The irresponsible promotion of e-cigarettes and Swaptober

The House of Commons Science and Technology Select Committee have launched an inquiry into e-cigarette impact, implications, and regulation.[1] National guidance for improving health should be evidence based, with a complete understanding of what is disseminated and encouraged. However, despite substantial gaps in research, e-cigarettes are promoted as part of smoking cessation efforts, including in the Public Health England (PHE) campaign, One You. Should the suggestion of e-cigarettes as a lesser evil be promoted when evidence of their long-term effect is insufficient?

Stoptober is a 28-day PHE initiative that occurs annually in October, with the aim of supporting smokers to quit the habit. In 2017, the campaign began promoting e-cigarettes, which, as stated by the National Institute of Clinical Excellence (NICE), are devices that are not understood in terms of the long-term health benefits or harms.[2] The promotion of e-cigarettes also features in the One You campaign. However, the addition of e-cigarettes to the 2017 mass-media promotion of Stoptober is even more surprising given that the evidence that e-cigarettes aid smoking cessation or reduction is of very low quality,[3] and data are insufficient for a confident estimation of their effectiveness.[4] Hence, the presentation of e-cigarettes alongside evidence-based medicinal products (licensed nicotine-replacement therapy) seems premature, and their portrayal as quitting aids under the Stoptober message of "if you can stop smoking for 28-days, you are five times more likely to quit" is misleading.[5] The Independent British Vape Trade Association sponsors Stoptober, which, among other activities, promotes the vape industry and thus presents a potential conflict of interest. A further concern is the evidence of e-cigarette use by UK children.[6] Preliminary evidence also suggests that e-cigarette use could have deleterious effects in relevant patient groups (eg, those with chronic obstructive pulmonary disease). Given that further understanding of the health implications of e-cigarettes is needed, promotion to the public, including young people and vulnerable populations at risk of shorter-term effects, is not an appropriate implementation strategy.

An emerging concern is Swaptober, another annual October initiative. Launched in 2016, Swaptober aims to convert smokers from traditional cigarettes to e-cigarettes, and is promoted in support of Stoptober. E-cigarettes are promoted as a healthier alternative to smoking, particularly as a first step towards smoking cessation for those finding it difficult to stop. However, e-cigarette companies do not encourage smoking cessation, but rather encourage a long-term swap. Thus, Swaptober, which occurs at the same time as Stoptober, could overshadow and reduce the effectiveness of Stoptober. In line with NICE guidance,[2] smoking cessation should be encouraged, not the swapping to an alternative that is not fully understood. PHE have reported and subsequently been key in publicising the expert opinion that e-cigarettes are 95% safer than tobacco.[7] The credibility of this estimate has been questioned, and has been referred to as a premature conclusion about devices that warrant rigorous safety assessment.[8]

NICE called for caution regarding recommendations for e-cigarettes as a suitable alternative because of the paucity of evidence regarding the long-term health effects.[2] This stance contradicts the views of PHE and the Royal College of Physicians,[7,9] both of whom advocate the wide promotion of e-cigarettes as a substitute for smoking. The contradictory stance of the UK's expert health organisations is likely to confuse public understanding. The inclusion of e-cigarettes in mass-media campaigns to help quit smoking is an example of short-term gain irrespective of the possible long-term consequences. Despite the divide in e-cigarette opinion, all health organisations should accept the need for a balanced approach to e-cigarette regulation. The House of Commons Science and Technology Select Committee inquiry[1] will probably highlight key gaps in the evidence regarding the health benefits or harms of e-cigarettes, which need to be addressed before any further public promotion of e-cigarettes. Until substantial evidence has been gathered on the health implications of e-cigarettes, the promotion of e-cigarettes by health organisations is irresponsible, unethical, and potentially harmful.

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Published **Online**
December 4, 2017
http://dx.doi.org/10.1016/S2213-2600(17)30473-3

For the **One You website** see https://www.nhs.ukoneyou/#7IGgkV475ATumckG.97

We declare no competing interests.

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See no evil, hear no evil, vape no evil; the irresponsible promotion of e-cigarettes and Swaptober

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Current word count: 599

The House of Commons Science and Technology Select Committee have launched an inquiry into e-cigarette impact, implications and regulation.[1] National guidance for improving health should be evidence-based, with a complete understanding of what is disseminated and encouraged. However, despite significant gaps in research, e-cigarettes are promoted as part of smoking cessation efforts including the Public Health England (PHE) Campaign, One You.[2] Should a suggested lesser evil in e-cigarettes, be promoted when there is insufficient evidence of their long-term impact?

Stoptober is a 28-day PHE initiative that occurs annually in October, with the aim of supporting smokers to quit the habit. In 2017, the campaign began promoting e-cigarettes, which as stated by the National Institute of Clinical Excellence (NICE), are devices that are not understood in terms of the long-term health benefits or harms.[3] Promotion of e-cigarettes features in the PHE campaign, One You.[2] The addition to this year's mass media is even more surprising when there is at best, very low-low quality evidence of e-cigarettes promoting smoking cessation or reduction,[4] and insufficient data for confident effect size estimation.[5] Hence, the presentation of e-cigarettes alongside evidence-based medicinal products (licensed nicotine-replacement therapy) seems premature and its portrayal under the message of being 'five times more likely to quit' is misleading. The Independent British Vape Trade Association sponsors Stoptober; which amongst other activity, promotes the vape industry and thus, presents a potential conflict of interest. A further concern is the evidence of e-cigarette use in UK children.[6] Preliminary evidence also suggests that e-cigarette use may have deleterious effects in relevant patient groups (e.g. COPD). Given that further understanding of the health implications of e-cigarettes is needed, promotion to the public including youth and vulnerable populations at risk of shorter-term effects, is not an appropriate implementation strategy.

An emerging concern is Swaptober, another annual October initiative. Launched in 2016, Swaptober aims to convert smokers from traditional cigarettes to e-cigarettes, and is promoted in support of Stoptober. E-cigarettes are promoted as a healthier alternative to smoking; particularly as a first step towards smoking cessation for people finding it difficult to stop. However, e-cigarette companies do not encourage smoking cessation, but alternatively to make a long-term swap. Thus, Swaptober, which occurs at the same time as Stoptober, could overshadow and reduce the effectiveness of Stoptober. In line with NICE guidance,[3] smoking cessation should be encouraged not to swap to an alternative that to date is not fully understood. PHE have reported and subsequently been key in publicising the expert opinion that e-cigarettes are 95% safer than tobacco.[7] The credibility of this estimate has been questioned, and referred to as a premature debate about devices that warrant rigorous safety assessment.

NICE called for caution regarding recommendations for e-cigarettes as a suitable alternative due to the lack of evidence regarding the long-term health effects.[3] This contradicts the views of PHE and the Royal College of Physicians,[7,8] advocating wide promotion of e-cigarettes as a substitute for smoking. The contradictory stance of the UK's expert health organisations is

likely to confuse public understanding. The inclusion of e-cigarettes in mass media campaigns is another example of short-term gain irrespective of the possible long-term pain. Despite the divide in e-cigarette opinion, all would accept the need for a balanced approach to e-cigarette regulation. The House of Commons Science and Technology Select Committee inquiry[1] will likely highlight key gaps of evidence regarding the health benefits or harms of e-cigarettes, which need addressing prior to any further public promotion. Until there is substantial evidence on the health implications of e-cigarettes, it is irresponsible, unethical and potentially harmful for health organisations to promote e-cigarettes.

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Studies: E-cigarettes Don’t Help Smokers Quit and They May Become Addicted to Vaping

September 2, 2020 | Yadira Galindo

E-cigarettes are now the most popular product used for smoking cessation in the United States, ahead of all U.S. Food and Drug Administration (FDA)-approved cessation aids combined, from nicotine patches and gum to prescription medications. However, two recently published analyses of a large nationally representative longitudinal study report that e-cigarettes are not effective in helping adults to quit smoking. However, more research is needed to identify whether these findings also extend to newer e-cigarette designs, which may deliver nicotine as effectively as cigarettes.

The analyses were led by University of California San Diego School of Medicine researchers using data from the Population Assessment of Tobacco and Health (PATH) Study, a longitudinal study of tobacco use and its effect on the health of people in the United States. The PATH Study, undertaken by the National Institute on Drug Abuse (NIDA) and the FDA Center for Tobacco Products under contract to Westat, enrolled a nationally representative sample of 45,971 adults and youth between September 2013 and December 2014 and re-interviewed them annually for the first four years.

The analysis, published online September 2, 2020 in the journal PLOS ONE, considered 2,770 daily smokers who reported trying to quit smoking during the first follow-up year; 23.5 percent used e-cigarettes in 2014-15 (before nicotine salt technology in e-cigarettes) to help with their quit attempt. At the second follow-up one year later, 9.6 percent of e-cigarette users had been abstinent from smoking over the previous 12 months compared to 9.5 percent who did not use an e-cigarette and 10.2 percent who used neither an e-cigarette or a pharmaceutical aid. There was no evidence that cessation rates differed between e-cigarette users and closely matched smokers who did not use e-cigarettes.

“Among this representative sample of U.S. smokers trying to quit, we found no evidence that e-cigarettes were helpful in the quit attempt,” said John P. Pierce, PhD, Professor Emeritus of Cancer Prevention at UC San Diego Moores Cancer Center and the study’s first author. “This lack of effectiveness was also apparent in the sub-sample who used e-cigarettes on a daily basis for this quit attempt.”

The second analysis, published online on July 27, 2020 in the *American Journal of Epidemiology*, considered 2,535 daily and non-daily smokers from the PATH Study’s wave 2 survey who reported making a quit attempt during the next follow-up year. Seventeen percent of these used e-cigarettes to help with the quit attempt in 2015-16 (also before the increase in sales of e-cigarettes with nicotine salt technology). At the subsequent wave 4 follow up survey, 13 percent reported not smoking for at least 12 months — a somewhat higher rate than the in first analysis (PLOS One paper), attributed to the inclusion of non-daily smokers who are known to have higher quit rates.

Again, study authors said there was no evidence that cessation rates differed from closely matched smokers who did not use e-cigarettes. However, in this analysis, it was clear that participants who used e-cigarettes to quit smoking were less likely to be nicotine-free at follow-up. This was largely because many of those who did quit smoking cigarettes were still using e-cigarettes, which also contain nicotine.

“In these analyses, we carefully matched each smoker who used e-cigarettes as a cessation aid with up to two similar smokers who tried to quit without using e-cigarettes,” said Karen Messer, PhD, professor of family medicine and public health, director of biostatics at UC San Diego Moores Cancer Center and senior author on both papers. “Our results suggest that these smokers would have been just as successful in quitting smoking without the use of e-cigarettes. However, without the use of e-cigarettes they would have been more successful in breaking their nicotine dependence.”

Co-authors for the *PLOS ONE* study, include: Tarik Benmarhnia, Ruifeng Chen, Martha White, Sheila Kealey. and Dennis R. Trinidad, all of UC San Diego; David B. Abrams and Raymond S. Niaura, of New York University; Bridget K. Ambrose, Nicolette Borek, Blair Coleman, James Henrie, Jean Limpert, Carolina Ramôa, Ethel Taylor, and Lisa D. Gardner, all of the Food and Drug Administration; Carlos Blanco, Kelvin Choi, Wilson M. Compton, and Heather L. Kimmel, all of the National Institutes of Health; K. Michael Cummings, Medical University of South Carolina; Cristine D. Delnevo and Michael B. Steinberg, of Rutgers Center for Tobacco Studies; Tara Elton-Marshall, Centre for Addiction and Mental Health; Maciej L. Goniewicz, Karin A. Kasza, and Maansi Bansal-Travers, all of Roswell Park Comprehensive Cancer Center; Shannon Gravely, University of Waterloo; Geoffrey T. Fong, University of Waterloo and Ontario Institute for Cancer Research; Dorothy Hatsukami, University of Minnesota; Eva Sharma and Cassandra A. Stanton, of Westat; Marushka L. Silveira, National Institutes of Health and Kelly Government Solutions; Andrew Hyland, Roswell Park Comprehensive Cancer Center and Westat; and Samir Soneji, Gillings School of Global Public Health.

This research was funded, in part, by the National Institute on Drug Abuse, National Institutes of Health and the Food and Drug Administration’s Center for Tobacco Products under contract to Westat (HHSN271201100027C).

Co-authors for the *American Journal of Epidemiology* study include: Ruifeng Chen, Eric C. Leas, Martha M. White, Sheila Kealey, David R. Strong, Dennis R. Trinidad, and Tarik Benmarhnia, all of UC San Diego.

This research was funded, in part, by the National Institutes of Health (RO1CA234539) as well as the California Tobacco-related Disease Research Program (28IR-0066).

Disclosures: Cummings has received payment as a consultant to Pfizer, Inc., for service on an external advisory panel to assess ways to improve smoking cessation delivery in health care settings. He also has served as paid expert witness in litigation filed against the tobacco industry. Goniewicz receives fees for serving on an advisory board from Johnson & Johnson and grant support from Pfizer. Compton reports long-term stock holdings in General Electric Company, 3M Company and Pfizer Incorporated, unrelated to this manuscript. Pierce and Strong report grants from National Cancer Institute during the conduct of the study. White reports grants from National Institutes of Health during the conduct of the study.

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edition.cnn.com /2022/02/07/health/e-cigarettes-quit-smoking-wellness/index.html

E-cigarettes were less effective than gum and other nicotine replacement aids, study says

Sandee LaMotte ⋮⋮ 8/2/2022

Nearly 60% of recent former smokers who were daily e-cigarette users had resumed smoking by 2019, a new study found.

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CNN —

People using e-cigarettes to quit smoking found them to be less helpful than more traditional smoking cessations aids, a new study found.

Vaping may raise the risk for erectile dysfunction, even in young men, a study found.

Vaping doubled the risk of erectile dysfunction in men age 20 and older, study finds

The study, published Monday in the journal BMJ, analyzed the latest 2017 to 2019 data from the Population Assessment of Tobacco and Health Study, which follows tobacco use among Americans over time.

“This is the first time we found e-cigarettes to be less popular than FDA-approved pharmaceutical aids, such as medications or the use of patches, gum, or lozenges,” said John P. Pierce, the director for

population sciences at the Moores Cancer Center at the University of California, San Diego.

“E-cigarettes were also associated with less successful quitting during that time frame,” said Pierce, a professor emeritus of family medicine and public health. In fact, nearly 60% of recent former smokers who were daily e-cigarette users had resumed smoking by 2019, the new study found.

“There’s no evidence that the use of e-cigarettes is an effective cessation aid,” Pierce said.

choice between cigarette and e-cigarette

Adobe Stock

Using e-cigarettes to prevent smoking relapse doesn't work well, study finds

A three-month randomized trial in the United Kingdom, published in 2019, found e-cigarettes, along with behavioral interventions, did help smokers quit tobacco cigarettes. In guidance published in late 2021, the UK National Institute for Health and Care Excellence decided to recommend that smokers use e-cigarettes to help them quit.

However, observational studies in the United States that study smoking in real-world environments have not found that to be true, Pierce said. A 2021 study by his team found people who quit smoking tobacco cigarettes between 2013 and 2016 by switching to e-cigs or other tobacco products were 8.5% more likely to resume smoking when compared with people who quit all tobacco products.

Uptick in use by teens

Proponents of e-cigarettes as a smoking cessation tool say higher-nicotine versions should assist tobacco cigarette smokersto quit tobacco cigarettes because they would be able to take fewer puffs off a vape than smoking the entire cigarette, Pierce said.

Vape teenager. Young pretty caucasian brunette girl smoking an electronic cigarette on the street in the spring. Deadly bad habit.

More than 2 million US teens use e-cigarettes, a quarter of them daily, CDC and FDA find

“In 2017, cigarette sales increased by 40%,” with a majority of the market share being held by new brands of e-cigarettes with very high nicotine levels, he said.

“We wanted to look at these new high-nicotine versions and see whether there’s any evidence that they helped people quit because the previous ones didn’t.”

Instead of an uptick in use by smokers, the study found use of e-cigarettes as a cessation aid dropped by 25% over the two-year period, Pierce said.

Did the higher-octane e-cigaretteshelp those who did use them to stop smoking?

“We can’t study the effectiveness of these high-nicotine e-cigarettes because no smokers were using them during the majority of the two-year period,” Pierce said. There was a small uptick in 2019, he added, which will need to be analyzed when the next PATH data are released.

If smokers weren’t driving the uptick in sales during 2017 to 2019, who was?

More teens were using vapes during that period, according to data collected by the US Food and Drug Administration. By September 2018, then-FDA Commissioner Dr. Scott Gottlieb was calling teen use of e-cigarettes “an epidemic.”

WHITE OAK, MD - JULY 20: A sign for the Food And Drug Administration is seen outside of the headquarters on July 20, 2020 in White Oak, Maryland.

Sarah Silbiger/Getty Images

Prior work by Pierce and his team have found e-cigarettes can function as a gateway drug for many teens. Youth ages 12 to 24 who used e-cigarettes were three times as likely to become daily cigarette smokers in the future, a 2021 study found.

In addition to a connection to later cigarette smoking, vapingby teens has also been linked to psychological issues, headaches, stomachaches and significant addictions to nicotine. In 2019, teens began to die from lung damage that was later connected to chemicals in vape liquids, including vitamin E acetate, according to the American Lung Association.

The FDA told CNN that the agency doesn’t comment on specific studies, but “evaluates them as part of the body of evidence to further our understanding about a particular issue and assist in our mission to protect public health.”

“The FDA is reviewing the findings of the paper,” said FDA press officer Alison Hunt via email.

OPEN ACCESS

Effectiveness of e-cigarettes as aids for smoking cessation: evidence from the PATH Study cohort, 2017–2019

Ruifeng Chen,[1] John P Pierce ,[1,2] Eric C Leas,[1] Tarik Benmarhnia,[3] David R Strong,[1,2] Martha M White,[2] Matthew Stone ,[1] Dennis R Trinidad,[1] Sara B McMenamin,[1] Karen Messer[1,2]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/tobaccocontrol-2021-056901).

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Received 6 July 2021
Accepted 12 November 2021

To cite: Chen R, Pierce JP, Leas EC, *et al*. *Tob Control* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/tobaccocontrol-2021-056901

ABSTRACT

Objective To assess the effectiveness of e-cigarettes in smoking cessation in the USA from 2017 to 2019, given the 2017 increase in high nicotine e-cigarette sales.

Methods In 2017, the PATH Cohort Study included data on 3578 previous year smokers with a recent quit attempt and 1323 recent former smokers. Respondents reported e-cigarettes or other products used to quit cigarettes and many covariates associated with e-cigarette use. Study outcomes were 12+ months of cigarette abstinence and tobacco abstinence in 2019. We report weighted unadjusted estimates and use propensity score matched analyses with 1500 bootstrap samples to estimate adjusted risk differences (aRD).

Results In 2017, 12.6% (95% CI 11.3% to 13.9%) of recent quit attempters used e-cigarettes to help with their quit attempt, a decline from previous years. Cigarette abstinence for e-cigarette users (9.9%, 95% CI 6.6% to 13.2%) was lower than for no product use (18.6%, 95% CI 16.0% to 21.2%), and the aRD for e-cigarettes versus pharmaceutical aids was −7.3% (95% CI −14.4 to −0.4) and for e-cigarettes versus any other method was −7.7% (95% CI −12.2 to −3.2). Only 2.2% (95% CI 0.0% to 4.4%) of recent former smokers switched to a high nicotine e-cigarette. Subjects who switched to e-cigarettes appeared to have a higher relapse rate than those who did not switch to e-cigarettes or other tobacco, although the difference was not statistically significant.

Conclusions Sales increases in high nicotine e-cigarettes in 2017 did not translate to more smokers using these e-cigarettes to quit smoking. On average, using e-cigarettes for cessation in 2017 did not improve successful quitting or prevent relapse.

INTRODUCTION

Electronic cigarettes (e-cigarettes), which were first sold in the USA in 2007, had become a popular cessation aid for US smokers by 2014–2016.[1 2] From 2013 to 2017 US sales of e-cigarettes almost doubled,[3] which was associated with rapid uptake among adolescents.[4] If there was a similar increase in e-cigarette usage attributed to smoking cessation (either as a cessation aid or an alternative nicotine source) and effectiveness was demonstrated, we would expect that successful cigarette cessation would increase in the population.

Randomised clinical trials (RCTs) are the optimal design to assess the efficacy of e-cigarettes as smoking cessation aids. To date, a number of RCTs have addressed the role of e-cigarettes as an aid to quitting cigarettes, and a recent systematic review concluded, with moderate certainty, that e-cigarettes improve cessation by an estimated four additional successful quitters per 100 quit attempters when compared with nicotine replacement therapy (NRT).[5] However, RCTs are usually conducted under optimal conditions, which means that they may not translate to the effectiveness of the product in community settings.[6] Analyses of the Population Assessment of Tobacco and Health (PATH) Study[7] have not found that e-cigarettes improve cessation.[8 9]

To date, no trials have been reported that test the hypothesis that cigarette smokers are able to switch to e-cigarettes and maintain their nicotine habit without relapsing to cigarette smoking. A recent PATH Study analysis found that those who switched to e-cigarettes between 2014 and 2016 were more likely to relapse to cigarette smoking by 2017 than those who were free from all tobacco including e-cigarettes between 2014 and 2016.[10] However, the e-cigarette market has changed dramatically since 2016. JUUL Labs introduced nicotine salt technology in 2015 and high nicotine concentration pods (ie, 5% nicotine by weight).[11] On the back of an innovative marketing campaign, JUUL became the most popular US e-cigarette in 2017[12 13] when over 50% of all e-cigarette products sold had high (>4%) nicotine concentrations.[3] Increasing the nicotine concentration in e-cigarette liquid increases nicotine exposure for users,[14–16] and high nicotine JUUL users have blood nicotine concentrations similar to cigarette smokers, which some argue may be a prerequisite for successfully switching to e-cigarettes.[17] Thus, in 2017, recent former smokers had the opportunity to switch to e-cigarettes with a much higher nicotine concentration than was possible for those in earlier years, which could reduce relapse to cigarette smoking.

The PATH Study is a nationally representative longitudinal study that can address questions on the effectiveness of e-cigarettes in reducing cigarette smoking. However, for longitudinal studies to address whether a product may cause an outcome such as smoking cessation requires careful analysis. The critical point is that groups must be as comparable as possible across variables that might be related to the study outcome.[18] In RCTs, randomisation of product usage usually achieves this effect.

In observational studies it is necessary to control for the variables associated with using e-cigarettes, particularly those that are also associated with longer term cigarette cessation (eg, motivation to quit). Some published analyses of PATH Study data[19–21] have not required that the control group has a recent quit attempt. Given that e-cigarettes are seen as a popular way to quit cigarettes,[1] such an analytical decision means that the control group will be very different from the e-cigarette user group as it will include many people who are not trying to quit, thus significantly biasing the conclusions in favour of an e-cigarette effect.[22]

In this paper, our starting population are PATH Study respondents who were established smokers in 2016. To address the hypothesis that e-cigarettes are an effective cigarette cessation aid, we limit our consideration to those who reported a quit attempt in the year prior to the 2017 (W4) survey and compare how cessation aids used were associated with 12+ months of cigarette/tobacco abstinence at the 2019 (W5) survey (see study flowchart in online supplemental file 1). To address whether switching to e-cigarettes improves maintenance of cigarette abstinence, we focus on those who were recent former smokers in 2017 (W4) and compare relapse to cigarette smoking in 2019 (W5) among those who switched to e-cigarettes versus those who did not use any tobacco or e-cigarette product.

METHODS

Data sources

The PATH Study is a US nationally representative cohort study. A screener survey of a stratified address-based sample of households oversampled tobacco users, young adults aged 18–24 and African Americans for the adult cohort.[7] The first four survey waves (W1–4) were at annual intervals starting in 2013–14 (W1), and W5 (2019) was conducted ~2 years after W4 (2017). The initial household screener had a 54% response rate and the adult survey response rates were 74.0%, 83.2%, 78.4% and 73.5% for W1–4, respectively. Among initial screened households, 27 757 adults were interviewed at W4 and an additional new replenishment sample of 6065 adults were added to the cohort to adjust for attrition and reset the cohort sample size, thus reducing the magnitude of weighting required to provide population estimates.[23] The weighted response rate for W4 replenishment household screener was 52.8% and the response rate of the adult survey was 68.0% at W4 and 88.0% at W5. The Westat Institutional Review Board approved the study and all respondents provided written informed consent. Data were obtained from available restricted use files.[23]

Study sample

The W4 (2017) total sample included both a continuing cohort and an added refreshment sample (see online supplemental file 1). For longitudinal analyses requiring earlier data we are limited to the continuing cohort subset (those with W1–W3 data). For each PATH survey, lifetime 100+ cigarette smokers were asked if they "currently smoke every day, some days, or not at all".[23] Thus, in this paper the continuing cohort are drawn from those who were current daily or some-day smokers at W3 (2016). For the added refreshment sample at W4 (2017), we assessed previous year smoking from: "Around this time 12 months ago, did you smoke cigarettes every day, some days or not at all?".

To investigate whether e-cigarettes are an effective cigarette cessation aid, we identified recent quit attempters from the W4 question: "In the past 12 months, have you tried to quit cigarettes completely?" A positive response was made by 3578 previous year established smokers. To investigate whether switching to e-cigarettes helps prevent relapse to cigarettes, we identified recent former smokers at W4 from a "not at all" response to the current cigarette smoking question among previous year established smokers (n=1323).

Use of e-cigarette or other products

To identify products used to help quit attempts, W4 quit attempters were asked: "Thinking back to the last time you tried to quit cigarettes in the past 12 months", followed by three separate types of questions: "did you use an e-cigarette/(other non-cigarette tobacco product) to help you quit?"; "did you use a nicotine patch, gum, inhaler, nasal spray, lozenge or pill?"; and "did you use Chantix, varenicline, Wellbutrin, Zyban or bupropion?".

To identify recent former smokers who had switched to an alternative nicotine source, we used the current use question (responses of every day, some days or not at all) for each of the following products: e-cigarettes, cigars, cigarillo, filtered cigars, pipes, hookah, snus and smokeless products. E-cigarette users were asked: "What concentration of nicotine do you usually use?" with eight response categories ranging from 0% to 4+%, as well as don't know.

Study outcome

At W5 (2019) current cigarette and other tobacco use was assessed from responses to the current use question for each product. To assess duration of abstinence from cigarettes, recent former smokers were asked: "In the past 12 months, have you smoked a cigarette/(used product), even one or two puffs/times?" Cigarette abstinence includes those who were using e-cigarettes or other tobacco products. Tobacco abstinence requires abstinence from all tobacco and e-cigarettes. This question was asked for all tobacco products as well as e-cigarettes. Duration of abstinence came from the question: "About how long has it been since you last smoked a cigarette/puffed from an electronic nicotine product?"

Study covariates

PATH Study investigators identified and measured potential confounders for e-cigarette and cessation analyses and demonstrated that these were mismatched between e-cigarette users and control participants.[9] Most of these variables were best measured when participants were still smokers at W3 (2016) and are only available for the continuing cohort. They include sociodemographic variables (age, sex, education, race, ethnicity, income), cigarette smoking status (daily or non-daily), tobacco dependence index,[24] time since last quit attempt, cigarette consumption, e-cigarette use status (any use or no use), interest in quitting cigarettes, self-efficacy about quitting, smoke-free home, exposure to smoking, perceived harm of cigarettes and e-cigarettes, cigarette pack-years, age began regular smoking, insurance status and health-related covariates (external/internal mental health symptoms, existence of smoking-related disease). Questions for each covariate and univariate distributions by product used in the quit attempt are shown in online supplemental file 2,3.

To test whether switching to e-cigarettes prevented relapse, we used the same set of covariates with the following exceptions: (1) we added duration of cigarette abstinence at W4 (2017); (2) we changed the source of the smoke-free home measure from W3 (2016) to W4 (2017). Details of these covariates with univariate distributions by product used are shown in online supplemental file 4,5.

Statistical analyses

All analyses were conducted in R (version 3.6.1). For unadjusted analyses using total samples (continuing + refreshment), estimates were weighted using W4 single wave weights[23] and variance estimates for confidence intervals were calculated using replicate weights constructed using a balanced repeated replications procedure with Fay adjustment (ρ=0.3).[7] Sample characteristics were explored using weighted proportions with 95% confidence limits. The adjusted analyses were restricted to the continuing cohort only and used W1–W5 longitudinal survey weights.[23]

For the adjusted propensity score matching analysis we created 1500 bootstrap samples for each hypothesis test. Within each bootstrap sample we used simple imputation (R package 'Mice') for missing data from all the covariates, and we identified the optimal set of covariates prior to estimating the propensity score as follows. To select variables we used the LASSO with the Akaike Information Criterion (AIC).[25 26] The optimal set of covariates was the one that returned the smallest AIC. Then, for each exposure separately, we calculated a propensity score for each participant by estimating the unweighted probability of membership in the e-cigarette use group using logistic regression adjusting for the optimised set of covariates. Using the estimated propensity score, we matched up to two controls for each case (nearest neighbour matching using R package 'Matchit')[27] within the a priori calliper distance of 0.1. Cases that did not have a match meeting these criteria were omitted from the sample (<10% for each matching). For each matched bootstrap sample we used logistic regression with survey weights (R package 'survey') to estimate the average risk difference between the two matched groups for each outcome. The model included an indicator of the matched pair (or triple) and an indicator of use of e-cigarettes or not. The risk difference was estimated by the bootstrap mean estimate and the confidence intervals were calculated using the 95% bootstrap quantiles. To assess e-cigarettes as a cigarette cessation aid we compared 12+ months of cigarette abstinence between (1) any e-cigarette for quit attempt versus anyone who did not use an e-cigarette; and (2) any e-cigarette versus NRT or pharmaceutical aid only for quit attempt. We also compared those who used e-cigarettes only versus NRT or pharmaceutical aid only in a sensitivity analysis. To assess if e-cigarettes prevent relapse to cigarettes, we estimated the risk difference in rates of relapse to cigarette smoking between any e-cigarette versus no e-cigarette at W4. Current use of NRT and pharmaceutical aids was only collected in relation to the last quit attempt.

RESULTS

Characteristics of tobacco use among recent quit attempters

There were no differences between the continuing cohort and the combined continuing cohort and refreshment sample (ie, total W4 sample) in any of the following key measures (table 1). In 2017 (W4), 32.8% (95% CI 31.8% to 33.9%) of previous year established smokers reported a recent quit attempt in the year prior to W4 and 12.4% (95% CI 11.6% to 13.3%) were recent former smokers at W4. Among recent quit attempters, 12.6% (95% CI 11.3% to 13.9%) reported using e-cigarettes to help in their last quit attempt (8.7% e-cigarettes only, 3.2% e-cigarettes and NRT/pharmaceutical aid, 0.5% e-cigarettes and other tobacco products, 0.2% used 3+ products); 2.5% (95% CI 1.9% to 3.1%) used non-e-cigarette tobacco products (2.1% non-e-cigarette tobacco products only); 20.6% (95% CI 18.9% to 22.3%) used NRT or a pharmaceutical aid only and 64.3% (95% CI 62.4% to 66.1%) did not use any product.

Among recent former cigarette smokers in 2017 (W4), 15.3% had switched to e-cigarettes (daily: 9.1% (95% CI 7.1% to 11.0%); non-daily: 6.2% (95% CI 4.7% to 7.7%); 10.4% e-cigarettes only) and 15.9% (95% CI 13.6% to 18.2%) reported

Table 1 Characteristics of PATH Study Wave 4 tobacco use

	W4 continuing cohort*			W4 continuing cohort+refreshment sample†		
	n	Wtd%	95% CI (%)	n	Wtd%	95% CI (%)
W4 population	24 905			30 970		
Smoking prevalence 12 months before W4	8564	19.6	(19.0 to 20.2)	10 614	19.7	(19.2 to 20.3)
Daily cigarette smokers	6286	74.1	(72.9 to 75.3)	7705	73.3	(72.1 to 74.4)
Non-daily cigarette smokers	2278	25.9	(24.7 to 27.1)	2909	26.7	(25.6 to 27.9)
Recent quit attempters (in year prior to W4)	2870	32.8	(31.6 to 33.9)	3578	32.8	(31.8 to 33.9)
Product used in quit attempt						
Any e-cigarettes	363	11.6	(10.2 to 13.0)	488	12.6	(11.3 to 13.9)
Non e-cigarette tobacco product‡	67	2.3	(1.7 to 2.9)	91	2.5	(1.9 to 3.1)
No tobacco product but any NRT§ or pharmaceutical aid¶	566	20.7	(18.9 to 22.5)	700	20.6	(18.9 to 22.3)
No product	1874	65.4	(63.4 to 67.4)	2299	64.3	(62.4 to 66.1)
Recent former smokers (RFS) at W4	1035	11.9	(10.9 to 12.8)	1323	12.4	(11.6 to 13.3)
Product used by RFS at W4						
Daily e-cigarettes	110	9.3	(7.1 to 11.5)	136	9.1	(7.1 to 11.0)
Non-daily e-cigarettes	61	5.3	(3.7 to 6.9)	94	6.2	(4.7 to 7.7)
Non-e-cigarette tobacco product‡	188	15.6	(13.0 to 18.1)	240	15.9	(13.6 to 18.2)
Tobacco-free	676	69.8	(66.5 to 73.1)	853	68.8	(65.9 to 71.8)

*The continuing cohort were interviewed on each of the previous PATH waves (W1, W2, W3).
†The W4 continuing cohort + refreshment sample includes all people interviewed for the PATH Study in 2017 (W4). The purpose of the refreshment sample (those first interviewed at W4) was to reset the size of the cohort and reduce the weighting needed to make estimates that were nationally representative of the US population.
‡Other products used by recent former smokers were those from the cigar family (traditional cigars, cigarillos and filtered cigars) and the smokeless family (snus pouches, loose snus, moist snuff, dip, spit and chewing tobacco).
§NRT (nicotine replacement therapy) includes nicotine patch, gum, inhaler, nasal spray, lozenge or pill.
¶Pharmaceutical aid includes Chantix, varenicline, Wellbutrin, Zyban or bupropion.
W4, Wave 4; Wtd, weighted US population estimate (W4 single-wave weights were used).

Table 2 Characteristics of recent quit attempters reported at PATH Wave 4 by use of non-cigarette tobacco products on last quit attempt prior to Wave 4

	No tobacco product use (n=2999)		Any e-cigarette use (n=488)		Other non-cigarette tobacco use* (n=91)	
Variable	**Wtd%**	**95% CI**	**Wtd%**	**95% CI**	**Wtd%**	**95% CI**
Age						
18–34	81.0	79.1 to 83.0	15.4	13.3 to 17.5	3.5	2.2 to 4.9
35–50	84.0	81.3 to 86.7	13.7	11.3 to 16.2	2.3	1.4 to 3.2
50+	89.7	87.8 to 91.5	8.8	7.1 to 10.4	1.6	0.7 to 2.4
Sex						
Male	84.6	82.7 to 86.5	12.0	10.3 to 13.8	3.4	2.5 to 4.3
Female	85.2	83.3 to 87.0	13.3	11.6 to 14.9	1.6	0.8 to 2.3
Education						
<High school	86.9	84.8 to 89.0	10.6	8.7 to 12.5	2.5	1.6 to 3.5
High school graduate	86.6	84.4 to 88.7	9.8	7.8 to 11.7	3.6	2.2 to 5.1
Some college+	82.9	81.0 to 84.9	15.3	13.4 to 17.1	1.8	1.0 to 2.6
Race/ethnicity						
Non-Hispanic white	82.5	80.5 to 84.4	15.3	13.4 to 17.2	2.2	1.6 to 2.9
Others	89.0	87.4 to 90.6	8.0	6.5 to 9.4	3.0	1.8 to 4.2
Income (US$)						
<35 000	86.5	84.7 to 88.3	10.6	9.0 to 12.1	2.9	2.0 to 3.8
≥35 000	82.7	80.3 to 85.1	15.6	13.2 to 17.9	1.7	1.0 to 2.4
Cigarette smoking status at W3						
Daily	83.4	81.7 to 85.1	13.9	12.3 to 15.5	2.7	1.9 to 3.4
Non-daily	88.2	86.3 to 90.1	9.7	7.7 to 11.7	2.1	1.1 to 3.0
E-cigarette use at W3						
Marked	66.0	61.5 to 70.5	30.8	26.4 to 35.1	3.2	1.4 to 5.1
Not marked	89.1	87.8 to 90.3	8.6	7.5 to 9.7	2.3	1.7 to 3.0
Time since last quit attempt						
<90 days	83.4	81.0 to 85.9	14.3	11.9 to 16.8	2.3	1.2 to 3.3
≥90 days	82.4	80.1 to 84.6	14.9	12.6 to 17.1	2.8	1.7 to 3.9

*Other non-cigarette tobacco: any use of cigar, cigarillo, filtered cigar, pipe, hookah, snus or smokeless tobacco.
PATH, Population Assessment of Tobacco and Health; W3, Wave 3; W4, Wave 4; Wtd, weighted US population estimate (W4 single-wave weights were used).

use of another tobacco product (11.5% cigar family, 2.9% smokeless, 3.6% other or multiple products) and 68.8% (95% CI 65.9% to 71.8%) reported not using any tobacco or e-cigarette. Among those who had switched to e-cigarettes, only 2.2% (95% CI 0.0% to 4.4%) reported using e-cigarettes with concentration >4% (see online supplemental file 6) and 1.9% (95% CI 0.4% to 3.4%) reported using JUUL e-cigarettes. This supplement also presents the 2019 (W5) data for recent former smokers who switched to e-cigarettes as this proportion increased to 22.0% (95% CI 19.6% to 24.5%) compared with the 15.3% observed at W4, with 19.9% of them using high nicotine content e-cigarettes.

Characteristics of recent quit attempters who used e-cigarettes

The use of e-cigarettes to aid a quit attempt was higher in 18–50-year-old subjects than in those aged 50+ years, higher in those who had attended college than in those who did not complete high school, higher in non-Hispanic white people than in other race ethnicities, higher in those with incomes >$35 000 than in those with lower incomes, higher in 2016 (W3) daily smokers than in non-daily smokers and higher in 2016 (W3) e-cigarette users (table 2). Similar use patterns were observed for recent former smokers (see online supplemental file 3, 5), although the lower sample size of recent former smokers resulted in some wide confidence intervals.

Successful quitting at W5 among quit attempters in year prior to W4

Unadjusted successful quitting in the total samples (continuing + refreshment)

Among those who used e-cigarettes in their last quit attempt prior to W4 (2017), 9.9% (95% CI 6.6% to 13.2%) were abstinent from cigarettes for 12+ months but not all tobacco at W5, which was lower than those who used NRT or pharmaceutical aid only (15.2%, 95% CI 12.3% to 18.1%) or those who did not use any product in the quit attempt (18.6%, 95% CI 16.0% to 21.2%), with similar patterns between the total sample and the continuing cohort (table 3). Considering abstinence for 12+ months from all tobacco including e-cigarettes, the proportion who used e-cigarettes for the quit attempt (3.5%, 95% CI 1.5% to 5.5%) was considerably lower than those who used NRT or pharmaceutical aid only (12.5%, 95% CI 9.6% to 15.4%) or who did not use any product when attempting to quit (13.9%, 95% CI 11.4% to 16.5%). For both abstinence from cigarettes and abstinence from all tobacco (including e-cigarettes), our data suggest that those who used e-cigarettes to help them quit had a similar outcome to those who used another non-cigarette combustible (eg, cigar) or smokeless tobacco product (eg, snus) (table 3).

Among recent former smokers who had switched to daily use of e-cigarettes in 2017 (W4), 43.2% (95% CI 32.5% to 54.0%) had successfully quit cigarette smoking by 2019 (W5), which

Table 3 Abstinence for 12+ months at Wave 5 among smokers who tried to quit prior to Wave 4 according to products used to assist during last quit attempt prior to Wave 4

Product used to assist during last quit attempt prior to W4	W4 sample type	Sample size	Abstinent* all tobacco (including e-cigarettes) at W5		Abstinent cigarettes, not all tobacco at W5†	
			Wtd%	95% CI	Wtd%	95% CI
E-cigarette	Continuing cohort‡	319	2.5	(0.5 to 4.5)	8.5	(5.1 to 11.8)
	Continuing cohort + refreshment sample§	401	3.5	(1.5 to 5.5)	9.9	(6.6 to 13.2)
Other tobacco product¶ but no e-cigarettes	Continuing cohort	58	2.8	(0 to 6.0)	13.5	(1.5 to 25.4)
	Continuing cohort + refreshment sample	77	2.5	(0.5 to 4.5)	14.1	(4.4 to 23.9)
No tobacco product or e-cigarettes but any NRT** or pharmaceutical aid††	Continuing cohort	489	13.2	(9.6 to 16.8)	16.2	(12.7 to 19.6)
	Continuing cohort + refreshment sample	582	12.5	(9.6 to 15.4)	15.2	(12.3 to 18.1)
No product	Continuing cohort	1613	14.7	(11.8 to 17.6)	19.2	(16.3 to 22.1)
	Continuing cohort + refreshment sample	1923	13.9	(11.4 to 16.5)	18.6	(16.0 to 21.2)
Total	Continuing cohort	2479	12.6	(10.6 to 14.7)	17.1	(15.0 to 19.2)
	Continuing cohort + refreshment sample	2983	12.0	(10.2 to 13.8)	16.7	(14.9 to 18.5)

*Abstinence = 12+ months, reported at Wave 5.
†Those abstinent from cigarettes could be using e-cigarettes or other tobacco products.
‡The continuing cohort were W4 respondents who had been surveyed at previous PATH Study waves (W1–W3).
§The W4 continuing cohort + refreshment sample includes all people interviewed for the PATH Study in 2017 (W4). The purpose of the refreshment sample (those first interviewed at W4) was to reset the size of the cohort and reduce the weighting needed to make estimates that were nationally representative of the US population.
¶Other products used by recent former smokers were those from the cigar family (traditional cigars, cigarillos and filtered cigars) and the smokeless family (snus pouches, loose snus, moist snuff, dip, spit and chewing tobacco).
**NRT (nicotine replacement therapy) includes nicotine patch, gum, inhaler, nasal spray, lozenge or pill.
††Pharmaceutical aid includes Chantix, varenicline, Wellbutrin, Zyban or bupropion.
W4, Wave 4; W5, Wave 5; Wtd, weighted US population estimate (W4 single-wave weights).

was similar to those who used e-cigarettes on a non-daily basis or to those who switched to another tobacco product, whether daily or non-daily (table 4). All estimates of successful quitting for those who switched to another nicotine source were below the lower confidence bound for those who reported no tobacco use in 2017 (W4) (52.9%, 95% CI 47.8% to 58.0%), although confidence intervals overlapped. Among those who had relapsed between 2017 (W4) and 2019 (W5), 15–20% had made another quit attempt (re-quit) and were abstinent at the time of the 2019 (W5) survey, although there were no differences across categories in the duration of these re-quit attempts.

Adjusted successful quitting in the continuing cohort

Propensity score matching achieved comparable study groups for variables associated with e-cigarette use at W4 (2017) (see online supplemental file 7-9). However, the perception that e-cigarettes were less harmful than cigarettes fell from 23.8% (95% CI 23.1% to 24.5%) in 2016 (W3) to 16.4% (95% CI 15.9% to 17.0%) in 2019 (W5) (see online supplemental file 10). Among quit attempters, those who used an e-cigarette as an aid had a lower 12+ month cigarette abstinence rate than those who did not (adjusted risk difference (aRD) −7.7, 95% CI −12.2 to −3.2). Similarly, using an e-cigarette as an aid resulted in a lower 12+ month cigarette abstinence rate than using NRT or a pharmaceutical aid (aRD −7.3, 95% CI −14.4 to −0.4) (figure 1A). When the outcome was 12+ months abstinence from cigarettes, e-cigarettes or any other tobacco product, these results were essentially the same with the aRD showing that e-cigarette use had between 7.4% and 6.4% lower abstinence than either not using e-cigarettes or using a pharmaceutical aid (figure 1B). The sensitivity analysis estimating the aRD between e-cigarette only users and NRT or pharmaceutical aid only users produced similar results.

Propensity score matching achieved highly comparable groups among recent former smokers who had switched to e-cigarettes compared with those who had not (online supplemental file 7). The e-cigarette group appeared to have a higher relapse rate by W5 (2019) than those who did not use any tobacco or e-cigarette product (aRD 9.4%, 95% CI −5.0% to 22.8%); however, this did not reach statistical significance.

DISCUSSION

In this analysis of the most recent PATH Study data, smokers who reported using e-cigarettes to help them in their most recent cigarette quit attempt were less rather than more likely than other quit attempters to achieve either successful cigarette cessation or to become tobacco and e-cigarette free. Rather than e-cigarettes adding four additional successful cigarette quitters per 100 quit attempters compared with pharmaceutical aid users as concluded by a systematic review of RCT data,[5] in this study e-cigarette use was associated with seven fewer successful quitters per 100 quit attempters. Furthermore, switching to e-cigarettes did not reduce the risk of relapse to cigarette smoking compared with other recent former smokers. Instead, nearly 60% of recent former smokers who were daily e-cigarette users had relapsed to cigarette smoking by 2019 (W5).

Between 2013 and 2018 there was a rapid increase in both the number of e-cigarette products available in the USA (now >800) and in the total unit sales, with over 40% sales growth between 2016 and 2017 alone.[3] This rapid growth has been attributed to

Table 4 Unadjusted cigarette smoking status at Wave 5 among recent former cigarette smokers* by use of non-cigarette tobacco products assessed at Wave 4

Exposure as RFS assessed in 2017 (W4)			Cigarette smoking status in 2019 (W5)							
			Successfully quit		Relapsed					
			12+ months, no puff		Significant re-quit† (3–12 months)		Re-quit (0–3 months)		Current smoker	
	Sample type	Sample size	Wtd%	95% CI	Wtd%	95% CI	Wtd%	95% CI	Wtd%	95% CI
Daily e-cigarette use	Continuing cohort‡	96	45.3	34.1 to 56.5	14.9	8.4 to 21.3	2.9	0.0 to 6.1	36.9	24.0 to 49.9
	Total W4 population§	115	43.2	32.5 to 54.0	17.4	11.0 to 23.7	3.0	0.1 to 5.9	36.4	24.9 to 47.9
Non-daily e-cigarette use	Continuing cohort	52	29.3	14.7 to 43.9	15.3	4.9 to 25.8	12.4	4.9 to 25.8	43.0	26.4 to 59.6
	Total W4 population	74	34.6	21.2 to 48.1	14.1	4.8 to 23.4	14.2	6.6 to 21.7	37.1	22.4 to 51.7
Daily use of other tobacco products¶	Continuing cohort	65	38.4	23.8 to 52.9	9.2	0.7 to 17.7	9.6	0.0 to 20.4	42.9	27.1 to 58.7
	Total W4 population	78	43.6	30.5 to 56.6	7.7	0.6 to 14.8	11.5	1.2 to 21.7	37.3	23.4 to 51.2
Non-daily use of other tobacco products	Continuing cohort	99	42.7	31.8 to 53.7	18.1	9.2 to 26.9	5.9	0 to 12.0	33.3	22.5 to 44.2
	Total W4 population	121	44.7	34.2 to 55.2	15.9	8.5 to 23.2	7.9	0.9 to 14.9	31.5	22.1 to 40.9
Any cigar use**	Continuing cohort	156	44.0	34.9 to 53.1	13.3	6.7 to 19.9	7.5	1.7 to 13.3	35.2	25.8 to 44.7
	Total W4 population	194	44.1	36.0 to 52.1	13.6	7.7 to 19.6	8.5	3.2 to 13.8	33.8	25.6 to 42.1
Any combusted tobacco product use††	Continuing cohort	178	40.9	32.2 to 49.5	13.8	7.7 to 19.9	8.5	2.4 to 14.6	36.7	27.4 to 46.1
	Total W4 population	224	42.6	34.1 to 51. 2	13.9	8.5 to 19.2	9.2	3.9 to 14.6	34.3	25.6 to 43.0
No tobacco use	Continuing cohort	576	52.8	47.5 to 58.0	9.8	7.3 to 12.4	4.3	2.0 to 6.6	33.1	28.1 to 38.1
	Total W4 population	701	52.9	47.8 to 58.0	10.7	8.1 to 13.4	5.2	2.8 to 7.6	31.2	26.8 to 35.7

Other tobacco product use: any use of other e-products, cigar, cigarillo, filtered cigar, pipe, hookah, snus or smokeless tobacco.
*Recent former cigarette smoker: those who were not smoking cigarettes at Wave 4 but who were established smokers 1 year earlier.
†Re-quit is a relapse to smoking since the previous survey followed by an additional quit attempt (we classify 3+ months off as a significant re-quit attempt).
‡The continuing cohort were W4 respondents who had been surveyed at previous PATH Study waves (W1–W3).
§The total W4 population is the continuing cohort + refreshment sample and includes all people interviewed for the PATH Study in 2017 (W4). The purpose of the refreshment sample (those first interviewed at W4) was to reset the size of the cohort and reduce the weighting needed to make estimates that were nationally representative of the US population.
¶Other tobacco use includes all other tobacco products including the combusted tobacco products and smokeless products, but not e-cigarettes.
**Any cigar use includes traditional cigars, cigarillo and filtered cigars.
††Any combusted tobacco product use: any use of cigar, cigarillo, filtered cigar, pipe or hookah.
RFS, recent former smokers; Wtd, weighted US population estimate.;

the introduction and effective marketing of high nicotine e-cigarettes, initially by JUUL Labs.[28] The high nicotine JUUL e-cigarette has been noted as the closest match to cigarettes in both nicotine delivery and user satisfaction,[29] which should make it one of the best candidates as a product to which smokers could switch in order to maintain their nicotine habit.[30] Thus, it was surprising that, just as sales for JUUL were surging in the marketplace, the use of e-cigarettes as a cessation aid fell from 17.4% of recent quit attempters in PATH W3[8] to 12.4% at PATH W4. However, by 2019 this situation had changed, at least among recent former smokers, with 22% switching to e-cigarettes and ~4% using high nicotine concentration e-cigarettes. Our analysis suggests that the 2017 JUUL marketing campaigns were not effective in encouraging smokers to use JUUL products to help with quit attempts, unlike their effectiveness in encouraging young people to initiate nicotine use with their products.[4 31 32] However, when we looked ahead to 2019, recent former smokers had started using high nicotine e-cigarettes. The effectiveness of high nicotine e-cigarettes at preventing relapse will require another follow-up PATH survey.

This study has both advantages and limitations. The PATH Study is a large cohort of a representative sample of the US population with a rigorous methodology, including biological samples to validate self-reported cigarette smoking.[7] In previous reports, biomarker concentrations indicate that self-reporting is valid.[33] This study included a large group of potential confounders that were measured prior to the target quit attempt and propensity score matching was used to achieve highly comparable groups. Each PATH survey collects detailed current use of a comprehensive set of tobacco products and detailed duration of abstinence of recently used products, allowing a comparison of the effectiveness of a wide range of potential products to help smokers quit. However, this study is observational and the exposure variable was not under experimental control. While our analytical

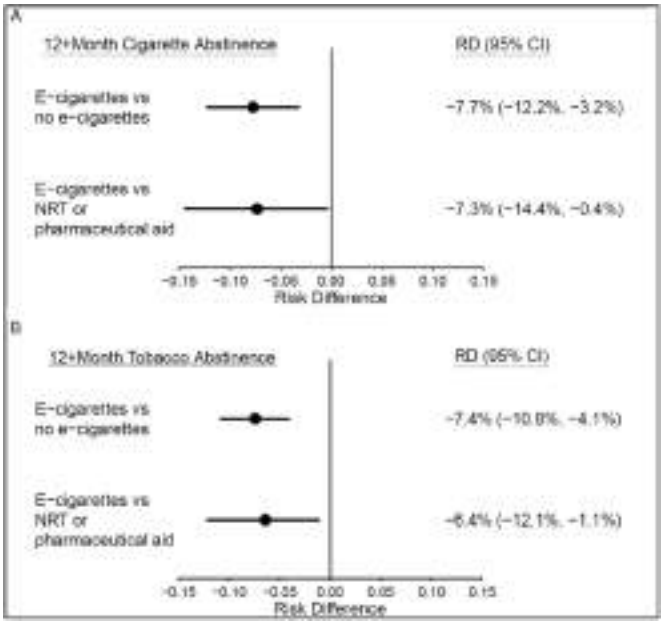

Figure 1 The adjusted risk difference (RD) in the rate of 12+ months of cigarette/tobacco abstinence for quit attempters by comparing the use of e-cigarettes versus no product use and the use of e-cigarettes versus use of nicotine replacement therapy (NRT) or pharmaceutical aid only during the last quit attempt in the year prior to Wave 4. (A) 12+ months of cigarette abstinence; (B) 12+ months of tobacco abstinence. Analyses using propensity score matching followed by logistic regression adjustment. Bootstrap samples were created to make statistical inference (details given in the section on Statistical Analyses). Covariates used for propensity score matching include: age, sex, education, race, ethnicity, income, cigarette smoking status at W3, time since last quit attempt, tobacco dependence index, cigarette consumption at W3, duration of previous quit attempt reported at W4, interest in quitting cigarettes, self-efficacy about quitting, smoke-free home, exposure to smoking, perceived harm of cigarettes and e-cigarettes, cigarette pack-years, age began regular smoking, insurance status, external mental health symptoms, internal mental health symptoms and existence of smoking-related disease. Missing data were imputed using simple imputation for each bootstrap sample. Cigarette abstinence does not include abstinence from e-cigarettes or other tobacco products. Tobacco abstinence includes no use of e-cigarette, cigar, cigarillo, filtered cigar, pipe, hookah, snus and smokeless tobacco.

design adjusted for potential confounding variables, other variables that were unmeasured confounders limit causal inference.

CONCLUSION

In 2017, a time of rapid growth in e-cigarette sales in the USA and increasing nicotine content in e-cigarette liquids, no such growth was seen in the use of e-cigarettes for cessation. In this study, smokers trying to quit or interested in switching to another nicotine delivery system were not early adopters of the high nicotine e-cigarettes such as JUUL, which have been reported as the closest products to resembling the experience of cigarette smoking. This analysis did not show a cessation benefit from using e-cigarettes either to help a cessation attempt or as a substitute for cigarette smoking. However, there is evidence that cigarette smokers were starting to use high nicotine e-cigarettes by 2019 and further follow-up in PATH is needed to see whether these changes result in future cessation benefit.

What this paper adds

What is already known on this subject?

- Randomised clinical trials indicate e-cigarettes have efficacy in helping smokers quit
- US cohort studies have not demonstrated effectiveness in the real world
- Starting in 2017, JUUL high nicotine e-cigarettes became the most popular e-cigarette brand and overall e-cigarette sales increased markedly

What important gaps in knowledge exist on this topic?

- The influence of the increased nicotine content of e-cigarettes on US smokers' ability to quit cigarette smoking is not known

What this study adds

- Despite a large increase in e-cigarette sales, the proportion who used e-cigarettes to help quit cigarettes declined and in 2017 only 2.2% of recent former smokers were using high nicotine e-cigarettes
- Those who used e-cigarettes to aid their cigarette quit attempt in the year prior to the 2017 survey were less likely to have successfully quit by 2019 compared with those who used a pharmaceutical aid or no product at all
- E-cigarette use did not prevent recent former smokers from relapsing to cigarettes
- However, the usage of high nicotine e-cigarettes for cessation increased in 2019, suggesting that this question needs to be addressed again in the 2021 PATH survey

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Contributors JPP is responsible for the overall content and is the guarantor of this paper. JPP and RC conceptualised and designed the study, drafted the initial manuscript and reviewed and revised the manuscript. JPP and TB acquired funding for the study. TB and KM had input into conceptualisation and supervised the methodology and all analyses undertaken. They also reviewed and revised the manuscript for important intellectual content. ECL, SBM, DRS, MDS, DT and MMW had input into the study conceptualisation and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding Supported by the National Institutes of Health (grant R01CA234539) and by the Tobacco-Related Disease Research ProgramProgramme of the University of California, Office of the President (grants 28IR-0066 and T31IR-1584).

Disclaimer Neither funding source had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Further, the funders of the PATH Study had no role in the analysis or interpretation of the data, its preparation, review or approval of this manuscript or decision to submit it for publication. All data used are available in a restricted public use file.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants but IRB for University of California San DiegoProject #181462 exempted this study Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The data are in a Restricted Use File that is available to approved researchers. National Addiction and HIV Data Archive Program. Population Assessment of Tobacco and Health (PATH) Study [United States] Restricted-Use Files (ICPSR 36231). NIH; National Institute on Drug Abuse.

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E-Cigarettes, as Consumer Products, Do Not Help People Quit Smoking, Study Finds

- Research
- December 22, 2020

By Vicky Stein

E-cigarette use has risen steeply and mostly without regulation over the past decade. The devices have diversified into a dizzying array of vape pens, tank systems, “mods,” and more, mass-marketed and sold to the public. The U.S. Food and Drug Administration (FDA) is in the midst of considering whether to approve thousands of pre-market applications for the sale of e-cigarettes as consumer products.

In these applications and related advertisements, the owners of e-cigarette brands claim that their products help smokers quit and can therefore be considered “appropriate for the protection of public health,” as stipulated by law. But a new systematic review by UC San Francisco researchers of the scientific literature on this topic puts those claims to the test.

In the new study, published Dec. 22, 2020, in the *American Journal of Public Health*, a team led by UCSF’s Richard Wang, MD, MAS, surveyed the scientific community’s understanding of e-cigarettes and found that, in the form of mass-marketed consumer products, they do not lead smokers to quit.

In their paper, the authors write, “If e-cigarette consumer product use is not associated with more smoking cessation, there is no population-level health benefit for allowing them to be marketed to adults who smoke, regardless of the relative harm of e-cigarettes compared with conventional cigarettes. Moreover, to the extent that people who smoke simply add e-cigarettes to their cigarette smoking

(becoming so-called dual users), their risk of heart disease, lung disease, and cancer could increase compared with smoking alone."

"The question we explored is of both scientific interest and public health interest," said Wang, assistant professor of medicine, "and we hope that the FDA will pay attention to our study as they try to make these decisions." Wang was joined in the study by co–first author Sudhamayi Bhadriraju, MD, a former UCSF postdoctoral fellow who is now a pulmonologist at Kaiser Permanente in Redwood City, Calif., and senior author Stanton A. Glantz, PhD, professor of medicine.

The authors searched the literature, compiling results from 64 studies to answer this question. The studies selected for formal analysis encompassed observational studies, in which participants were surveyed, but not directed, about their use of e-cigarettes, as well as clinical trials in which smokers who were trying to quit were given free e-cigarettes under medical supervision.

Richard Wang, MD, MAS

This distinction mattered for their analysis, Wang noted. "In observational studies, you're basically asking people 'out in the wild' about their use of e-cigarettes that they've purchased themselves from a corner store, without specific guidance to quit. But in a randomized trial you're testing a product, treating it like a therapy – a medicine – to see if an e-cigarette or some other product is more conducive to quitting."

In their analysis of observational studies that involved groups of people who already smoked and used e-cigarettes, whether or not they wanted to quit, the team found no appreciable effect of e-cigarettes on participants' ability to quit. In the next group of studies, which surveyed smokers using e-cigarettes who did indicate a desire to quit, the researchers also found no effect.

Then the team tried to tease apart the effects of frequency of use – whether people who used e-cigarettes daily might quit at different rates than people who used them less often. The researchers found that daily users quit at a higher rate than more infrequent users, although they cautioned that most participants in U.S. studies fall into the second category.

Finally, they examined nine clinical trials, which provided some type of e-cigarette, for free, to participants who were specifically encouraged to use the devices to help them quit. Though the devices and the controls employed in the studies differed, Wang concluded that being provided with certain e-cigarette products in a clinical trial context led to more quitting than some other therapies.

The 2009 Family Smoking Prevention and Tobacco Control Act (TCA) charges the FDA with only allowing e-cigarettes on the market when manufacturers can prove their tobacco-based products are "appropriate for the protection of public health." But the FDA delayed enforcing the law until a federal court order required companies to submit pre-market approval applications to the agency before September 2020 in order to continue selling e-cigarettes to consumers. The FDA is now evaluating thousands of such applications to sell e-cigarettes.

"It's important to recognize that in clinical trials, when certain e-cigarette devices are treated more like medicine, there may actually be an effect on quitting smoking," said Wang. "But that needs to be balanced against the risks of using these devices. Also, only seven e-cigarette devices were studied in

the clinical trials. Whether the effect observed with these seven devices is the same or different than that of the thousands of different e-cigarette products available for sale is unknown."

In addition, he said, the new study does not analyze the increase in youth and teen smoking as a result of e-cigarette marketing and availability, nor does it compare the negative health effects of e-cigarettes to traditional tobacco products.

With regard to the current decision before the FDA, Wang said, "The standards that the FDA has to apply to approve e-cigarettes as consumer products or therapeutic devices are fundamentally different."

Funding: The work was supported by National Heart, Lung, and Blood Institute (F32HL144063, K12HL143961, T32HL007185, and cooperative agreement U54HL147127 from the National Heart, Lung, and Blood Institute and the Food and Drug Administration Center for Tobacco Products.

Disclosures: The authors report no conflicts of interest.

The University of California, San Francisco (UCSF) is exclusively focused on the health sciences and is dedicated to promoting health worldwide through advanced biomedical research, graduate-level education in the life sciences and health professions, and excellence in patient care. UCSF Health, which serves as UCSF's primary academic medical center, includes top-ranked specialty hospitals and other clinical programs, and has affiliations throughout the Bay Area.

Editorial Commentary

Electronic cigarettes: not evidence-based cessation

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Submitted Mar 13, 2019. Accepted for publication Mar 21, 2019.
doi: 10.21037/tlcr.2019.03.08
View this article at: http://dx.doi.org/10.21037/tlcr.2019.03.08

Despite extensive efforts, smoking remains a modern-day epidemic with profound health consequences. In 1984, Dr. C. Everett Koop, the Surgeon General of the US at that time, presented an important speech on the hazards of smoking. In his speech he stated "*The ultimate goal should be a smoke-free society by the year 2000.*" Unfortunately, we did not achieved that goal. Shortly after the target date for a smoke-free society as proposed by Dr. Koop, a new product was successfully introduced to the world, electronic cigarettes, or e-cigarettes, with the plan to provide a healthier alternative to smoking burnt tobacco. Unlike combustible cigarettes, e-cigarettes are battery-operated and use a heating element to heat an e-liquid releasing a chemical-filled aerosol. E-cigarettes also include e-pens, e-pipes, e-hookah, and e-cigars and are collectively known as electronic nicotine delivery systems (ENDS).

The first patent for a smokeless tobacco cigarette was filed in 1963 by the inventor Herbert Gilbert but it was not until the early 2000s when the world learned the commercial potential of e-cigarettes. E-cigarettes were successfully invented by Hon Lik, a Chinese pharmacist whose father died of lung cancer, with the goal of delivering nicotine with a smoke-free vapour. The assumption was that by eliminating the toxic chemicals found in combustible tobacco, these products would have less impact on smokers' health and minimize the health-related consequences. After first being patented and then introduced into the Chinese market in 2003 these products appeared on the market in the US and UK 4 years later. E-cigarettes have quickly grown into a billion-dollar industry. In 2018 Americans will spend 4 billion dollars on e-cigarettes compared with 12 billion dollars in annual sales of burnt tobacco and is projected to outsell burnt tobacco products within the next 5 to 10 years (1). Currently in the US, e-cigarettes are the fastest growing patent class followed by 3-D printing and artificial intelligence (2).

Our relationship with smoking is complex. Historically smoking has been a symbol of cool (James Dean), a symbol of aspiration (Winston Churchill) and associated with genius (Albert Einstein). But once one starts smoking, despite the known detrimental health effects, quitting is not easy. In fact, it takes an average of 30 quit attempts over a smokers' lifetime before quitting successfully (3). As Mark Twain once said, "Giving up smoking is the easiest thing in the world. I know because I've done it thousands of times." In Ontario, Canada, the cessation rate, the proportion of smokers who remain abstinent for 12 months, is only 1.9% and has remained unchanged for several years (4).

In addition to being marketed as a safe alternative to burnt tobacco, e-cigarettes are marketed as an effective smoking cessation product without sufficient data to support these claims. Currently, the medical community is divided on its opinion about the use of e-cigarettes as a smoking cessation device. The scientific evidence that e-cigarettes are a useful aid for smoking cessation remains limited. In this review, we examined the current literature for evidence that could support or deny these claims to determine whether e-cigarettes can be a useful aid in combatting smoking addiction.

While some research shows e-cigarettes to be useful in quit attempts (5-7), results from a US national survey conducted of 729 current and former smokers showed that smokers are unsatisfied with the new devices and return to smoking tobacco cigarettes or maintain dual use of e-cigarettes and conventional cigarettes (8). The dissatisfaction may in part be due to the design evolution

of e-cigarettes. First-generation e-cigarettes were aptly named "cig-a-likes" because they closely resembled traditional cigarettes and were smoked the same way. First generation e-cigarette users would inhale the way they would with a traditional cigarette. This inhalation activated the atomizer to heat the e-liquid in the cartridge and convert the liquid to a vapor. Inhaling this vapor through the mouthpiece delivered nicotine to the lungs, and the user exhaled vapor that looks much like a cloud of cigarette smoke. As the technology has advanced, e-cigarettes have taken on new shapes. Current e-cigarettes have evolved into personal devices where users are able to tailor their devices to suit their personal smoking preferences. E-cigarette users, or "vapers", are now able to adjust the strength and temperature of their devices. The variety of e-liquids available means that there is a flavor to suit anyone's tastes and preferences. E-cigarettes have quickly evolved from a smoking alternative to a cloud-chasing, flavour phenomenon. Overall, these third-generation devices are highly modifiable and, in order to accommodate the modifications, have become much bulkier where the smoking style is highly unique.

To date, two randomized controlled trials have shown that e-cigarettes are not effective smoking-cessation tools (9,10). The first study was conducted in New Zealand and recruited smokers who were motivated to quit through newspaper advertisements and found that e-cigarettes were not superior to the patch as a smoking cessation tool. Subjects (657 motivated smokers who met the inclusion criteria) were randomly assigned to receive nicotine e-cigarettes (with cartridges containing 10 to 16 mg of nicotine per milliliter), nicotine patches (21 mg patch, one daily), or placebo (non-nicotine e-cigarettes). There were no statistical differences in 6-month quit rates between the three groups; the verified quit rates were 7.3% with nicotine e-cigarettes, 4.1% with non-nicotine e-cigarettes, and 5.8% with nicotine patches (9). Overall the abstinence rates were low in this study, perhaps due to lack of counselling and support. The trial also showed that dual use of tobacco cigarettes and e-cigarettes persisted amongst one third of the subjects at 6 months; dual use also occurred among patch users but at a lower level (7%) (9).

The results of another randomized controlled trial recently published in the *NEJM* also suggest that e-cigarettes are not effective for smoking cessation (10). The purpose of this study was to determine whether usual care (i.e., counselling and support), the 7 Food and Drug Administration (FDA) approved cessation aids, e-cigarettes provided by NJOY, or financial incentives promote smoking cessation among unselected smokers. In this study, 6,006 smokers working for major US companies were assigned to one of 5 study groups. Overall, the abstinence rates were very low at 0.1, 0.5, 1, 2, and 2.9 in the whole population but in the engaged population, that is smokers motivated to quit, the abstinence rates were 4–6 times higher. Interestingly, redeemable deposits plus free cessation aids were superior to free e-cigarettes (P=0.008) (10). This was no surprise as we know people can be highly motivated by monetary incentives. Free e-cigarettes were not superior to usual care (P=0.20) or to free cessation aids (P=0.43) (10).

Hajek *et al.* has recently shown that e-cigarettes were more effective for smoking cessation than nicotine-replacement therapy, when both products were accompanied by behavioral support in a randomized trial where motivated smokers had some free reign over the products they used (7). This one-year study showed that e-cigarettes improved abstinence rates from 9.9% with nicotine replacement alone *vs.* 18.0% in the e-cigarette group. However, the authors defined abstinence as a self-report of not smoking more than five cigarettes over a 26-week period. Biochemical confirmation of cessation was not assessed over time. Instead, a one-time measurement of exhaled carbon monoxide at 52 weeks was used to confirm smoking status. This is especially problematic since the study was not blinded. Positive expectations have limited effects on long-term abstinence but exhaled carbon monoxide normalizes within 24 hours of smoke exposure. Study participants may have stopped smoking prior to the scheduled time to meet the expectations of the investigators. Moreover, this study failed to address the potential detrimental health effects of e-cigarettes (11-13). Of note, a study in mice found that a 4-month inhalational exposure to nebulized e-cigarette liquid containing nicotine promoted distal airspace enlargement and airway hyperreactivity (14).

Three population-based, longitudinal studies have also not shown associations between e-cigarette use and smoking cessation (15-17). Vickerman *et al.* surveyed a large group of tobacco users, approximately 3,000 participants, seeking support from 6 state tobacco quitlines. Overall, 30.9% of callers had used e-cigarettes, and smoking cessation was the most frequently reported reason for e-cigarette use (51.3%) (15). Among motivated smokers accessing the quitline for support the results show that e-cigarette users were less likely to have quit traditional smoking at 7 months compared with nonusers of e-cigarettes (16.6% e-cigarettes *vs.* 31.3% nonusers) (15).

Similarly, Adkison *et al.* conducted a longitudinal, international study with 1-year follow-up that involved data collected from the International Tobacco Control Four-Country Survey (16). This study found that the majority of smokers, 85%, used e-cigarettes to help them quit smoking. However, the results from this study showed that e-cigarette users did not quit smoking more frequently than nonusers (P=0.52) (16).

Furthermore, in a paper by Grana *et al.*, they provided more evidence that e-cigarette use was not associated with higher rates of smoking cessation (17). This study involved a longitudinal analysis of a national sample of current US smokers to determine whether e-cigarette use predicted successful quitting or reduced cigarette consumption and found that the self-reported quit rate was not higher among smokers using e-cigarettes as a smoking cessation device. In fact, the results showed that e-cigarette users had lower quit rates and a lower reduction in cigarette consumption (17). Importantly, further analysis showed that intention to quit [OR, 5.59 (95% CI, 2.41–12.98); P<0.001] and cigarettes smoked per day [OR, 0.97 (95% CI, 0.94–0.99); P=0.02] significantly predicted quit status but past 30-day e-cigarette use did not [OR, 0.76 (95% CI, 0.36–1.60); P=0.46] (17).

Further doubts about the usefulness of e-cigarettes for facilitating smoking cessation were raised by the systematic review and meta-analysis performed by Kalkhoran *et al.* (18). The aim of this study was to assess the association between e-cigarette use and smoking cessation among adult cigarette smokers, irrespective of their motivation for using e-cigarettes. Surprisingly, this study found that e-cigarette use may lower the odds of an individual quitting smoking combustible tobacco products by 28% (18).

And finally, when looking at a targeted group, current smokers with cancer, 1,074 were referred to a tobacco cessation program and it was found that e-cigarette users were twice as likely to be smoking at follow-up (6 months) as compared with nonusers, after adjusting for nicotine dependence, quit attempts, and cancer diagnosis (19). In this study, e-cigarette users were more nicotine dependent than nonusers, had more prior quit attempts, and were more likely to be diagnosed with thoracic and head or neck cancers, possibly suggesting that this group of patients would have more difficulty quitting without a tapering dose of nicotine. In addition to the other studies presented, this raises doubts concerning the usefulness of e-cigarettes for facilitating smoking cessation among smokers in general or patients with cancer more specifically.

The studies summarized in this article are not without biases and limitations. Survey studies were not designed to specifically address the effect of e-cigarettes on smoking cessation. Their uncontrolled nature and other potential confounding factors could limit the ability to see a treatment effect. As discussed previously, the largest randomized controlled trial was limited by its lack of blinding and failure to confirm the smoking status of its participants. Unfortunately, most of the studies were underpowered and the studies both supporting and opposing e-cigarettes as a smoking cessation tool were biased by what stage a person may be on the Transtheoretical Model of Behavior Change (20), the number of quit attempts, and the other smoking cessation techniques they were currently using or have used in the past. While there may be a subset of users that still needs to be identified where e-cigarettes may be effective at improving abstinence, overall, we currently lack evidence supporting the use of e-cigarettes as effective smoking cessation devices.

The health and economic effects of smoking cessation are well established as tobacco use is the leading preventable cause of disease globally. Despite extensive research, smoking cessation rates are still at unacceptably low levels. For example, Ontario's smoking cessation rate has remained for many years at 1.9% (4). When it comes to quitting, most smokers quit on their own without the aid of formal treatment (i.e., medication and counselling) (21).

Smokers' efforts to quit smoking may be undermined by the promotion of smoking cessation products because these products reduce their confidence in their ability to quit on their own by implying that quitting cannot be achieved successfully without the use of these aids (22). The truth is, the majority of smokers do not want to quit smoking and we need to figure out why. Sixty-five percent of smokers refused participation in the study by Zhu *et al.* (22). The same is true for vapers; the majority do not want to quit (23). Developing and promoting interventions to improve smokers' odds of success has been the focus of smoking cessation efforts for so long that the field has largely neglected to investigate how to get more smokers to try to quit and to try more frequently. Increasing the quit attempt rate is a key goal for tobacco control efforts and critical to further reducing smoking (4). E-cigarettes are not the answer to this complex problem, and we need to be very careful about the role these nicotine delivery devices have in our society.

Acknowledgments

AM Wallace would like to thank Dr. Gail Darling for her support and for the opportunity to present at the IASLC WCLC. We would also like to thank Dr. John McDonough

for his support and editing assistance.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Wallace AM, Foronjy RE. Electronic cigarettes: not evidence-based cessation. Transl Lung Cancer Res 2019;8(Suppl 1):S7-S10. doi: 10.21037/tlcr.2019.03.08

EDITORIAL

E-Cigarettes to Assist with Smoking Cessation

Belinda Borrelli, Ph.D., and George T. O'Connor, M.D.

The prevalence of tobacco smoking in the United States has declined to 14.0% but still exceeds 25% among high-risk subgroups.[1,2] Electronic cigarettes (e-cigarettes) are not approved by the Food and Drug Administration (FDA) for smoking cessation, but Americans trying to quit smoking use these products more frequently than FDA-approved cessation aids.[3] Comparative-effectiveness trials are needed to learn whether smokers have a better chance of quitting with e-cigarettes. Previous trials have had methodologic shortcomings, used first-generation e-cigarettes, or did not assess long-term outcomes.

Hajek et al.[4] now report in the *Journal* the results of a multicenter, pragmatic, randomized trial of e-cigarettes, as compared with nicotine-replacement therapy, as a smoking-cessation treatment within the U.K. National Health Service smoking-cessation program. In addition to behavioral support, participants received either a second-generation refillable e-cigarette or a 3-month supply of whichever nicotine-replacement products they preferred. After 1 year, the rate of abstinence from smoking tobacco, validated by exhaled carbon monoxide concentration, was higher in the e-cigarette group (18.0%) than in the nicotine-replacement group (9.9%). Trial limitations include a lack of objective and validated measures of adherence and the possibility that smoking-cessation counselors who were aware of the treatment assignments may have influenced patient expectations.

These findings must be considered in the context of FDA-approved medications for smoking cessation that have acceptable safety profiles. Treatment with nicotine-replacement therapy and bupropion achieves abstinence rates of approximately 25 to 26% at 6 months and 20% at 1 year,[5] with slightly higher abstinence rates for combination therapy than for monotherapy.[6] Varenicline has been shown to outperform bupropion, all forms of nicotine-replacement therapy, and placebo, with a 26% abstinence rate through 24 weeks of follow-up among participants without psychiatric diagnoses.[7] The 1-year abstinence rate of 18% reported by Hajek et al. for the e-cigarette group is similar to these outcomes.

This evidence of effectiveness must be balanced against the short-term and long-term safety of e-cigarettes. With regard to the former, the data from Hajek et al. are reassuring: the e-cigarette group had greater declines in the incidence of cough and phlegm than the nicotine-replacement group, no excess wheezing or dyspnea, and only a small incidence of oropharyngeal irritation. More frequent respiratory serious adverse events in the e-cigarette group than in the nicotine-replacement group (5 vs. 1) did not appear to be related to e-cigarette use. A limitation of this pragmatic trial is the lack of information on the presence of asthma or chronic obstructive pulmonary disease, which could confer a predisposition to short-term adverse respiratory health effects, although previous reports have suggested short-term clinical benefit among patients with these conditions who switch from tobacco smoking to e-cigarette use.[8] The use of e-cigarettes by pregnant women, who were excluded from the trial by Hajek et al., raises special safety concerns. Although nicotine-patch use during pregnancy is associated with a higher rate of smoking cessation and better child-development outcomes than placebo,[9] there are no such reassuring data for e-cigarettes.

A key finding of Hajek et al. is that among participants with sustained abstinence at 1 year,

63 of 79 (80%) in the e-cigarette group were still using e-cigarettes, whereas only 4 of 44 (9%) in the nicotine-replacement group were still using nicotine replacement. This differential pattern of long-term use raises concerns about the health consequences of long-term e-cigarette use. E-cigarette vapor contains many toxins and exerts potentially adverse biologic effects on human cells in vitro or in animal models, although toxin levels and biologic effects are generally lower than those of tobacco smoke.[10] A study involving humans showed an altered bronchial epithelial proteome in association with e-cigarette use, including some protein alterations also seen among tobacco smokers.[11] In a mouse model, inhalational exposure to nebulized e-cigarette liquid containing nicotine resulted in distal airspace enlargement that was consistent with pulmonary emphysema.[12] These findings argue against complacency in accepting the transition from tobacco smoking to indefinite e-cigarette use as a completely successful smoking-cessation outcome.

An additional societal consideration is the effect of adult e-cigarette use on children and young adults. Adult use may not only expose children to e-cigarette vapor but also models addictive behavior. There is substantial evidence that e-cigarette use by youth increases the risk of smoking combustible tobacco cigarettes,[10] and the U.S. Surgeon General has recently declared e-cigarette use among youth "an epidemic."[13]

A consensus has emerged that e-cigarettes are safer than traditional combustible cigarettes,[10] but it remains controversial whether e-cigarettes should be recommended as a first-line treatment to assist smoking cessation, alongside FDA-approved treatments. The appropriate duration of e-cigarette "treatment" for smokers trying to quit is also uncertain. We recommend that e-cigarettes be used only when FDA-approved treatments (combined with behavioral counseling) fail, that patients be advised to use the lowest dose needed to manage their cravings, and that there be a clear timeline and "off ramp" for use. Use of e-cigarettes should be monitored by health care providers, like other pharmacologic smoking-cessation treatments. The efficacy and safety of e-cigarettes need to be evaluated in high-risk subgroups, and further research on the health consequences of long-term e-cigarette use is needed.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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This editorial was published on January 30, 2019, at NEJM.org.

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DOI: 10.1056/NEJMe1816406

Can nicotine e-cigarettes be used for smoking cessation

Unveil what you inhale

There is an absence of strong evidence supporting the use of nicotine e-cigarettes as a smoking cessation tool. Given the known risks and the unknown health impacts, Lung Foundation Australia does not support the use of nicotine e-cigarettes as a smoking cessation tool.

Medical regulations

Nicotine e-cigarettes have not been approved by the Therapeutic Goods Administration (TGA), nor by any equivalent foreign medicine regulator, as a proven smoking cessation tool. The TGA is part of the Australian Government Department of Health and is responsible for regulating therapeutic goods including prescription medications, vaccines, sunscreens, vitamins and minerals, medical devices, blood and blood products. The role of the TGA is to ensure products meet an acceptable level of safety and quality.

Nicotine e-cigarettes are an unapproved product, meaning that unlike other forms of nicotine replacement therapy, they have not been assessed by the TGA for safety, quality and efficacy. From the 1st of October 2021, you may be able to access the unapproved product if your GP or healthcare practitioner thinks it might be right for you as part of a plan to quit smoking. As they are unapproved, it is essential that they only be used under medical supervision, and as a last-line smoking cessation aid.

Seeking expert advice

Speaking to your GP or healthcare practitioner about your intention to quit smoking will provide you with the opportunity to discuss the proven and safe options and strategies available to help you quit smoking.

Replacing cigarette smoking with an unapproved product that is inhaled into your lungs, like nicotine e-cigarettes, will present an ongoing risk to your lung health. The human lungs are designed to breath in clean air, not toxins and carcinogenic substances of any type.

People may take up nicotine e-cigarettes because they believe these products are “less damaging” than tobacco cigarettes. However, no formal assessment or regulation of nicotine e-cigarettes has been undertaken by the TGA and therefore they cannot be considered a safe or to have less risk than traditional tobacco cigarettes.

The previous ‘safer’ products manufactured since the 1950s by the tobacco industry (i.e. filter, light, low tar cigarettes) have not improved smokers’ health. It also cannot be ignored that nicotine e-cigarettes are primarily manufactured by the tobacco industry.

Proven smoking cessation

If you or someone you know is trying to quit smoking tobacco cigarettes, there are proven, safe and effective methods available to you. Speak to your doctor or a trained Quitline counsellor about strategies to support you on your quit journey including anti-smoking medications and nicotine replacement therapy (sprays, patches, lozenges, chews and gums). Quitting can be tough but seeking support from your healthcare professional will give you the motivation, resources and practical skills you need.

Your GP will discuss with you a range of therapies to assist you to quit. Please note that nicotine e-cigarettes are considered second line therapy by the Royal Australian College of General Practitioners (the peak body for GPs), which means they should be recommended as a last resort when all other therapies have not been successful.

Learn more about quitting smoking

Helpful links

Tobacco in Australia

A comprehensive review of the major issues in smoking and health in Australia, compiled by the Cancer Council Victoria.

View Link →

QuitCoach

QuitCoach is free and has helped thousands to achieve their goal of becoming a nonsmoker.

View Link →

iCanQuit

Join a supportive community for free to help you quit for good.

View Link →

Quitline

Quitline Specialists are trained to listen carefully to you to help meet your needs.

View Link →

Smoking Hazards

Electronic Cigarettes

What are electronic cigarettes (e-cigarettes)

- E-cigarettes include electronic nicotine delivery systems and electronic non-nicotine delivery systems. Some are similar to conventional cigarettes in appearance, while some are similar to daily appliances, such as pen and USB flash.
- E-cigarettes heat a chemical mixture (e-liquid), which does not contain tobacco, to produce aerosol for users to inhale. With nicotine or not, the aerosol contains various harmful substances.
- E-cigarettes are available in over 15,000 flavours, and are marketed as a healthy and trendy product, satisfying the curiosity and desire for novel experience in young people.
- E-cigarettes can be a gateway to conventional cigarette smoking, particularly in young people. Research found that young people who had ever used e-cigarette were 4 times as likely to initiate cigarette smoking as never users.
- Nicotine has been detected in even e-cigarettes labelled as “nicotine-free”.

Health risks

- All smoking products, including e-cigarettes, are harmful. E-liquids are a mixture of propylene glycerol, glycerin, flavourings, nicotine and other additives. The aerosol generated contains a wide range of harmful substances and carcinogens such as nicotine, formaldehyde, acetaldehyde, tobacco-specific nitrosamines (TSNAs), polycyclic aromatic hydrocarbons, acrolein, acrylamide, heavy metals and volatile organic compounds, etc.
- E-cigarette use is associated with increased risks of cancers (e.g. lung cancer and bladder cancer), respiratory diseases (e.g. chronic obstructive pulmonary disease, asthma, obliterative bronchiolitis (also known as “popcorn lung”)), cardiovascular diseases and reproductive system diseases.
- COSH commissioned the Hong Kong Baptist University to evaluate 13 e-cigarettes that were available on the Hong Kong market. The evaluation detected various harmful chemicals, and was the first to detect polybrominated diphenyl ethers (PBDEs), which disrupts thyroid stimulating hormone release and affects fertility and fetal development. See COSH Report No.20 for more details
- Ever e-cigarette users have 4 to 6 times higher risks of contracting COVID-19 than never users (including e-cigarettes and conventional cigarettes).
- In the United States (US) in late 2019, there was an outbreak of lung injuries potentially caused by e-cigarettes that hospitalization and deaths after using e-cigarettes surged. The US Center for Disease Control and Prevention named the illness as “E-cigarette, or vaping, e-product use associated lung injury” (EVALI). As at February 2020, nearly 3,000 cases, including 68 deaths, were reported. Similar cases were also reported in the United Kingdom, Canada, the Philippines and Taiwan.

- E-cigarettes may explode, leading to burns and body damages. The risk is particularly high for low quality battery, improper storage and device modifications by users. Media have reported different levels of burns, bone fracture and even deaths due to e-cigarette explosions.

Secondhand smoke and third-hand smoke

- Similar to conventional cigarettes, e-cigarettes expose bystanders to secondhand aerosol.
- Secondhand aerosol of e-cigarettes exposes bystanders to a wide range of harmful substances such as nicotine, formaldehyde, acetaldehyde and TSNAs, etc.
- Similar to secondhand smoke of conventional cigarettes, secondhand aerosol of e-cigarettes may linger on dust and surfaces before re-mitted into the air, leading to third-hand aerosol exposure.

E-cigarettes do not help smoking cessation

- E-cigarettes do not help smoking cessation although they are often marketed as an alternative to conventional cigarette smoking. E-cigarettes should not be considered as another option for smoking.
- Dual users, who smoke conventional cigarettes and use e-cigarettes simultaneously, tend to use e-cigarettes as a complementary product to satisfy the desire for nicotine when smoking is not allowed or suitable. They may thus be exposed to more nicotine and other harmful substances.
- Research shows that e-cigarette use is not associated with smoking cessation, even in smokers who intend to quit conventional cigarettes.
- Smokers should abstain from all tobacco and nicotine products. If needed, they should seek recognized cessation aid, such as cessation counselling and nicotine replacement therapy.

Situation in Hong Kong

- According to the Thematic Household Survey Report No. 70 published by Census and Statistics Department, about 7,200 people aged 15 years or above were daily users of e-cigarettes in 2019, 0.1% of the Hong Kong population. In Primary 4-6 and Secondary 1-6 students, 0.2% and 0.8% were current e-cigarette users in 2018/19, respectively.
- According to Smoking (Public Health) Ordinance (Cap. 371), e-cigarette use in statutory no-smoking areas is prohibited. Offenders are liable for a fixed penalty of HK$1,500 fine.
- Since 30 April 2022, it is an offence to import, promote, manufacture, sell or possess for commercial purposes e-cigarettes. Offenders are liable for a HK$50,000 fine and 6-month imprisonment. Broadcast of an e-cigarette advertisement is liable for a HK$50,000 fine, with an extra HK$1,500 fine per day for continuing offences.

Stance of overseas and regulatory bodies and health authorities

- At least 100 countries and regions have regulations on e-cigarettes, including around 30 countries and regions (e.g. Brazil, India, Singapore, Thailand, Turkey and Macau) with a total ban on all types of e-cigarettes.
- The World Health Organization (WHO) stated that e-cigarettes are not harmless, non-smokers should be prevented from e-cigarette use while non-e-cigarette users should be protected against the secondhand aerosol. There is no sufficient evidence for a blanket recommendation to use any

type of e-cigarettes to help smoking cessation. WHO recommends to impose strict regulation, including prohibition, on e-cigarettes to protect health of people.

- International Union Against Tuberculosis and Lung Disease recommended protective and preventive bans on e-cigarettes in low and middle income countries, where there is strong potential for e-cigarettes to overwhelm the governments and exacerbate the tobacco epidemic.
- European Respiratory Society stated that no evidence shows that e-cigarettes are safe. The “harm reduction” strategy is based on incorrect or undocumented claims or assumptions (e.g. smokers cannot quit cigarettes, e-cigarettes help quitting, smokers will completely switch to e-cigarettes). Any products that can damage lung and human health cannot be recommended.
- European Society of Cardiology stated that e-cigarette use affects cardiovascular health, and the long-term impacts on health and smoking cessation are still unclear. Smokers should consider recognized cessation aids first.
- American Lung Association is concerned about the potential impacts of e-cigarettes on public health, including the gateway effect and cessation claims. Smokers should quit with recognized methods, but not e-cigarettes.

To prevent the use of e-cigarettes and the potential health risks associated with the secondhand aerosol, as well as to prevent e-cigarettes from being a gateway to smoking in youths, COSH suggests to impose a total ban on e-cigarettes as soon as possible.

Download the Q&A information sheet on alternative smoking products

Download the brochure on alternative smoking products (Only available in Chinese)

Should flavoured vaping products be banned?

The Upfront Team ⋮⋮ 15/4/2023

The news on Wednesday that e-cigarette manufacturer Juul Labs has agreed to pay $462m (€420m) to settle claims by six US states after being accused of targeting teenagers has brought the regulation of vaping products in Ireland back into focus.

In November the Irish Government approved a ban on the sale of e-cigarettes to minors, it's expected to take effect at some point this year.

The bill will also prohibt the advertisement of e-cigarettes on public transport, in cinemas and near schools in an effort to limit children's exposure to commercial messages normalising e-cigarettes.

While the sale of flavoured e-cigarettes to minors is restricted under the new bill, some don't believe its gone far enough and have called for an outright ban on these flavoured products because of their appeal to younger people.

As part of The Conversation from RTÉ's Upfront with Katie Hannon, we asked two people to join our WhatsApp group to discuss whether flavoured e-cigarettes products should be banned.

Alex Pescar is a founding member of the Irish Vape Vendors Association (IVVA) and managing director of an e-cigarette retailer and wholesaler.

Professor Luke Clancy is the Director General of the TobaccoFree Research Institute Ireland (TFRI).

Luke Clancy: Our research at the TobaccoFree Research Institute Ireland has shown that 39% of 16 year olds had tried e-cigarettes in 2019 up from 23% in 2015.

We believe that e-cigarettes should not be used by children, teenagers and young adults.

Flavours are mainly used to attract these young people and they obviously work so one way to prevent that is to ban flavours. We think this is worth a try.

Alex Pescar: In Ireland the legislation which ban sales of e-cigarettes to persons under the age of 18 has not yet been brought into law by the Irish government. The industry has called on the government repeatedly to pass this legislation over the course of eight years.

Over 70% of adult smokers use flavored e-liquids and not tobacco flavour when using vaping to quit smoking.

The banning of flavours would cause a large percentage of vapers to go back to smoking and to find alternative ways to obtain flavoured e-liquids which may be unregulated.

Luke Clancy: Only 6% of people in Ireland (aged 15 years and over) use e-cigarettes, according to the 2022 Healthy Ireland figures and we know that the highest prevalence is in those under 25 years*.

*[*Editor's note: This figure is taken from a Healthy Ireland Survey, published in December 2022].*

A fifth of adults report using e-cigarettes as a quitting aid while four-fifths do not, and two-thirds of all successful quitters use nothing. Only 10% of people who use e-cigarettes to quit are successful.

Only 3% of teenagers who use e-cigarettes report that they use them to quit smoking. While we want people to quit smoking, we do not think it is worth risking the health of our young people for the possible gain of a few extra quitters when we know that other forms of nicotine are often as good as e-cigarettes in randomised control trials for helping people to quit.

Alex Pescar: We agree that it is very important that young people who do not smoke should not take up vaping.

However, we have to consider that a very large percentage of adults have taken up vaping with the sole aim of quitting smoking, or at least as a method of harm reduction as vaping is proven to be at least 95%* safer than smoking traditional cigarettes in various studies.

Vaping is intended to be used as a quit smoking aid for existing adult smokers.

*[*Editor's note: This statistic is from a 2015 study conducted by Public Health England].*

It is also worth mentioning that vaping is not yet recognised as a successful form of harm reduction by major Irish health bodies and organisations.

While other countries have proven that vaping is as effective, if not more effective than existing nicotine replacement therapies. Again, in response to youth vaping, we circle back to our calls for legislation banning sales of vaping products to persons under 18 years of age.

Without this legislation, it is very difficult to control the correct selling of these products. Also, there is no licensing system in place for the sale of vaping products, meaning any retailer can sell vaping products, even those who are not aware of correct practices.

Luke Clancy: In our research young people reported that one of the three main reasons they used e-cigarettes was because of flavours and it is mainly young people who use e-cigarettes.

We support the legislation, and it will help but unfortunately, whatever the legislation, if flavoured e-cigarettes are available many young people will get them and use them because that is what attracts them.

There is no doubt that the main reason the industry supports flavours is not because they will help people to quit smoking but because they will attract children.

We have no idea what damage inhaled flavours will do. We should not be fooled by the fact that when these substances are eaten they are not harmful. Inhaling them into the lungs is a very different matter.

Alex Pescar: All flavours for sale in the Republic of Ireland are strictly regulated as per the Irish Tobacco Products Directive (TPD).

Within the TPD, it is required that all flavours must undergo strict toxicity tests. It must be noted that flavours are available not to appeal to young people, but to appeal to adults.

This argument on flavours being enticing to young people can also be made with traditional nicotine replacement therapies currently available, which are available in different flavours.

Furthermore, looking at the alcohol industry, flavours are used here as well.

Research has been conducted and will continue to be conducted on the potential harms of vaping to the body.

As it stands, once again, vaping is proven to be 95% safer than smoking.

While we know that inhaling flavours is different than consuming them, it must be emphasised that traditional cigarettes, which are proven to contain thousands of carcinogens, are still available for sale. Harm reduction must be considered.

Luke Clancy: There is not one single empirical study showing that e-cigarettes are 95% safer than cigarettes. Toxicity tests on flavours are not done by inhalation. If it was considered safe to add flavours to inhalers it would be done with regular medicines such as asthma treatments. It is not because of known and feared toxicity.

While I do not accept that the flavours are made to appeal to adults, remember that in Ireland e-cigarettes are mainly used by under 25s, a group whose brains are known to be damaged by inhaled nicotine and

who are susceptible to nicotine addiction and whom we have shown to be twice as likely to take up smoking if they have tried e-cigarettes.

Smoking has increased in adults. For the first time in 25 years smoking has increased in children.

If e-cigarettes had a beneficial effect on reducing smoking in society, this would not have occurred at the same time as the introduction of e-cigarettes and their dramatic increase in usage over the last few years.

I have no doubt that the influence of e-cigarettes long term will not be beneficial and will not result in the elimination of cigarette smoking or even its reduction.

Alex Pescar: We have all the research cited with references available for all major studies proving our earlier fact that vaping is safer than traditional cigarettes.

Not only young people are using flavours.

We agree that an increase in smoking rates among children needs to be put a stop to.

However, we know that vaping is safer than smoking, and can be used as a tool to quit smoking and also as a method of harm reduction.

This cannot be ignored and must be used as a tool to combat smoking rates.

Furthermore, the young generation has to be protected by enacting legislation prohibiting access to tobacco products electronic cigarettes included if under the age of 18.

Read last week's edition of The Conversation, where we asked whether** Good Friday should be recoginsed as an official public holiday, here**.

Addiction
SSA SOCIETY FOR THE STUDY OF ADDICTION
RESEARCH REPORT
doi:10.1111/add.12917

Is the use of electronic cigarettes while smoking associated with smoking cessation attempts, cessation and reduced cigarette consumption? A survey with a 1-year follow-up

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ABSTRACT

Aims To use a unique longitudinal data set to assess the association between e-cigarette use while smoking with smoking cessation attempts, cessation and substantial reduction, taking into account frequency of use and key potential confounders. **Design** Web-based survey, baseline November/December 2012, 1-year follow-up in December 2013. **Setting** Great Britain. **Participants** National general population sample of 4064 adult smokers, with 1759 (43%) followed-up. **Measurements** Main outcome measures were cessation attempt, cessation and substantial reduction (≥50% from baseline to follow-up) of cigarettes per day (CPD). In logistic regression models, cessation attempt in the last year (analysis $n = 1473$) and smoking status ($n = 1656$) at follow-up were regressed on to baseline e-cigarette use (none, non-daily, daily) while adjusting for baseline socio-demographics, dependence and nicotine replacement (NRT) use. Substantial reduction ($n = 1042$) was regressed on to follow-up e-cigarette use while adjusting for baseline socio-demographics and dependence and follow-up NRT use. **Findings** Compared with non-use, daily e-cigarette use at baseline was associated with increased cessation attempts [odds ratio (OR) = 2.11, 95% confidence interval (CI) = 1.24–3.58, $P = 0.006$], but not with cessation at follow-up (OR = 0.62, 95% CI = 0.28–1.37, $P = 0.24$). Non-daily use was not associated with cessation attempts or cessation. Daily e-cigarette use at follow-up was associated with increased odds of substantial reduction (OR = 2.49, 95% CI = 1.14–5.45, $P = 0.02$), non-daily use was not. **Conclusions** Daily use of e-cigarettes while smoking appears to be associated with subsequent increases in rates of attempting to stop smoking and reducing smoking, but not with smoking cessation. Non-daily use of e-cigarettes while smoking does not appear to be associated with cessation attempts, cessation or reduced smoking.

PLOS ONE

RESEARCH ARTICLE

Are electronic nicotine delivery systems helping cigarette smokers quit? Evidence from a prospective cohort study of U.S. adult smokers, 2015–2016

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OPEN ACCESS

Citation: Weaver SR, Huang J, Pechacek TF, Heath JW, Ashley DL, Eriksen MP (2018) Are electronic nicotine delivery systems helping cigarette smokers quit? Evidence from a prospective cohort study of U.S. adult smokers, 2015–2016. PLoS ONE 13(7): e0198047. https://doi.org/10.1371/journal.pone.0198047

Editor: Raymond Maura, Legacy, Schroeder Institute for Tobacco Research and Policy Studies, UNITED STATES

Received: February 12, 2018

Accepted: May 12, 2018

Published: July 9, 2018

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This study was supported by grant number P50DA036128 (to Michael P Eriksen) from the National Institutes of Health, National Institute of Drug Abuse (NIH/NIDA) and Food and Drug Administration, Center for Tobacco Products (FDA CTP). The content is solely the responsibility of the

Abstract

Background

The potential of electronic nicotine delivery systems (ENDS) to reduce the cardiovascular and other disease risks of smoking is of great interest. While many smokers report using ENDS for cessation, their impact under real-world use patterns and conditions on adult smokers' quitting behavior is uncertain. The objective of this study was to generate more recent and comprehensive evidence on the effect of "real world" ENDS use on the population quit rates of adult smokers while taking account of frequency and duration of use, device type, e-liquid flavor, and reasons for use.

Methods and findings

We conducted a population-based, prospective cohort study of a random probability sample of 1284 U.S. adult smokers recruited in August/September 2015 and re-contacted one-year later (September 2016) from GfK's KnowledgePanel, a national, probability-based web-panel designed to be representative of non-institutionalized U.S. adults. Among the 1081 baseline smokers who remained members of KnowledgePanel, 858 completed the follow-up survey. The primary outcome was smoking abstinence for at least 30 days prior to follow-up. Secondary outcomes were making a quit attempt during the 12-month study period and number of cigarettes smoked per day at follow-up. The adjusted odds of quitting smoking were lower for those that used ENDS at baseline (9.4%, 95% CI = 5.22%-16.38%; AOR = 0.30, 95% CI = 0.13–0.72) compared to smokers who did not use at ENDS (18.9%, 95% CI = 14.24%-24.68%). Smokers who used ENDS daily at some point during the study period were also less likely to quit smoking than nonusers (AOR = 0.17; 95% CI = 0.04–0.82).

Conclusions

We found no evidence that ENDS use, within context of the 2015–2016 US regulatory and tobacco/vaping market landscape, helped adult smokers quit at rates higher than smokers who did not use these products. Absent any meaningful changes, ENDS use among adult smokers is unlikely to be a sufficient solution to obtaining a meaningful increase in population quit rates. Additional research is needed to reconcile the divergent literature and monitor the impact of ENDS in an environment of rapidly evolving markets and regulatory policies.

World's largest and longest study – 200,000 e-cigarette users monitored over 10 consecutive years.

Open access Research

BMJ Open

Is prevalence of e-cigarette and nicotine replacement therapy use among smokers associated with average cigarette consumption in England? A time-series analysis

Emma Beard,[1,2] Jamie Brown,[1,2] Susan Michie,[2] Robert West[1]

To cite: Beard E, Brown J, Michie S, *et al*. Is prevalence of e-cigarette and nicotine replacement therapy use among smokers associated with average cigarette consumption in England? A time-series analysis. *BMJ Open* 2018;8:e019046. doi:10.1136/bmjopen-2017-019046

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-019046).

Received 23 January 2017
Revised 21 June 2017
Accepted 11 September 2017

ABSTRACT

Objectives Many smokers use e-cigarettes and licensed nicotine replacement therapy (NRT), often in an attempt to reduce their cigarette consumption. We estimated how far changes in prevalence of e-cigarette and NRT use while smoking were accompanied by changes in cigarette consumption at the population level.

Design Repeated representative cross-sectional population surveys of adults aged 16+ years in England.

Methods We used Autoregressive Integrated Moving Average with Exogeneous Input (ARIMAX) modelling of monthly data between 2006 and 2016 from the Smoking Toolkit Study. Prevalence of e-cigarette use and NRT use in current smokers, and specifically for smoking reduction and temporary abstinence, were input variables. Mean daily cigarette consumption was the dependent variable. Analyses involved adjustment for mass media expenditure and tobacco-control policies.

Results No statistically significant associations were found between changes in use of e-cigarettes (β −0.012, 95% CI −0.026 to 0.002) or NRT (β 0.015, 95% CI −0.026 to 0.055) while smoking and daily cigarette consumption. Neither did we find clear evidence for an association between e-cigarette use (β −0.010, 95% CI −0.025 to 0.005 and β 0.011, 95%–0.027 to 0.004) or NRT use (β 0.006, 95%–0.030 to 0.043 and β 0.022, 95%–0.020 to 0.063) specifically for smoking reduction and temporary abstinence, respectively, and changes in daily cigarette consumption.

Conclusion If use of e-cigarettes and licensed NRT while smoking acted to reduce cigarette consumption in England between 2006 and 2016, the effect was likely very small at a population level.

Strengths and limitations of this study

- This is the first time series study to assess the population-level impact of the use of nicotine replacement therapy and e-cigarettes for harm reduction on cigarette consumption.
- This study uses a large representative sample of the population in England and considers both smoking reduction and temporary abstinence.
- A wide range of confounders are adjusted for including population-level interventions.
- In countries with weaker tobacco control, or stricter regulation of using products for harm reduction, different effects may be observed.
- Data are observational and so strong conclusions regarding cause and effect cannot be made.

attempts to cut down) or during periods of temporary abstinence (ie, during periods of time when one is unable to smoke).[1] Outside of the clinical setting where little behavioural support is provided, the use of NRT during attempts to cut down smoking appears to increase smoker's propensity to quit, but does not result in significantly large reductions in cigarette consumption.[2–4] Explanations for this include the lack of behavioural support and possible poor compliance with the medical regimen.[3 5]

In recent years, there has been an increase in the overall use of nicotine-containing

Conclusion

In conclusion, the increased prevalence of e-cigarettes use among smokers in England has not been associated with a detectable change in cigarette consumption per day. The decline in the use of NRT has also not been associated with a change in mean cigarette intake. If use of e-cigarettes and licensed NRT while smoking act to reduce cigarette consumption, the effect is probably small.

American Journal of
Preventive Medicine

RESEARCH ARTICLE

E-cigarettes Associated With Depressed Smoking Cessation: A Cross-sectional Study of 28 European Union Countries

Margarete C. Kulik, PhD, Nadra E. Lisha, PhD, Stanton A. Glantz, PhD

Introduction: Electronic cigarettes (e-cigarettes) are often promoted to assist with cigarette smoking cessation. In 2016–2017, the relationship between e-cigarette use and having stopped smoking among ever (current and former) smokers was assessed in the European Union and Great Britain by itself.

Methods: Cross-sectional logistic regression of the association between being a former smoker and e-cigarette use was applied to the 2014 Eurobarometer survey of 28 European Union countries controlling for demographics.

Results: Among all ever smokers, any regular ever use of nicotine e-cigarettes was associated with lower odds of being a former smoker (unadjusted OR=0.34, 95% CI=0.26, 0.43, AOR=0.43, 95% CI=0.32, 0.58) compared with smokers who had never used e-cigarettes. In unadjusted models, daily use (OR=0.42, 95% CI=0.31, 0.56); occasional use (OR=0.25, 95% CI=0.18, 0.35); and experimentation (OR=0.24, 95% CI=0.19, 0.30) of nicotine e-cigarettes were associated with lower odds of being a former smoker compared with having never used nicotine-containing e-cigarettes. Comparable results were found in adjusted models. Results were similar in Great Britain alone. Among current smokers, daily cigarette consumption was 15.6 cigarettes/day (95% CI=14.5, 16.7) among those who also used e-cigarettes versus 14.4 cigarettes/day (95% CI=13.4, 15.4) for those who did not use them ($p < 0.05$).

Conclusions: These results suggest that e-cigarettes are associated with inhibiting rather than assisting in smoking cessation. On the population level, the net effect of the entry of e-cigarettes into the European Union (and Great Britain) is associated with depressed smoking cessation of conventional cigarettes.

Am J Prev Med 2018;▮(▮):▮▮▮–▮▮▮

E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis

Sara Kalkhoran, Stanton A Glantz

Summary

Background Smokers increasingly use e-cigarettes for many reasons, including attempts to quit combustible cigarettes and to use nicotine where smoking is prohibited. We aimed to assess the association between e-cigarette use and cigarette smoking cessation among adult cigarette smokers, irrespective of their motivation for using e-cigarettes.

Methods PubMed and Web of Science were searched between April 27, 2015, and June 17, 2015. Data extracted included study location, design, population, definition and prevalence of e-cigarette use, comparison group (if applicable), cigarette consumption, level of nicotine dependence, other confounders, definition of quitting smoking, and odds of quitting smoking. The primary endpoint was cigarette smoking cessation. Odds of smoking cessation among smokers using e-cigarettes compared with smokers not using e-cigarettes were assessed using a random effects meta-analysis. A modification of the ACROBAT-NRSI tool and the Cochrane Risk of Bias Tool were used to assess bias. This meta-analysis is registered with PROSPERO (number CRD42015020382).

Findings 38 studies (of 577 studies identified) were included in the systematic review; all 20 studies with control groups (15 cohort studies, three cross-sectional studies, and two clinical trials) were included in random effects meta-analysis and sensitivity analyses. Odds of quitting cigarettes were 28% lower in those who used e-cigarettes compared with those who did not use e-cigarettes (odds ratio [OR] 0·72, 95% CI 0·57–0·91). Association of e-cigarette use with quitting did not significantly differ among studies of all smokers using e-cigarettes (irrespective of interest in quitting cigarettes) compared with studies of only smokers interested in cigarette cessation (OR 0·63, 95% CI 0·45–0·86 *vs* 0·86, 0·60–1·23; p=0·04). Other study characteristics (design, population, comparison group, control variables, time of exposure assessment, biochemical verification of abstinence, and definition of e-cigarette use) were also not associated with the overall effect size (p≥0·77 in all cases).

Interpretation As currently being used, e-cigarettes are associated with significantly less quitting among smokers.

Funding National Institutes of Health, National Cancer Institute, FDA Center for Tobacco Products.

Lancet Respir Med 2016

Published Online
January 14, 2016
http://dx.doi.org/10.1016/S2213-2600(15)00521-4

See Online/Comment
http://dx.doi.org/10.1016/S2213-2600(15)00553-6

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Vaping no boost to quit rates in smokers, study suggests

eurekalert.org/pub_releases/2018-11/osu-vnb112018.php

Public Release: 20-Nov-2018

'Dual users' no more likely to kick habit

Ohio State University

COLUMBUS, Ohio - People who vape and smoke cigarettes are no more likely to drop the nicotine habit than those who just smoke, a new study suggests.

Researchers at The Ohio State University studied 617 tobacco users and found no differences in quit rates for "dual users" of both traditional and electronic cigarettes.

This research adds important information to the conversation as public health and medical professionals grapple with the role vaping might play in reducing cigarette smoking, said study senior author Mary Ellen Wewers, a professor emeritus of health behavior and health promotion, and a member of Ohio State's Center of Excellence in Tobacco Regulatory Science.

Participants in the study were part of a larger group of about 1,200 rural and urban Ohioans whose habits are being followed by researchers. All of them are considered heavy tobacco users - those who smoke every day or at least some days every week.

The study appears in the journal *Nicotine & Tobacco Research*.

The researchers sat down with participants every six months for 18 months to ask them about tobacco use, interest in quitting and quit attempts they'd made. They also documented what type of tobacco products the participants used.

At the first check-in, six months into the study, the dual users were more likely to have stopped using tobacco, but that difference disappeared by the 1-year and 18-month interviews. By the end of the study, most dual users were back to smoking cigarettes exclusively.

"The initial difference we saw might be due to a higher interest in quitting among the dual users, but that higher quit rate vanished with time," said lead author Laura Sweet, a graduate student in Ohio State's College of Public Health.

"Tobacco is such a huge killer, and if these products help people quit, that could be really significant for public health. But in this study it looks like they don't, and we need to know that as well," Sweet said.

Though electronic products still deliver nicotine and much remains unknown about their long-term health effects, there's general agreement that they are less harmful than cigarettes in adults.

"The hope would be that adult cigarette smokers are trying e-cigarettes because they want to stop cigarettes and are looking for alternatives to help them," Wewers said, adding that she and others who work on tobacco prevention are concerned that younger people who vape will start there and transition to cigarettes down the road.

The researchers can't be sure what factors contributed to their findings, but the results prompted Sweet to wonder if many adults who smoke and vape are doing so because vaping is more accepted in certain environments, rather than because vaping might help them drop nicotine altogether, she said.

Wewers, a member of the Cancer Control Research Program at Ohio State's Comprehensive Cancer Center, said she wasn't surprised to see a higher likelihood of quitting cigarettes at six months in the dual users, because that group expressed greater interest in quitting overall.

"It makes sense that during the first few months they may do better at quitting, but given that cigarette smoking is

such a cyclical thing - people quit and resume all the time - it's not surprising that they went back to smoking after a year," she said.

Because this study didn't assess light smokers or those who consider themselves "social" smokers, it's hard to say what role vaping might play in quitting, Wewers said.

But for health care providers trying how best to help heavy smokers quit, this study could help inform those doctor-patient conversations, she said.

"Providers get questions about trying e-cigarettes all the time from people who want to quit. Our paper would suggest that it's not a promising approach - the majority don't quit, and most of them go back to combustible products exclusively," Wewers said.

"This reinforces the recommendation that there are good, approved medications and nicotine-replacement products out there now and that those should be the first-line approach to helping smokers quit."

The study findings are limited in that the researchers relied on self-reported information from the smokers and did not conduct tests to confirm whether someone had quit. But the study is stronger than some other similar work, because it used a randomly selected sample of smokers in both an urban Ohio county and in six Appalachian counties in the state, Wewers said.

Next, Wewers said she's interested in exploring the role of flavored products for those who vape, and wants to know more about what motivates smokers to pick up e-cigarettes.

"Is it because e-cigarettes haven't been banned to the same extent as cigarettes? Is it that there's so much advertising? We'd really like some answers to these questions."

###

Theodore Brasky, Sarah Cooper, Nathan Doogan, Alice Hinton, Elizabeth Klein, Haikady Nagaraja, Amanda Quisenberry and Wenna Xi - all of Ohio State - also worked on the study.

The National Institutes of Health and the Food and Drug Administration supported the research.

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Bloomberg Business

E-Cigs Breed More Smokers Than They Stop

While the device helps some adults quit the habit for good, research suggests nicotine vaping leads to many more tobacco users.

By *Janine Wolf*

March 15, 2018, 2:00 AM GMT+8

https://www.bloomberg.com/news/articles/2018-03-14/e-cigarette-study-says-they-lead-to-more-smokers-than-they-stop

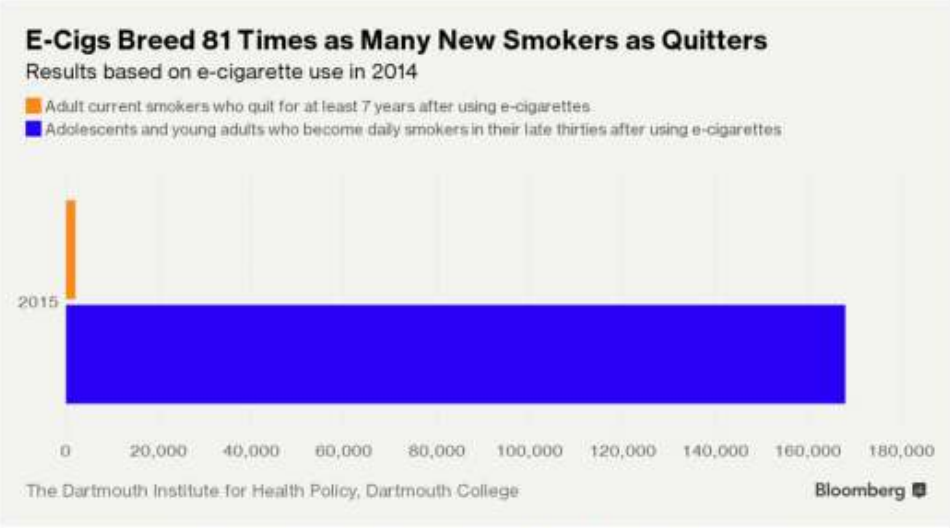
Electronic cigarettes have long been touted not only as a safer alternative to cigarettes but as a potential avenue by which existing smokers might quit. The industry, now worth $11.4 billion, hasn't been hurt by this one-two pitch of safety and good public policy.

New research shows, however, that e-cigarettes are hurting a lot more than they help.

Researchers at Dartmouth College's Norris Cotton Cancer Center said vaping has led more people to start a real smoking habit, rather than avoid tobacco or quit in favor of e-cigarettes, according to a study published Wednesday.

Using 2014 census data, published literature and surveys on e-cigarette usage to build a model, the scientists were able to estimate that about 2,070 cigarette-smoking adults in America quit in 2015 with the help of the electronic devices. However—and **perhaps more alarming**—the model estimated that, **at the same time, an additional 168,000 adolescents and young adults who had never smoked cigarettes began smoking and eventually became daily cigarette smokers after first using e-cigarettes.**

The model estimates that e-cigarette use in 2014 would eventually lead to about 1,510,000 years of life lost—a figure based on an optimistic 95 percent relative harm reduction of using e-cigarettes compared to traditional cigarettes.



The Dartmouth Institute for Health Policy, Dartmouth College

Samir Soneji, an associate professor of health policy at Dartmouth's Geisel School of Medicine and the paper's lead author, said that advertising e-cigarettes as a means to quit or reduce smoking has done damage, mostly to young people. E-cigarettes use cartridges of chemicals, including nicotine, that are transformed into vapor. Despite a federal requirement that purchasers be at least 18 years of age, use of the product in popular culture, combined with its fruity flavors, have proved a strong draw to younger, would-be vapers. These

characteristics have been at the core of keeping youths interested in the devices, Soneji said, and should be the focus of restriction efforts by the U.S. Food and Drug Administration.

"The harms of e-cigarette use among adolescents and young adults are serious," he said. "Kids who vape are more likely to start smoking cigarettes—notably kids who were otherwise not at a high risk of starting to smoke." Currently, Soneji said, the risk of initiating cigarette smoking is three times as high for adolescents who vape than for those who do not.

In 2015, 68 percent of Americans who smoked wanted to quit, with about 55.4 percent of them doing so successfully for at least one day, according to the Centers for Disease Control and Prevention. That same year, 45.5 percent of high school-aged cigarette smokers said they had tried to stop smoking over the previous 12 months. After first regulating the devices in 2016, the FDA embraced vaping as a way for smokers to quit.

Last July, a study published in the British Medical Journal found that e-cigarette users were indeed more likely than non-users to attempt to quit smoking—and be more successful at doing so. However, at around the same time the survey was conducted, e-cigarette use among high school students was jumping from 1.5 percent in 2011 to 16 percent in 2015, making the products the most commonly used tobacco product by young people in the U.S.

"E-cigarettes could, indeed, provide more population benefit if they were more effective as a cessation tool."

Current research already points toward e-cigarettes being a public health risk because of the chemicals they use, making the new research even more problematic for the industry. However, the Dartmouth researchers point out that a future in which e-cigarettes do help people quit isn't impossible—as long as they're kept out of the hands of young people.

"E-cigarettes could indeed provide more population benefit if they were more effective as a cessation tool," Soneji said. "For example, if smokers who used e-cigarettes to help quit were twice as likely to actually quit compared to smokers who used nicotine-replacement therapy, then the benefits of e-cigarette use would approximately balance the harms of e-cigarette use."

Representatives from Reynolds American Inc., which owns market-leading e-cigarette Vuse, and competitor Altria Group Inc., maker of MarkTen and APEX, didn't immediately respond to requests for comment.

Alex Clark, executive director of Consumer Advocates for Smoke-Free Alternatives Association, an e-cigarette industry lobby group, called the study's results "surprising," given government studies showing an overall decline in smoking. (A recent CDC study shows that while smoking has declined, vaping has increased.) Clark said his organization prefers that e-cigarette makers be truthful in advertisements by marketing products as "less risky alternatives" to smoking that have the ability to help smokers quit.

The government has made some effort to dissuade young adopters, with a new requirement for product warnings set to take effect this summer. In October, the FDA addressed youth use of e-cigarettes and other electronic nicotine-delivery systems (ENDS) through its "The Real Cost" campaign. Commissioner Scott Gottlieb said in a statement that vaping devices are by far the most common source of experimentation with tobacco products among children.

"While we continue to encourage innovation of potentially less harmful forms of nicotine delivery for currently addicted adult smokers, we can all agree no child should be using any nicotine-containing product," he said.

Michael Bloomberg, the majority owner of Bloomberg LP, parent of Bloomberg News, provides philanthropic support to anti-smoking campaigns and other health initiatives.

Nicotine & Tobacco Research, 2018, 1–7
doi:10.1093/ntr/nty222
Original investigation
Received April 23, 2018; Editorial Decision October 10, 2018; Accepted October 16, 2018
Advance Access publication October 20, 2018

Original investigation

Quitting Behaviors Among Dual Cigarette and E-Cigarette Users and Cigarette Smokers Enrolled in the Tobacco User Adult Cohort

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Abstract

Purpose: We examined quitting behaviors among a cohort of dual users (cigarettes and electronic cigarettes [e-cigarettes]) and exclusive cigarette smokers for: (1) cigarette smoking reduction, (2) quit attempts, (3) abstinence from cigarettes, and (4) abstinence from all tobacco products.

Methods: Participants enrolled in the Tobacco User Adult Cohort and categorized as "daily" user of cigarettes and "daily" or "some days per week" use of e-cigarettes (ie, dual users; $n = 88$) or "daily" user of cigarettes only (ie, cigarette smokers; $n = 617$) served as the analytic sample. Participants were interviewed face to face every 6 months, through 18 months. Data on self-reported current product(s) used, cessation interest, quit attempts and abstinence from cigarettes, and all tobacco products were collected.

Results: No difference in reduction of cigarette consumption over time was noted between groups. Rates of reporting an attempt to quit all tobacco products (≥ 24 hours of not using any tobacco in an attempt to quit) also did not differ by group. Compared to cigarette smokers, dual users were more likely to report abstinence from cigarettes at 6 months (OR = 2.54, $p = .045$) but not at 12 or 18 months. There was no significant difference in abstinence from all tobacco products by group at 6, 12, or 18 months.

Conclusions: Although dual use of e-cigarettes has been cited as a potential cessation tool for cigarette smokers, our findings indicated that this association was only observed in the short term. We also found no evidence of any association between dual use and eventual abstinence from all tobacco products.

Implications: Our study observed that, in the natural environment, dual users of cigarettes and e-cigarettes were more likely than cigarette smokers to quit cigarettes in the short term but no more likely to quit using cigarettes and all tobacco products over time.

Teen vapers smoke just as much as youth who don't use e-cigarettes

businessinsider.com/r-teen-vapers-smoke-just-as-much-as-youth-who-dont-use-e-cigarettes-2018-11

Reuters 18h

By Lisa Rapaport (Reuters Health) - E-cigarettes aren't likely to keep kids away from traditional cigarettes, a U.S. study suggests.

Instead, researchers found, adolescents who experimented with e-cigarettes ended up smoking traditional cigarettes just as much as teens who never tried vaping.

FILE PHOTO: Man exhales e-cigarette vapour in park in Kiev Thomson Reuters

"The findings show that e-cigs do nothing to deter the amount of combustible smoking in youth," said lead study author Jessica Barrington-Trimis of the Keck School of Medicine at the University of Southern California in Los Angeles. "On the contrary, they increase the likelihood that vaping teens will start smoking."

In the initial phase of the study, researchers surveyed 6,258 high schoolers in Southern California and Connecticut about their vaping and smoking usage. Roughly 14 to 17 percent had used traditional cigarettes and 23 to 29 percent had tried e-cigarettes.

Next, researchers surveyed the teens again one year later. Overall, 7 percent of the teens who had never tried cigarettes had started smoking traditional combustible cigarettes, researchers report in Pediatrics. But the proportion was higher - at 21 percent - among the teens who had been using e-cigarettes.

Compared to the youth who never tried vaping, those who did were more than four times more likely to be dabbling with cigarettes or smoking one to two days a month by the end of the study.

And vapers were also more than three times more likely to be frequent smokers by the end of the study.

Teens who were using both combustible and e-cigarettes were more likely to continue using both than to switch to vaping only.

Big tobacco companies, including Altria Group Inc, Lorillard Tobacco Co and Reynolds American Inc, are all developing e-cigarettes. The battery-powered devices feature a glowing tip and a heating element that turns liquid nicotine and other flavorings into a cloud of vapor that users inhale.

Some previous research has suggested e-cigarettes might help some adult smokers cut back on traditional cigarettes or quit altogether.

"The research on e-cigarettes for smoking cessation among adults is mixed," said Benjamin Chaffee, a researcher at the University of California San Francisco who wasn't involved in the study. Some adults may be able to use e-cigarettes as a cessation aid, but some studies suggest vaping may make it harder to quit, he said.

The picture for teens is even murkier.

"We know very little about e-cigarettes and smoking cessation among adolescents," Chaffee added. "Smoking cessation does not appear to be a major reason that youth try e-cigarettes."

Instead, the current study offers fresh evidence that vaping may lure some young people to tobacco who might otherwise avoid it or make it harder for them to stop using these tobacco products once they start.

"These findings did not provide strong evidence of transition away from cigarette smoking as a potential public health benefit of e-cigarette use," Barrington-Trimis said by email. "Collectively, findings from this paper suggest that e-cigarette use may result in an overall adverse impact to the public health of youth and young adults."

The study wasn't a controlled experiment designed to prove whether or how vaping might directly lead to smoking or impact teen cigarette use.

Still, the results suggest vaping won't help teens stop smoking, said Janet Audrain-McGovern of the Perelman School of Medicine at the University of Pennsylvania in Philadelphia.

"This important study tells us that youth who use e-cigarettes are more likely to continue to use combustible cigarettes after initiating," Audrain-McGovern, who wasn't involved in the study, said by email. "Youth who smoke cigarettes and use e-cigarettes do not appear to be quitting smoking."

SOURCE: http://bit.ly/2SO9xeg Pediatrics, online November 5, 2018.

E-cigarette Use and Subsequent Smoking Frequency Among Adolescents

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abstract

BACKGROUND AND OBJECTIVES: Electronic cigarette (e-cigarette) use is associated with cigarette initiation among adolescents. However, it is unclear whether e-cigarette use is associated with more frequent cigarette use after initiation. Also, the extent to which cigarette or dual cigarette and e-cigarette users transition to exclusive e-cigarette use or to the nonuse of either product is not yet known.

METHODS: Data were pooled from 3 prospective cohort studies in California and Connecticut (baseline: 2013–2014; follow-up: 2014–2016; $N = 6258$). Polytomous regression models were used to evaluate the association of baseline e-cigarette use (never or ever) with cigarette use frequency at follow-up (experimental: initiation but no past-30-day use; infrequent: 1–2 of the past 30 days; frequent: 3–5 or more of the past 30 days). Polytomous regression models were also used to evaluate transitions between baseline ever or past-30-day single or dual product use and past-30-day single or dual product use at follow-up.

RESULTS: Among baseline never smokers, e-cigarette users had greater odds of subsequent experimental (odds ratio [OR] = 4.58; 95% confidence interval [CI]: 3.56–5.88), infrequent (OR = 4.27; 95% CI: 2.75–6.62) or frequent (OR = 3.51; 95% CI: 1.97–6.24) cigarette use; the 3 OR estimates were not significantly different. Baseline past-30-day exclusive cigarette use was associated with higher odds at follow-up of exclusive cigarette or dual product use than of exclusive e-cigarette use.

CONCLUSIONS: Tobacco control policy to reduce adolescent use of both e-cigarettes and cigarettes is needed to prevent progression to more frequent tobacco use patterns and reduce combustible cigarette use (with or without concurrent e-cigarette use) to lessen the adverse public health impact of e-cigarettes.

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Dr Barrington-Trimis formulated the research question, interpreted the results, wrote and edited the manuscript, and is the guarantor; Ms Liu and Ms Mayer contributed to formulating the research question, conducted the analyses, interpreted the results, and edited the manuscript; Drs Kong and Cruz contributed to formulating the research question, the interpretation of results, and the editing of the manuscript; Drs Leventhal, Krishnan-Sarin, and McConnell designed the study (each cohort), collected data, contributed to formulating the research question and the interpretation of the results, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

DOI: https://doi.org/10.1542/peds.2018-0486

Accepted for publication Sep 11, 2018

WHAT'S KNOWN ON THIS SUBJECT: Electronic cigarette (e-cigarette) use is associated with cigarette initiation. However, it is unclear whether e-cigarette use is associated with more frequent cigarette use after initiation or whether adolescent cigarette or dual product users transition to exclusive e-cigarette use or nonuse.

WHAT THIS STUDY ADDS: Adolescent e-cigarette users appear to follow similar trajectories of cigarette smoking frequency as nonusers. Exclusive cigarette or dual product users are more likely to continue using cigarettes than to transition away from smoking to exclusive e-cigarette use or to nonuse.

To cite: Barrington-Trimis JL, Kong G, Leventhal AM, et al. E-cigarette Use and Subsequent Smoking Frequency Among Adolescents. *Pediatrics*. 2018;142(6):e20180486

There's even more evidence that e-cigarettes can expose you to dangerous toxins

IN thisisinsider.com/e-cigs-dangerous-toxins-2018-12

Julia Naftulin 6h

The Food and Drug Administration (FDA) has been cracking down on adolescent tobacco use with new e-cigarette and flavored tobacco product regulations, and a new study reinforces how dangerous these products can be to a person's health.

On December 14, JAMA released an investigative report that looked at potential exposure to harmful toxins in e-cigarettes versus traditional cigarettes and found that both contain high amounts of toxins like nicotine, lead, cadmium, and pyrene.

While the study found that people who used traditional cigarettes or a mixture of traditional and e-cigarettes had the highest level of toxins, the report also stressed that people who exclusively use e-cigarettes have a considerable amount of harmful chemicals in their bodies.

E-cigarette users had fewer toxins when compared with traditional smokers, but still had "measurable exposure."

The study, which found all types of smokers are susceptible to dangerous levels of toxins, highlights a major sticking point of e-cigarettes: their helpfulness among people trying to quit smoking.

People who combined traditional and electronic cigarettes had the highest levels of toxins in their bodies, according to the study.
Mesk Photography/Shutterstock

According to the study, 84% of adult e-cigarette users are former traditional cigarette users who are using the devices to quit smoking, but "reducing smoking-related health risks requires complete cessation," the study's authors wrote. While people who solely used e-cigarettes had less exposure to toxins and nicotine, researchers said "measurable exposure" still existed.

People who combined traditional and electronic cigarettes had the highest levels of toxins in their bodies, according to the study.

Vapes are being used more readily and can lead to serious health problems

As studies on the effects of vaping and e-cigarettes continue to be released, e-cigs like the Juul are being scrutinized for their negative health effects. Not only do these trendy products contain lead and in some cases traces of diacetyl, but they are also being marketed to teenagers who may not realize the addictive nature of vaping.

Risk of Heart Attacks is Double for Daily E-Cigarette Users

ucsf.edu/news/2018/08/411476/risk-heart-attacks-double-daily-e-cigarette-users

By Elizabeth Fernandez

New Analysis Shows Five-Fold Risk for People Who Use Both Cigarettes and E-Cigarettes Daily

Use of e-cigarettes every day can nearly double the odds of a heart attack, according to a new analysis of a survey of nearly 70,000 people, led by researchers at UC San Francisco.

The research also found that dual use of e-cigarettes and conventional cigarettes – the most common use pattern among e-cigarette users – appears to be more dangerous than using either product alone. The study found that the risks compound, so that daily use of both e-cigarettes and conventional cigarettes raises the heart attack risk five-fold when compared to people who don't use either product.

This is the first study to examine the relationship between e-cigarette use and heart attacks, and begins to fill the understanding of the effects of e-cigarettes on long-term health. The study was published Aug. 22, 2018, in the *American Journal of Preventive Medicine*. The data were first presented in February in Baltimore at the 2018 annual meeting of the Society for Research on Nicotine and Tobacco.

"Most adults who use e-cigarettes continue to smoke cigarettes," said senior author Stanton Glantz, PhD, a UCSF professor of medicine and director of the UCSF Center for Tobacco Control Research and Education.

"While people may think they are reducing their health risks, we found that the heart attack risk of e-cigarettes adds to the risk of smoking cigarettes," Glantz said. "Using both products at the same time is worse than using either one separately. Someone who

Vaping no boost to quit rates in smokers, study suggests

medicalxpress.com/news/2018-11-vaping-boost-smokers.html

Credit: CC0 Public Domain

People who vape and smoke cigarettes are no more likely to drop the nicotine habit than those who just smoke, a new study suggests.

Researchers at The Ohio State University studied 617 tobacco users and found no differences in quit rates for "dual users" of both traditional and electronic cigarettes.

This research adds important information to the conversation as public health and medical professionals grapple with the role vaping might play in reducing cigarette smoking, said study senior author Mary Ellen Wewers, a professor emeritus of health behavior and health promotion, and a member of Ohio State's Center of Excellence in Tobacco Regulatory Science.

Participants in the study were part of a larger group of about 1,200 rural and urban Ohioans whose habits are being followed by researchers. All of them are considered heavy tobacco users—those who smoke every day or at least some days every week.

The study appears in the journal *Nicotine & Tobacco Research*.

The researchers sat down with participants every six months for 18 months to ask them about tobacco use, interest in quitting and quit attempts they'd made. They also documented what type of tobacco products the participants used.

At the first check-in, six months into the study, the dual users were more likely to have stopped using tobacco, but that difference disappeared by the 1-year and 18-month interviews. By the end of the study, most dual users were back to smoking cigarettes exclusively.

"The initial difference we saw might be due to a higher interest in quitting among the dual users, but that higher quit rate vanished with time," said lead author Laura Sweet, a graduate student in Ohio State's College of Public Health.

"Tobacco is such a huge killer, and if these products help people quit, that could be really significant for public health. But in this study it looks like they don't, and we need to know that as well," Sweet said.

Though electronic products still deliver nicotine and much remains unknown about their long-term health effects, there's general agreement that they are less harmful than cigarettes in adults.

"The hope would be that adult cigarette smokers are trying e-cigarettes because they want to stop cigarettes and are looking for alternatives to help them," Wewers said, adding that she and others who work on tobacco prevention are concerned that younger people who vape will start there and transition to cigarettes down the road.

The researchers can't be sure what factors contributed to their findings, but the results prompted Sweet to wonder if many adults who smoke and vape are doing so because vaping is more accepted in certain environments, rather than because vaping might help them drop nicotine altogether, she said.

Wewers, a member of the Cancer Control Research Program at Ohio State's Comprehensive Cancer Center, said she wasn't surprised to see a higher likelihood of quitting cigarettes at six months in the dual users, because that group expressed greater interest in quitting overall.

"It makes sense that during the first few months they may do better at quitting, but given that cigarette smoking is such a cyclical thing—people quit and resume all the time—it's not surprising that they went back to smoking after a year," she said.

Because this study didn't assess light smokers or those who consider themselves "social" smokers, it's hard to say what role vaping might play in quitting, Wewers said.

But for health care providers trying how best to help heavy smokers quit, this study could help inform those doctor-patient conversations, she said.

"Providers get questions about trying e-cigarettes all the time from people who want to quit. Our paper would suggest that it's not a promising approach—the majority don't quit, and most of them go back to combustible products exclusively," Wewers said.

"This reinforces the recommendation that there are good, approved medications and nicotine-replacement products out there now and that those should be the first-line approach to helping smokers quit."

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JOURNAL OF ADOLESCENT HEALTH

www.jahonline.org

Original article

Polytobacco Use Among a Nationally Representative Sample of Adolescent and Young Adult E-Cigarette Users

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Article History: Received October 19, 2017; Revised March 2, 2018; Accepted April 18, 2018
Keywords: E-cigarette; Adolescence; Epidemiology; Polytobacco use

ABSTRACT

Purpose: Electronic nicotine delivery systems (ENDS) are adolescents' most commonly used tobacco product and young adults' second most used. Little is known about ENDS use alongside other tobacco products (polytobacco use) and whether exclusive ENDS users differ from polytobacco ENDS users.
Methods: In spring 2016, we surveyed a nationally representative sample of 3,517 13–25-year olds (36.9% 13–17-year olds), and examined sociodemographic and relative risk perceptions between two groups of past 30-day ENDS users: exclusive (only ENDS) and polytobacco (ENDS and at least one other tobacco product).
Results: 4.5% of adolescents and 10% of young adults reported past 30-day ENDS use (n = 281; analytic sample). ENDS users were 38.8% female and 70.6% white. Over half (55.9%) were polytobacco ENDS users. The most common patterns of polytobacco ENDS use were ENDS and cigarettes (11.5%), ENDS and cigars (7.7%), and ENDS, cigars, and waterpipe (5.2%). Those who perceived ENDS to be less harmful than cigarettes were more likely to be exclusive ENDS users than those who perceived ENDS to be as or more harmful than cigarettes (adjusted odds ratio = 2.6, confidence interval = 1.2, 5.7). There were no differences between ENDS groups on age, race, sex, parental education, sexual orientation, or ENDS use frequency.
Conclusions: Just over half of ENDS users also used other tobacco products, increasing their risk for nicotine addiction and other health harms. The Food and Drug Administration is responsible for communicating product risk to consumers and should consider common patterns of use and relative risk perceptions in its ENDS public education efforts.

IMPLICATIONS AND CONTRIBUTION

Over half of ENDS users also used other tobacco products, most often cigarettes, cigars, and waterpipe; however, the study identified few sociodemographic differences between exclusive ENDS users and polytobacco ENDS users. Prevention efforts should consider educating about ENDS alongside other tobacco products and prioritize educating adolescents and young adults about the harms of polytobacco use.

Tobacco use remains the leading preventable cause of disease and death, contributing to over 480,000 deaths annually within the U.S. [1]. Decades of prevention and policy efforts have reduced cigarette smoking rates, but the introduction of non–cigarette tobacco products has led to increased use of multiple tobacco products, or polytobacco use [2]. Polytobacco use is common among U.S. adolescents and young adults; 63% of tobacco users reported past 30-day polytobacco use in the 2014 National Youth Tobacco Survey [3].

Polytobacco use is common for several potential reasons. First, tobacco companies continue to introduce products that are appealing to youth. Often, these products come in a variety of flavors and are perceived as less harmful than cigarettes, which make them more attractive to young people [4–6]. Second, non–cigarette

Conflict of interest: No authors have conflicts of interest to report.
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1054-139X/
https://doi.org/10.1016/j.jadohealth.2018.04.010

E-Cigs are Gateway to Cigarette Smoking

natlawreview.com/article/e-cigs-are-gateway-to-cigarette-smoking

Wednesday, March 15, 2017

A recent University of *Michigan* study revealed that e-cigarette use may act as a bridge to traditional tobacco use. The study showed that teens who vape are four times more likely to start smoking traditional tobacco cigarettes within a year of smoking e-cigs. Scientists attribute the gateway effect to "desensitization" to the dangers of tobacco smoking ostensibly because e-cigarettes have a relatively low smoke output and are touted as being relatively "safe" in comparison to traditional cigarettes. The study results support that restriction of e-cigarette use in minors is critical to prevent long-term smoking behaviors.

Contradicting the study are scientists from a previously released College of London study that showed e-cigarettes are safer than traditional smoking. These and other U.K. scientists denounce the University of Michigan results as either misleading or "exaggerated" to support a U.S. "moral crusade" against e-cigarettes. In reality, it is just a matter of understanding statistics and study results.

The University of Michigan study is not wrong; it just doesn't distinguish between those who would never try to smoke (e-cigs or otherwise), and those who will. Those who will never try cigarettes may never try e-cigarettes. However, the Michigan study shows that those who will, and do try e-cigarettes are four times more likely to smoke regular cigarettes later—and that throws hot water on the belief that e-cigarettes are benign.

The UK scientists continued their criticism and the attempt to bolster their "e-cigarettes are safe" study with mention of the 22,000 people per year who quit smoking regular tobacco cigarettes by using e-cigarettes. Unfortunately, that figure is not very compelling—it equates to only a fraction of a percent (0.06%) of U.S. smokers, which, as of 2015, was still 36.5 million adults. Data points from the CDC tend to support the Michigan study:

- Smoking harms nearly every organ of the body.
- 1% of all adults (36.5 million people): 16.7% of males, 13.6% of females were current cigarette smokers in 2015.
- Thousands of young people start smoking cigarettes every day
- Use of multiple tobacco products increases the risk of nicotine dependence and long-term tobacco use.

E-cigarettes are included in the list of "multiple tobacco products," and are now regulated in the U.S. in the same way as other "tobacco." In fact, according to the CDC figures, the use of e-cigarettes is on such a rise that it almost matches that of regular tobacco use. Refer to the CDC table below to see how fast e-cigarettes have risen to the levels of traditional cigarette use in students.

Tobacco Use* Among High School Students in 2015[5]

Tobacco Product	Overall	Females	Males
Any tobacco product†	25.3%	20.3%	30.0%
Electronic cigarettes	16.0%	12.8%	19.0%
Cigarettes	9.3%	7.7%	10.7%
Cigars	8.6%	5.6%	11.5%
Hookahs	7.2%	6.9%	7.4%
Smokeless tobacco	6.0%	1.8%	10.0%
Pipes	1.0%	0.7%	1.4%
Bidis	0.6%	0.4%	0.9%

Tobacco Use* Among Middle School Students in 2015[5]

Tobacco Product	Overall	Females	Males
Any tobacco product†	7.4%	6.4%	8.3%
Electronic cigarettes	5.3%	4.8%	5.9%
Cigarettes	2.3%	2.2%	2.3%
Hookahs	2.0%	2.0%	1.9%
Smokeless tobacco	1.8%	1.1%	‡
Cigars	1.6%	1.4%	1.8%
Pipes	0.4%	-	-
Bidis	0.2%	-	-

*"Use" is determined by respondents indicating that they have used a tobacco product on at least 1 day during the past 30 days.

†"Any tobacco product" includes cigarettes, cigars, smokeless tobacco (including chewing tobacco, snuff, dip, snus, and dissolvable tobacco), tobacco pipes, bidis, hookah, and electronic cigarettes.

‡Where percentages are missing, sample sizes were less than 50 and thus considered unreliable.

Source: CDC. Tobacco Use Among High School Students in 2015

The main author of the College of London study, Professor Robert West, was reported to have said that "virtually all users of e-cigarettes were past smokers, not the other way around." The CDC numbers contradict this statement. Instead it shows young people are now starting tobacco use with e-cigarettes, e.g., see above where 5.3% of middle schoolers have vaped. This data seems to support the University of Michigan finding that, "Vaping as a risk factor for future smoking is a strong, scientifically-based rationale for restricting youth access to e-cigarettes."

It is unclear why the U.K. scientists from the previous study are adamant that e-cigarettes are healthy when the use of this type of tobacco delivery system is still in its infant stage. It is also unclear why the U.K. made such an outcry when their study compared the safety to traditional cigarettes (apples) rather than determining if e-cigarettes acted as a gateway to other tobacco use (oranges). If they haven't been misquoted, one might ask if they have a crusade to preserve e-cigarette use for the sake of their "study" reputation rather than taking a moment to recognize potential dangers brought forth in the more current Michigan study. The only clear information at this point is that dangers of e-cigarette use continue to be revealed over time.

In addition to the potential danger as a gateway to long term tobacco use, e-cigarettes also pose a danger from inhaling diacetyl and other chemicals known to be in e-cigarette liquids. There is also the growing incidence of explosions attributed to product delivery system, i.e., electronic vaporizers and the lithium batteries that enable nicotine inhalation. The explosion incidents alone are responsible for serious chemical and heat burns that require months of hospitalization as well as skin grafts, bone grafts, and ongoing medical care for physical damage and psychological trauma.

Teens who vape at increased risk for future cigarette smoking

news.umich.edu/teens-who-vape-at-increased-risk-for-future-cigarette-smoking

February 7, 2017

ANN ARBOR—Among high school seniors who have never smoked a cigarette, those who vape are more than four times more likely to smoke a cigarette in the following year than their peers who do not vape.

Part of the reason vaping may be associated with future smoking is that it changes teens' perceptions of the risks of smoking, according to a new University of Michigan study. In fact, vapers are more likely to move away from the view that smoking poses a great risk of harm than nonvapers, says Richard Miech, the study's lead author and research professor at U-M's Institute for Social Research.

The results come from U-M's annual Monitoring the Future study, which conducts nationally representative surveys of 12th-graders. A subset of the respondents is randomly selected to continue participation in the study and is periodically re-surveyed in later years. The results are based on 347 respondents who were initially surveyed in their senior year of high school in 2014 and then followed up a year later in 2015.

Vaping involves the use of battery-powered devices with a heating element that produce an aerosol, or vapor, inhaled by users. The vapors come in thousands of flavors, such as bubble gum and milk chocolate cream, which are attractive to teens. They may or may not contain nicotine, per the user's choice, and contain fewer chemicals known to be harmful to humans than traditional cigarette smoke. Vaping devices include e-cigarettes, "mods" and e-pens.

Vaping has become popular in a short time, and has grown from near-zero prevalence in 2011 to one of the most common forms of substance use among teens today, Miech says.

"These findings contribute to a growing body of evidence showing that teens who vape are more likely to start smoking than their peers who don't vape," he said. "At the very least, teens who vape should be considered at high risk for future smoking, even if they believe they are vaping only flavoring."

Vaping could lead to future smoking through entirely social means. Miech says that kids who vape may believe that smoking is not dangerous if they do not detect any immediate health effects from their vaping. And teens who vape may also be more likely to join peer

groups of smokers, which put youth at heightened risk for smoking.

Richard Miech. "It is possible that among teens vaping, it could lead former smokers back to smoking," Miech said.

The study also looked at seniors who had previously smoked cigarettes, but had no recent smoking activity at the time of the initial survey in 12th grade. Among these seniors, those who vaped were twice as likely to smoke in the next year as compared to those who did not vape.

The results did not find strong evidence for vaping as an effective means for cigarette cessation, at least among teens. Among the 12th-graders who smoked at the initial survey, those who vaped were just as likely to have smoked cigarettes in the following year than those who did not vape, Miech says.

The findings appear in the current issue of Tobacco Control.

More information:

- Study abstract (PDF): E-cigarette use as a predictor of cigarette smoking: results from a 1-year follow-up of a national sample of 12th grade students
- Richard Miech

TC Online First, published on February 6, 2017 as 10.1136/tobaccocontrol-2016-053291

E-cigarette use as a predictor of cigarette smoking: results from a 1-year follow-up of a national sample of 12th grade students

Richard Miech, Megan E Patrick, Patrick M O'Malley, Lloyd D Johnston

▸ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/tobaccocontrol-2016-053291).

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Received 30 June 2016
Revised 22 November 2016
Accepted 27 November 2016

ABSTRACT

Objective To prospectively examine vaping as a predictor of future cigarette smoking among youth with and without previous cigarette smoking experience. A secondary aim is to investigate whether vaping may desensitise youth to the dangers of smoking.

Methods Analysis of prospective longitudinal panel data from the nationally representative Monitoring the Future study. The analysis is based on 347 12th grade students who were part of a randomly selected subsample that completed in-school surveys in 2014 and were resurveyed 1-year later.

Results Among youth who had never smoked a cigarette by 12th grade, baseline, recent vapers were more than 4 times (relative risk (RR)=4.78) more likely to report past-year cigarette smoking at follow-up, even among youth who reported the highest possible level of perceived risk for cigarette smoking at baseline. Among 12th grade students who had smoked in the past but had not recently smoked at baseline, recent vapers were twice (RR=2.15) as likely to report smoking in the past 12 months at the follow-up. Vaping did not predict cessation of smoking among recent smokers at baseline. Among never-smokers at baseline, recent vapers were more than 4 times (RR=4.73) more likely to move away from the perception of cigarettes as posing a 'great risk' of harm, a finding consistent with a desensitisation process.

Conclusions These results contribute to the growing body of evidence supporting vaping as a one-way bridge to cigarette smoking among youth. Vaping as a risk factor for future smoking is a strong, scientifically-based rationale for restricting youth access to e-cigarettes.

INTRODUCTION

Use of e-cigarettes (vaping) among US high school students has increased rapidly in recent years. Any vaping in the past 30 days as of 2015 was 16% among 12th graders, 14% among 10th graders, and 10% among 8th graders.[1] This is rapid growth from a 30-day prevalence of near 1% among secondary school students in 2011.[2] As prevalence has increased so too has concern that vaping among school-aged adolescents may be a bridge to future use of traditional combustible cigarettes.

Evidence is building to bolster this concern. Prospective observational studies provide some of the strongest possible scientific evidence to assess vaping as a risk factor for smoking. To date, five such studies based on US samples have examined the issue and all find vaping to be an independent predictor of smoking initiation. Among youth who had never smoked at baseline, the odds of incident smoking were 1.75–2.87 times higher among youth who vaped compared with those who did not among 9th and 10th grade students,[3–5] and odds were >6 among 12th grade students.[6] Among a panel of Hispanic youth at mean age 23, odds of incident smoking 1-year later were more than three times higher among vapers.[7]

This finding is robust across research designs. The studies noted above are all school-based samples that originally surveyed respondents in schools and then followed them longitudinally. An analysis that used random digit dialling to recruit participants nationally throughout the USA found odds of incident smoking to be more than eight times higher for vapers among a sample aged 16–26.[8]

Importantly, in all these studies vaping remains a significant predictor of smoking incidence after taking into account potential confounders such as baseline smoking susceptibility. In fact, a recent analysis indicates that vaping had the greatest predictive power for incident smoking among adolescents who had the *lowest* propensity to smoke at baseline.[9]

This study focuses on vaping as a risk factor for smoking among 12th grade students originally surveyed in schools in 2014 and contributes to the field in three ways. First, to the best of our knowledge we report the first results on this topic from a sample of schools selected to be nationally representative. All current school-based samples on the topic sample a specific US state or city, and replication of results from existing studies with a national, school-based sample strengthens the case for all these studies to directly inform national policy and regulation.

Second, the analysis examines perceived risk of harm from cigarette use as both a baseline confounder and also a possible intervening mechanism connecting vaping with future smoking. Perceived risk of harm predicts use of a wide variety of substances[10–12] and is substantially associated with cigarette smoking.[13] Evidence that baseline levels of perceived risk from cigarette smoking do not 'explain away' the finding of vaping as an independent predictor of future smoking would show that the finding is robust across different, major measures of smoking propensity. In addition, evidence that vaping predicts later reductions in perceived risk of smoking would be an important step towards the identification of a possible desensitisation process that would help explain how vaping is connected to later smoking. Finally, we examine vaping as a predictor of future smoking among

To cite: Miech R, Patrick ME, O'Malley PM, *et al*. *Tob Control* Published Online First: [*please include* Day Month Year] doi:10.1136/tobaccocontrol-2016-053291

youth with past cigarette smoking experience, a group that has received relatively less attention than never-smokers. This is a preliminary step to consider whether vaping leads this group of youth away from smoking or not.

METHODS

Data

Data come from the annual Monitoring the Future (MTF) study, which since 1975 has used questionnaires administered in classrooms to survey nationally representative samples of US 12th graders in the 48 contiguous states.[12 14] The project has been approved by the University of Michigan Institutional Review Board. The target sample is all schools in the contiguous USA that enrol 25 or more 12th grade students, and in 2014 the study surveyed 122 schools (105 public and 17 private). In 2014, 13 015 12th grade students completed questionnaires, for a response rate of 82%. Almost all non-response was due to school absences. This non-response did not lead to a substantial upward or downward bias of the study's prevalence estimates for smoking and vaping in comparison to other nationally representative, school-based surveys.[15 16]

The geographical areas sampled included the 28 largest metropolitan areas containing about one-third of the nation's population, as well as 136 other primary areas. In 2014, either an original school or a replacement school was obtained in 92% of the sample units.

This analysis uses information from 347 follow-up participants in 2015. Figure 1 presents information on how they were selected. Every year a random subsample of 2450 members of the 12th grade class is selected to participate in a panel that receives follow-up surveys. Questions on vaping were included on four of the six forms of the survey (the forms are randomly distributed in equal proportions). Consequently, 1643 (~2/3) of the 2450 respondents selected for follow-up were eligible for the analyses. To reduce respondent burden the panel is split into two random halves, with one half receiving questionnaires in even years and the other in odd years. In 2015 out of the 822 target panel respondents 347 provided sufficient information to be included in the analyses, for a response rate of 42% at modal age 19. Only respondents who had complete information on their 2015 cigarette smoking status were retained in the final analyses (97% of responders). Of these, the average length of the follow-up period was 13.40 months (with a 95% CI of 13.23 to 13.57). Online supplementary tables A1 and A2 in the Appendix provide more detailed information on the sample size of the analysis pool.

Statistical analysis

We developed and used attrition weights to control the potential influence of panel attrition. The attrition weight was the inverse of the predicted probability of follow-up response, based on a regression equation modelling panel retention as a function of respondents' baseline characteristics, which are defined in table 1. Final weights were calculated as this attrition weight multiplied by a weight used to control the panel's intentional oversampling of individuals with higher levels of illicit drug use at baseline.[17]

Online supplementary table A3 in the Appendix shows that with use of the attrition weights none of the baseline variables differed for the follow-up responders as compared with the target sample. The attrition weights took into account a higher likelihood of response for women and whites, as well as respondents with lower levels of substance use.

To control for missing item-level data among follow-up respondents the analysis used multiple imputation with 20 imputed data sets,[18] in conjunction with the survey weights. The imputation process had little effect on the study results because item-level missing data were uncommon (92% of the 347 respondents had complete information on all analysis variables). In a parallel analysis that used list-wise deletion instead of multiple imputations all statistically significant differences remained, in the same direction, across the two analyses. Likewise, all significant differences remained and were in the same direction when the attrition weights were not used, both in analyses with and without multiple imputation.

The main analyses consist of two main components. First, tables 2 and 3 examine vaping as a predictor of future smoking (detailed results presented in the online supplementary tables A4 and A5). The predictive power of vaping may differ by respondents' past level of smoking experience and/or perceived risk of harm from smoking cigarettes, and consequently the analyses are stratified by these factors. Stratification also controls any potential differential sample attrition by these factors. The multivariable models include additional controls for demographics as well as baseline levels of marijuana use and binge drinking, which serve as measures of proclivity for general substance use. The second component of the analyses examines vaping as a predictor of decreases in perceived risk of smoking, to examine whether vaping desensitises youth to the dangers of smoking cigarettes.

RESULTS

Table 1 presents the proportions and definitions of the study variables. The prevalence of vaping ranked among the highest of all substance use,[19] and prevalence of recent vaping (in the past 30 days) was about 50% higher than prevalence of recent smoking (smoked combustible cigarettes in the past 30 days). Cigarette smoking was considered harmful by most, with the percentage seeing great risk in smoking one or more packs of cigarettes per day over 80% at both the baseline and follow-up surveys.

Table 2 presents incidence of cigarette smoking among respondents who had never smoked a cigarette up to the time of the 12th grade survey. For this group, the incidence of smoking within the past 12 months in 2015 was about four times higher for youth who vaped at baseline as compared with those who did not, at 31% and 7%, respectively (model 1). This difference remained after statistically controlling the potential confounders of sex, race, and parental education. Among the group of new smokers at follow-up who had recently vaped at baseline, all reported that they had smoked cigarettes at the level of 'once or twice' in the past 12 months at follow-up.

Model 2 of table 2 presents results for the subgroup of never-smokers who at baseline saw great risk in cigarette smoking. This group would presumably be the least likely to consider cigarette smoking in the future. Even among this group, recent vaping at baseline strongly predicted incidence of cigarette smoking in the following year.

Table 3 presents prevalence of any cigarette smoking in the past 12 months among respondents who had ever smoked a cigarette by the time of the 12th grade survey. For this group the prevalence of past 12-month smoking at follow-up was more than twice as high for baseline recent vapers compared with non-vapers at baseline, at 80% and 37%, respectively. This difference was statistically significant in bivariate and multivariable analyses.

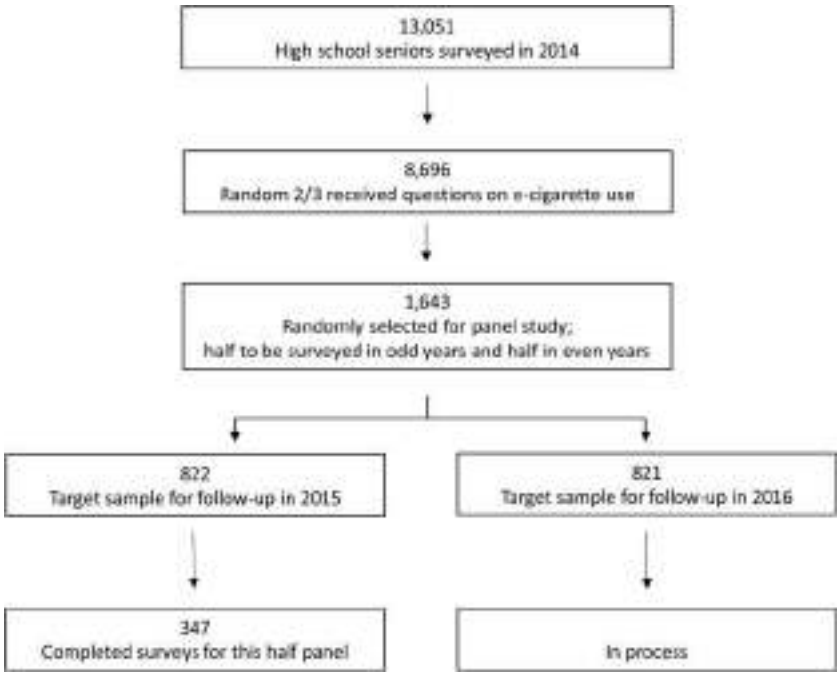

Figure 1 Flow chart for selection in the panel study.

Table 3 also presents results stratified by smoking activity in the 30 days prior to the 12th grade survey. Vaping significantly predicted cigarette smoking in the past 12 months at follow-up among youth who had smoked in the past but not recently (63% vs 27%), but did not reach significance among youth who had smoked recently (95% vs 77%). To test whether the predictive power of vaping was significantly different across these two groups of youth we modelled past 12-month prevalence at follow-up as a function of baseline recent vaping, baseline recent smoking, and the multiplicative interaction between these two dichotomies. The significance level of the interaction term was $p<0.062$, which meets criteria as 'statistically significant' to the extent that multiplicative interaction terms warrant higher probability cut-offs.[20]

Among youth with past smoking experience the analysis examined potential differences by level of past cigarette use (analyses not presented in the tables). About half (50.73%, SE=5.06) of the non-recent smokers in 12th grade were experimental smokers who reported that they had smoked a cigarette just 'once or twice' in their life. For this subgroup vaping was a significant predictor of past-year smoking at the follow-up survey (bivariate relative risk=2.75; 95% CI 1.17 to 6.76). The other half of youth with past smoking experience reported that before 12th grade they smoked 'occasionally but not regularly' or 'regularly in the past'. For this subgroup vaping was not a significant predictor of past-year smoking in the follow-up survey (bivariate relative risk=1.60; 95% CI 0.88 to 2.91). However, the relative risk estimates did not significantly differ across the two groups, making these differences across the two groups only suggestive (relative risk differences tested with a multiplicative interaction term in a model that included all past smokers).

Table 4 presents baseline recent vaping as a predictor of changes in perception of cigarette smoking away from 'great risk' to a lower level during the study period. Among respondents who had never smoked a cigarette by the 12th grade survey, recent vapers compared with non-vapers were four times more likely to move away from the view that cigarette smoking poses a 'great risk'. This predictive association was statistically significant in bivariate and multivariable models both of all never-smokers as well as never-smokers who saw 'great risk' in cigarette smoking at the baseline survey. No predictive association for recent vaping on risk perception was present among respondents who had ever smoked cigarettes at the baseline survey.

DISCUSSION

Two aims motivated this study. The first was to examine vaping in 12th grade as a predictor of future smoking of traditional combustible cigarettes, among youth with and without smoking experience at baseline. The second was to examine whether youth who vaped later downgraded their perception of the risks of smoking. Study participants were drawn from a nationally representative sample of students in US private and public schools in 2014 and followed up 1 year later in 2015.

Among 12th grade students who had never smoked combustible cigarettes, vaping strongly predicted smoking initiation a year later. First use of a combustible cigarette at follow-up was reported by 31% of those who had recently vaped at the baseline survey, as compared with 7% among those who did not. The analysis also examined the group of non-smokers who at baseline reported the highest level of perceived risk for smoking; these adolescents would be expected to have the lowest predisposition to start smoking cigarettes. Even among this group, recent vaping was a strong predictor of smoking initiation, which was 33% for vapers as compared with 7% among non-vapers.

Desensitisation to the dangers of smoking may play a role in explaining how vaping can progress to smoking among youth who have no history of cigarette use. Youth who begin to vape primarily to experiment and because vaping tastes good (the most common reasons for vaping[21]) may detect no immediate health consequences and conclude that the dangers of smoking are exaggerated. Empirical support for a desensitisation process comes from this study's finding that youth who vaped were significantly more likely to change their perception of the dangers of smoking away from 'great risk', among those who had never smoked at baseline.

Table 1 Definitions and sample proportions for analysis variables (SEs in brackets)*

Variable	Percentage of follow-up subsample n=347
Variables measured at baseline in 2014	
Recently vaped	15.60
Coded 1 for response of at least 1 to the question 'During the last 30 days, on how many days (if any) have you used electronic cigarettes (e-cigarettes)?'.	(1.97)
See 'great risk' in smoking	80.88
Coded 1 for the response of 'great risk' to the question 'How much do you think people risk harming themselves (physically or in other ways) if they smoke 1 or more packs of cigarettes per day?'.	(2.28)
Never smoked a cigarette	71.05
Coded 1 for the response 'never' to the question 'Have you ever smoked cigarettes?'.	(2.49)
Recently smoked	10.13
Coded 1 for a response of '<1 cigarette a day' or more to the question 'How frequently have you smoked cigarettes in the past 30 days?'.	(1.68)
Female	56.26
Coded 1 for female respondents	(2.80)
Non-white†	39.89
Coded 1 for respondents who did not report that they were 'white (Caucasian)'.	(2.77)
Binge drinking in past 2 weeks	16.12
Coded 1 for a response of at least one to the question 'Think back over the last 2 weeks. How many times (if any) have you had 5 or more drinks in a row?'.	(2.00)
Recently smoked marijuana	18.93
Coded 1 for a response of at least 1 to the question 'On how many occasions (if any) have you used marijuana (weed, pot) or hashish (hash, hash oil) during the last 30 days?'.	(2.09)
Variables measured at follow-up in 2015	
See 'great risk' in smoking	83.05
Coded 1 for the response of 'great risk' to the question 'How much do you think people risk harming themselves (physically or in other ways) if they smoke one or more packs of cigarettes per day?'.	(2.13)
Changed perception of risk of smoking away from 'great risk'	11.12
Coded 1 for respondents who saw 'great risk' in smoking at baseline but not at follow-up.	(1.82)
Smoked in last 12 months at 1-year follow-up	21.75
Coded 1 for respondents who responded 'smoked once or twice', or more, to the question 'What best describes your cigarette smoking in the last 12 months?'.	(2.27)

Baseline questions on cigarettes ask about lifetime and past 30-day smoking, but not smoking in the past year.
*Estimates weighted for oversample of 12th grade students with high levels of drug use and for attrition.
†More detailed measures of race/ethnicity are precluded by small sample size.

Table 2 Smoking incidence at 1-year follow-up among 12th grade students who had never smoked traditional, combustible cigarettes, by baseline vaping (SEs and 95% relative risk CIs in brackets)†

Model	(1) All	(2) See 'great risk' in smoking cigarettes
n (weighted)	**246**	**204**
Recently vaped at time of 12th grade survey		
No	6.75 (1.70)	7.15 (1.96)
Yes	31.07 (14.00)	32.92 (14.99)
Bivariate relative risk‡	4.60** (1.71 to 12.34)	4.59** (1.67 to 12.63)
Adjusted relative risk‡	4.78** (1.91 to 11.96)	4.64** (1.66 to 12.93)

**p<0.01.
†Estimates weighted.
‡Differences across e-cigarette use groups modelled in a binomial regression with a log link. See online supplementary table A4 for detailed presentation of the controls in the models for adjusted relative risk.

The analysis also examined vaping as a predictor of cigarette smoking among students with smoking experience by 12th grade. Among those who had not recently smoked at the baseline survey, vaping strongly predicted any cigarette smoking in the past 12 months at the follow-up. In contrast, among students who were recent smokers at the baseline survey, the prevalence of past 12-month smoking at the follow-up did not differ significantly by vaping at baseline.

Health policy implications

Developing a rationale to regulate youth access to e-cigarettes will require more than a simple extension of the arguments used to regulate combustible cigarettes. Currently lacking for e-cigarettes is a developed body of scientific evidence documenting their health dangers, a body of evidence that exists for combustible cigarettes and plays a central role in the rationale for their regulation. The development of such evidence for the direct effects of

Table 3 Prevalence of past 12-month smoking at 1-year follow-up among 12th grade students who had ever smoked, by baseline vaping status (SEs and 95% relative risk CIs in brackets)†

	All	Non-recent smoking at 12th grade survey‡	Recent smokers at 12th grade survey‡
n (weighted)	101	66	35
Recently vaped at time of 12th grade survey			
No	37.44 (6.73)	27.45 (6.78)	76.93 (13.72)
Yes	80.18 (5.78)	62.70 (10.62)	94.86 (3.69)
Bivariate relative risk§	2.14** (1.46 to 3.14)	2.28** (1.27 to 4.10)	1.23 (0.87 to 1.73)
Adjusted relative risk§	2.15* (1.49 to 3.12)*	2.26** (1.22 to 4.18)	1.32 (0.89 to 1.96)

*p<0.05; **p<0.01.
†Estimates weighted.
‡Non-recent smoking defined as youth who smoked at some time in the past but not in 30 days prior to the 12th grade survey, and recent smokers defined as those who smoked in the 30 days prior to the 12th grade survey.
§Differences across e-cigarette use groups modelled in a binomial regression with a log link. Not all controls could be included in each adjusted model due to convergence issues; see online supplementary table A4 for detailed presentation of multivariable models.

e-cigarettes may require many years or even decades (as it did for regular cigarettes), and once this body is developed e-cigarette manufacturers could change their ingredients and the process may need to start all over again. In addition, recent research shows that the majority of youth who vape report that they vape 'just flavouring' and not nicotine.[22] Consequently, regulations and policies based on a rationale of nicotine regulation may not necessarily apply to youth e-cigarette use in a straightforward way.

One important rationale to regulate e-cigarettes is that they lead to use of combustible cigarettes among youth. This rationale builds on the already-existing consensus and political will to reduce youth cigarette smoking, given that most people would favour age restrictions on sale of devices that lead youth to smoke.

This study strengthens the evidence that vaping is a risk factor for cigarette smoking among youth in three ways. First, it contributes the first findings based on a sample of schools selected to be nationally representative of the USA to the growing body of evidence linking vaping to later smoking incidence among youth who had never smoked at baseline. Now four studies have used school-based samples of adolescents to investigate this topic longitudinally, and all support vaping as an independent predictor of smoking incidence, taking into account predisposition to smoke at baseline.[3 4 6] These findings are particularly important given that vaping is one of the most common forms of substance use among youth who have never smoked, with a current prevalence of 4% for this group.

Second, the study's evidence for a potential role for perceived risk is an important step in the identification of mechanisms that link vaping to later smoking incidence among never smokers. The intervening mechanisms at work may not necessarily be linked to chemical addiction and may operate even if the substance vaped in e-cigarettes is not addictive or physically harmful. Other candidate intervening mechanisms include smoking expectancies, peer smoker affiliations, and attitudes toward smokers.[23] The planned, future addition of a third wave of data will allow testing of a formal mediation model.

Finally, this study is one of few to consider the possibility that vaping may lead youth with past smoking experience to return to smoking. Among youth who had smoked in the past but had not recently smoked at the time of survey, those who vaped were about twice as likely to have smoked at least one cigarette in the past 12 months at the follow-up. Vaping did not divert this group away from smoking.

We note four limitations of this study. First, the analyses do not take into account what substances youth vaped in their e-cigarettes. Such questions were asked in more recent surveys, so in the future it will be possible to test if the overall predictive power of vaping for future smoking incidence differs among subgroups who vape different types of substances.

A second limitation is that the sample size of the analysis did not allow detailed examination of important subgroups. For example, analysis of racial/ethnic categories beyond white and non-white led to groupings that were too small to support

Table 4 Percentage who changed their perceived risk of smoking away from 'great risk' at follow-up wave (SEs and 95% relative risk CIs in brackets)†

Smoking status:	Never smoked by 12th grade		Smoked by 12th grade
	All	See 'great risk' in smoking cigarettes	All
n (weighted)	246	204	101
Recently vaped at time of 12th grade survey			
No	9.01 (2.04)	10.92 (2.44)	14.12 (5.05)
Yes	41.27 (16.58)	41.73 (16.68)	11.65 (5.70)
Bivariate relative risk‡	4.56** (1.87 to 11.11)	3.81** (1.57 to 9.21)	0.82 (0.29 to 2.83)
Adjusted relative risk‡	4.73** (2.07 to 10.82)	3.74** (1.57 to 8.89)	0.69 (0.19 to 2.49)

Analysis includes five cases with imputed data for the dependent variable. Results changed only trivially when these five cases were removed from the analysis. See online supplementary table A5 for detailed presentation of multivariable models.
**p<0.01.
†Estimates weighted.
‡Differences across e-cigarette use groups modelled in a binomial regression with a log link. Adjusted relative risk controls sex, parental education, and race (white vs non-white).

statistical analysis. The sample size also did not allow analysis by different frequency of vaping in the past 30 days at baseline. In future years, the sample size will grow considerably with the addition of new cohorts that can be combined with this one, which will allow more detailed analysis of possible differences in the overall findings across specific subgroups.

A third limitation is that not all target follow-up respondents returned surveys, which introduces the possibility of response bias. Subgroups that are more likely to respond may exert a larger influence than their size warrants on the study results. In particular, for this study any differential sampling response by groups with high predisposition to smoke cigarettes at baseline or smoking experience at baseline have potential to confound the results. To address this possibility the analyses stratify by these factors, with perceived risk of smoking as an indicator of predisposition to smoke. Stratification of analyses by key groups takes into account both substantive confounding as well as any confounding that results from their potentially different levels of survey response. Confidence that response bias does not seriously confound the study results is strengthened both by the stratification procedure as well as the finding from the attrition analyses that the stratified subgroups showed no major difference in proportionate size among follow-up responders as compared with the target panel sample. To be thorough, the study's attrition weighting addresses the small differences in response rates by groups, and this attrition weighting did not change the study's substantive results or conclusions.

A fourth limitation is that the data do not contain specific questions related to tobacco use such as smoking susceptibility, smoking expectations, rebelliousness, affiliation with smokers in the community, and perception of friends' attitudes toward smoking. Such questions would allow more comprehensive, statistical control of the predisposition of youth to smoke cigarettes. The analyses control for these influences in part by controlling general substance use at baseline, through which many of these influences would act, and still find support for vaping as an independent predictor of future smoking. These results are consistent with other school-based studies in this literature that include controls for these factors[3 4 6] and still find that vaping significantly predicts future smoking. Taken together, existing studies suggest that it is unlikely that predisposition to smoke can 'explain away' the association of vaping with future cigarette smoking.

In conclusion, these results bolster findings for vaping as a one-way bridge to cigarette smoking among adolescents. To the best of our knowledge, the risk for future cigarette smoking is currently one of the strongest, scientifically-based rationales for restricting youth access to e-cigarettes.

What this paper adds

This paper contributes to the growing body of evidence that e-cigarette use is an independent risk factor for future smoking, both among youth who are non-smokers and also among youth with past smoking experience. Results support a desensitisation process, whereby youth who vape lower their perceived risk of cigarette smoking.

Contributors LDJ is the principal investigator of the Monitoring the Future Study, and the other authors are all co-investigators. RM developed the paper plan, performed the data analysis, and drafted the manuscript, assisted by MEP. All authors contributed to drafts of the manuscript.

Funding This study was supported by the National Institute on Drug Abuse, part of the National Institutes of Health, by grants numbers R01DA001411 and R01DA016575.

Competing interests None declared.

Ethics approval University of Michigan Institutional Review Board, approval number HUM00063656.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The data are drawn from a wider survey that examines trends in the use of a variety of substances among adolescents, as well as trends in many substance use related variables. Each year a de-identified version of the previous year's data is made publicly available and can be downloaded for no charge at: http://www.icpsr.umich.edu/icpsrweb/NAHDAP/index.jsp. Researchers wishing to use sensitive data that cannot be publicly released should send a request to mtfinformation@umich.edu to start the application process.

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E-cigarettes are 'one way bridge to tobacco'

dailymail.co.uk/health/article-4202072/E-cigarettes-one-way-bridge-tobacco.html

February 8, 2017

Electronic cigarettes are a ‘one-way bridge’ to smoking tobacco among teenagers, experts have claimed.

The study, by scientists at the University of Michigan, last night fuelled a growing row over the benefits and dangers of e-cigarettes.

The US team said using the nicotine gadgets ‘desensitised’ teenagers as to the harms of tobacco, meaning they were four times as likely to go on to smoke cigarettes.

But British researchers criticised the design of the study and dismissed its findings as ‘trivial’.

A study by the University of Michigan has claimed electronic cigarettes 'desensitise' teenagers to the harms of tobacco, making them four times more likely to smoke the real thing (file picture)

Just yesterday a major study by University College London reported e-cigarettes were significantly safer than tobacco and would help people quit cigarettes.

The senior author of that study, Professor Robert West, said it was ‘frustrating’ that research which highlighted the danger of e-cigarettes are given so much publicity.

He said virtually all users of e-cigarettes were past smokers – not the other way around.

And he accused US researchers of waging a ‘moral crusade’ against e-cigarettes, claiming many scientists exaggerated their findings to achieve publicity and recognition.

E-cigarettes contain a liquid form of nicotine that is heated into vapour to be inhaled, avoiding the harm caused by tobacco smoke.

Nearly three million adults in Britain have used e-cigarettes in the decade they have been on the market.

Health experts agree that the devices are much safer than smoking tobacco – and the gadgets are thought to have helped 22,000 people quit smoking each year.

But many are concerned about unresolved safety concerns, while others are worried they provide a ‘gateway’ for teenagers to go on to smoke tobacco.

The latest study, published in the journal Tobacco Control, examined data from American pupils in their final year of high school in 2014 and again a year later.

Questioning 17 and 18 year olds, the researchers found that those who had used e-cigarettes but had never smoked tobacco, were more than four times as likely to try cigarette smoking in the next year.

Those who tried ‘vaping’ were also more likely to move away from the perception of cigarettes as posing a ‘great risk’ of harm, the authors added.

They said this finding was ‘consistent with a desensitisation process’.

But a major study by University College London reported e-cigarettes were significantly safer than tobacco and would help people quit cigarettes (file picture)

Watchdog said e-cigarettes don't help quit smoking
0:00
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‘These results contribute to the growing body of evidence supporting vaping as a one-way bridge to cigarette smoking among youth,’ the scientists wrote.

‘Vaping as a risk factor for future smoking is a strong, scientifically-based rationale for restricting youth access to e-cigarettes.’

But the findings were criticised by UK scientists.

Professor Peter Hajek, director of the Tobacco Dependence Research Unit at Queen Mary University of London, said: ‘This paper just shows that teenagers who try cigarettes are more likely to also try e-cigarettes - and the other way round - compared to teenagers who do not do such things. This is trivial.

‘People who read sci-fi novels are also more likely to watch sci-fi movies than people who do not like sci-fi. There is no reason why these activities should be performed in one order only.’

Professor Linda Bauld of the University of Stirling added: ‘If trying an e-cigarette causes regular smoking, then we should be alarmed.

‘However, this study and previous American studies which have made similar assertions have not found this, and so we must be very cautious about jumping to such a conclusion on the basis of this study.’

Espacenet search results on 13-12-2018 09:39

Approximately 29 results found in the Worldwide database for:
txt = PETER and txt = HAJEK using Smart search
Displaying selected publications

Publication	Title	Page
GB2376885 (A)	Method to aid smoking cessation	2
GB2376884 (A)	Helping smokers stop	3

(12) UK Patent Application (19) GB (11) 2 376 885 (13) A

(43) Date of A Publication 31.12.2002

(21) Application No 0115568.8

(22) Date of Filing 26.06.2001

(51) INT CL[7]
A61K 31/351 31/341 , A61P 25/34

(52) UK CL (Edition T)
A5B B180 B23Y B230 B44Y B442 B443 B50Y B502 B54Y B540 B565 B566
U1S S1328

(56) Documents Cited
None

(58) Field of Search
UK CL (Edition R) A5B BHA BJA
INT CL[7] A61K 31/341 31/351
Other: DATA-BASE:WPI, EPODOC, PAJ

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(54) Abstract Title
Method to aid smoking cessation

(57) The present invention concerns methods of treating patients for nicotine and tobacco addiction, for alleviating nicotine withdrawal, for improving the effects of other smoking cessation therapies and as long-term smoking cessation maintenance therapy. The invention comprises pharmaceutical compositions comprising dextrose monohydrate and/or laevulose in combination with amfebutamone (or with any other non-nicotine smoking cessation method whose efficacy can be enhanced by addition of dextrose or laevulose). Specific combinations of drugs (dextrose and/or laevulose combined with amfebutamone) as well as dextrose and/or laevulose in combination with certain drug classes (e.g. stimulant drugs, anti-depressants, drugs used in treatment of psychoactive substance use disorders) comprise the pharmaceutical compositions disclosed. These compositions are also contemplated for use in the treatment of alcoholism, cocaine dependence and other drug dependencies.

GB 2 376 885 A

(12) UK Patent Application (19) GB (11) 2 376 884 (13) A

(43) Date of A Publication 31.12.2002

(21) Application No 0115668.2

(22) Date of Filing 26.06.2001

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(51) INT CL[7]
A61K 31/465 , A61P 25/34

(52) UK CL (Edition T)
A5B B190 B327 B541 B565 B595 B621 B623 B627 B634
U1S S1328

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EP 1107738 A2 **WO 1995/011679 A1**
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(58) Field of Search
INT CL[7] **A61K 31/465**
Other: **DATA-BASE: WPI, EPODOC, PAJ**

(54) Abstract Title
Helping smokers stop

(57) The present invention concerns a new way of using nicotine replacement treatment to enhance its efficacy in treating patients for nicotine and tobacco addiction and for alleviating nicotine withdrawal. The invention includes providing nicotine replacement treatment in one or more forms for a period of time prior to cessation of smoking to de-condition the link between smoking behaviour and its pharmacological reinforcement, and to habituate the user to the nicotine replacement products. After stopping smoking, nicotine replacement treatment is used in the usual way.

GB 2 376 884 A

Estimating the population impact of e-cigarettes on smoking cessation in England

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Conflict of Interest declaration: RW undertakes research and consultancy for companies that market smoking cessation medicines but not e-cigarettes. He is honorary advisor to the UK's national Centre for Smoking Cessation and Training. His salary is funded by Cancer Research UK. JB received an unrestricted research grant from Pfizer in 2012 to study smoking cessation trends in England. LS has received a research grant, an honorarium for a talk and travel expenses to attend meetings and workshops from a pharmaceutical company that makes smoking cessation products (not e-cigarettes).

Funding: RW is funded by Cancer Research UK. JB is funded by the Society for the Study of Addiction.

An important consideration when assessing the public health impact of e-cigarettes is how far they contribute to, or detract from, smoking cessation in the population. There has been speculation about this (1), but without engaging appropriately with the relevant data and based on unreliable assumptions. England has data that can help to address this question, at least so far. Addiction's readers may be interested in the following analysis. It focuses on 2014, the most recent year for which full data are available. It leads to an estimate of 16K-22K as the number of additional long-term quitters generated by e-cigarettes in that year.

Estimation

1. At the start of 2014 there were approximately 8.46 million adult smokers in England (19.3% of 43.83 million people aged 16+) (2)
2. The percentage of smokers in 2014 who reported that they had tried to stop at least once is estimated at 37.3% (3.16 million people) (3)
3. The percentage of those who tried to quit who used an e-cigarette (and not a prescription medicine or behavioural support) in 2014 was 28.2% (891K people) (3)
4. The expected long-term (1 year) success rates of a quit attempt made without assistance or using a licensed nicotine product (LNP) bought from a shop is approximately 5% (4, 5). Note that in England no benefit has been found for LNPs bought from a shop whereas they have been associated with increased success rates when accompanied by at least some professional support (5, 6).
5. Evidence from RCTs and from surveys in England indicate that using an e-cigarette in *a quit attempt* increases the probability of success on average by approximately 50% compared with using no aid or LNP bought from a shop – similar to use of a licensed medicine with limited behavioural support but less than medication plus specialist behavioural support (6, 7).
6. Therefore it is estimated that 2.5% of the smokers who used an e-cigarette in their quit attempt in England (**22K** people) succeeded who would have failed if they had used nothing or LNP bought from a shop.
7. As e-cigarette usage has increased, use of prescription stop-smoking medications and specialist behavioural support has decreased (3). The decline in these methods of stopping

since e-cigarettes started to become popular is approximately 10% of quit attempts which represent 3.7% of smokers in 2014 (313K smokers). The trajectories of the declines have not mirrored the increase in e-cigarette use so there may be no connection. However, we consider that an upper estimate for the contribution of e-cigarettes to that decline is 80%, which represents 250,000 smokers (313K×0.8).

8. Therefore, if e-cigarettes have detracted from the use of methods of stopping that are equally effective or more effective, the net increase in smokers using a method of stopping yielding an approximately 50% increase in long-term success is approximately 630K people (880K-250K). The net number estimated to have quit in England during 2014 who would not have quit if e-cigarettes had not been available would therefore be **16K** (630K*0.025).

Comments and caveats

1. Estimated prevalence of e-cigarette use in a quit attempt as a proportion of all smokers is subject to 95% confidence intervals of ±1%.
2. There have been highly publicised studies purporting to have found that e-cigarettes promote uptake of cigarettes, or are taken up in substantial numbers by, people who would not have smoked and that this outweighs any impact of e-cigarettes on quitting. These claims are undermined by highly plausible alternative explanations (8). In England and the US, the evidence thus far contradicts the hypothesis: regular use of e-cigarettes by never smokers is extremely rare and the decline in smoking prevalence in young people has been as great or greater than in previous years (8).
3. Our estimate does not take account of any effect of e-cigarettes on the incidence of quit attempts. Since e-cigarettes became popular the incidence of quit attempts has risen and then fallen again (3) so a causal connection is unlikely.
4. It has been proposed that using an e-cigarette while continuing to smoke may reduce subsequent quitting so that, even if using an e-cigarette in a quit attempt increased the chances of success of that attempt, the net effect of having e-cigarettes on the market has reduced quitting (9). However, smokers who use e-cigarettes may have a lower pre-existing ability to stop smoking (10). If the proposal were correct, one would expect a reduction in population quitting rates as dual use of e-cigarettes among smokers increased, whereas in England the overall rate of smoking cessation in 2014 was *higher* than in any of the previous 7 years (3).
5. It is possible that smokers who quit with the aid of an e-cigarette may be at greater risk of longer term relapse to smoking. However, it is also possible that they are at lower risk, or similar risk. This is an issue that requires further study.
6. The figures relate to the population as a whole, not individual smokers.
7. No differentiation can be made between different types of e-cigarette because of the lack of trial and population level data on relative effectiveness and usage.
8. For smokers who used more than one method of quitting in their quit attempt, we counted the method that evidence indicated would be most effective (6).
9. The figure of approximately 16K-22K is much lower than the population estimates of e-cigarette users who have stopped smoking (approximately 560K in England at the last count according to the Smoking Toolkit Study). However, the reason for this can be understood from the following:
    a. Only some e-cigarette users who have stopped smoking will have done so in the past year; 3.6% (252K) of the 7.01 million long-term ex-smokers (16% of adult population in 2014) used e-cigarettes according to the Smoking Toolkit Study (leaving 308K).

b. Some 9% (28K) of the 3.11 million recent ex-smokers (according to Smoking Toolkit Study) started their e-cigarette use after they stopped smoking, possibly to avoid relapse to smoking (leaving 280K).
c. It has to be assumed on the basis of the evidence (6, 7) that only a third of e-cigarette users who stopped smoking would not have succeeded had they used no cessation aid (leaving 93K).
d. It is assumed that, as with other smoking cessation aids, 70% of those recent ex-smokers who use e-cigarettes will relapse to smoking in the long term (11) (leaving 28K).
e. Some people (estimated at 6K based on the calculations in 7. and 8. of our estimate) who stopped smoking with the aid of an e-cigarette may otherwise have used a prescription medicine and/or behavioural support (leaving 22K).
f. So by this alternative method the range is 22K-28K which is only slightly higher than the 16K-22K estimated earlier.
g. It is, of course, important to appreciate that estimates of the numbers of e-cigarette users are subject to quite wide margins of error. Nevertheless, the population figure for numbers of additional ex-smokers generated by e-cigarettes in 2014 in England looks to be in the tens of thousands.

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GB2461008 (A)
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Bibliographic data: GB2461008 (A) — 2009-12-23

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Nicotine inhaler with flavour source

Page bookmark	GB2461008 (A) - Nicotine inhaler with flavour source
Inventor(s):	MCEWEN ANDREW [GB]; WEST ROBERT [GB]; WEST MATTHEW [GB] +
Applicant(s):	EXCHANGE SUPPLIES LTD [GB] +
Classification:	**- international:** ***A61M15/06***
	- cooperative: **A24F47/002**; **A61M15/06** → more
Application number:	GB20060024579 20061208
Priority number(s):	GB20060024579 20061208
Also published as:	GB2461008 (B)

Abstract of GB2461008 (A)

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There is provided a nicotine inhalation device comprising a tubular housing (2) and first and second end caps (18, 8), engageable with inlet and outlet ends (6, 4) of the housing (2) respectively. The second end cap (8) has a rod-like central core (14) extending from its inner face, and also has a plurality of holes (12); each hole (12) is for supporting a nicotine cartridge, wherein the nicotine cartridges are arranged to surround the central core (14) radially. A body (16), made of porous material, is supported between the first end cap (18) and the housing (2), and can be impregnated with menthol to improve the taste of the inhaled nicotine.

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Bibliographic data: GB2376885 (A) — 2002-12-31

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Method to aid smoking cessation

Page bookmark	GB2376885 (A) - Method to aid smoking cessation
Inventor(s):	WEST ROBERT [GB]; HAJEK PETER [GB] +
Applicant(s):	WEST ROBERT [GB]; HAJEK PETER [GB] +
Classification:	**- international:** ***A61K31/341; A61K31/351; A61K31/7004; A61P25/34;*** (IPC1-7): A61K31/341; A61K31/351; A61P25/34
	- cooperative: **A61K31/341**; **A61K31/351**; **A61K31/7004** → more
Application number:	GB20010015568 20010626
Priority number(s):	GB20010015568 20010626

Abstract of GB2376885 (A)

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The present invention concerns methods of treating patients for nicotine and tobacco addiction, for alleviating nicotine withdrawal, for improving the effects of other smoking cessation therapies and as long-term smoking cessation maintenance therapy. The invention comprises pharmaceutical compositions comprising dextrose monohydrate and/or laevulose in combination with amfebutamone (or with any other non-nicotine smoking cessation method whose efficacy can be enhanced by addition of dextrose or laevulose). Specific combinations of drugs (dextrose and/or laevulose combined with amfebutamone) as well as dextrose and/or laevulose in combination with certain drug classes (e.g. stimulant drugs, anti-depressants, drugs used in treatment of psychoactive substance use disorders) comprise the pharmaceutical compositions disclosed. These compositions are also contemplated for use in the treatment of alcoholism, cocaine dependence and other drug dependencies.

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Bibliographic data: GB2376884 (A) — 2002-12-31

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Helping smokers stop

Page bookmark	GB2376884 (A) - Helping smokers stop
Inventor(s):	HAJEK PETER [GB]; WEST ROBERT [GB] +
Applicant(s):	HAJEK PETER [GB]; WEST ROBERT [GB] +
Classification:	**- international:** ***A61K31/465; A61P25/34;*** *A61K9/00; A61K9/70;* (IPC1-7): A61K31/465; A61P25/34
	- cooperative: **A61K31/465**; A61K9/0043; A61K9/7023
Application number:	GB20010015566 20010626
Priority number(s):	GB20010015566 20010626

Abstract of GB2376884 (A)

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The present invention concerns a new way of using nicotine replacement treatment to enhance its efficacy in treating patients for nicotine and tobacco addiction and for alleviating nicotine withdrawal. The invention includes providing nicotine replacement treatment in one or more forms for a period of time prior to cessation of smoking to de-condition the link between smoking behaviour and its pharmacological reinforcement, and to habituate the user to the nicotine replacement products. After stopping smoking, nicotine replacement treatment is used in the usual way.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6020958/

Is prevalence of e-cigarette and nicotine replacement therapy use among smokers associated with average cigarette consumption in England? A time-series analysis

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Is prevalence of e-cigarette and nicotine replacement therapy use among smokers associated with average cigarette consumption in England? A time-series analysis

BMJ Open. 2018; 8(6): e016046.

Published online 2018 Jun 19. doi: [10.1136/bmjopen-2017-016046]
PMCID: PMC6020958

PMID: 29921676

,[1,2] ,[1,2] ,[2] and [1]

Abstract

Objectives

Many smokers use e-cigarettes and licensed nicotine replacement therapy (NRT), often in an attempt to reduce their cigarette consumption. We estimated how far changes in prevalence of e-cigarette and NRT use while smoking were accompanied by changes in cigarette consumption at the population level.

Design

Repeated representative cross-sectional population surveys of adults aged 16+ years in England.

Methods

We used Autoregressive Integrated Moving Average with Exogeneous Input (ARIMAX) modelling of monthly data between 2006 and 2016 from the Smoking Toolkit Study. Prevalence of e-cigarette use and NRT use in current smokers, and specifically for smoking reduction and temporary abstinence, were input variables. Mean daily cigarette consumption was the dependent variable. Analyses involved adjustment for mass media expenditure and tobacco-control policies.

Results

No statistically significant associations were found between changes in use of e-cigarettes (β −0.012, 95% CI −0.026 to 0.002) or NRT (β 0.015, 95% CI −0.026 to 0.055) while smoking and daily cigarette consumption. Neither did we find clear evidence for an association between e-cigarette use (β −0.010, 95% CI −0.025 to 0.005 and β 0.011, 95%–0.027 to 0.004) or NRT use

(β 0.006, 95%−0.030 to 0.043 and β 0.022, 95%−0.020 to 0.063) specifically for smoking reduction and temporary abstinence, respectively, and changes in daily cigarette consumption.

Conclusion

If use of e-cigarettes and licensed NRT while smoking acted to reduce cigarette consumption in England between 2006 and 2016, the effect was likely very small at a population level.

Keywords: time series, arimax, smoking, e-cigarette, nrt

Strengths and limitations of this study

- This is the first time series study to assess the population-level impact of the use of nicotine replacement therapy and e-cigarettes for harm reduction on cigarette consumption.
- This study uses a large representative sample of the population in England and considers both smoking reduction and temporary abstinence.
- A wide range of confounders are adjusted for including population-level interventions.
- In countries with weaker tobacco control, or stricter regulation of using products for harm reduction, different effects may be observed.
- Data are observational and so strong conclusions regarding cause and effect cannot be made.

Introduction

Randomised controlled trials have shown that use of non-tobacco nicotine-containing products (eg, nicotine replacement therapy; NRT) are efficacious for harm-reduction attempts.[1] Harm reduction is defined as any attempt to reduce the harm from smoking without an intention to quit completely, such as, the use of NRT for smoking reduction (ie, during attempts to cut down) or during periods of temporary abstinence (ie, during periods of time when one is unable to smoke).[1] Outside of the clinical setting where little behavioural support is provided, the use of NRT during attempts to cut down smoking appears to increase smoker's propensity to quit, but does not result in significantly large reductions in cigarette consumption.[2–4] Explanations for this include the lack of behavioural support and possible poor compliance with the medical regimen.[5 6]

In recent years, there has been an increase in the overall use of nicotine-containing products for harm reduction, with a growth in e-cigarettes more than offsetting a decline in the use of NRT.[7–9] Previous studies suggest that e-cigarettes which contain nicotine reduce cravings more effectively than NRT,[7 10 11] have better adherence rates[7 12] and deliver clinically significant levels of nicotine into the blood, at least for some smokers.[10 11 13] Thus, although further studies are needed it is possible that e-cigarettes may be a more effective aid for smoking reduction than licensed nicotine products.[14 15] However, it also remains possible that e-cigarettes will not result in clinically significant reductions in cigarette intake at a population level.

The aim of this study was to assess the association between changes in prevalence of e-cigarettes and NRT with changes in mean cigarette consumption per day using a time-series approach. Time-series analysis allows us to take into account underlying trends, the effect of other tobacco-control interventions, autocorrelation (whereby data collected at points closer in time tend to be more similar), and to consider possible lag effects of the independent variable on the dependent variable.[16] Where associations are found, they cannot unequivocally establish a causal association but can be indicative, as has been the case with estimating the effect of price of cigarettes on population consumption,[17] mass-media expenditure on use of specialist stop-smoking services[18] and introduction of varenicline to the market on prevalence of use of smoking cessation medication.[19] Where associations are not found, or they go in a direction opposite to that expected, this can also be informative.

Specifically, this paper assesses the association between mean cigarette consumption per day and:

1. Current e-cigarette use among smokers for any purpose, current use specifically for smoking reduction and current use specifically for temporary abstinence.

2. Current NRT use among smokers for any purpose, current use specifically for smoking reduction and current use specifically for temporary abstinence.

Sensitivity analyses will examine the effect of focusing only on daily e-cigarette and NRT use, given previous associations between extent of non-tobacco nicotine-containing product use and the effectiveness of harm-reduction attempts.[6]

Methods

Design

We used Autoregressive Integrated Moving Average with Exogeneous Input (ARIMAX) modelling of monthly data between 2006 and 2016 primarily from the Smoking Toolkit Study. The smoking toolkit study (STS) is a monthly survey of a representative sample of the population in England aged 16+ years.[20] This has been collecting data on smoking patterns among smokers and recent ex-smokers since November 2006. Questions on the use of e-cigarettes among all smokers were introduced in May 2011 and as aids to a quit attempt among smokers attempting to stop in July 2009. The STS involves monthly household surveys using a random location sampling design, with initial random selection of grouped output areas (containing 300 households), stratified by ACORN (sociodemographic) characteristics (https://acorn.caci.co.uk/) and region. Interviewers then choose which houses within these areas are most likely to fulfil quotas based on the probability of individuals being at home in different regions and conduct face-to-face computer-assisted interviews with one member per household. Participants from the STS appear to be representative of the population in England, having similar sociodemographic composition as other large national surveys, such as the Health Survey for England.[20]

Measures

Explanatory variables

Daily and non-daily smokers were asked the following questions:

1. Which, if any, of the following are you currently using to help you cut down the amount you smoke?
2. Do you regularly use any of the following in situations when you are not allowed to smoke?
3. Can I check, are you using any of the following either to help you stop smoking, to help you cut down or for any other reason at all?

All three questions had the following response options: nicotine gum, nicotine replacement lozenges\tablets, nicotine replacement inhaler, nicotine replacement nasal spray, nicotine patch, electronic cigarette, nicotine mouth spray, other, none.

Current e-cigarette use was derived by an 'electronic cigarette' response to any of the three questions; e-cigarette use for smoking reduction by a response to the first question; and e-cigarette use for temporary abstinence by a response to the second question.

Current NRT use was derived by an NRT product response ('nicotine gum, nicotine replacement lozenges\tablets, nicotine replacement inhaler, nicotine replacement nasal spray, nicotine patch or nicotine mouth spray') to any of the three questions; NRT use for smoking reduction by an NRT product response to the first question; and NRT use for temporary abstinence by an NRT product response to the second question.

Data were not recorded on NRT use for temporary abstinence between November 2006 and January 2007 and was imputed using prevalence data from February 2007.

Data were only available on the prevalence of use of electronic cigarettes among smokers from April 2011 although use specifically during a recent quit attempt were available from July 2009. Thus, prevalence of electronic cigarette use among smokers between July 2009 and April 2011 was estimated from data on use during a quit attempt; use of electronic cigarettes among smokers between November 2006 and June 2009 was assumed to be 0.1% of smokers based on other surveys which found their use to be very rare before 2009.[21 22]

Daily NRT and e-cigarette users were classified as those who reported that they used the product(s) at least once per day in response to the question: How many times per day on average do you use your nicotine replacement product or products? This question was introduced in July 2010. Prior to this time, prevalence of daily NRT use was assumed to be 60% of all users,[6] while e-cigarette prevalence was computed as above using prevalence during a quit attempt or 0.1%.

Outcome variables

Smokers taking part in the STS were also asked how many cigarettes they smoke on average per day. Non-daily smokers were asked how many cigarettes they smoked per week which was then converted to a daily figure.

Co-variables

In England, tobacco mass media campaigns have been run as part of a national tobacco-control programme. Spending was almost completely suspended in 2010 and then reintroduced in 2011 at a much lower level. Previous studies have shown that such cuts were associated with a decreased use of smoking cessation support.[18 23] Thus, advertising expenditure will be adjusted for using data obtained from Public Health England. Data on mass media expenditure was available monthly from May 2008, and yearly prior to this period, and so a monthly average was assumed. For a number of months, spending was effectively zero and was imputed as 0.1 to allow the analysis to run.

A number of tobacco-control policies were adjusted for. These included the move in commissioning of stop-smoking services to local authorities in April 2013,[24] introduction of a smoking ban in July 2007,[25] licensing of NRT for harm reduction in December 2009, [26] the publication of National Institute for Health and Care Excellence guidance on harm reduction in June 2013[27] and change in the minimum age of sale of cigarettes in October 2007. [28] Price of cigarettes is correlated 0.99 with time and will thereby be taken into account by use of differencing (ie, using the differences between consecutive observation rather than observations themselves) to make the series stationary.

Analysis

The analysis plan was registered on the Open Science Framework prior to data analysis (https://osf.io/6swk3/). All data were analysed in R V.3.2.4[29] using ARIMAX modelling.[16 30 31] Data were weighted prior to the analyse to match the population in England using a rim (marginal) weighting technique. This involves an iterative sequence of weighting adjustments whereby separate nationally representative target profiles are set (for gender, working status, children in the household, age, social grade and region). This process is then repeated until all variables match the specified targets.[20]

Two waves of data were collected in March 2007 and March 2013. These waves were averaged. No data were collected in December 2008. Mean cigarette consumption, NRT use and e-cigarette use during this period were calculated as an average of the month before and the month after. For a few months (May 2012, July 2012, September 2012, November 2012, January 2013, March 2013), data on electronic cigarettes and NRT use among smokers were not recorded. For these months, the average of the previous and next month was imputed.

The Granger causality test suggested that there was some evidence for the violation of the assumption of weak exogeneity (ie, Y can depend on the lagged values of X but the reverse must not be true) between the input and the output series. However, caution has been advised when using this and similar tests on data across a long time series,[32 33] and there was no theoretical reason we could identify for a bidirectional relationship between e-cigarette use and cigarette consumption. It was assumed that the association was spurious and likely removed following adjustment for other covariates.

Both unadjusted and fully adjusted models are reported which regressed onto mean cigarette consumption per day: (1) use of e-cigarettes among current smokers; (2) use of e-cigarettes for smoking reduction; (3) use of e-cigarettes for temporary abstinence; (4) use of NRT for harm reduction; (5) use of NRT for temporary abstinence and (6) use of NRT for smoking reduction. Sensitivity analyses were conducted which constrained the analysis to only those reporting daily e-cigarette and NRT use. We followed a standard ARIMAX modelling

approach.[16 34] The series were first log-transformed to stabilise the variance, and if required, first differenced and seasonally differenced. The autocorrelation and partial autocorrelation functions were then examined in order to determine the seasonal and non-seasonal moving average (MA) and autoregressive terms (AR). For example, AR(1) means that the value of a series at one point in time is the sum of a fraction of the value of the series at the immediately preceding point in time and an error component; while MA(1) means that the value of a series at one point in time is a function of a fraction of the error component of the series at the immediately preceding point in time and an error component at the current point in time. To identify the most appropriate transfer function (ie, lag) for the continuous explanatory variables, the sample cross-correlation function was checked for each ARIMAX model. Coefficients can be interpreted as estimates of the percentage change in cigarette consumption for every (a) percentage increase in use of e-cigarettes and NRT, (b) percentage increase in mass media expenditure and (c) implementation of tobacco-control policies.

Bayes factors (BFs) were derived for non-significant findings using an online calculator[35] to disentangle whether there is evidence for the null hypothesis of no effect (BF <1/3rd) or the data are insensitive (BF between 1/3rd and 3). A half-normal distribution was assumed with a percentage change in the outcomes of interest for every percentage increase in the input series of 0.009% based on the effect detectable with 80% power (see sample size). Sensitivity analyses were conducted using a much larger percentage change of 0.1. This was based on a meta-analysis assessing the efficacy of non-tobacco nicotine replacement products for harm reduction which reported that 21.8% of the experimental group had reduced consumption by more than 50% at final follow-up compared with 16.5% receiving placebo.[1] We therefore assumed that a 5% change in prevalence of NRT and e-cigarettes would be associated with a 0.5% change in overall cigarette consumption.

Strengthening the Reporting of Observational Studies in Epidemiology guidelines for the reporting of observational studies were followed throughout.[36]

Sample size

Simulation-based power analyses suggested that this study would have 80% power to detect a change in the output series of 0.009% for every 1% change in the input series, assuming 113 monthly data collection points, MA (1) autocorrelation,[37] a baseline proportion for the input series of 0.005,[9] a baseline mean (SD) for the output series of 12.3 [38] and a total change over time for the input series of 30%.[38]

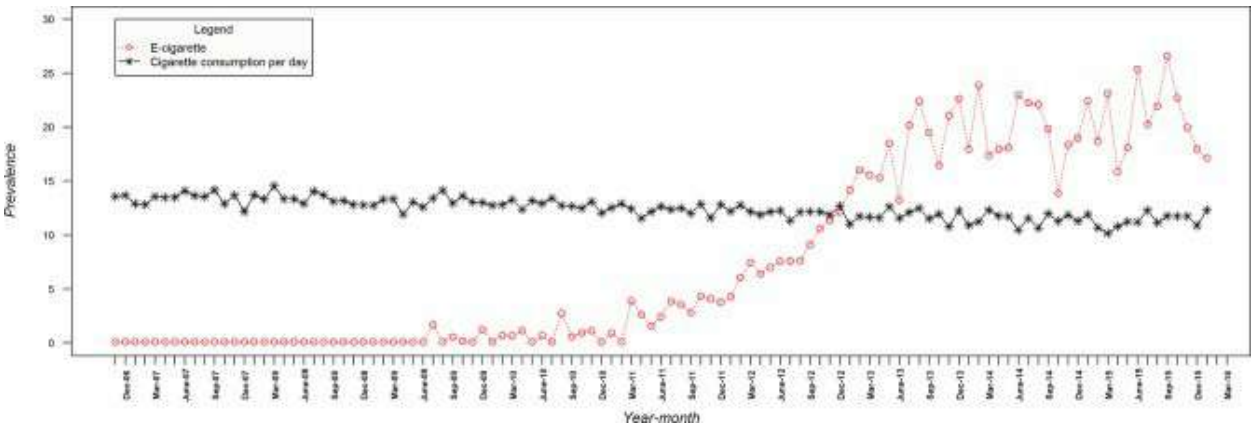
Results

Sample characteristics

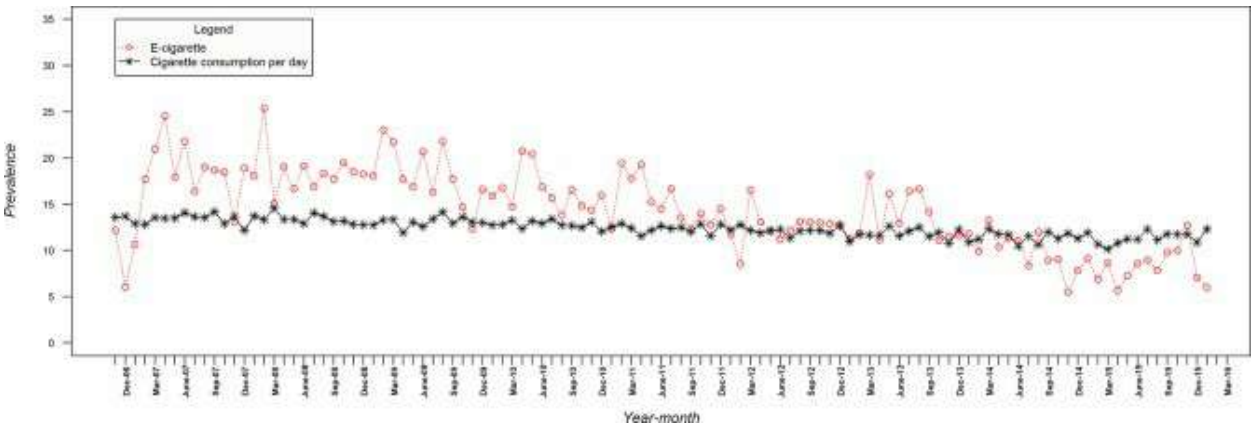
Data were collected on 199 483 adults aged 16+ years taking part in the STS who reported their smoking status between November 2006 and March 2016. Of these, 43 608 (20.8%, 95% CI 20.6 to 21.0) were current smokers. Fifty-two per cent (95% CI 52% to 53%) of the smokers were male and 60.4% (95%CI 60% to 60.1%) were in routine or manual positions or were unemployed. The average age of smokers in this study was 42.1 years (95% CI 42.0 to 42.1).

Main analysis

shows that cigarette consumption declined over the study period from 13.6 to 12.3 (mean 12.4, SD 0.92). This figure also shows that current use of e-cigarettes among smokers for harm reduction increased from negligible use in the last quarter of 2006 to 17.1% at the end of the study (mean 7.8%, SD 8.82). shows that there was also a decline in the use of NRT for harm reduction from 12.2% to 6% (mean 14.4%, SD 4.36). Online supplementary figures 1 and 2 show the changes in e-cigarette and NRT use for smoking reduction and temporary abstinence, respectively.



Monthly prevalence of cigarette consumption and e-cigarettes for harm reduction among smokers.



Monthly prevalence of cigarette consumption and nicotine replacement therapy use for harm reduction among smokers.

Supplementary data

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show the results of the ARIMAX models assessing the association between cigarette consumption per day with (1) e-cigarette use among current smokers and NRT use for harm reduction; (2) e-cigarette and NRT use for smoking reduction and (3) e-cigarette and NRT use for temporary abstinence. The findings were inconclusive as to whether an association was present between use of e-cigarettes and NRT for any purpose and cigarette consumption.

Table 1

Estimated percentage-point changes in mean cigarette consumption per day as a function of e-cigarette use and NRT use among smokers from November 2006 to March 2016, based on ARIMAX models

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Any current use of e-cigarettes (immediate impact)	−0.011 (−0.025 to 0.002) 0.097		−0.012 (−0.026 to 0.002) 0.091	−0.010 (−0.024 to 0.004) 0.149		−0.011 (−0.026 to 0.003) 0.130
NRT use for harm reduction (immediate impact)		0.012 (−0.028 to 0.053) 0.546	0.015 (−0.026 to 0.055) 0.475		0.003 (−0.019 to 0.025) 0.794	0.005 (−0.017 to 0.027) 0.672
Mass media expenditure (immediate impact)			<0.001 (−0.001 to 0.001) 0.984			<0.001 (−0.001 to 0.001) 0.880
	Total percentage change due to the exposure (95% CI) P values					
Smoking ban (pulse effect)			0.015 (−0.070 to 0.101) 0.724			0.013 (−0.072 to 0.099) 0.756
Increase in age-of-sale (pulse effect)			−0.041 (−0.126 to 0.044) 0.342			−0.043 (−0.128 to 0.042) 0.324
Move to local authority control (pulse effect)			−0.019 (−0.105 to 0.067) 0.662			−0.027 (−0.112 to 0.058) 0.533
Licensing for NRT for harm reduction (pulse effect)			0.021 (−0.067 to 0.110) 0.639			0.020 (−0.069 to 0.109) 0.661
NICE guidance on harm reduction (pulse effect)			−0.024 (−0.109 to 0.061) 0.578			−0.028 (−0.114 to 0.057) 0.512
Best fitting model	ARIMAX(0,1,1) $(0,0,0)^{12}$	ARIMAX(0,1,1) $(0,0,0)^{12}$	ARIMAX(0,1,1) $(0,0,0)^{12}$	ARIMAX(0,1,1) $(0,0,0)^{12}$	ARIMAX(0,1,1) $(0,0,0)^{12}$	ARIMAX(0,1,1) $(0,0,0)^{12}$
Non-seasonal AR p value	NA	NA	NA	NA	NA	NA

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Non-seasonal MA p value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Seasonal AR p value	NA	NA	NA	NA	NA	NA
Seasonal MA p value	NA	NA	NA	NA	NA	NA
R^2	0.65	0.65	0.66	0.65	0.64	0.66
Bayes factor e-cigarette (0.009 (0.1))	2.44 (0.46)		2.68 (0.55)	1.95 (0.35)		2.12 (0.41)
Bayes factor NRT (0.009 (0.1))		0.77 (0.14)	0.74 (0.13)		0.69 (0.09)	0.63 (0.08)

Table 2

Estimated percentage point changes in mean cigarette consumption per day as a function of e-cigarette use and NRT use among smokers for cutting down from November 2006 to March 2016, based on ARIMAX models

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Use of e-cigarettes for cutting down (immediate impact)	−0.010 (−0.024 to 0.005) 0.191		−0.010 (−0.025 to 0.005) 0.191	−0.008 (−0.023 to 0.006) 0.256		−0.009 (−0.024 to 0.006) 0.229
NRT use for cutting down (immediate impact)		0.002 (−0.033 to 0.037) 0.917	0.006 (−0.030 to 0.043) 0.732		−0.002 (−0.016 to 0.013) 0.825	−0.002 (−0.017 to 0.013) 0.786
Mass media expenditure (immediate impact)			<0.001 (−0.001 to 0.001) 0.885			<0.001 (−0.001 to 0.001) 0.860
	Total percentage change due to the exposure (95% CI) P values					
Smoking ban (pulse effect)			0.014 (−0.072 to 0.099) 0.755			0.012 (−0.073 to 0.097) 0.782

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Increase in age-of-sale (pulse effect)			−0.043 (−0.128 to 0.042) 0.323			−0.042 (−0.127 to 0.043) 0.329
Move to local authority control (pulse effect)			−0.025 (−0.110 to 0.061) 0.571			−0.029 (−0.115 to 0.056) 0.499
Licensing for NRT for harm reduction (pulse effect)			0.018 (−0.072 to 0.108) 0.694			0.015 (−0.074 to 0.103) 0.747
NICE guidance on harm reduction (pulse effect)			−0.028 (0.058 to <0.001) 0.529			−0.027 (−0.112 to 0.059) 0.541
Best fitting model	ARIMAX(0,1,1) $(0,0,0)^{12}$	ARIMAX(0,1,1) $(0,0,0)^{12}$	ARIMAX(0,1,1) $(0,0,0)^{12}$	ARIMAX(0,1,1) $(0,0,0)^{12}$	ARIMAX(0,1,1) $(0,0,0)^{12}$	ARIMAX(0,1,1) $(0,0,0)^{12}$
Non-seasonal AR p values	NA	NA	NA	NA	NA	NA
Non-seasonal MA p values	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Seasonal AR p values	NA	NA	NA	NA	NA	NA
Seasonal MA p values	NA	NA	NA	NA	NA	NA
R^2	0.64	0.64	0.65	0.64	0.64	0.65
Bayes factor e-cigarette (0.009 (0.1))	1.87 (0.34)		1.79 (0.32)	1.46 (0.23)		1.61 (0.27)
Bayes factor NRT (0.009 (0.1))		0.86 (0.16)	0.81 (0.15)		0.76 (0.10)	0.76 (0.10)

Table 3

Estimated percentage point changes in mean cigarette consumption per day as a function of e-cigarette use and NRT use among smokers for temporary abstinence from November 2006 to March 2016, based on ARIMAX models

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Use of e-cigarettes for temporary abstinence (immediate impact)	−0.010 (−0.024 to 0.005) 0.150		−0.011 (−0.027 to 0.004) 0.146	−0.010 (−0.024 to 0.004) 0.159		−0.011 (−0.026 to 0.003) 0.135
NRT use for temporary abstinence (immediate impact)		0.023 (−0.016 to 0.062) 0.241	0.022 (−0.020 to 0.063) 0.303		0.006 (−0.015 to 0.028) 0.563	0.006 (−0.016 to 0.028) 0.585
Mass media expenditure (immediate impact)			<0.001 (−0.001 to 0.001) 0.873			<0.001 (−0.001 to 0.001) 0.942
	Total percentage change due to the exposure (95% CI) P values					
Smoking ban (pulse effect)			0.017 (−0.069 to 0.103) 0.696			0.014 (−0.071 to 0.099) 0.750
Increase in age-of-sale (pulse effect)			−0.036 (−0.122 to 0.050) 0.415			−0.040 (−0.125 to 0.044) 0.350
Move to local authority control (pulse effect)			−0.016 (−0.102 to 0.071) 0.721			−0.026 (−0.111 to 0.060) 0.556
Licensing for NRT for harm reduction (pulse effect)			0.023 (−0.067 to 0.114) 0.615			0.019 (−0.070 to 0.108) 0.670
NICE guidance on harm reduction (pulse effect)			−0.021 (−0.106 to 0.065) 0.638			−0.030 (−0.116 to 0.055) 0.483
Best fitting model	ARIMAX(0,1,1) $(0,0,0)^{12}$	ARIMAX(0,1,1) $(0,0,0)^{12}$	ARIMAX(0,1,1) $(0,0,0)^{12}$	ARIMAX(0,1,1) $(0,0,0)^{12}$	ARIMAX(0,1,1) $(0,0,0)^{12}$	ARIMAX(0,1,1) $(0,0,0)^{12}$

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Non-seasonal AR P values	NA	NA	NA	NA	NA	NA
Non-seasonal MA P values	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Seasonal AR P values	NA	NA	NA	NA	NA	NA
Seasonal MA P values	NA	NA	NA	NA	NA	NA
R^2	0.65	0.65	0.65	0.65	0.64	0.65
Bayes factor e-cigarette (0.009 (0.1))	1.01 (0.59)		1.94 (0.38)	1.97 (0.35)		2.15 (0.41)
Bayes factor NRT (0.009 (0.1))		0.15 (0.02)	0.69 (0.11)		1.05 (0.18)	0.61 (0.08)

BFs were between one-third and three when assuming a 0.009% change in cigarette consumption for every percentage change in the input series, suggesting the data are insensitive to detect very small reductions in cigarette consumption. Most BFs were less than one-third, when assuming a 0.1% change in cigarette consumption for every percentage change in the input series, suggesting evidence for the null hypothesis that NRT use and e-cigarette use among smokers has not resulted in large reductions in cigarette intake.

Sensitivity analysis

Current daily use of e-cigarettes among smokers for harm reduction increased from negligible use in the last quarter of 2006 to 11.1% at the end of the study (mean 4.5%, SD 4.91). There was also an increase in e-cigarette use specifically for temporary abstinence (from 0.1% to 8.4%; mean 3.5% SD 3.81) and smoking reduction (from 0.1% to 8.3%; mean 3.3% SD 3.64).

In contrast, there was a decline in the use of NRT for harm reduction from 7.3% to 2.9% (mean 6.5%, SD 2.35) and a decline in NRT use specifically for temporary abstinence (from 7.3% to 1.8%; mean 4.7% SD 2.29) and smoking reduction (from 6.8% to 2.6%; mean 5.8%, SD 2.46).

also show the results of the sensitivity analyses restricted to those smokers using NRT or e-cigarettes daily. The findings were inconclusive as to whether or not an association was present between the daily use of e-cigarettes and NRT for any purpose and cigarette consumption. BFs suggested the data are insensitive to detect very small reductions in cigarette consumption, but there is evidence for the null hypothesis that NRT use and e-cigarette use among smokers have not resulted in large reductions in cigarette intake.

Discussion

To our knowledge, this is the first empirical study to estimate the population association between the use of e-cigarettes and NRT among current smokers on cigarette consumption per day, using a time-series approach. There was evidence that there was no substantial association between the rise in use of e-cigarettes and decline in NRT use and changes in cigarette consumption per day.

Strengths and limitations

A strength of the study is the use of a large representative sample of the population in England, stratification of results by daily use, and the consideration of both temporary abstinence and smoking reduction. Previous studies have shown that reductions in cigarette intake are dependent on the extent of NRT use and differ as a function of the specific harm-reduction behaviour, that is, an attempt to cut down or restraining from smoking during periods of brief abstinence.[2 6]

The study had a number of limitations. First, caution should be taken when interpreting estimates of the covariates, that is, impact of some of the tobacco-control policies, as interrupted explanatory variables with short time-periods prior to their introduction in ARIMAX-type models often give inaccurate estimates of the SEs.[28] Thus, although the increase in age-of-sale has been previously associated with a decline in smoking prevalence,[24] the short lead-in period may have masked any true association.[27] Second, the STS required participants to recall their average daily cigarette intake which is likely to have been somewhat inaccurate. Third, the findings may not generalise to other countries. England has a strong tobacco-control climate and relatively liberal attitude towards harm reduction and e-cigarette use. In countries with weaker tobacco control, or stricter regulation of using products for harm reduction, different effects may be observed. Fourth, although we are unaware of any other major population-level interventions or other events during the study period, we cannot rule out residual confounding. Fifth, participants were not asked questions regarding potentially important features of the e-cigarette (eg, nicotine content, flavouring, device type) or frequency and duration of use. It is likely that these factors may play a role in their effectiveness and should be considered in future studies.[15 39] Finally, as data were not collected on current e-cigarette use prior to April 2011, prevalence was estimated from use during a quit attempt or from previous studies.[21 22] This was necessary to ensure that the time series was long enough for an ARIMAX analysis and is an appropriate approach when data are missing completely at random.[16 40] As prevalence was low and relatively stable during this period, it is unlikely to have impacted on the reported results.

Implications of findings

The findings are in line with previous studies which show that reductions in cigarette consumption observed in clinical trials of NRT for harm reduction do not appear to generalise beyond the closely controlled trial setting.[1 2] It was hypothesised that e-cigarettes may be associated with population mean cigarette intake given that they reduce cravings more effectively than NRT,[7 10 11] have better adherence rates[7 12] and deliver clinically significant levels of nicotine into the blood.[10 11 11 13]

The finding that e-cigarette use was not associated with reductions in consumption at a

population level is consistent with previous real-world studies at the individual level. These have found little change in consumption among ever e-cigarette users[41] and that only a minority of daily users manage to reduce by a substantial amount which is not likely to be detected at a population level.[42] The findings of a recent pragmatic controlled trial, whereby 60% of participants using e-cigarettes had managed to reduce by over 50% by 6 months' follow-up, suggests that the lack of effectiveness at a population level may not be the consequence of poor behavioural support.[11]

Of course, it remains plausible that e-cigarettes may still be associated with a small effect on mean population cigarette consumption,[15] and that a reduction in harm from smoking at a population level could be seen through their promotion of quit attempts[37] or by reducing smoke intake from each cigarette.[5]

Conclusion

In conclusion, the increased prevalence of e-cigarettes use among smokers in England has not been associated with a detectable change in cigarette consumption per day. The decline in the use of NRT has also not been associated with a change in mean cigarette intake. If use of e-cigarettes and licensed NRT while smoking act to reduce cigarette consumption, the effect is probably small.

Supplementary data

bmjopen-2017-016046supp002.jpg

Supplementary Material

Reviewer comments:
Click here to view.(184K, pdf)
Author's manuscript:
Click here to view.(1.8M, pdf)

Footnotes

Contributors: EB, JB, SM and RW designed the study. EB wrote the first draft and conducted the analyses. All authors commented on this draft and contributed to the final version.

Funding: The Smoking Toolkit Study is currently primarily funded by Cancer Research UK (C1417/A14135; C36048/A11654; C44576/A19501) and has previously also been funded by Pfizer, GSK and the Department of Health. JB's post is funded by a fellowship from the Society for the Study of Addiction and CRUK also provides support (C1417/A14135). RW is funded by Cancer Research UK (C1417/A14135). EB is funded by a fellowship from the NIHR SPHR (SPHR-SWP-ALC-WP5) and CRUK also provides support (C1417/A14135). SW is funded by Cancer Research UK (C1417/A14135) and NIHR SPHR (SPHR-SWP-ALC-WP5) also provide support. SPHR is a partnership between the Universities of Sheffield; Bristol; Cambridge; Exeter; UCL; The London School for Hygiene and Tropical Medicine; the LiLaC collaboration between the Universities of Liverpool and Lancaster and Fuse; The Centre for Translational Research in Public Health, a collaboration between Newcastle, Durham, Northumbria, Sunderland and Teesside Universities.

Disclaimer: The views expressed are those of the authors(s) and not necessarily those of the NHS, NIHR or Department of Health. No funders had any involvement in the design of the study, the analysis or interpretation of the data, the writing of the report or the decision to submit the paper for publication.

Competing interests: RW undertakes consultancy and research for and receives travel funds and hospitality from manufacturers of smoking cessation medications but does not, and will not take funds from e-cigarettes manufacturers or the tobacco industry. RW and SM are honorary co-directors of the National Centre for Smoking Cessation and Training. RW is a Trustee of the stop-smoking charity, QUIT. RW's salary is funded by Cancer Research UK. SM's salary is funded by Cancer Research UK and by the National Institute for Health Research (NIHR)'s School for Public Health Research (SPHR). EB and JB have received unrestricted research funding from Pfizer. EB and JB are funded by CRUK. EB is also funded by NIHR's SPHR and JB by the Society for the Study of Addiction. RW has received travel funds and hospitality from, and undertaken research and consultancy for pharmaceutical companies that manufacture or research products aimed at helping smokers to stop. These products include nicotine replacement therapies, Champix (varenicline) and Zyban (bupropion). This has led to payments to him personally and to his institution.

Patient consent: Obtained.

Ethics approval: Ethical approval for the Smoking Toolkit Study was granted by the UCL Ethics Committee (ID 0498/001).

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: For access to the data please contact the lead author, EB (e.beard@ucl.ac.uk).

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ENDS Not Effective as Tobacco Cessation Method, Says Study

July 31, 2018 08:39 am News Staff – Users of electronic nicotine delivery systems (ENDS) who also smoke cigarettes are not more likely to quit smoking than smokers who don't use ENDS devices.
https://www.aafp.org/news/health-of-the-public/20180731endsstudy.html

That's among findings of a study by researchers at Georgia State University's (GSU's) School of Public Health that was published July 9 in the *PLOS ONE* journal.(journals.plos.org)

The researchers found no evidence to indicate that ENDS marketed and used in the United States are effective at helping cigarette smokers quit at a population level, even though anecdotally, some smokers have said they found ENDS useful in their cessation efforts.

Study Details

The researchers conducted a population-based, prospective cohort study of a random probability sample of 1,284 U.S. adult smokers initially recruited in 2015 and recontacted a year later. The patient panel was drawn from GfK's KnowledgePanel,(www.gfk.com) a probability-based web panel designed to represent noninstitutionalized U.S. adults.

This specific sample of established smokers was made up of respondents to the 2015 (August-September) Tobacco Products and Risk Perceptions Survey on their smoking and ENDS use.

Story Highlights

A study recently published in *PLOS ONE* found that users of electronic nicotine delivery systems (ENDS) who also smoked cigarettes were not more likely to quit smoking than smokers who didn't use ENDS.

At the end of the one-year study, researchers found that 90 percent of "dual users" (participants who used both ENDS and traditional cigarettes at the beginning of the study at baseline) were still smoking.

"Many smokers are using ENDS in their smoking quit attempts, but these devices may not be providing a sufficiently satisfying nicotine delivery and overall user experience to completely supplant their smoking," the study's lead author suggested.

Of the 1,081 baseline smokers who remained in KnowledgePanel at the one-year mark, 858 completed the follow-up survey.

The primary outcome of interest from the study was smoking abstinence for at least 30 days before follow-up. Secondary outcome variables were making a quit attempt during the 12-month study period and, for those who continued to smoke at follow-up, number of cigarettes smoked per day.

At the end of the study, researchers found that the odds of quitting smoking were lower for those who used ENDS at baseline (9.4 percent) compared with smokers who did not use ENDS (18.9 percent). The researchers also found that smokers who used ENDS daily at any point during the study were less likely to quit smoking than nonusers.

Moreover, 90 percent of "dual users" (participants who used both ENDS and traditional cigarettes at the beginning of the study) were still smoking at follow-up, according to the study's authors. Among those baseline dual users, nearly 54 percent were smoking cigarettes as well as using ENDS after a year, and more than 37 percent were still smoking cigarettes but had stopped using ENDS.

Among smokers who didn't use ENDS at baseline, 73.5 percent smoked daily compared with 70.5 percent among smokers who did use ENDS at baseline. Similarly, no statistically significant difference was seen between daily smokers who used ENDS at any point during the study and those who did not (74.7 percent and 71.4 percent, respectively).

Compared to smokers who did not use ENDS, those who used ENDS during the study period were younger (age 41.5 versus 45.1) and were more likely to recognize their addiction to smoking cigarettes (87.7 percent versus 78 percent) and report a history of psychiatric/psychological therapy (50.1 percent versus 38.2 percent).

Also of note, less than one-third of both ENDS users and nonusers (32.8 percent and 25.9 percent, respectively) said they had ever used an approved nicotine replacement therapy or pharmaceutical drug to quit smoking.

Additional Findings

Although the researchers found that users of ENDS were more likely to try to quit smoking, this didn't translate into greater success.

For example, study participants who specifically said they were using ENDS to help stop smoking -- which was most ENDS-using respondents -- were actually less likely to quit than those who didn't use the devices.

"Many smokers are using ENDS in their smoking quit attempts, but these devices may not be providing a sufficiently satisfying nicotine delivery and overall user experience to completely supplant their smoking," said lead author Scott Weaver, Ph.D., assistant professor of epidemiology and biostatistics at GSU, in a news release.(news.gsu.edu)

"Coordinated regulation aimed at improving the appeal and satisfaction of ENDS available to smokers, while reducing the nicotine levels in combustible tobacco products to nonaddictive levels, may be necessary for ENDS to have a meaningful role in reducing the staggering public health burden of smoking."

The authors noted that limitations of the study included having a limited ability to draw causal inferences from the observational design and a lack of biochemical verification of quitting smoking or ENDS use. They recommended that additional research be conducted to monitor rapidly changing ENDS market and usage patterns.

Study Suggests E-cigarettes Cause More Harm Than Good

Some Adults May Quit Smoking Traditional Cigarettes, But More Teens and Young Adults Will Start

March 30, 2018 11:30 am Michael Devitt – For years, e-cigarettes have been promoted not only as a less harmful alternative to traditional cigarettes, but also as an option for current smokers to quit or reduce their use of tobacco. New research indicates, however, that e-cigarettes may have the opposite effect, especially in younger individuals who have never smoked.

https://www.aafp.org/news/health-of-the-public/20180330e-cigstudy.html

In a March study published in *PLOS ONE,(journals.plos.org)* researchers from the Norris Cotton Cancer Center at Dartmouth College concluded that although e-cigarettes may be of some benefit in adults who are trying to quit smoking combustible cigarettes, they may act as a gateway product in other people. In particular, the study findings suggest that e-cigarette use may be associated with teenagers and young adults starting to smoke traditional cigarettes and, eventually, becoming daily smokers.

Study Model and Results

In the study, the authors constructed a population-level risk model using 2014 U.S. census data, previously published study results on e-cigarette use and its association with smoking cessation or initiation, and national health or tobacco use surveys on e-cigarette use. Unlike previous studies, the model considered multiple population subgroups, including current smokers and individuals who had never smoked cigarettes. For current smokers, the authors reviewed information on adults ages 25 to 69; for never-smokers, the authors analyzed data on adolescents and young adults ages 12 to 29.

The model attempted to measure the benefits or harms of e-cigarette use through three estimated outcomes: the number of current combustible cigarette smokers who would quit smoking through the use of e-cigarettes and remain abstinent for seven or more years; the number of adolescents and young adults who never smoked but began smoking after using e-cigarettes and eventually became long-term daily smokers later in life; and the total number of years of life gained or lost by these groups through e-cigarette use.

Story Highlights

Results of a recent study indicate that e-cigarette use by teenagers and young adults may be associated with these individuals taking up smoking traditional cigarettes as they get older.

Using a population model, the study authors estimated that individuals who transitioned from using e-cigarettes to becoming daily combustible cigarette smokers would lose about 1.5 million years of life.

The authors suggest that e-cigarette use may confer more harm than good and note that to provide real benefit, the effectiveness of e-cigarettes as a smoking cessation tool would need to be considerably higher than it currently is.

Data drawn from the information sources cited above indicated that in 2014, 3,490,000 current adult cigarette smokers who had attempted to quit smoking in the past year had also currently used e-cigarettes. Additionally, 3,640,000 never-cigarette smoking adolescents and young adults had ever used e-cigarettes. The authors validated the model against one-year intermediate outcomes from 2013 data sources.

Based on the available information, the study model estimated that using e-cigarettes in 2014 would help an additional 2,070 current adult smokers quit in 2015 and remain abstinent from smoking for at least seven years compared with those who did not currently use e-cigarettes. **The model also estimated that about 168,000 never-cigarette smoking adolescents and young adults who used e-cigarettes in 2014 would start smoking combustible cigarettes during the following year and would become daily smokers by age 35-39, compared with those who never used e-cigarettes**.

Although current adult cigarette smokers may experience a relative benefit from using e-cigarettes to quit smoking compared with current smokers who never used e-cigarettes, the net effect remains in the red. Specifically, the model estimated that the 2,070 additional long-term quitters would gain -3,000 years of life -- still an overall negative loss of life.

Finally, the model estimated that the adolescents and young adults who transitioned from using e-cigarettes to becoming daily cigarette smokers would lose about 1.5 million years of life. This estimate was based on a 95 percent relative harm reduction of e-cigarette use compared with smoking traditional cigarettes, a figure the authors called "optimistic" given the current lack of evidence on the harms of e-cigarettes. Additional analysis showed that the total number of years of life lost increased as the relative harm reduction of e-cigarette use dropped, reaching 1.6 million years when the relative harm reduction was decreased to about 50 percent.

"Based on the most up-to-date published evidence, our model estimated that e-cigarette use in 2014 represents a population-level harm of about 1.6 million years of life lost over the lifetime of all adolescent and young adult never-cigarette smokers and adult current cigarette smokers in the 2014 U.S. population," the authors wrote. "Our model also estimated even greater population-level harm if e-cigarette use confers long-term health risks."

Although the study authors suggested that e-cigarettes could provide some benefits if they were more effective in helping people quit smoking, they cautioned that e-cigarettes also carry their own health risks. Previous research(pubs.acs.org) has shown, for example, that e-cigarettes contain a number of harmful and potentially harmful ingredients, including heavy metals and chemicals such as diacetyl, which has been linked to lung disease.

Study results have also shown that e-cigarette use can negatively affect the immune system(www.ncbi.nlm.nih.gov) and significantly impair respiratory(www.atsjournals.org) and cardiovascular(jaha.ahajournals.org) function.

The authors noted several limitations to their study, including uncertainty regarding whether e-cigarette use directly causes cigarette smoking in adolescents and young adults; inability to identify the types of e-cigarettes, each of which may deliver different levels of nicotine, used by adults who are current smokers; no consideration of the possibility that e-cigarette use in current smokers may cause a decline in the number of traditional cigarettes smoked per day; and no consideration of potential harms or benefits resulting from e-cigarette use among former smokers at the population level because of a lack of evidence regarding whether e-cigarette use among former cigarette smokers led to higher or lower rates of relapse.

Despite these limitations, the authors concluded that their study "suggests that e-cigarettes pose more harm than they confer benefit at the population level."

"If e-cigarettes are to confer a net population-level benefit in the future, the effectiveness of e-cigarettes as a smoking cessation tool will need to be much higher than it currently is," the authors stated.

Implications and Related Studies

Jennifer Frost, M.D., medical director for the AAFP's Health of the Public and Science Division, told *AAFP News* that the study highlights the potential negative health impact of e-cigarettes. She encouraged family physicians to ask patients about their use of e-cigarettes as well as traditional cigarettes.

"Family physicians should remember e-cigarettes when asking their patients whether or not they smoke," Frost said. 'This may mean not only asking, 'Do you smoke?' but also asking, 'Do you vape or use electronic

cigarettes?'" Frost added that although many people promote e-cigarettes as less harmful than traditional cigarettes, it's important to recognize that the true harms of these products still are not known.

Several other recently published studies have documented similar associations between e-cigarette use and tobacco smoking.

In January, the National Academies of Sciences, Engineering and Medicine published a comprehensive report(www.nap.edu) on the health effects of e-cigarettes, and found "substantial evidence" to show that e-cigarette use by adolescents and young adults increases the risk of ever using traditional cigarettes.

A March *Annals of Internal Medicine* study(annals.org) of more than 1,300 recently hospitalized smokers who planned to discontinue smoking found that using e-cigarettes intermittently and concurrently with other tobacco cessation treatments "did not seem to aid quitting and may have hampered" the efforts of some individuals to quit.

E-cigarettes tied to less smoking cessation

businessinsider.com/r-e-cigarettes-tied-to-less-smoking-cessation-2018-3

Reuters Mar. 22, 2018, 2:31 PM

By Lisa Rapaport

A man uses an IQOS e-cigarette at an outlet in London Thomson Reuters

(Reuters Health) - Smokers who also use e-cigarettes may be half as likely to give up tobacco as smokers who never vape at all, a European study suggests.

Even when smokers only occasionally experimented with vaping, they were about 67 percent less likely to become ex-smokers, the study found. Daily e-cigarette use was associated with 48 percent lower odds of having quit regular cigarettes.

"This is important because e-cigarettes are widely promoted as a smoking cessation tool," said senior author Stanton Glantz, director of the Center for Tobacco Control Research and Education at the University of California, San Francisco.

"And, while there is no question that some smokers do successfully quit with e-cigarettes, they keep many more people smoking," Glantz said by email.

Smokers in the study also used more cigarettes a day when they vaped than when they avoided e-cigarettes altogether, researchers report in the American Journal of Public Health.

People smoked an average of about 14 cigarettes a day when they didn't vape, and around 16 cigarettes a day when they did.

Researchers analyzed data from a 2014 survey of more than 13,000 current or former smokers in the European Union. About 2,500 participants said they had tried vaping at least once.

Overall, they were 50 years old on average, 46 percent of the participants were former smokers and 19 percent currently or previously used e-cigarettes.

Among these people who had all been cigarette smokers at some point, the researchers looked at the likelihood of being an ex-smoker at the time of the survey based on whether a person used e-cigarettes.

Some past research has suggested that using e-cigarettes may help smokers cut down on use of traditional tobacco products, or even transition entirely away from tobacco.

"The findings are concerning because they suggest the idea that e-cigarettes are an even more effective cessation tool than nicotine replacement therapy - an idea aggressively marketed by e-cigarette and tobacco companies - may not be true in practice," said Samir Soneji, a health policy researcher at Dartmouth College in Hanover, New Hampshire, who wasn't involved in the study.

Most adult smokers express a desire to quit, and many try and fail, Soneji said by email. E-cigarettes might seem like an appealing cessation tool because the devices in some ways mimic the smoking, but nicotine gum or patches may be more effective.

"Most of the scientific evidence to date, including this study, finds that e-cigarette use does not lead to higher rates of smoking cessation compared to standard cessation tools," Soneji said by email.

Big U.S. tobacco companies are all developing e-cigarettes. The battery-powered gadgets feature a glowing tip and a heating element that turns liquid nicotine and flavorings into a cloud of vapor that users inhale.

The study wasn't a controlled experiment designed to prove whether or how e-cigarette use might influence the success of any smoking cessation efforts. The survey also did not ask current smokers whether they were trying to quit or cut down on tobacco use, or if they were using e-cigarettes for that purpose.

Another drawback is that researchers lacked data on when ex-smokers had quit, and it's possible some of them stopped before e-cigarettes were widely available.

A bigger question about e-cigarettes - whether they're safe or at least safer than traditional cigarettes - also isn't answered by the current study.

When e-cigarettes contain nicotine, they can be addictive like traditional cigarettes. Even without nicotine, some previous research suggests that flavorings and other ingredients in e-liquids used for vaping could be linked to serious breathing problems.

"Whether they are safer than cigarettes is almost a trick question because tobacco cigarettes are one of the most harmful substances known to medicine," said Thomas Wills, director of the Cancer Prevention in the Pacific Program at the University of Hawaii Cancer Center in Honolulu.

"It would be hard to find anything more harmful to long-term health except maybe arsenic," Wills, who wasn't involved in the study, said by email. "But this does not mean that e-cigarettes are safe."

SOURCE: https://bit.ly/2IKjpAv American Journal of Preventive Medicine, online February 12, 2018.

American Journal of
Preventive Medicine

RESEARCH ARTICLE

E-cigarettes Associated With Depressed Smoking Cessation: A Cross-sectional Study of 28 European Union Countries

Margarete C. Kulik, PhD, Nadra E. Lisha, PhD, Stanton A. Glantz, PhD

Introduction: Electronic cigarettes (e-cigarettes) are often promoted to assist with cigarette smoking cessation. In 2016–2017, the relationship between e-cigarette use and having stopped smoking among ever (current and former) smokers was assessed in the European Union and Great Britain by itself.

Methods: Cross-sectional logistic regression of the association between being a former smoker and e-cigarette use was applied to the 2014 Eurobarometer survey of 28 European Union countries controlling for demographics.

Results: Among all ever smokers, any regular ever use of nicotine e-cigarettes was associated with lower odds of being a former smoker (unadjusted OR=0.34, 95% CI=0.26, 0.43, AOR=0.43, 95% CI=0.32, 0.58) compared with smokers who had never used e-cigarettes. In unadjusted models, daily use (OR=0.42, 95% CI=0.31, 0.56); occasional use (OR=0.25, 95% CI=0.18, 0.35); and experimentation (OR=0.24, 95% CI=0.19, 0.30) of nicotine e-cigarettes were associated with lower odds of being a former smoker compared with having never used nicotine-containing e-cigarettes. Comparable results were found in adjusted models. Results were similar in Great Britain alone. Among current smokers, daily cigarette consumption was 15.6 cigarettes/day (95% CI=14.5, 16.7) among those who also used e-cigarettes versus 14.4 cigarettes/day (95% CI=13.4, 15.4) for those who did not use them ($p < 0.05$).

Conclusions: These results suggest that e-cigarettes are associated with inhibiting rather than assisting in smoking cessation. On the population level, the net effect of the entry of e-cigarettes into the European Union (and Great Britain) is associated with depressed smoking cessation of conventional cigarettes.

Am J Prev Med 2018;▮(▮):▮▮▮–▮▮▮.

INTRODUCTION

Electronic cigarettes (e-cigarettes) are promoted to assist with cigarette-smoking cessation, including by the National Health Service in England,[1] by Public Health Wales,[2] and, more tentatively, by NHS Health Scotland,[3] and cessation is one of the major reasons smokers use them.[4,5] Public health institutions in other European Union (EU) countries do not endorse e-cigarettes as cessation devices. RCTs on efficacy for smoking cessation are limited, and their results have been equivocal.[6,7] Most studies have been based on e-cigarette use in the real world, which, taken together, show that e-cigarettes are associated with significantly less quitting.[8–11] Some studies, however, suggest that intensive use of e-cigarettes (daily use of tank systems,[12] daily use for at least 1 month,[13] long-term use,[14] and use among established current smokers and recent quitters[15]) is associated with more quitting. E-cigarettes are mass-marketed consumer products, not medicines

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0749-3797/$36.00
https://doi.org/10.1016/j.amepre.2017.12.017

administered as part of a medically supervised cessation attempt. Thus, rather than asking the clinically relevant question "Are e-cigarettes effective when used as part of an organized cessation attempt?" this paper asks, "What effect is use of e-cigarettes having on smoking cessation in the real world as they are actually used?"

One limitation of the available literature is that the sample sizes are relatively small and often do not have detailed assessment of e-cigarette use patterns. Filippidis et al.[16] used the Eurobarometer, a cross-sectional household survey performed in a representative sample of the population of the EU, to assess increases in e-cigarette use between 2012 and 2014, and Farsalinos and colleagues[17] used the 2014 Eurobarometer[18] to assess cigarette smoking behavior among e-cigarette users. As Farsalinos and colleagues noted, the Eurobarometer survey is useful for evaluating e-cigarette use by the EU population because it is representative of the entire EU region (28 countries), and the 2014 Eurobarometer makes a clear distinction between regular and occasional use and between nicotine-containing and nicotine-free e-cigarettes. Using the Eurobarometer, they found that 35% of current e-cigarette users reported smoking cessation. Although Farsalinos and colleagues[17] specifically examined the relationship between intensity of e-cigarette use and being a former smoker among e-cigarette users, they did not include people who did not use e-cigarettes as the control group, so they did not estimate the effect of e-cigarette use on smoking cessation. This is a major shortcoming as their study did not assess the association of any e-cigarette use with cigarette smoking status. The same dataset is used to assess the relationship between e-cigarette use and having stopped smoking among all ever (current and former) smokers.

METHODS

Study Population

Following Farsalinos and colleagues,[17] data from Eurobarometer 82.4 (Special Eurobarometer 429) was used, a survey conducted in all 28 EU states in November and December 2014. Interviews took place in participants' homes in their native language. The multistage probability sample of Europeans aged ≥15 years was based on the total population of a country and population density. A weighting procedure was applied for all countries by using official population figures provided by Eurostat or national statistic offices. For the analyses using all the countries, generalizability was achieved using the weighting variable for the full EU population.[18] The total sample size for the survey is 27,801; a total of 12,608 current and former smokers were used for the analyses. Because health authorities have endorsed e-cigarettes in England and Wales, and tentatively in Scotland, a separate analysis for the 411 current and former smokers in Great Britain (GB) was also run. For use with the GB subsample, the weight for the United Kingdom was adjusted to apply to GB only, excluding Northern Ireland.

Measures

The main outcome variable was being a former smoker, defined by the answer to the question, *Regarding smoking cigarettes, cigars, cigarillos or a pipe, which of the following applies to you?* with the following response options: *you used to smoke, but you have stopped* (former smoker, coded 1) or *you currently smoke* (current smoker, coded 0).

The primary independent variable was nicotine-containing e-cigarette use, quantified in two different ways: (1) nicotine e-cigarette use (dichotomous, excluding experimenters who had only used e-cigarettes once or twice), and (2) intensity of nicotine e-cigarette use. Experimenters were excluded on the assumption that they did not use e-cigarettes enough to have an impact on smoking behavior. Nicotine-containing e-cigarette ever use was measured with the question, *How often do you or did you use the following products: Nicotine-containing electronic cigarettes or similar electronic devices?* after participants previously endorsed using e-cigarettes or similar electronic devices (e-shisha, e-pipe), having used e-cigarettes in the past or having tried e-cigarettes in the past. Those who used e-cigarettes every day, weekly, monthly, or less than monthly were coded as 1. The people who endorsed having never used e-cigarettes were coded as 0 (non-users). The 80 people who responded *don't know* were excluded. Intensity of nicotine e-cigarette use was measured using the same question to create a four-level variable: (1) daily use; (2) occasional use (weekly, monthly, less than monthly); (3) experimentation (used once or twice); and (4) never use (the reference group).

Covariates included age (continuous); sex; cigarettes per day (continuous from the item: *On average, how many cigarettes do you or did you or did you [before you stopped smoking] smoke each day?*); marital status (single, divorced/separated/widowed, with married/living with a partner as reference); and age at which respondents completed their education (16–19 years, ≥20 years, still studying, with no formal education as reference). People who only used non-nicotine e-cigarettes (201/2,430=8% in the EU and 6/118=5% in GB) were coded as never users of nicotine-containing e-cigarettes.

Statistical Analysis

Weighted logistic regression models were run using former smoking as the outcome variable using Mplus, version 8.[19] Predictors included one of two variables: (1) e-cigarette ever use (dichotomous, excluding people who only experimented with e-cigarettes) and (2) intensity of nicotine e-cigarette use. Sensitivity analyses were also run only including current e-cigarette use (not shown), which gave similar results. All models were run using all the countries unadjusted and adjusting for the control variables listed above.

Cigarette consumption was compared among all current smokers who did and did not currently use e-cigarettes using a *t*-test.

Missing data were handled using full-information maximum likelihood, which allows all observations to be used,[20] including those with some missing data. The full-information maximum likelihood method produces more accurate effect size estimates and smaller SEs than listwise deletion by using all the available information, including from incomplete records.[21–23] Country was

entered using the CLUSTER option with TYPE = COMPLEX in Mplus.[24] The same analyses were also conducted for GB alone using GB-specific weights.

Sensitivity analyses were run for the EU without GB and excluding 509 smokers (4% of sample) who only used cigars, cigarillos, or a pipe. The results remained essentially the same. Data analysis was done in 2016 and 2017.

RESULTS

The overall sample of ever smokers in the EU had a mean age of 49.9 years (SD=16.8); 55.6% were male; >65% were married or living with a partner; and >36% had finished education at age ≥20 years or were currently studying. Overall, 45.6% were former smokers. They smoked on average 14.8 cigarettes per day as smokers, and 19.4% had used or currently used any e-cigarettes, whereas 15.5% had used nicotine-containing e-cigarettes. The GB sample of ever smokers was slightly older (p=0.009); less likely to be married ($p<0.001$); less educated ($p<0.001$); and more likely to use ($p<0.001$) e-cigarettes and use them more frequently ($p<0.001$); and tended to smoke fewer cigarettes/day (p=0.055) than the entire EU sample (including GB) by t-test or chi-square. Gender (p=0.696) and being a former smoker (p=0.429) were similar (Table 1).

Among ever smokers any regular use of nicotine e-cigarettes was associated with lower odds of being a former smoker (unadjusted OR=0.34, 95% CI=0.26, 0.43; AOR=0.43, 95% CI=0.32, 0.58). In unadjusted models, daily use (OR=0.42, 95% CI=0.31, 0.56); occasional use (OR=0.25, 95% CI=0.18, 0.35); and experimentation (OR=0.24, 95% CI=0.19, 0.30) of nicotine e-cigarettes were all associated with lower odds of being a former smoker compared with having never used nicotine-containing e-cigarettes. Similar results were found in the adjusted models (daily use: OR=0.52, 95% CI=0.36, 0.73; occasional use: OR=0.33, 95% CI=0.23, 0.47; and experimentation: OR=0.32, 95% CI=0.25, 0.41; Table 2).

Data from GB revealed similar results (unadjusted OR=0.33, 95% CI=0.18, 0.64; AOR=0.42, 95% CI=0.20, 0.87) for any regular nicotine-containing e-cigarette use. Likewise, daily use (OR=0.42, 95% CI=0.20, 0.84); occasional use (OR=0.15, 95% CI=0.03, 0.68); and experimentation (OR=0.28, 95% CI=0.12, 0.66) were all related to lower odds of being a former smoker compared with having never used nicotine-containing e-cigarettes. Similar results were found in the adjusted models, though the result for daily use was not statistically significant (daily use: OR=0.55, 95% CI=0.25, 1.21,

Table 1. Sample Characteristics

Characteristic	European Union	Great Britain
Total sample (ever smokers),[a] *n*	12,608	411
Demographics		
Age	49.9 (16.8)	52.1 (18.6)
Male	7,010 (55.6)	224 (54.5)
Marital status		
Married/living with partner	8,278 (65.8)	218 (53.4)
Single	2,072 (16.5)	99 (24.3)
Divorced/separated/widowed/other	2,241 (17.8)	91 (22.3)
Education		
No full-time education / ≤15 years at completion	1,931 (15.5)	99 (24.2)
16–19 years	6,012 (48.3)	211 (51.6)
≥20 years	3,986 (32.0)	89 (21.8)
Still studying	514 (4.1)	10 (2.4)
Smoking variables		
Former smoker	5,743 (45.6)	196 (47.7)
Cigarettes per day, M (SD)	14.8 (5.0)	13.7 (1.2)
Any ever e-cigarette users	2,430 (19.4)	118 (28.9)
Frequency of nicotine containing e-cigarette use		
Daily use	430 (3.4)	46 (11.3)
Occasional use (weekly, monthly, less than monthly)	383 (3.1)	17 (4.2)
Experimentation (used once or twice)	1,132 (9.0)	38 (9.3)
Never	10,571 (84.5)	307 (75.3)

Note: Values are *n* (%) unless otherwise noted.
[a]96% of the entire European Union sample are cigarette smokers (including 30% who are dual users with cigars, cigarillos, or pipes); and 4% are cigar, cigarillo, or pipe users only.

Table 2. Odds (95% CI) of Being a Former Smoker (Logistic Regression)

	European Union		Great Britain	
Predictor	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Ever nicotine-containing e-cigarette use (excluding experimenters), *n*	11,384	11,384	370	370
Used e-cigarette (ref=never)	0.34 (0.26, 0.43)	0.43 (0.32, 0.58)	0.33 (0.18, 0.64)	0.42 (0.20, 0.87)
Female (ref=male)		1.13 (0.98, 1.31)		1.39 (0.83, 2.33)
Cigarettes per day (per 10 cigs)		1.04 (0.96, 1.12)		1.13 (0.89, 1.44)
Age (per 10 years)		1.51 (1.43, 1.59)		1.68 (1.42, 2.00)
Education				
No formal education		1.00 (ref)		1.00 (ref)
16–19 years at completion		1.23 (1.08, 1.40)		2.35 (1.27, 4.35)
≥20 years at completion		2.27 (1.82, 2.82)		4.58 (2.15, 9.77)
Still studying		2.71 (2.00, 3.69)		4.22 (0.85, 20.98)
Marital status				
Married/living with partner		1.00 (ref)		1.00 (ref)
Single		0.80 (0.69, 0.93)		0.47 (0.25, 0.89)
Divorced/separated/widowed/other		0.63 (0.54, 0.72)		0.39 (0.19, 0.79)
Intensity of nicotine-containing e-cigarette use, *n*	12,528	12,528	408	408
Intensity of e-cigarette use				
Never	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Daily use	0.42 (0.31, 0.56)	0.52 (0.36, 0.73)	0.42 (0.20, 0.84)	0.55 (0.25, 1.21)
Occasional use	0.25 (0.18, 0.35)	0.33 (0.23, 0.47)	0.15 (0.03, 0.68)	0.19 (0.04, 0.84)
Experimentation	0.24 (0.19, 0.30)	0.32 (0.25, 0.41)	0.28 (0.12, 0.66)	0.32 (0.11, 0.93)
Female (ref=male)		1.08 (0.94, 1.24)		1.20 (0.72, 1.98)
Cigarettes per day (per 10 cigs)		1.02 (0.94, 1.10)		1.04 (0.85, 1.27)
Age (per 10 years)		1.48 (1.41, 1.56)		1.57 (1.33, 1.85)
Education				
No formal education		1.00 (ref)		1.00 (ref)
16–19 years at completion		1.23 (1.08, 1.40)		2.02 (1.12, 3.62)
≥20 years at completion		2.25 (1.82, 2.78)		3.56 (1.71, 7.40)
Still studying		2.87 (2.08, 3.96)		2.64 (0.59, 11.80)
Marital status				
Married/living with partner		1.00 (ref)		1.00 (ref)
Single		0.80 (0.69, 0.93)		0.52 (0.28, 0.96)
Divorced/separated/widowed/other		0.64 (0.55, 0.74)		0.43 (0.23, 0.83)

occasional use: OR=0.19, 95% CI=0.04, 0.84; and experimentation: OR=0.32, 95% CI=0.11, 0.93). The AORs from GB did not differ significantly from the EU excluding GB (p=0.93).

EU current smokers consumed 14.5 cigarettes a day (95% CI=13.6, 15.5), whereas former smokers smoked 15.2 cigarettes/day (95% CI=14.0, 16.4, p=0.05). Among all EU current smokers, daily cigarette consumption was 15.6 cigarettes/day (95% CI=14.5, 16.7) among those who also used e-cigarettes versus 14.4 cigarettes/day (95% CI=13.4, 15.4) for those who did not use them ($p<0.05$).

DISCUSSION

These results, based on a large cross-sectional study of EU countries conducted in 2014, found that nicotine e-cigarette use was associated with lower odds of being a former smoker. The finding that on the EU level even daily use of e-cigarettes is associated with lower odds of being a former smoker differs from three earlier smaller longitudinal studies,[12–14] which found increased quitting for intensive users, a national cross-sectional sample from the U.S.[15] and an ecological analysis of time series behavior in England.[25] The International Tobacco Control Four-Country Surveys, based on data collected from 2010 to 2014 and hence relatively early in the e-cigarette era, showed that there appear to be differences in the effectiveness of e-cigarettes as cessation devices, depending on the degree to which e-cigarettes are regulated. E-cigarettes seem to facilitate quitting (abstinence for at least 30 days) in less restrictive environments (United Kingdom, U.S.), while inhibiting sustained abstinence in

more restrictive ones (Australia, Canada).[26] The findings in this paper are, however, consistent with most other real-world studies of e-cigarette use.[8,27,28]

England, Scotland, and Wales, unlike other EU countries, have embraced e-cigarettes as a smoking cessation aid.[1–3] As of May 2017, the National Health Service website advised patients, "Research has found that e-cigarettes can help you give up smoking, so you may want to try them rather than [NRT and other] medications.… There are no e-cigarettes currently available on prescription. But once medicinally licensed e-cigarette products become available, GPs and stop smoking services will be able to prescribe them."[1] This recommendation is consistent with recommendations from the Royal College of Physicians[29] and Public Health England.[30] In January 2017, Public Health Wales updated their position to state that e-cigarettes "may prove helpful in achieving a successful quit from tobacco although they are not currently licensed as a medicine for this purpose."[2] In September 2017, NHS Scotland said, "e-cigarettes are useful for public health and health service purposes only as a potential route towards stopping smoking."[3] In contrast to these recommendations, Eurobarometer data from GB indicated that regular e-cigarette use was associated with lower odds of being a former smoker.

The fact that the ORs in the unadjusted and adjusted models are similar suggests that confounding by other factors is unlikely to be an important effect on the results. Although the authors do not have an explicit measure of dependence, cigarettes per day are used as an approximation.

As shown above, current cigarette smokers who also use e-cigarettes smoke significantly more cigarettes per day than smokers who do not use e-cigarettes. This finding, combined with e-cigarette use being associated with less quitting, is inconsistent with the hypothesis that e-cigarettes have a positive net public health effect.

Limitations

The major limitation of this study is that the Eurobarometer is a cross-sectional survey that cannot determine causation. An important concern with this analysis is that the survey does not contain information on when smokers quit smoking and hence the sample includes people who quit before e-cigarettes were available. However, if quitting patterns are stable over time beyond any effects of e-cigarettes, this effect will bias the estimate of the effect of e-cigarette use on quitting smoking toward the null,[31] which would make the fact that a significant depression was found in the odds of being a former smoker even more reliable. EU quit ratios (former smokers/ever smokers) have increased over time, from 0.32 in 2002[32] to 0.43 in 2009[33] before the advent of e-cigarettes, then remained at 0.43 through 2014, the year this study analyzes. Thus, for the 5 years prior to the survey the quit ratio remained stable, which is consistent with the conclusion that the results are biased toward the null. To the extent that some people in the cross-sectional sample quit before 2009, the odds of quitting associated with e-cigarette use will be biased upward (in absolute terms) because some of the quitting as a result of long-term secular trends will be inappropriately associated with e-cigarettes, which biases the results against the conclusion that e-cigarettes are associated with less quitting. In addition, other cross-sectional population-level studies that examined the same association in which data were only collected after e-cigarettes were available show results similar to those presented here.[34–36]

The Eurobarometer survey also used self-reported e-cigarette and cigarette use without any biomarker verification use status or duration of smoking cessation. An earlier meta-analysis,[8] however, showed similar results for the relationship between e-cigarette use and smoking cessation between cross-sectional and longitudinal studies and independent of biomarker validation of smoking status. Changes in cigarette consumption between people who did and did not use e-cigarettes could not be compared because the question on changes in consumption was only asked to e-cigarette users. Self-selection to use e-cigarettes might be likely skewed toward those with higher dependence and lower self-efficacy for quitting without a cessation aid. However, the meta-analysis by Kalkhoran and Glantz[8] included a sensitivity analysis that examined sociodemographic factors associated with such a self-selection and found that they were not significantly associated with the results.

CONCLUSIONS

These results, based on a large data set from the EU, suggest that e-cigarettes are associated with inhibiting rather than assisting in smoking cessation. The net effect of the entry of e-cigarettes into the EU (and GB) is associated with depressed smoking cessation of conventional cigarettes.

ACKNOWLEDGMENTS

Dr. Kulik was supported by the University of California Tobacco Related Disease Research Program Grant 25FT-0004, and the William Cahan Endowment funded by the Flight Attendant Medical Research Institute provided to Dr. Glantz. Dr. Lisha's work on this publication was supported by grant P50CA180890 from the National Cancer Institute and U.S. Food and Drug

Administration Center for Tobacco Products. Drs. Glantz and Lisha's work was supported by P50CA180890. Dr. Glantz was also supported by National Institute on Drug Abuse grant R01DA043950. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the U.S. Food and Drug Administration. The funding agencies played no role in the conduct of the research or preparation of the manuscript.

MCK and NEL conducted statistical analyses. MCK drafted the methods and results sections, consulted on the data set and revised all original manuscript sections. SAG advised on the statistical analysis and drafted original versions of the introduction and discussion sections. All authors edited subsequent manuscript versions.

No patients were involved in the design or conduct of this study. Because this research is based on a de-identified public use data set, there is no way to notify participants of the results of this paper beyond publication of the paper itself.

All Eurobarometer data and questionnaires are publically available and can be obtained through the Leibniz Institute for the Social Sciences: http://zacat.gesis.org/webview/.

All authors state that they do not have any financial relationships with any organizations that might have an interest in the submitted work or any other relationships or activities that could appear to have influenced the submitted work.

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Addiction
RESEARCH REPORT
doi:10.1111/add.12917

Is the use of electronic cigarettes while smoking associated with smoking cessation attempts, cessation and reduced cigarette consumption? A survey with a 1-year follow-up

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ABSTRACT

Aims To use a unique longitudinal data set to assess the association between e-cigarette use while smoking with smoking cessation attempts, cessation and substantial reduction, taking into account frequency of use and key potential confounders. **Design** Web-based survey, baseline November/December 2012, 1-year follow-up in December 2013. **Setting** Great Britain. **Participants** National general population sample of 4064 adult smokers, with 1759 (43%) followed-up. **Measurements** Main outcome measures were cessation attempt, cessation and substantial reduction (≥50% from baseline to follow-up) of cigarettes per day (CPD). In logistic regression models, cessation attempt in the last year (analysis $n = 1473$) and smoking status ($n = 1656$) at follow-up were regressed on to baseline e-cigarette use (none, non-daily, daily) while adjusting for baseline socio-demographics, dependence and nicotine replacement (NRT) use. Substantial reduction ($n = 1042$) was regressed on to follow-up e-cigarette use while adjusting for baseline socio-demographics and dependence and follow-up NRT use. **Findings** Compared with non-use, daily e-cigarette use at baseline was associated with increased cessation attempts [odds ratio (OR) = 2.11, 95% confidence interval (CI) = 1.24–3.58, $P = 0.006$], but not with cessation at follow-up (OR = 0.62, 95% CI = 0.28–1.37, $P = 0.24$). Non-daily use was not associated with cessation attempts or cessation. Daily e-cigarette use at follow-up was associated with increased odds of substantial reduction (OR = 2.49, 95% CI = 1.14–5.45, $P = 0.02$), non-daily use was not. **Conclusions** Daily use of e-cigarettes while smoking appears to be associated with subsequent increases in rates of attempting to stop smoking and reducing smoking, but not with smoking cessation. Non-daily use of e-cigarettes while smoking does not appear to be associated with cessation attempts, cessation or reduced smoking.

Keywords Electronic cigarettes, electronic nicotine delivery systems, harm reduction, smoking cessation, tobacco, quit attempts.

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Submitted 22 July 2014; initial review completed 28 October 2014; final version accepted 4 March 2015

INTRODUCTION

In electronic cigarettes, a battery-powered heating element heats a solution, usually containing nicotine, to produce a aerosol. The use of e-cigarettes has increased dramatically in the last few years; users are almost exclusively smokers or former smokers, with fewer than 1% of never-smokers using them regularly [1–8]. The vast majority of e-cigarette users report using them to stop smoking tobacco [6,9] and in England, for example, smokers attempting to stop smoking now use e-cigarettes more often than any other aid, including nicotine replacement therapy (NRT) [10]. Smoking prevalence in England has been declining from 20% in 2012 to 18.4% in 2014 (up to October), and in 2014 smoking cessation rates were the highest since at least 2008 [10,11]. This simultaneous increase in e-cigarette use and cessation may be coincidental, and it is therefore vitally important for longitudinal studies to be conducted to assess the impact of e-cigarette usage on quitting behaviour.

Evidence on NRT supports the possibility of a link between using e-cigarettes that deliver nicotine and attempts to stop smoking. Use of NRT while smoking is associated

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doi:10.3390/toxics6030046

Article

Aldehydes in Exhaled Breath during E-Cigarette Vaping: Pilot Study Results

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Received: 6 June 2018 / Accepted: 3 August 2018 / Published: 7 August 2018

Abstract: Several studies have shown the presence of aldehydes (i.e., formaldehyde, acrolein) in mainstream emissions of some e-cigarettes. For this reason, concerns have been raised regarding potential toxicity. The purpose of this research was to measure levels of carbonyls in exhaled breath of e-cigarette users during “vaping” sessions and estimate the respiratory tract (RT) uptake of specific aldehydes, including formaldehyde and acetaldehyde. We measured concentrations of 12 carbonyls in e-cigarette aerosols produced directly by e-cigarettes and in the exhaled breath of 12 participants (19 sessions). Carbonyls were sampled on 2,4-dinitrophenylhydrazine (DNPH) cartridges and analyzed with high performance liquid chromatography (HPLC) coupled with a UV/Vis photodiode detector. We found that in most cases, levels of aldehydes and methyl ethyl ketone (MEK) were significantly higher (2–125 times) in exhaled e-cigarette breaths than in pre-exposed breath. Exposure levels for the most abundant individual carbonyls in e-cigarette emissions—formaldehyde, acetaldehyde,

acrolein—were between the limit of quantification (LOQ) and 24.4 μg·puff^{-1}. The mean retention of formaldehyde in the respiratory tract was 99.7 ± 0.9% for all participants, while acetaldehyde retention was 91.6 ± 9.9%. Within the limitation of a small number of participants, our results showed that there is an increase in breath carbonyls during e-cigarette use.

Keywords: aldehydes; breath analysis; e-cigarette emissions; respiratory tract retention; exposure

1. Introduction

An electronic cigarette (e-cigarette) is a nicotine delivery device that has become one of the most popular alternatives to conventional tobacco cigarettes in recent years [1,2,3]. This device produces aerosolized nicotine in vapor form (e-vapor) by heating e-cigarette liquid (or e-liquid), which is typically composed of propylene glycol (PG), vegetable glycerin (VG), nicotine, and flavoring compounds [4]. A number of studies have shown that in addition to nicotine and flavorings, e-cigarette vapors may also contain carbonyl compounds, including potentially harmful species such as formaldehyde, acetaldehyde, and acrolein [5,6,7,8,9] as well as diacetyl [10]. Although many

studies have reported aldehyde emissions from e-cigarettes, there are ongoing debates within the scientific, tobacco control, and tobacco manufacturing communities about whether these compounds are present in sufficient quantities in inhaled vapor to be harmful to e-cigarette users. Variability in these quantities can be explained by the difference in tested e-cigarette devices (type of coil, power output, and composition of flavored liquid) that causes a large variability in concentrations of emitted carbonyls [5,11,12]. Some investigators have argued [13] that dangerously high aldehyde concentrations in mainstream e-cigarette aerosols occur only during so-called “dry puff” conditions that are avoided by users because of the associated acrid taste, thus eliminating or minimizing aldehyde exposure during realistic e-cigarette use. However, high concentrations of aldehydes have been detected in e-cigarette emissions that have no option of power control (e.g., CE4 or V2) [11] and at power settings typically selected by e-cigarette users. Therefore, it is critical to further evaluate aldehyde e-cigarette exposure to better understand toxicological significance.

To our knowledge, research on human respiratory track (RT) retention of carbonyls, specifically formaldehyde and acetaldehyde, during e-cigarette use is

lacking. RT uptake of aldehydes has been studied for conventional cigarettes [14,15], but the retention of aldehydes in e-cigarette users' RT could differ from that of cigarette smokers. Large amounts of PG/VG aerosols can cause certain aldehyde compounds to partition into the particle phase, thus modifying RT retention efficiency. Long et al. [16] performed analysis of carbonyls in exhaled e-vapors and found no significant difference between exhaled e-cigarette breath. However, considering that mainstream e-cigarette carbonyls were not measured in the Long study, the exposure could not be estimated, and the low levels of carbonyls in exhaled e-cigarette breaths are most likely because of high carbonyl retention rates (above 95%) in the human RT [17,18].

The goal of this study was to estimate the extent to which carbonyl exposures occurred during realistic e-cigarette use conditions. With the limited number of participants, we aimed to determine if levels of carbonyls, including potentially harmful compounds such as formaldehyde and acrolein, were elevated in exhaled breath of e-cigarette users and confirm that carbonyl's formation is not a laboratory artifact. For this purpose, concentrations of 12 aldehydes and butanone (methyl ethyl ketone [MEK]) were measured in mainstream and exhaled e-cigarette

aerosols under real-life conditions and then accessed for carbonyl retention in participants' RT.

2. Experimental

2.1. Materials

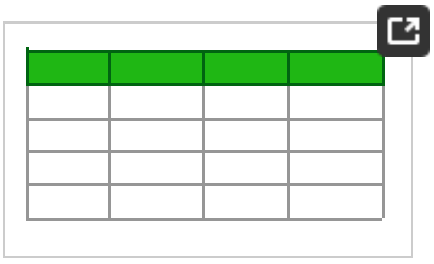
Carbonyl standards were purchased from AccuStandard, Inc. (New Haven, CT, USA). Acetonitrile (high performance liquid chromatography grade) was obtained from Fisher Scientific (Fair Lawn, NJ, USA). High purity grade water (18 MΩ·cm^{-1}) was produced using a NanoPure system (Barnstead, Thermo Scientific, Dubuque, IA, USA). Cartridges loaded with 2,4-dinitrophenylhydrazine (DNPH, Sep-Pak DNPH-Silica Short Body Cartridges, part WAT047205) were obtained from Waters Corporation (Milford, MA, USA). Aerosol breath bags were purchased from Allied Healthcare Products, Inc. (St. Louis, MO, USA). Air (ultra-zero grade) was provided by Airgas, Inc. (Radnor, PA, USA). Detailed descriptions of e-cigarette devices and used e-liquid are summarized in Table S1 (Supplementary Material).

2.2. Participants

Twelve e-cigarette users (seven females and five males) in the age range of 21 to 65 years were recruited for sampling background and exhaled e-cigarette aerosol breaths (Table 1). The protocol for the collection of human

breath (study ID number: 994577-1) was approved by the University of Nevada, Reno (UNR, Reno, NV, USA) Office of Human Research Protection (OHRP, Reno, NV, USA), approval date: 14 June 2016. One male volunteer participated seven times and one female volunteer participated two times using different e-cigarette devices or e-liquids (Table 1). Therefore, we had 19 paired samples of background breath and exhaled e-cigarette breath. All participants were asked not to vape at least two hours prior to breath collection, and no other specific limitations were required. Participants used their own e-cigarette devices and e-liquids except sessions #6–10. Participants of sessions #6–10 used a brand new e-cigarette provided in the laboratory (Table 1). Each volunteer signed a written informed consent approved by the local UNR institutional review board (IRB, UNR, Reno, NV, USA).

Table 1. A summary of data on participants and e-cigarettes.



2.3. Sampling and Measurements

Breath sampling was conducted using

the sampling setup presented in Figure S1 (Supplementary Material). The participants were asked to exhale their breath into a disposable 700 mL aerosol breath bag (Blowout Medical LLC, Evanston, WY, USA) using an exchangeable sterile mouthpiece. A sterile, one-way valve was incorporated between mouthpiece and air bag connected to the rest of the sampling system, such that participants were not able to inhale back anything from the sampling system. The exhaled breath was immediately pumped from the bag to minimize loss of exhaled carbonyls. The sample was pulled though the DNPH-coated cartridge with a flow rate of ~1 $L \cdot min^{-1}$. All samples were collected under the same conditions (flow rate, sampling system, type of air bag, sampling media, etc.) in the same laboratory room to minimize variation in inhaled background air and errors between samples. Before the vaping session, background breath was collected for each participant. Five breaths were sampled into one DNPH cartridge, and 2–3 replicate cartridges were collected. Exhaled e-cigarette breaths were collected the same way.

We collected mainstream e-cigarette emissions using an approach similar to the exhaled breath collection sampling system (Figure S1b), and it is described in Khlystov and Samburova [11]. Briefly, the operator/participant manually

depressed the e-cigarette power button while the laboratory operator simultaneously switched a stainless steel, three-way valve to sample position (Figure S1b). The sample air was drawn by a pump through a mass flow controller (MassTrak 810C-DR-13-V1S0, Sierra Instruments Inc., Monterey, CA, USA). The puff duration during the sampling of the direct e-cigarette emissions varied between subjects and it was 3 ± 1 s on average. All samples were collected in triplicates (3 DNPH cartridges) with 3 puffs per one DNPH cartridge. However, to accurately measure direct emissions from tested e-cigarettes and thus subjects' exposure, it was important to know the vaping topography parameters such as flow rate, puff duration, and puff profile. To investigate how flow rate and puff duration affect aldehyde emissions, additional experiments were performed. We tested an e-cigarette (Aspire Cleito) at three flow rates (0.4, 1.0, and 1.5 $L \cdot min^{-1}$) and three typical puff durations: 2, 3, and 4 s [19,20]. We found that the amount of emitted aldehydes was insensitive to flow rate but increased linearly with puff duration (data not presented). Aldehyde amounts emitted during a 4-s puff were no more than three times higher than during 2-s puffs. Given the common puff duration range [19], this represented about 50% maximum uncertainty. To minimize this

uncertainty, we asked participants to manually depress the e-cigarette power button. For all subjects, the puff duration was within 2 and 4 s. The samples were collected with a flow rate of 0.4 L·min^{-1}.

Collected DNPH cartridges were kept at 4 °C immediately after sampling, eluted within two hours to avoid chemical transformations of unsaturated carbonyls [21], and analyzed within 24 h with high performance liquid chromatography (HPLC, Waters 2690 Alliance System, Milford, MA, USA) coupled with a UV/Vis detector (Waters 996 photodiode array detector). A detailed description of the analytical method is in Khlystov and Samburova's work [11]. Briefly, collected cartridges were eluted with 2 mL of acetonitrile and analyzed for 12 aldehydes (formaldehyde, acetaldehyde, acrolein, propionaldehyde, crotonaldehyde, methacrolein, n-butyraldehyde, benzaldehyde, valeraldehyde, glyoxal, m-tolualdehyde, hexaldehyde) and one ketone (MEK) by HPLC-UV/Vis detector. The compounds were separated on a Polaris HPLC column (C18-A, 100 × 2.0 mm, particle size: 3 µm) and quantified based on six-point external calibration for each analyte with an R^2 value above >0.99 (median value of error for each curve point was ~5% for all analyzed carbonyls). The limit of detection (LOD) values were in the range of 0.001–0.01 µg·puff^{-1} (or µg·breath^{-1}).

3. Results

3.1. Mainstream Concentrations

Table 1 summarizes concentrations of carbonyl compounds detected in aerosols sampled directly from participants' e-cigarettes. The content of carbonyls varied among e-cigarette devices and e-liquid flavors [11]. Formaldehyde and acetaldehyde were the most abundant carbonyls detected in all e-cigarette vapor samples, ranging from 0.059 ± 0.006 to 24.4 ± 2.3 $\mu g \cdot puff^{-1}$ and from 0.022 ± 0.008 to 22.5 ± 6.2 $\mu g \cdot puff^{-1}$, respectively. The highest concentrations of formaldehyde and acetaldehyde were generated by the CE4 e-cigarette with Bubble Gum flavored e-liquid. Acrolein, glyoxal, and propionaldehyde were above their LOD in more than one half of the collected samples, and their concentration levels were from 0.012 ± 0.003 to 1.37 ± 0.35 $\mu g \cdot puff^{-1}$, from 0.019 ± 0.004 to 1.62 ± 0.39 $\mu g \cdot puff^{-1}$, and from 0.019 ± 0.008 to 4.2 ± 1.2 $\mu g \cdot puff^{-1}$, respectively. Overall, the highest concentration of total aldehydes and MEK were observed for the CE4 e-cigarette (0.97–53.3 $\mu g \cdot puff^{-1}$), while BLU and V2 e-cigarettes generated lower aldehyde levels (0.4–14.1 $\mu g \cdot puff^{-1}$), in good agreement with results from other studies [8,22].

We detected benzaldehyde in seven out of 16 e-cigarette vapor samples in

the range of 0.11 ± 0.03 and 3.9 ± 1.2 μg·puff^{-1}. Concentrations of eight carbonyls (crotonaldehyde, methacrolein, butyraldehyde, methylglyoxal, valeraldehyde, m-tolualdehyde, and hexaldehyde) were below their LODs. All of the detected aldehydes have been previously found in e-cigarette mainstream samples [5,11,23,24]. Although concentrations of individual compounds varied from device to device, our results are consistent with previously reported data [8,12]. For example, concentrations of formaldehyde, acetaldehyde, and acrolein measured in our study (Table 1) were within the range presented in Gillman et al. [5], where five different e-cigarette devices were tested at various power levels and 0.07–51 μg·puff^{-1} of formaldehyde, 0.03–41 μg·puff^{-1} of acetaldehyde, and 0.02–5.5 μg·puff^{-1} of acrolein were detected in direct e-cigarette emissions.

3.2. Concentrations in Exhaled E-Cigarette Breath

Concentrations of 12 aldehydes and MEK were measured in participants' breath prior to each session (background breath or $C_{background}$) and in exhaled e-cigarette breath ($C_{e\text{-}cig\ breath}$). Background formaldehyde concentrations ranged between being below LOD and 0.012 ± 0.003 μg·breath^{-1} (mean: 0.003 ± 0.004

μg·breath^{-1}). Background levels of acetaldehyde were higher than formaldehyde levels, in the range of 0.002–0.035 μg·breath^{-1} (mean: 0.015 ± 0.009 μg breath^{-1}). The measured background levels of carbonyls were compared with those in exhaled e-cigarette breaths.

Figure 1 (Table S2) shows differences between carbonyl concentrations in exhaled e-cigarette breath relative to background levels ($\Delta C = C_{e\text{-}cig\ breath} - C_{background}$; units: μg breath^{-1}). In 14 out of 19 sessions, total concentrations of aldehydes and MEK were higher in exhaled e-cigarette breath ($\Delta C > 0$) than those in the background breath. We detected a factor of 1.4 to 53 increase (factor of 13 on average) above the formaldehyde background level in aerosols exhaled in seven sessions (#6–10, 12, and 15), where the highest $\Delta C_{formaldehyde}$ values were observed for participants in sessions #8 (0.4 μg·breath^{-1}), #10 (0.07 μg·breath^{-1}), and #12 (0.08 μg·breath^{-1}). Note that formaldehyde concentration levels were found to be hundreds of times higher in direct e-cigarette emissions (Table 1) than in exhaled e-cigarette breaths (Figure 1). This large difference between mainstream aerosol and breath formaldehyde levels is most likely because of the high retention of the formaldehyde in the users' RT [14,17]. Deviations in vaping topography during

e-cigarette use by volunteers and during collection of vapors directly from e-cigarettes can also contribute to the observed differences in aldehyde concentrations between exhaled and mainstream aerosols. As discussed in "*Sampling and Measurements*", however, errors in reproducing topography are not more than a factor of two, especially given that during mainstream aerosol measurements, the participants were asked to reproduce puff durations that they normally use during vaping. We calculated the RT aldehyde uptake for the two most abundant aldehydes (acetaldehyde and formaldehyde) in e-cigarette emissions [6,8] and present these results in Figure 1.

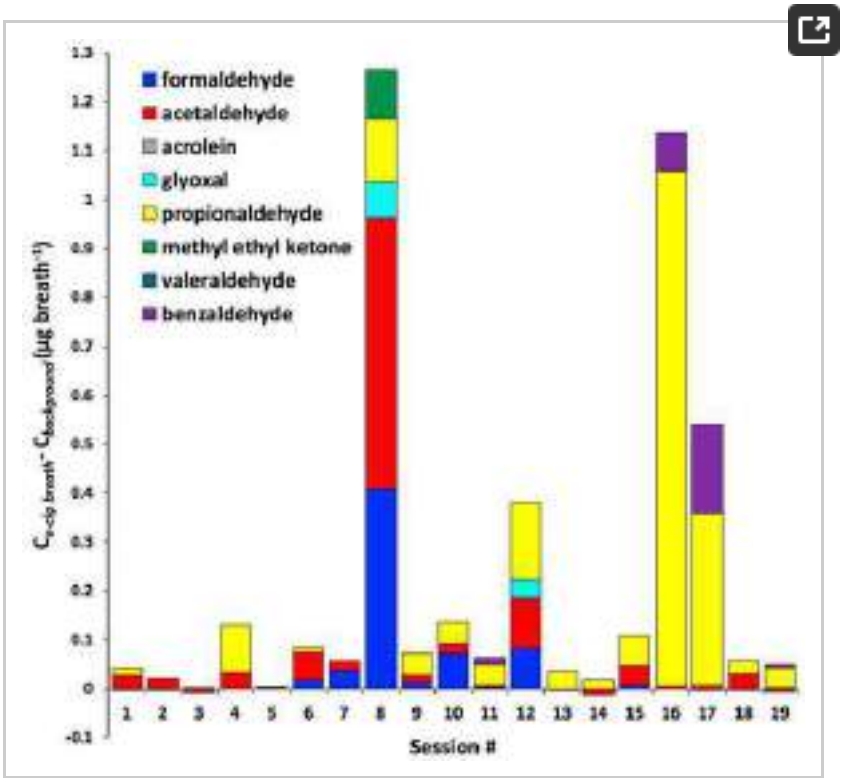


Figure 1. Difference in carbonyl concentrations between exhaled e-cigarette breath ($C_{e\text{-}cig\ breath}$) and background breath ($C_{background}$); units: μg breath^{-1}; the concentrations are also presented in Table S2.

Concentrations of acetaldehyde for the majority of participants were higher in exhaled e-cigarette breaths (1.2–62 times; mean: 8.9) than in background breaths with $\Delta C_{acetaldehyde}$ from 0.003 ± 0.015 to 0.56 ± 0.11 μg·breath^{-1}. The highest acetaldehyde concentration in exhaled e-cigarette breath was observed for participants in sessions #8 and 12, where $\Delta C_{acetaldehyde}$ values were 0.56 ± 0.11 and 0.10 ± 0.02 μg·breath^{-1}, respectively (Figure 1, Table S2). Similar to formaldehyde, acetaldehyde concentrations in mainstream e-cigarette vapors were higher (~50 times on average), which is most likely because of great absorption of acetaldehyde in participants' RT [14,17,18].

We also observed higher concentrations in exhaled e-cigarette breath samples than in background breath samples for propionaldehyde (Figure 1). In 15 of the 19 sessions, $\Delta C_{propionaldehyde}$ was positive and ranged from 0.010 ± 0.002 to 1.05 ± 0.08 μg·breath^{-1}. For sessions #2, 3, 5, and 7, no propionaldehyde was detected

in either background or exhaled e-cigarette breath samples. Propionaldehyde is one of the possible products of thermal decomposition of flavoring compounds that was detected in vapors emitted by e-cigarettes [8,11]. Breaths of participants during sessions #12 ($\Delta C_{propionaldehyde}$ = 0.16 μg·breath^{-1}), #16 ($\Delta C_{propionaldehyde}$ = 1.05 μg·breath^{-1}), and #17 ($\Delta C_{propionaldehyde}$ = 0.35 μg·breath^{-1}) contained greater levels of propionaldehyde relative to other sessions (Figure 1, Table S2). At the same time, high propionaldehyde concentrations were measured in direct emissions of e-cigarette devices used by volunteers in sessions #12 (0.19 ± 0.04 μg·puff^{-1}), #16 (12.1 ± 2.7 μg·puff^{-1}), and #17 (0.18 ± 0.04 μg·puff^{-1}) (Figure S2, Supplementary material). In comparison, the propionaldehyde level in direct e-cigarette emissions for the rest of cases (except e-cigarette #8) was lower, in the range of 0 to 0.10 ± 0.02 μg·puff^{-1}. Although it seems like there is an association between high propionaldehyde concentration in direct e-cigarette emission and elevated propionaldehyde level ($\Delta C_{propionaldehyde}$) in participants' e-cigarette exhaled breath, no significant correlation was observed (Spearman $r = 0.16$, $p = 0.53$).

We detected several aldehydes (benzaldehyde and glyoxal) only in exhaled e-cigarette breaths, while being

below LOD in all background breath samples. Benzaldehyde is one of the flavoring compounds that is widely used in e-cigarette liquids [4,7]. It was detected in exhaled e-cigarette breaths ($\Delta C_{benzaldehyde}$) of #11, 16, 17, and 19 samples ranging between 0.007 and 0.18 μg·puff^{-1}. Glyoxal, an aldehyde with acute toxic effects [25], has been detected in the mainstream of many e-cigarette devices [11,23], including e-cigarettes tested in this study (Table 1). Glyoxal was found in exhaled e-cigarette breaths of two subjects (sessions #8 and 12) and was below LOD in background breath. Interestingly, in mainstream e-cigarette emissions, glyoxal was below LOD in only five out of 19 (Table 1) samples, meaning that absorption of this aldehyde by RT is close to 100% in the majority of cases. Acrolein is another potentially hazardous carbonyl compound, the inhalation of which can cause severe pulmonary diseases [26,27]. We detected acrolein in 12 mainstream e-cigarette samples (Table 1), but its concentration was below LOD for all breath samples pointing to high absorption of acrolein by human RT.

Overall, the variation of aldehydes and MEK levels in participants' breath varied substantially (Figure 1). This variability can be explained by the following factors: (i) use of different e-liquid flavors and e-cigarette devices; (ii)

variability in age, gender, physical condition, and lung function of participants; (iii) difference in participants' vaping style.

3.3. Exposure and RT Retention

Next we examined the level of exposure by calculating the difference between aldehyde concentrations in mainstream e-cigarette emissions ($C_{mainstream}$, μg puff^{-1}) and elevated aldehyde levels in exhaled breath (ΔC) during e-cigarette use (Figure 2, Table S3). The highest levels of exposure to total aldehydes and MEK were observed for sessions #3 (14.2 μg·puff^{-1}), #7 (53.2 μg·puff^{-1}), and #16 (12.8 μg·puff^{-1}). For formaldehyde and acetaldehyde, we found the highest exposure levels in six cases (sessions #3, 6, 7, 9, 10, and 12) in the concentration range of 0.33–24.4 μg·puff^{-1}. Exposure to acrolein was observed in 12 out of 18 sessions, ranging between 0.01 and 1.4 μg·puff^{-1} (Figure 2, Table S3).

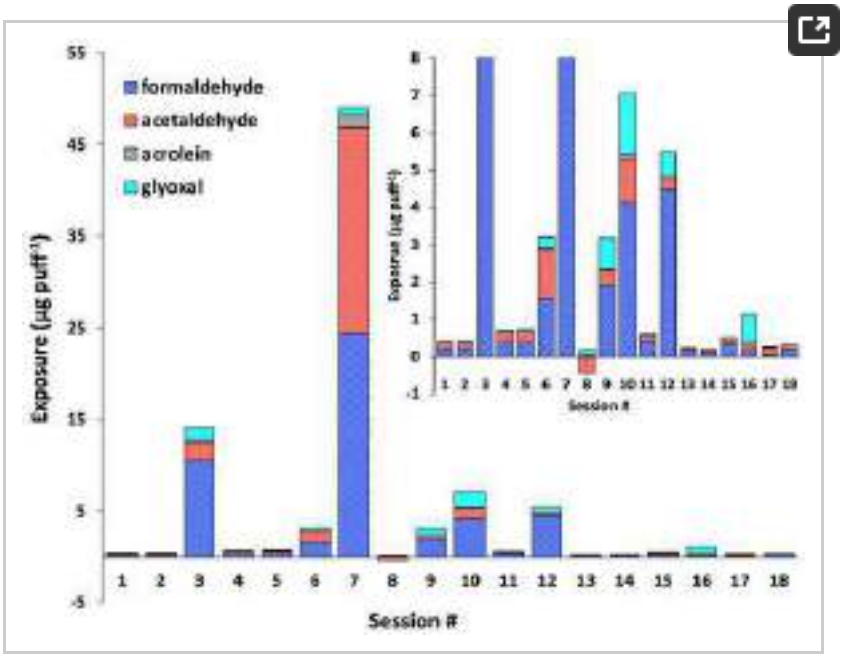


Figure 2. Level of exposure to selected carbonyls (formaldehyde, acetaldehyde, acrolein, and glyoxal); data are not available for session #19; these results are also presented in Table S3.

In order to estimate how much aldehyde was retained in human RT, we calculated the aldehyde retention fraction (F_{RT}) using the following formula:

$$F_{RT} = C_{mainstream} - \Delta C_{mainstream}$$

where F_{RT}—fraction of aldehyde retained by RT, $C_{mainstream}$—aldehyde concentration measured in direct e-cigarette emissions, ΔC—concentration of aldehyde in subject's breath during vaping ($\Delta C = C_{e\text{-}cig\ breath} - C_{background}$).

Figure 3 shows the retention fraction of inhaled formaldehyde for three groups

of participants: (a) users of BLU personal e-cigarette devices, (b) participants who were asked to use unfamiliar e-cigarette devices (V2 or CE4), and (c) participants who used their personal three-battery vaping devices (Aspire Cleito and Sigelei). As can be seen for all three groups, the amount of formaldehyde retained by RT was above 97% with mean percentile values of 99.8 ± 0.6% (BLU), 99.2 ± 0.8% (V2 + CE4), and 99.8 ± 1.2% (Aspire Cleito and Sigelei). Such a significant uptake of formaldehyde was expected since it is a highly water-soluble compound and thus is well retained by the RT hydrophilic surface. Our results are in good agreement with previously reported data. For example, Overton et al. [18] used two dosimetry models and predicted that more than 95% of the inhaled formaldehyde would be retained in the RT. Close to 100% of formaldehyde uptake was also reported by J.L. Jr. Eagle [28], who measured formaldehyde in dog RTs. Moldoveanu et al. reported 95–100% formaldehyde RT retention values for cigarette smokers [15].

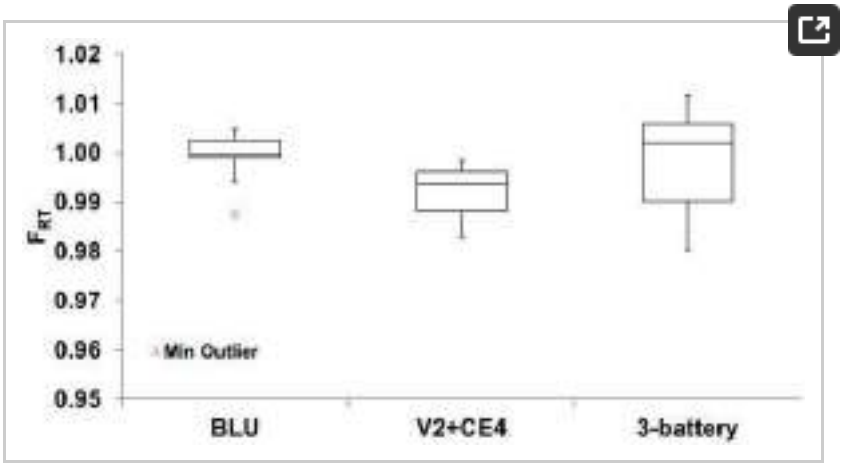


Figure 3. Formaldehyde retained by participants' respiratory tracts (RTs). Error bars represent minimum and maximum values; boxes represent upper (75%) and lower (25%) quartiles, midline—median value.

Although no significant difference in formaldehyde uptake among three groups of participants (Figure 3, $p > 0.21$) was observed in our study, slightly lower formaldehyde retention was observed in the second group (V2 and CE4 users). Participants in this group were asked to vape an e-cigarette and e-liquid that was unfamiliar to them. Although we do not have puff topography measurements, we observed that group 2 participants were cautious to deeply inhale the unfamiliar flavor generated by a new e-cigarette device. We suspect that an unfamiliar e-cigarette was the reason for the slightly lower formaldehyde uptake. Overall, the mean value of formaldehyde RT retention for all participants was 99.7 ±

0.9% (Figure 4a). In the case of acetaldehyde, average uptake by the RTs was 91.6 ± 10% with minimum and maximum values 72.4 and 100%, respectively (Figure 4a). Except for session #7 (uptake: 72.4%), retention of acetaldehyde in the RT was found to be above 75% for all participants' sessions. No significant difference in formaldehyde (p = 0.36) and acetaldehyde (p = 0.09) RT retention was observed between female and male participants (Figure 4b,c).

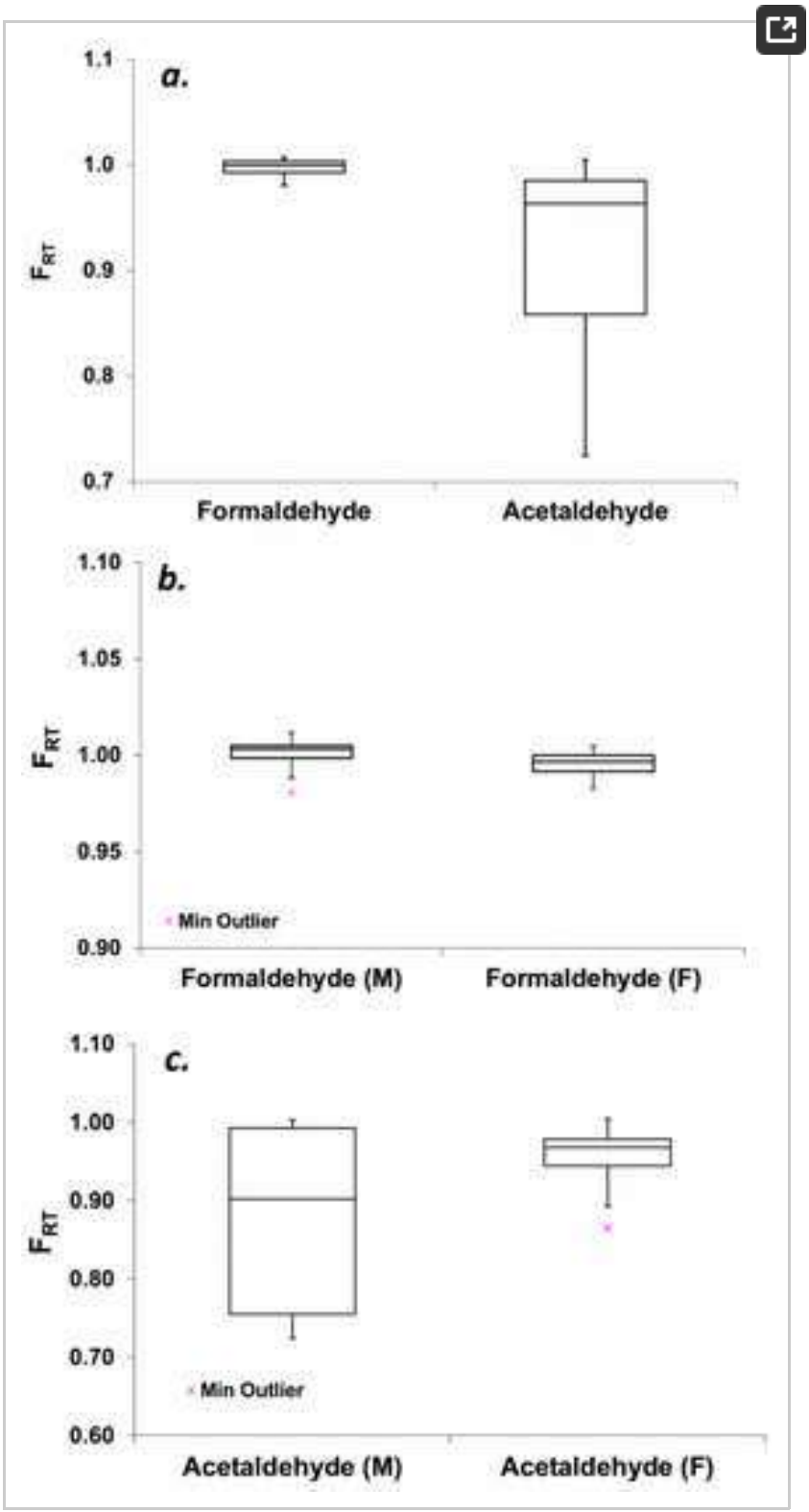


Figure 4. Fraction (F_{RT}) of aldehydes retained by human RTs: (**a**) F_{RT} of acetaldehyde and formaldehyde measured for all participants; F_{RT} of (**b**) formaldehyde and (**c**) acetaldehyde for male (M) and female participants (F).

Compared to formaldehyde, acetaldehyde RT uptake was lower, which can be explained by acetaldehyde's lower water solubility (~400-fold lower than formaldehyde). Moreover, the presence of formaldehyde in particulate phase (mainly in PG/VG aerosols) [29] may increase RT retention of this aldehyde. To our knowledge, there is limited research on pulmonary retention of acetaldehyde in either humans or animals. In 1969, Dalhamn et al. [14] presented retention of different compounds, including acetaldehyde, in RTs during cigarette smoking and showed a 99 ± 1.2% acetaldehyde RT uptake. This value is about 7.5% higher than medium acetaldehyde uptake measured in our study. The RT retention of acetaldehyde reported by Moldoveanu et al. [15] for conventional cigarettes (94–99%) is close to our values but still above average RT uptake (91.6 ± 10%). The difference in acetaldehyde RT retention during e-cigarette use can be explained by the presence of PG/VG particles in e-cigarette aerosol that could affect gas-particle phase partitioning of acetaldehyde and, therefore, its deposition mechanism in the human pulmonary system. Moreover, smoking and vaping topographies are different [30], which could also affect RT uptake of aldehydes. For example, several studies [31,32] showed that puff durations for e-cigarettes are longer

than those for conventional cigarettes. In addition, a different vacuum is needed for e-cigarette activation than for smoking traditional cigarettes [33]. Thus, intake of e-cigarette aldehydes and associated health effects cannot be extrapolated using data on conventional cigarettes, and assessment of "real-world" e-cigarette exposure is important.

3.4. Mainstream Aldehydes vs. $\Delta C_{aldehyde}$

We performed a comparison between elevated aldehyde concentrations in exhaled breath during e-cigarette use ($\Delta C_{aldehyde}$) and mainstream e-cigarette aerosols for the three most abundant aldehydes in all samples: formaldehyde, acetaldehyde, and propionaldehyde. A positive correlation was observed for formaldehyde with Spearman r of 0.76 ($p = 0.0003$). Unlike formaldehyde, we found no apparent correlation between elevated exhaled acetaldehyde (Spearman's $r = 0.10$, $p = 0.70$) during vaping ($\Delta C_{acetaldehyde}$) and direct acetaldehyde emissions from e-cigarettes. No significant correlation was observed for propionaldehyde (Spearman $r = 0.16$, $p = 0.53$) either. The poor correlation is perhaps because of the limited number of recruited participants and use of different e-cigarette devices and flavoring liquids. For this reason, we compared the same

correlations (Table S5) within each group of e-cigarettes (Table 1): (i) BLU and V2 (sessions #1–6), (ii) CE4 (sessions #7–10), and (iii) three-battery vaporizers Aspire Cleito and Sigelei (sessions #11–19). For BLU and V2 e-cigarettes, a positive Spearman's "Mainstream aldehydes vs. $\Delta C_{aldehyde}$" correlation was observed only for formaldehyde ($r = 0.948$, $p = 0.013$). A positive formaldehyde correlation was also found for the three-battery vaporizers Aspire Cleito and Sigelei ($r = 0.695$, $p = 0.056$). In the case of the CE4 device, no significant correlations were found for all three aldehydes ($-0.800 < r < -0.02$, $p > 0.330$).

4. Discussion

Our results showed that concentrations of analyzed carbonyls were higher in exhaled e-cigarette breaths than in background breaths in the majority of participants' sessions. The total carbonyl concentration, on average, was 10.5 times higher in exhaled e-cigarette breaths than in background breaths. Our results clearly showed that high carbonyl concentrations—including those of potentially hazardous formaldehyde, acetaldehyde, and acrolein—were not limited to dry puff conditions [13], since participants were using their e-cigarettes in their typical "vaping" style. None of the participants using their own

or the provided e-cigarette with a flavored e-liquid complained of unpleasant sensations during vaping sessions. The only complaint was received from a participant who was offered unflavored pure PG/VG liquids that were found to be “unpleasant.” High RT uptake of acetaldehyde (mean: 91.6 ± 9.9%) and formaldehyde (mean: 99.7 ± 0.9%) was obtained for all cases, and no significant difference was observed for RT uptake of these aldehydes between male and female participants. High exposure to formaldehyde (1.53–24.4 $\mu g \cdot puff^{-1}$; mean: 7.8 $\mu g \cdot puff^{-1}$) was observed in six (out of 18) cases, and the mean value of these exposure levels is comparable with exposure to conventional cigarette formaldehyde (~5 $\mu g \cdot puff^{-1}$) [34]. The Acute Exposure Guideline Levels (AEGL-1) for formaldehyde, acetaldehyde, and acrolein are 1.1, 81, and 0.070 $mg \cdot m^{-3}$, respectively, for 10 min exposure [35]. We converted our aldehyde levels into $mg \cdot m^{-3}$ for 10 min exposure (Supplementary Material, Table S4) and found that formaldehyde concentrations were above the AEGL-1 for sessions #3 (1.93 $mg \cdot m^{-3}$) and #7 (4.44 $mg \cdot m^{-3}$) and were close to the AEGL-1 for participants’ sessions #10 (0.76 $mg \cdot m^{-3}$) and #12 (0.84 $mg \cdot m^{-3}$). Acetaldehyde levels didn’t exceed the AEGL-1 for any participants. In the case

of acrolein, the exposure level (0.250 $mg \cdot m^{-3}$) was 3.6 times higher than the AEGL-1 for participant session #7.

The observed large variability in aldehyde concentrations was most likely because of differences in e-cigarette conditions (type of e-liquid and e-cigarette, e-cigarette settings) and volunteers' vaping styles (or vaping topography).

The present study has several limitations. First, the sample size was rather limited, considering the observed variability among participants in their vaping styles, used e-cigarettes, and e-liquid flavors. Twelve e-cigarette users were recruited; one male and one female participant were engaged seven and two times, respectively. Thus, 19 experimental sessions were performed during the study (Table 1). The sample size was sufficient, however, to detect a significant increase in aldehydes and MEK concentration in exhaled e-cigarette breaths relative to background breaths. Second, the puff duration of individual participants was measured with a timer as no topography devices were available, making puff duration measurements less accurate (±1 s). Among all participants, the puff duration varied from 2 to 4 s. Given a linear dependence of carbonyl emissions on puff duration and that the mean puff duration was 3 s, our estimates of inhaled carbonyls could be up to 50%

uncertain. In order to reduce this uncertainty during the sampling of mainstream e-cigarette emissions, we asked participants to manually depress the e-cigarette power button for the duration they use when vaping. This way, the puff duration during e-cigarette use by a participant is expected to be close to the puff duration for direct e-cigarette emissions generation, thus significantly reducing the uncertainty. We need to emphasize that in future studies, it is important to use a vaping topography device to minimize the uncertainty in carbonyl generation during e-cigarette use. Third, no losses of breath aerosols onto sampling bag walls (Figure S1a) or chemical transformations undergone by carbonyls during the sampling were evaluated. To avoid the chemical transformation of unsaturated carbonyls [21], the samples were eluted within two hours after the sampling and analyzed within 24 h. Another limitation in relation to overall health impact assessment was that this study focused only on analysis of aldehydes, while other chemicals (e.g., toluene, lead, naphthalene, flavorings) have also been found in e-cigarette vapors [36,37] and may have a substantial impact on human health. In addition, our recent experiments with DNPH cartridges and DNPH impregnated filters showed that even though the DNPH-cartridge is an effective medium

to collect gas-phase carbonyls [38], levels of particle phase carbonyls can be underestimated (~30%). More details on efficiency of different sampling media to collect gas and particle phase e-cigarette carbonyls will be presented in a following paper.

5. Conclusions

This pilot study underlines a potential health risk associated with carbonyls (i.e., formaldehyde, acetaldehyde, acrolein) generated by e-cigarettes. Concentrations of 12 aldehydes and MEK were measured directly in exhaled e-cigarette breaths of human volunteers, and RT uptakes were estimated for the most abundant in e-cigarette emissions carbonyls (formaldehyde and acetaldehyde).

Results of this study suggest: (1) concentrations of carbonyls, such as formaldehyde and acetaldehyde, are higher (2–125 times) in exhaled e-cigarette aerosols than in background breath of e-cigarette users, (2) since most of the recruited volunteers used their personal e-cigarette devices, this study confirms that significant amounts of carbonyls are indeed produced during normal e-cigarette use and that high carbonyl emissions observed in numerous laboratory studies [5,6,8,9] cannot be dismissed as laboratory artifacts, (3) e-cigarette aldehyde exposure needs to be assessed in future

studies that include a larger set of participants and (4) for an accurate health risk assessment, it is important to correlate aldehyde exposure with the "vaping topography", type of e-cigarette, e-cigarette settings, and chemical composition of e-liquids.

Supplementary Materials

The following are available online at http://www.mdpi.com/2305-6304/6/3/46/s1, Table S1: Used e-cigarette devices, Table S2: Difference (ΔC) in carbonyl concentrations between exhaled e-cigarette breath ($C_{e\text{-}cig\ breath}$) and background breath ($C_{background}$), Table S3: Level of exposure to different aldehydes, Table S4: Exposure levels in $mg \cdot m^{-3}$ for 10 min, Table S5: Spearman correlations between elevated aldehyde levels in exhales e-cigarette breath ($\Delta C_{aldehyde}$) for three groups of e-cigarettes, Figure S1: Sampling systems for collection of (a) exhaled breath and (b) mainstream e-cigarette emissions, Figure S2: Propionaldehyde concentrations in (a) "vape" breath ($\Delta C = C_{e\text{-}cig\ breath} - C_{background}$) and (b) direct e-cigarette emissions, Figure S3: Fraction of formaldehyde and acetaldehyde retained by human RT measured for one male volunteer, Figure S4: Correlations between elevated aldehyde levels in exhales e-cigarette breath ($\Delta C_{aldehyde}$) and aldehyde concentration in mainstream of e-

cigarette aerosol.

Author Contributions

V.S., C.B., and A.K. designed experiments. V.S. and C.B. performed data collection. V.S. summarized data and wrote the paper. A.K., M.S., L.D., Y.S., and J.A. provided input on interpretation of results. V.S., A.K., and Y.S. revised the manuscript.

Funding

This research received no external funding.

Acknowledgments

This work was supported by the DRI. We thank all the volunteers who participated in this study. We also thank Anna Cunningham and Mark McDaniel for technical assistance with sampling and analysis of carbonyls.

Conflicts of Interest

The authors declare no conflict of interest.

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Environmental Science & Technology

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Flavoring Compounds Dominate Toxic Aldehyde Production during E-Cigarette Vaping

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Supporting Information

ABSTRACT: The growing popularity of electronic cigarettes (e-cigarettes) raises concerns about the possibility of adverse health effects to primary users and people exposed to e-cigarette vapors. E-Cigarettes offer a very wide variety of flavors, which is one of the main factors that attract new, especially young, users. How flavoring compounds in e-cigarette liquids affect the chemical composition and toxicity of e-cigarette vapors is practically unknown. Although e-cigarettes are marketed as safer alternatives to traditional cigarettes, several studies have demonstrated formation of toxic aldehydes in e-cigarette vapors during vaping. So far, aldehyde formation has been attributed to thermal decomposition of the main components of e-cigarette e-liquids (propylene glycol and glycerol), while the role of flavoring compounds has been ignored. In this study, we have measured several toxic aldehydes produced by three popular brands of e-cigarettes with flavored and unflavored e-liquids. We show that, within the tested e-cigarette brands, thermal decomposition of flavoring compounds dominates formation of aldehydes during vaping, producing levels that exceed occupational safety standards. Production of aldehydes was found to be exponentially dependent on concentration of flavoring compounds. These findings stress the need for a further, thorough investigation of the effect of flavoring compounds on the toxicity of e-cigarettes.

INTRODUCTION

Electronic cigarettes (or e-cigarettes) are battery-operated electronic devices that deliver nicotine or nicotine-free "vapors" to smokers in aerosol form. Since their introduction to the market in 2003, e-cigarettes have been increasing in popularity, especially among the younger population, including school-age children.[1] According to the 2015 report[2] of the National Center for Health Statistics (NCHS), approximately 3.7% adults in the United States use e-cigarettes on a regular basis while 12.6% of adults had tried an e-cigarette. The Adult Tobacco Survey (ATS), prepared by the Centers for Disease Control and Prevention (CDC), reported that the number of adult e-cigarette users doubled between 2010 and 2013,[3] while several studies showed that e-cigarette use is higher among 18−24-year-olds.[3,4] Bunnell et al.[5] reported the number of young e-cigarette users who never smoked before more than tripled (from 79000 to more than 263000) during the period of 2011−2013. According to Singh et al.,[1] in 2015, 25.3% of high school students have regularly used (one or more times per 30 days) any tobacco products (cigarettes, cigars, hookahs, pipes, etc.), with e-cigarettes being the most popular nicotine delivery device (16.0%). A similar pattern was observed among middle school smokers, where e-cigarette user group was dominant, 5.3%.[1] The popularity of e-cigarettes among young people raises serious concerns that e-cigarette usage could cause a future nicotine addiction and facilitate transition to regular cigarettes.

The growing popularity of e-cigarettes could be explained by marketing of these devices as a less harmful or even "healthy" alternative to traditional tobacco products. These claims are based on the assumption that "vapor" produced by "atomization" of e-cigarette liquid (or e-liquid) is harmless, because the e-liquid that is used for vaping is composed mostly of nontoxic components. However, with the exception of ultrasonic brands, e-cigarettes produce vapors using a heating element, which can lead to decomposition of e-liquid constituents. Thermal decomposition does indeed take place, resulting in the production of aldehydes[6−9] and other toxic compounds.[10] Toxic compounds produced by pyrolysis of e-liquid constituents could be the cause of immune and inflammatory response gene suppression in nasal epithelial cells observed in e-cigarette users.[11]

The studies hypothesized that the main source of carbonyl compounds is thermal decomposition of propylene glycol (PG) and/or vegetable glycerin (VG); each serves as a solvent for nicotine and flavoring compounds in e-liquids. Indeed, neat PG and VG were shown to produce aldehydes during vaping, with PG reportedly contributing more to aldehyde production.[6,7] The power and construction of e-cigarettes were also shown to

Received: August 8, 2016
Revised: October 20, 2016
Accepted: October 27, 2016

DOI: 10.1021/acs.est.6b05145
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have a strong effect on aldehyde emissions.[6,8,9,12] In addition to PG, VG, and nicotine, e-liquids often contain large quantities of flavoring compounds.[13] So far, only two studies have investigated the contribution of flavorings to toxic aldehyde emissions during vaping.[14,15] These studies have investigated direct emission due to evaporation of flavoring compounds, such as benzaldehyde and diacetyl. Thermal decomposition of flavoring compounds and its contribution to the production of aldehydes in e-cigarette vapor have been overlooked so far.

Because the operating temperature of e-cigarettes is sufficient to decompose small molecules, such as PG and VG, it is possible that flavoring compounds could decompose, too. Many flavoring additives are aldehydes,[16] often containing unsaturated bonds. It was demonstrated that thermal decomposition of "chocolate" aldehyde (2-methylbutyraldehyde) leads to formation of formaldehyde, acrolein, and other aldehydes.[17] Another study has shown that unsaturated 2-alkenals and 2,4-alkadienals, while relatively stable in neat form, decompose at 200 °C in the presence of air and/or buffer, producing formaldehyde, acetaldehyde, and other small aldehydes.[18] Flavoring compounds, thus, could be an additional source of toxic aldehydes in e-cigarette emissions, which could explain the recent studies showing that flavorings significantly affect the inhalation toxicity of e-cigarette aerosols.[19,20]

In this study, we have investigated whether flavoring compounds could affect e-cigarette emissions of small, toxic aldehydes, such as formaldehyde, by measuring aldehyde concentrations in aerosols produced by vaping flavored and unflavored liquids.

MATERIALS AND METHODS

We have measured concentrations of 12 aldehydes in e-cigarette aerosols produced by flavored and unflavored liquids. To determine the role of flavoring compounds, in each experiment, we fixed all potentially important parameters that could affect aldehyde production (e-cigarette design, power output, and liquid PG/VG ratio)[6−9,12] and varied only the type and concentration of flavors. Under these conditions, any differences in aldehyde emissions could be due only to differences in the type and concentration of e-liquid flavor.

While comparison between e-cigarette brands was not the aim of this study, we have tested three popular brands of e-cigarettes to investigate whether results are not limited to one e-cigarette brand or construction type. The selected e-cigarette brands were chosen to represent the three most common types of e-cigarette "atomizers": bottom and top coil "clearomizers" and a "cartomizer". Two of the brands were single-coil types, while one was a double-coil type. General characteristics of the three types of e-cigarette devices that were tested in this study are listed in Table 1. The brands were chosen on the basis of ease of availability among the most popular brands to represent the three most common types of e-cigarette "atomizers".

Brand I was a double-bottom coil "clearomizer"; brand II was a single-coil "cartomizer", and brand III was a single-top coil "clearomizer". Though brand I offered a possibility to adjust output voltage (and thus power) between 3.2 and 4.8 V, it was operated at 4 V, the lowest common power setting according to the retailer. Brands II and III have a fixed, manufacturer-set power output. Thus, the possibility of overheating e-liquids during vaping that could lead to excessive aldehyde production (the so-called "dry puff") is excluded. Per the manufacturer's instructions, e-cigarettes were kept horizontal during sampling. Cartridges of brand I and III e-cigarettes were sampled with fresh coils, whose resistance was verified to be within the manufacturers' specifications, and filled up to two-thirds of their tank capacity. This was done to avoid wick starvation, which could also lead to "dry puff". Brand II was sampled with fresh manufacturer-prefilled cartridges.

Table 1. List of Tested E-Cigarette Devices

	brand I	brand II	brand III
brand	Kangertech eVod Glass[a]	V2 Standard	E-Cig CE4
type	bottom double coil clearomizer	single coil cartomizer	top single coil clearomizer
voltage (V)	4.0[b]	4.2[c]	3.9[d]
resistance (Ω)	1.5	3.4	3.1
power (W)	10.7	5.2	4.9
PG (%)/VG (%)	60/40	80/20	80/20
[nicotine] (mg mL^{-1})	12	18	12

[a]Used with a SmokTech Winder battery. [b]Voltage used for experiments. [c]Manufacturer-set voltage that cannot be modified by the user. [d]Used with a 1100 mAh eGo-T battery, a manufacturer-set voltage that cannot be modified by the user. Voltage and power are nominal values.

E-Cigarette vapor was produced by 4 s, 40 mL controlled "puffs" with a 30 s resting period between each puff. This protocol was adapted to simulate the most common vaping conditions.[14,21] E-Cigarettes were operated according to instructions from the manufacturer and retailer to mimic the most common vaping conditions. The schematic of the sampling setup is given in Figure 1. E-Cigarettes were operated manually to better represent real-life conditions. The operator manually depressed the e-cigarette power button, simultaneously switching a stainless steel three-way valve to sample position. The sample air was drawn by a pump through a mass flow controller (MassTrak 810C-DR-13-V1-S0, Sierra Instruments Inc., 0−50 sccm flow range, 810 ms response time constant) at a rate of 10 mL s^{-1}. The stability of the sample flow was monitored using the mass flow controller display and was checked before and after each experiment using a Gillibrator (Sensodyne, LP). After 4 s, on a signal from an electronic timer, the power button was released and the valve switched to the flush position, during which time the sampling

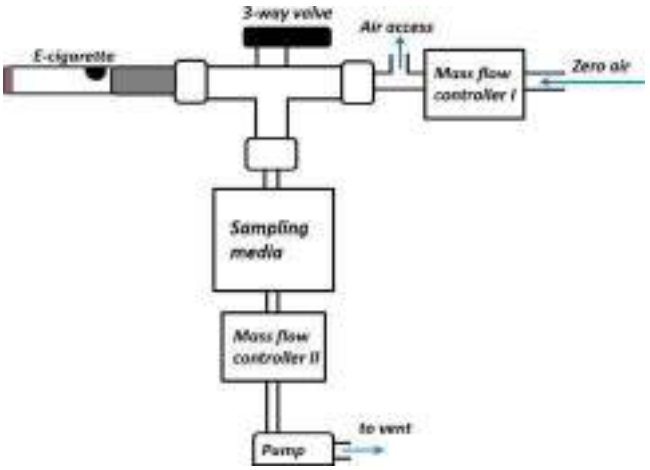

Figure 1. Schematics of the sampling system for e-cigarette emissions. The three-way valve was heated to 40 °C to prevent deposition and/or condensation of gaseous species.

DOI: 10.1021/acs.est.6b05145
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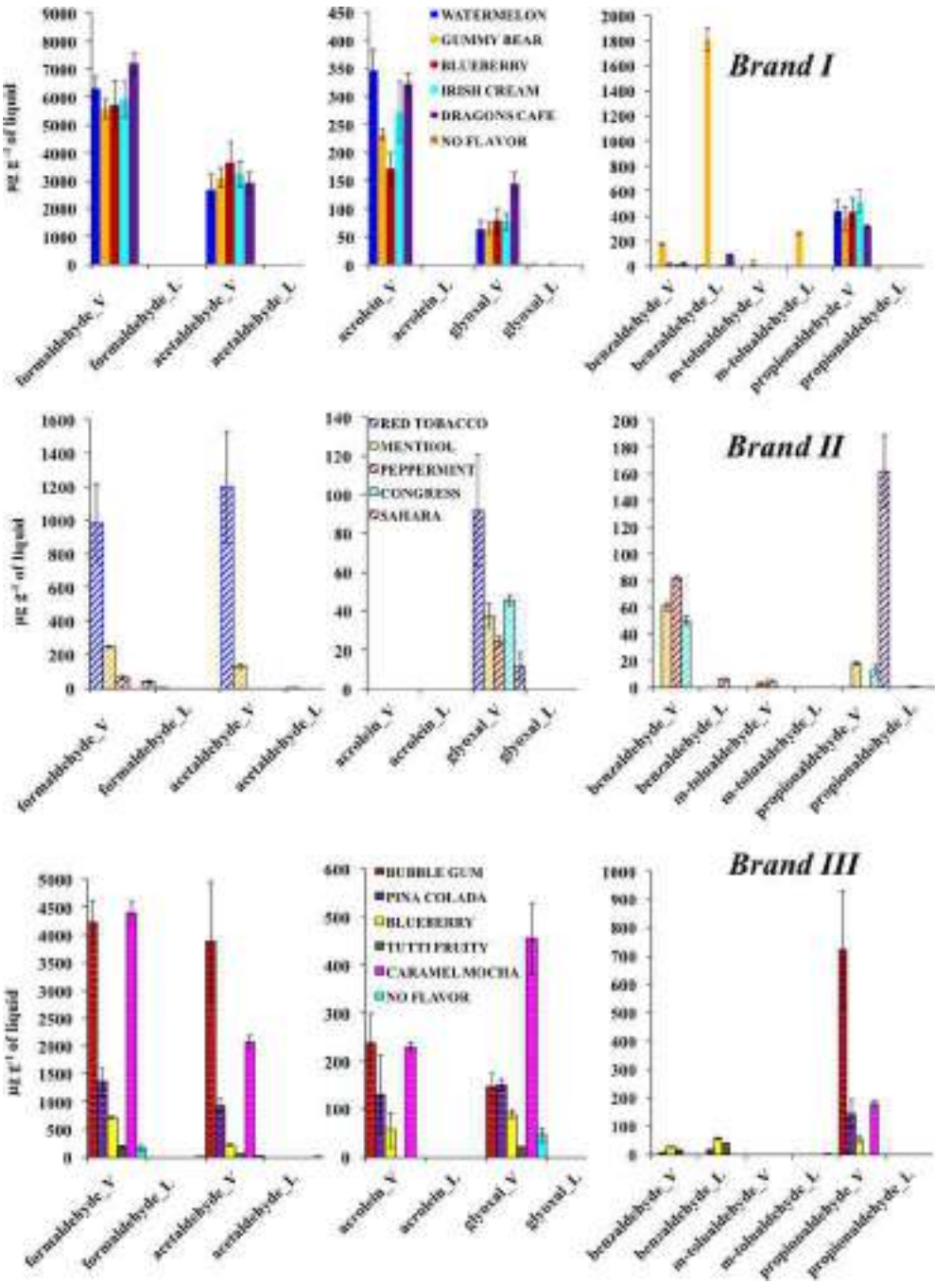

Figure 2. Amounts of aldehydes produced per gram of e-liquid. Error bars represent one standard deviation of triplicate measurements ($N = 3$). "V" designates "vapor" (aerosol), and "L" designates liquid.

line was flushed with zero air. All parts of the sampling system were made of stainless steel and were heated to 40 °C to minimize wall losses.

After 15 warm-up puffs, which are necessary to bring e-cigarette output to steady state,[9] two puffs were sampled directly into 2,4-dinitrophenylhydrazine (DNPH) cartridges (Sep-Pak DNPH-Silica Short Body Cartridges, part WAT047205, Waters, Milford, MA) using the sampling setup presented in Figure 1. All samples were collected in triplicate; i.e., three DNPH cartridges were collected for each liquid. To verify the collection efficiency of DNPH cartridges, several tests were carried out with two cartridges in series. No aldehydes were detected in the second cartridge, indicating quantitative collection of aldehydes. Blank measurements were performed before and after experiments and showed no presence of aldehyde.

Because some aldehydes measured in this study, such as benzaldehyde, could be found as flavoring compounds in liquids and not produced during vaping, we have tested the aldehyde content of liquids. An aliquot (100 μL) of e-liquid was directly run through a DNPH cartridge, which was then extracted in a manner similar to that used for cartridges collected during vaping. Using DNPH cartridges to collect aldehydes from liquids has been reported elsewhere.[12]

Sampled cartridges were eluted with 2 mL of acetonitrile [high-performance liquid chromatography (HPLC) grade,

DOI: 10.1021/acs.est.6b05145
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EMD Millipore Corp., Billerica, MA] within a few hours of sampling and analyzed with a HPLC system (Waters 2690 Alliance System with a model 996 photodiode array detector) equipped with a Polaris column (C18-A, 3 μm, 100 mm × 2.0 mm HPLC column, Agilent). The following HPLC parameters were used: flow rate of 0.2 mL min^{-1}, injection volume of 2 μL, solvent A of ultrapure water, and solvent B of acetonitrile. The HPLC gradient was as follows: 50% A and 50% B for 10 min, 30% A and 70% B for 8 min, and 100% B for 1 min. The run time was 31 min. The photodiode array detector was operated in the range of 210−400 nm. The detection wavelength was set to 360 nm. Full spectrum readings were used to verify the identity of individual compounds by comparing spectra of individual peaks with the spectra of calibration compounds (DNPH−aldehyde adducts). The HPLC response is calibrated in micrograms per milliliter with a certified calibration mixture purchased from AccuStandard Inc. (New Haven, CT) that contains all 12 DNPH species listed in Table S1. Six-point external calibration was run prior to analysis, and one calibration check was run every 24 h. If the response of an individual compound is more than 10% off, the system is recalibrated, which did not occur during this study. Calibration curves for all aldehydes were linear with R^2 values of >0.99. Recovery rates for 12 standard aldehydes were 94.1−109%. The limit of detection for analyzed free (as opposed to DNPH adducts) aldehydes varied between 0.003 and 0.01 μg mL^{-1} (Table S1). Given the elution volume of 2 mL and the total of two puffs collected per cartridge, this translated into minimal detection limits of 0.003−0.01 μg/puff.

To investigate whether flavoring additives affect aldehyde production during vaping, five flavored e-liquids per each device were tested. In addition to flavored e-liquids, brands I and III were tested with unflavored e-liquids provided by the manufacturers. Brand II did not provide unflavored e-liquids. The relative amount of PG and VG in e-liquids was reported to have an effect on aldehyde production.[6,7,12] To control for this variable, e-liquids for each e-cigarette brand had the same PG/VG ratio. No information about the concentration or composition of flavoring compounds was provided by any of the manufacturers.

To determine whether the concentration of flavoring compounds affects aldehyde production, a series of experiments were performed with Brand III using "bubblegum" e-liquid diluted with the unflavored e-liquid of the same manufacturer and the same PG/VG content; 25, 50, and 75% dilutions were tested in addition to undiluted "bubblegum" and the unflavored e-liquids.

All measured aldehyde concentrations were normalized to the amount of e-liquid consumed. For this purpose, the amount of e-liquid per puff was determined by weighing cartridges before and after each experiment and dividing the weight change by the number of puffs made during each experiment. The liquid consumption per puff is reported in Table S2.

RESULTS

Figure 2 shows aldehyde concentrations detected in e-liquids and in aerosols ("vapors") measured in this study. Among the tested brands, brand I produced the most aldehydes per liquid consumed (Figure 2) and per puff (Table S3) while brand II produced the least. There is anecdotal evidence that bottom coil construction is less prone to dry puffs, yet a bottom coil e-cigarette (brand I) produced the most aldehydes among the tested brands. This reflects the effect of power output on aldehyde production reported by other researchers, as brand I was the most powerful of the three tested brands (Table 1).

While a direct comparison with other studies is difficult because of the differences in e-cigarette construction, power setting, and e-liquid composition, amounts of aldehydes per puff observed in this study (Table S3) are in the range of or higher than those reported elsewhere.[8,9,12,15,22] For example, maximal formaldehyde emissions observed in this study are approximately 2−7 times lower than the steady-state emissions measured by Sleiman et al.,[9] who reported values ranging from 13000 to 48200 ng/mg. In terms of emissions per puff, our formaldehyde data [0.12−50 μg/puff (Table S3)] are comparable to values of 0.05−50 μg/puff reported by Gillman et al.[6] and 30−100 μg/puff reported by Sleiman et al.[9] Several earlier studies have reported significantly lower concentrations. Those studies, however, have used no warm-up puffs. As Sleiman et al. have shown,[9] the first few puffs significantly underestimate the actual emissions. This could be a reason for the low concentrations reported in those studies.

With the exception of benzaldehyde and tolualdehyde, common flavoring compounds, aerosols contained significantly more aldehydes per gram of e-liquid consumed than the liquids used to produce these vapors did. None of the flavored liquids contained formaldehyde, acetaldehyde, or acrolein. Aerosols produced by flavored liquids, however, contained large amounts of these toxic aldehydes. This clearly demonstrates that these aldehydes are formed not by evaporation but by chemical breakdown of e-liquid components. This is consistent with several previous studies.[6,7,9]

Remarkably, there is a significant variation in the amount and relative abundance of individual aldehydes in vapors within each brand. It should be kept in mind that for each e-cigarette brand, the e-cigarette coil construction and power are the same; the e-liquid carrier composition (i.e., the PG/VG ratio) was also kept constant within each brand. These parameters could not explain the observed variations. Thus, the observed variations in emissions of individual aldehydes observed within each brand are not due to pyrolysis of carrier e-liquids (PG and VG). The only variable within one e-cigarette brand is the type of e-liquid flavor. This strongly suggests that flavoring compounds contribute to the production of aldehydes during vaping.

A comparison of aldehyde concentrations found in flavored and unflavored vapors shows that, in fact, decomposition of flavoring compounds dominates production of aldehydes during vaping. Unflavored brand I e-liquid produced detectable amounts of only glyoxal (2.53 ± 1.16 μg/g of e-liquid) and benzaldehyde (6.77 ± 1.05 μg/g of e-liquid); 11 other aldehydes were not detected (ND). In contrast, flavored brand I e-liquids produced large amounts of formaldehyde (5570 ± 330 to 7210 ± 410 μg/g of e-liquid), acetaldehyde (2670 ± 600 to 3640 ± 750 μg/g of e-liquid), acrolein (172 ± 27 to 347 ± 37 μg/g of e-liquid), glyoxal (64.2 ± 14.3 to 146 ± 18 μg/g of liquid), propionaldehyde (320 ± 10 to 518 ± 89 μg/g of e-liquid), and benzaldehyde (ND to 176 ± 7 μg/g of e-liquid). Brand III unflavored e-liquid produced formaldehyde (159 ± 54 μg/g of e-liquid), glyoxal (46.0 ± 14.5 μg/g of liquid), and acetaldehyde (26.9 ± 9.49 μg/g of e-liquid). Brand III flavored e-liquids produced formaldehyde (176 ± 18 to 4400 ± 200 μg/g of e-liquid), acetaldehyde (58.4 ± 1.1 to 3880 ± 1080 μg/g of e-liquid), acrolein (ND to 237 ± 61 μg/g of e-liquid), glyoxal (22.0 ± 3.4 to 455 ± 74 μg/g of e-liquid), propionaldehyde (ND to 722 ± 204 μg/g of e-liquid), and

DOI: 10.1021/acs.est.6b05145
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benzaldehyde (ND to 58.8 ± 3.2 μg/g of e-liquid). Because unflavored e-liquids produced relatively "clean" vapors, the large amounts of aldehydes found in flavored vapors must be due to pyrolysis of flavoring compounds.

It should be noted that our results do not suggest that PG or VG produces no aldehydes, but that flavoring compounds are responsible for the main part of the emitted toxic aldehydes. Nondetects for unflavored liquids reported in this study are likely due to the small number of puffs that we have used in our measurements. By collecting more puffs per measurement, we could have quantified emissions for unflavored liquids. This quantification, however, is of minor consequence, as the flavored liquids produce significantly more aldehydes than unflavored ones do.

To the best of our knowledge, only two studies have reported emissions from both flavored and unflavored liquids. Kosmider et al.[12] measured both flavored commercially available liquids and liquids containing only PG, VG, water, and nicotine. With the exception of butanal, detectable aldehyde concentrations were found only in flavored liquids. Gillman et al.[6] used 48% (w/w) PG and glycerin with 2% nicotine; it is not clear what the remaining 2% consisted of. For an atomizer that was identical to our brand III e-cigarette, but operated at a higher power setting (5.3 W), they reported formaldehyde emissions of 8.5 ± 8.9 μg/puff. Formaldehyde emissions from unflavored liquid measured in our study are 0.64 ± 0.22 μg/puff. Given the very large uncertainty in the data of Gillman et al. and the sample size (six) used in that study, the difference from our data is not statistically significant.

To provide further proof that flavoring compounds, not the carrier e-liquid (PG and/or VG), dominate production of aldehydes during vaping, we have performed a series of experiments in which a flavored brand III e-liquid ("bubblegum") was diluted with different amounts of the unflavored brand III e-liquid. Amounts per puff of formaldehyde, acetaldehyde, acrolein, and propionaldehyde as a function of the volume fraction of the flavored e-liquid are shown in Figure 3. Aldehyde concentrations increase exponentially with the concentration of flavoring compounds. While the reason for the superlinear relationship is not clear, it emphasizes the dominant effect of flavoring compounds on aldehyde concentration in e-cigarette vapors.

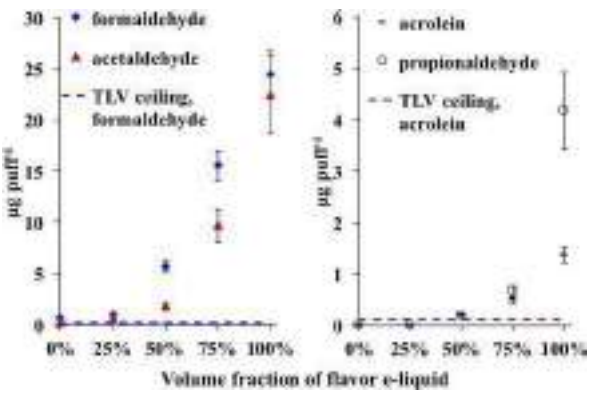

Figure 3. Amounts of formaldehyde, acetaldehyde, acrolein, and propionaldehyde as a function of flavored e-liquid volume fraction after dilution with unflavored e-liquid. Also shown are TLV ceiling levels for formaldehyde and acrolein, assuming each puff is diluted in 500 mL of air (a typical lung tidal volume). Error bars represent one standard deviation of triplicate measurements (N = 3).

It should be stressed that the amount of aldehydes produced by pyrolysis of flavoring compounds is dangerously large. The American Conference of Governmental Industrial Hygienists (ACGIH) establishes Threshold Limit Values (TLVs) for various hazardous chemicals. The ACGIH defines the threshold limit value-ceiling (TLV-C) as the concentration that should not be exceeded during any part of the working exposure,[23] thus representing a limit to instantaneous, not time-averaged, exposure. For formaldehyde, the TLV-C is 0.3 mg m^{-3}, and for acrolein, it is 0.23 mg m^{-3}. To compare exposure to these aldehydes from one puff, we have divided the amount per puff by 500 mL, the average tidal volume of a healthy adult.[24]

All flavored brand I vapors exceeded the ACGIH formaldehyde ceiling level by factors of 190−270 and the acrolein ceiling level by factors of 11−24, depending on the flavor used. Three of five liquids of brand II vapors exceeded the formaldehyde ceiling level by 2.0−13-fold, depending on the e-liquid flavor. No acrolein was detected in brand II vapors. All flavored brand III vapors exceeded the formaldehyde ceiling level by 2.9−66-fold. Four of brand III flavored vapors exceeded the acrolein ceiling by 1.5−6.0-fold, while no acrolein was detected in one of the liquids ("tutti fruity"). In other words, one puff of any of the tested flavored e-cigarette liquids exposes the smoker to unacceptably dangerous levels of these aldehydes, most of which originates from thermal decomposition of flavoring compounds.

In summary, our observations demonstrate that thermal decomposition of flavoring compounds is the main source of aldehydes in vapors produced by e-liquids tested in this study. These results demonstrate the need for a further thorough study of the contribution of flavoring additives to the formation of aldehydes and other toxic compounds in e-cigarette vapors. A study of the thermal behavior of individual flavoring compounds was beyond the scope of this paper and is part of a larger ongoing study, which also includes other decomposition products in addition to aldehydes. The dependence of toxic emissions on flavor concentration in e-liquids is another facet that needs attention. The results of our experiments indicate an exponential dependence of aldehyde emission strength on the concentration of flavoring compounds. For example, by diluting the flavored liquid by a factor of 4 in our experiments, we decreased the acrolein concentration below the TLV-C level (Figure 3). A better understanding of this dependence could offer a way to reduce the toxicity of vapors by controlling concentrations of flavoring compounds in e-liquids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.6b05145.

Information about detection limits per compound, the average liquid consumption for each of the tested flavors, and a table with aldehyde concentrations per puff for each of the e-cigarette brands and e-liquids tested in this study (PDF)

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Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.est.6b05145
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■ ACKNOWLEDGMENTS

This work has been carried out with Desert Research Institute (DRI) internal funding. We thank Anna Cunningham of DRI for technical assistance with chemical analysis of collected samples. We also thank Dr. Marc Pitchford of DRI and Dr. Jeffrey E. Angermann, Dr. Matthew Strickland, and Dr. Lyndsey Darrow of the University of Nevada, Reno (Reno, NV), for their useful suggestions during the preparation of the manuscript.

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DOI: 10.1021/acs.est.6b05145
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

SUPPORTING INFORMATION

Flavoring Compounds Dominate Toxic Aldehyde Production During E-cigarette Vaping

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3 pages, 3 tables

Supplemental information

Tables

Table S1. Minimum detection limits for HPLC determination of free aldehydes.

Aldehyde	***MDL, μg/mL***
formaldehyde	0.009
acetaldehyde	0.007
acrolein	0.01
propionaldehyde	0.013
crotonaldehyde	0.008
methacrolein	0.008
n-butyraldehyde	0.009
benzaldehyde	0.009
valeraldehyde	0.011
glyoxal	0.003
m-tolualdehyde	0.008
hexaldehyde	0.007

Table S2. Average liquid consumption per puff for e-cigarette brands and e-liquids tested in this study. Liquid consumption within triplicate measurements did not vary by more than 20%.

Brand	***Flavor***	***Liquid consumption, mg/puff***
Brand I	Watermelon	7.85
	Gummy Bear	6.25
	Blueberry	7.627
	Irish Cream	7.027
	Dragon's Cafe	6.38
	No flavor	13.85
Brand II	Peppermint	6.19
	Menthol	4.6
	Congress	5.138
	Sahara	3.06
	Red Tobacco	2.456
Brand III	Bubble Gum	5.785
	Pina Colada	6.115
	Blueberry	5.988
	Tutti Frutti	6.117
	Caramel Mocha	3.319
	No flavor	4.04

Table S3. Concentration of aldehydes (units: μg puff^{-1}) in e-cigarette emissions from three e-cigarette devices, n/a – e-liquid was not available; ND – not detected (below detection limit); each sample was collected and analyzed in triplicates (N=3)

Aldehyde	***Flavors (concentration level in vapor emission)***					
Brand I	***No flavor***	***Watermelon***	***Gummy Bear***	***Blueberry Pomegranate***	***Kahlua & Irish Cream***	***Dragon Café***
formaldehyde	ND	49.5±3.2	34.8±2.1	43.8±6.6	41.57±4.5	46.0±2.6
acetaldehyde	ND	20.9±4.7	19.5±2.1	27.7±5.7	22.79±3.3	18.63±2.5
acrolein	ND	2.72±0.29	1.45±0.06	1.31±0.21	1.91±0.38	2.05±0.13
propionaldehyde	ND	3.44±0.72	2.38±0.59	3.28±0.83	3.64±0.62	2.04±0.08
crotonaldehyde	ND	ND	ND	ND	ND	ND
methacrolein	ND	ND	ND	ND	ND	ND
butyraldehyde	ND	ND	ND	ND	ND	ND
benzaldehyde	0.09±0.01	ND	1.10±0.05	0.15±0.05	0.06±0.02	0.13±0.10
glyoxal	0.04±0.02	0.50±0.11	0.40±0.06	0.60±0.16	0.54±0.10	0.93±0.79
valeraldehyde	ND	ND	ND	ND	ND	ND
m-tolualdehyde	ND	ND	0.15±0.10	ND	ND	ND
hexanaldehyde	ND	ND	ND	ND	ND	ND
Brand II	***No flavor***	***Sahara***	***Red Tobacco***	***Peppermint***	***Menthol***	***Congress***
formaldehyde	n/a	0.12±0.01	2.41±0.58	0.37±0.07	1.14±0.03	ND
acetaldehyde	n/a	ND	2.95±0.82	ND	0.60±0.06	ND
acrolein	n/a	ND	ND	ND	ND	ND
propionaldehyde	n/a	0.038±0.012	0.40±0.07	ND	0.080±0.003	ND
crotonaldehyde	n/a	ND	ND	ND	ND	ND
methacrolein	n/a	ND	ND	ND	ND	ND
butyraldehyde	n/a	ND	ND	ND	ND	ND
benzaldehyde	n/a	ND	ND	0.51±0.01	0.28±0.01	0.26±0.02
glyoxal	n/a	0.035±0.021	0.22±0.07	0.15±0.02	0.17±0.03	0.23±0.04
valeraldehyde	n/a	ND	ND	ND	ND	ND
m-tolualdehyde	n/a	ND	ND	0.030±0.001	0.012±0.005	ND
hexanaldehyde	n/a	ND	ND	ND	ND	ND
Brand III	***No flavor***	***Bubble Gum***	***Pina Colada***	***Blueberry***	***Tutti Fruity***	***Caramel Mocha***
formaldehyde	0.64±0.22	24.4±2.3	8.34±1.54	4.27±0.16	1.08±0.11	14.6±0.7
acetaldehyde	0.11±0.04	22.5±6.2	5.67±0.75	1.35±0.13	0.36±0.01	6.88±0.38
acrolein	ND	1.37±0.35	0.80±0.49	0.34±0.22	ND	0.76±0.03
propionaldehyde	ND	4.18±1.18	0.88±0.31	0.32±0.06	ND	0.59±0.04
crotonaldehyde	ND	ND	ND	ND	ND	ND
methacrolein	ND	ND	ND	ND	ND	ND
butyraldehyde	ND	ND	ND	ND	ND	ND
benzaldehyde	ND	ND	0.036±0.002	0.15±0.01	0.091±0.008	ND
glyoxal	0.19±0.06	0.85±0.16	0.92±0.07	0.54±0.05	0.14±0.02	1.51±0.25
valeraldehyde	ND	ND	ND	ND	ND	ND
m-tolualdehyde	ND	ND	ND	ND	ND	ND
hexanaldehyde	ND	ND	ND	ND	ND	ND

Otolaryngology: Open Access

Nguyen et al., Otolaryngol (Sunnyvale) 2017, 7:2
DOI: 10.4172/2161-119X.1000304

Case Report Open Access

Oral Carcinoma Associated with Chronic Use of Electronic Cigarettes

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Received date: April 14, 2017; **Accepted date:** April 19, 2017; **Published date:** April 26, 2017

Abstract

The electronic cigarette (E-cigarette) is a handheld electronic device that vaporizes a nicotine-containing fluid for inhalation. Invented in 2003 by Chinese pharmacist Hon Lik, the E-cigarette was developed as a substitute for tobacco cigarettes. The use of E-cigarettes continues to grow in popularity in most parts of the world, and many consider their use and the use of other electronic nicotine delivery systems (ENDS) to be healthier than smoking tobacco cigarettes. There is a paucity of medical research, however, to support that notion. In particular, the impact of chronic use of E-cigarettes and ENDS has not been studied adequately. Herein, we report two cases of oral carcinoma associated with chronic use of E-cigarettes. These highlight the need for increased awareness of this important, and potentially fatal, risk. Physicians, dentists and other health care providers must be made aware and should consider regularly-scheduled, comprehensive oral examinations of their patients that regularly use E-cigarettes or ENDS. In the United States, the Food and Drug Administration (FDA) collects adverse effect and safety data at their Safety Reporting Portal for Tobacco Products (https://www.fda.gov/TobaccoProducts/PublicHealthScienceResearch). Adverse effects suspected to be related to the use of E-cigarettes or ENDS should be reported to the FDA or to analogous regulatory governances in other countries.

Keywords: E-cigarette; Electronic cigarette; Electronic nicotine delivery systems; ENDS; Oral carcinoma; Oral cancer; Squamous cell carcinoma

Introduction

Hookah pens, vaporizers, vape pens, E-cigarettes and E-pipes are some of the many type of Electronic Nicotine Delivery Systems (ENDS). In addition to liquid containing nicotine, propylene glycol, glycerin, flavorings and water are vaporized into an aerosol that the user inhales [1-4]. Many ENDS are commercial manufactured to look like conventional cigarettes or cigars, but some are manufactured to resemble everyday items (e.g. pens), and other types of ENDS (e.g. hookah devices) bear no resemblance to cigarettes or cigars. Claims that ENDS contain "only water vapour and nicotine" are false: the vapour has been found to contain varying amounts of heavy metals (Nickel, Tin, Silver, Aluminum, Mercury and Chromium) as well as carbonyls and other organic volatile compounds [4].

Herein we describe two cases of oral carcinoma associated with chronic E-cigarette use in otherwise healthy individuals. In both cases, their use of E-cigarettes began in 2003 and continued for more than 10 years. Neither patient had a family history of oral carcinoma nor did either have a history of known risk factors for oral carcinoma (e.g. hematopoietic stem-cell transplant, chronic heavy alcohol consumption, smoking or Human Papilloma Virus infection) [5,6]. Neither patient had diagnoses of acute or chronic oral infections caused by other microorganisms (e.g. fungi, bacteria, virus). Neither patient had a history of consumption/chewing of tobacco, paan (betel leaf mixed with areca nut) or other leaf types. Importantly, both presented with the same triad of symptoms - unintended weight loss, dry mouth, and difficulty swallowing. As the popularity of E-cigarettes and ENDS continues to increase across the world, health care providers need to be aware of the possible increased risk of oral carcinoma [6].

Case Reports

Case 1

A 66-year-old male presented to the out-patient office (otolaryngology) with chief complaints of unintended weight loss, dysphagia and xerostomia. His immunization records were up to date for Human Papilloma Virus, Varicella Zoster Virus and Hepatitis B Virus. His past medical history was unremarkable other than a social history positive for use of E-cigarettes (20 times per day for past 13 years). Examination of the oral cavity was consistent with xerostomia, and there were several areas of induration and paresthesia of the tongue. Several exophytic masses were present with surrounding hyperkeratotic areas with histological features of lichen planus. As infection or carcinoma were the chief suspects, the following clinical laboratory tests were ordered: complete blood count; complete blood chemistry panel; and blood calcium, liver enzymes, ferritin, urea, alpha-antitrypsin and alpha-anti-glycoprotein levels. Importantly, increased levels of serum ferritin, alpha-antitrypsin, and alpha-anti-glycoprotein are often associated with later stages of oral cancer. A tissue biopsy was performed and reported as follows: A small piece of tissue was cut from an abnormal paraesthesia, keratotic region at the anterior aspect of the tongue. This incisional biopsy was taken at the office, and neither general anesthesia nor localized anesthesia were needed. The removed tissue was cut into thin sections, placed on slides and stained before further processing to "frozen section" and "permanent section". Histopathology revealed a moderately

collagenous connective tissue stroma infiltrated with nests and islands of tumor epithelial cells. The tumor cells exhibited a basaloid appearance with hyperchromatic nuclei and scanty cytoplasm and were arranged in a lobular configuration. Occasional squamous differentiation was also noted and a large number of mitotic figures with nuclear atypia were observed. A diagnosis of basaloid squamous cell carcinoma was given. Oncologist was notified to follow-up.

Case 2

A 59-year-old male presented to an out-patient otolaryngology office with a chief complaint of a 9-month history of a non-healing ulceration of the lower lip. No pain or discomfort was reported by the patient, but the patient reported having some difficulty swallowing and severe dry mouth. No history of trauma to the area was reported and the patient denied a history of alcohol use. The patient reported consistent, routine dental care throughout his life but reported that he had smoked 30 E-cigarettes per day for the past 13 years. The patient's health history was otherwise unremarkable. Other than an ulcerative lesion (1-cm in diameter) on the vermilion of the lower lip, examination of the head and neck region was without abnormalities. Vitals signs were within normal limits, and no palpable lymph nodes were detected. No other abnormal extra oral findings were noted, and palpation of the lesion revealed induration at the periphery of the lesion. Basal squamous cell carcinoma was suspected, and the following clinical laboratory tests were ordered: complete blood count; complete blood chemistry panel; and blood calcium, liver enzymes, ferritin, urea, alpha-antitrypsin and alpha-anti-glycoprotein levels. Again, it is important to note that increased levels of serum ferritin, alpha-antitrypsin and alpha-anti-glycoprotein are often associated with later stages of oral cancer. An incisional tissue biopsy was examined for histologic analysis, and histopathological examination revealed a dysplastic stratified squamous epithelium infiltrating into underlying moderately collagenous connective tissue. The infiltrating tumor cells had a basaloid appearance. Nuclear atypia was observed and pleomorphisms with large numbers of mitotic figures were noted. A diagnosis of basaloid squamous cell carcinoma was made, and an Oncologist was scheduled for follow-up.

Summary

Clinical findings

Oral cancer may occur on the floor of the mouth, the lining of the cheek, the gingiva (gums), the lips or the palate (roof of the mouth) [7]. Early-stage symptoms can include persistent red or white patches, a non-healing ulcer, progressive swelling or enlargement, unusual surface changes, sudden tooth mobility without apparent cause, unusual oral bleeding or epitaxis and prolonged hoarseness. Late-state symptoms can include induration of affected areas(s), paresthesia/dysesthesia of the tongue or lips, airway obstruction, chronic serous otitis media, dysphagia, cervical lymphadenopathy, ánd persistent pain. Oral cavity cancers can manifest as a red lesion (erythroplakia), a granular ulcer with fissuring or raised exophytic margins, a non-healing extraction socket or as a lesion fixed to deeper tissues [8].

Laboratory findings

A diagnosis of oral cancer is confirmed by tissue-biopsy microscopy. As more than 90% of oral cancers are squamous cell carcinoma, a FOXM1-based diagnostic test, quantitative malignancy diagnostic system (qMIDS), is used to confirm diagnosis and quantify the aggressiveness of squamous cell carcinomas [9,10]. Bacterial identification testing also has some predictive value: *C. gingivalis*, *P. melaninogenica* and *S. mitis* have a predictive value of about 80% for oral squamous cell carcinoma. About 5% of oral cancer are verrucous carcinoma, a very slow-growing cancer also comprised of squamous cells and the remainder (<5%) of oral carcinomas are either minor salivary gland carcinoma or lymphoma [9,10].

Treatment

Surgical excision can be curative for oral cancers limited in size. Inoperable tumors are treated with radiation +/- chemotherapy, and more definitive treatment often combines these with surgery (e.g. maxillectomy, mandibulectomy, glossectomy and radical neck dissection) [8].

Pathophysiology

Tobacco is a known risk factor for oral cancer, and about 80% of patients with oral cancers have a history of smoking or chewing tobacco. An interaction between redox-active metals in saliva and the low reactive free radicals in tobacco smoke that results in saliva losing much of its antioxidant capacity [8]. Other known risk factors include gender (males are twice as likely as females to develop oral cancer), routine alcohol consumption (70% of patients with oral cancer regularly consume alcohol), chewing betal quid (a leaf from the betel plant wrapped around areca nut and lime) combined or without tobacco, human papilloma viruses (HPV) infection (about 25% of patients with oral cancer have HPV, particularly HPV-16), immune-system suppression, lichen planus infection (itchy rash +/- white lines or spots in oral cavity) and graft-verse-host disease (secondary to stem-cell transplant) [3,6,9].

Discussion

Nicotine solutions commercially available for use with ENDS and E-cigarettes can contain up to 100mg/mL of nicotine (as little as 1mg of nicotine can cause symptoms in a toddler and 6 to 13 mg/kg can be lethal in toddlers) [4]. In addition to nicotine, diethylene glycol, ethylene glycol, ethanol, formaldehyde, acrolein and various amounts of heavy metals (nickel, tin, silver, aluminum, mercury and chromium) comprise the inhaled vapour [4]. The effects of chronic exposure to these chemicals are unknown but should not be considered benign (several have known toxicity). Patients seeking smoking cessation should consider approved nicotine replacement delivers products (gums, patches, lozenges) instead of the use of E-cigarettes or ENDS.

Conclusion

Tobacco cigarette smoking is a known risk for cancers, including oral cancer. Patients and clinicians (physicians, dentist and nurses) need to be aware that the use of electronic-cigarettes (E-cigarettes) or other electronic nicotine delivery systems (ENDS) may also be associated with an increased risk of oral cancer. Here we describe two patients, with positive history for chronic E-cigarette use, that developed oral cancer without any identifiable risk factors other than E-cigarette use. Further investigation is warranted.

Acknowledgement

The authors are thankful to faculty and staff members at the Departments of Otolaryngology and Obstetrics & Gynecology at Ho Chi Minh City School of Medicine and Pharmacy (Ho Chi Minh City, Vietnam) and at the Ohio State University Department of Biological Chemistry and Pharmacology (Columbus, Ohio, USA).

Funding

None

Conflict of Interest

None

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E-cigarette smoke damages DNA and reduces repair activity in mouse lung, heart, and bladder as well as in human lung and bladder cells

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Edited by Bert Vogelstein, Johns Hopkins University, Baltimore, MD, and approved December 20, 2017 (received for review October 17, 2017)

E-cigarette smoke delivers stimulant nicotine as aerosol without tobacco or the burning process. It contains neither carcinogenic incomplete combustion byproducts nor tobacco nitrosamines, the nicotine nitrosation products. E-cigarettes are promoted as safe and have gained significant popularity. In this study, instead of detecting nitrosamines, we directly measured DNA damage induced by nitrosamines in different organs of E-cigarette smoke-exposed mice. We found mutagenic O^6-methyldeoxyguanosines and γ-hydroxy-1,N^2-propano-deoxyguanosines in the lung, bladder, and heart. DNA-repair activity and repair proteins XPC and OGG1/2 are significantly reduced in the lung. We found that nicotine and its metabolite, nicotine-derived nitrosamine ketone, can induce the same effects and enhance mutational susceptibility and tumorigenic transformation of cultured human bronchial epithelial and urothelial cells. These results indicate that nicotine nitrosation occurs in vivo in mice and that E-cigarette smoke is carcinogenic to the murine lung and bladder and harmful to the murine heart. It is therefore possible that E-cigarette smoke may contribute to lung and bladder cancer, as well as heart disease, in humans.

E-cigarettes | DNA damage | DNA repair | lung–bladder–heart | cancer

E-cigarettes (E-cigs) are designed to deliver the stimulant nicotine, similar to conventional cigarettes, through an aerosol state. In E-cigs, nicotine is dissolved in relatively harmless organic solvents, such as glycerol and propylene glycol, then aerosolized with the solvents by controlled electric heating. Hence, E-cig smoke (ECS) contains mostly nicotine and the gas phase of the solvents (1–4). In contrast, conventional tobacco smoke (TS), in addition to nicotine and its nitrosamine derivatives, contains numerous (>7,000) incomplete combustion byproducts, such as polycyclic aromatic hydrocarbons (PAHs), aromatic amines, aldehydes, and benzene, many of which are human carcinogens, irritants, and allergens (5, 6). TS also has a strong scent. Therefore, TS is both harmful and carcinogenic to smokers, as well as being unpleasant and harmful to bystanders (7). Because of these effects, TS has become an unwelcome social habit and is no longer acceptable in many social settings and public domains (8). E-cigs have been promoted as an alternative to cigarettes that can deliver a TS "high" without TS's ill and unpleasant effects. Since it appears that ECS contains neither carcinogens, allergens, nor odors that result from incomplete combustion, as a result of these claims, E-cigs have become increasingly popular, particularly with young people (9). However, the question as to whether ECS is as harmful as TS, particularly with regard to carcinogenicity, remains a serious public health issue that deserves careful examination.

It is well established that most chemical carcinogens, either directly or via metabolic activation, can induce damage in genomic DNA, that unrepaired DNA damage can induce mutations, and that multiple mutations can lead to cancer (10). Many chemical carcinogens can also impair DNA-repair activity (11–13). Therefore, in this study, as a step to understanding the carcinogenicity of ECS, we determined whether ECS can induce DNA damage in different organs of a mouse model and whether ECS can affect DNA-repair activity. We then characterized the chemical nature of ECS-induced DNA damage and how ECS affects DNA repair. Last, we determined the effect of ECS metabolites on the susceptibility to mutations and tumorigenic transformation of cultured human cells.

Results

ECS Induces O^6-Methyl-Deoxuguanosine in the Lung, Bladder, and Heart. Nicotine is the major component of ECS (3). The majority (80%) of inhaled nicotine in smoke is quickly metabolized into cotinine, which is excreted into the bloodstream and subsequently into urine (14). Cotinine is generally believed to be nontoxic and noncarcinogenic (15); however, a small portion (<10%) of inhaled nicotine is believed to be metabolized into nitrosamines in vivo (16–18). Nitrosamines induce tumors in different organs in animal models (6, 19). Inhaled nitrosamines are metabolized into *N*-nitrosonornicotine (NNN) and nicotine-derived nitrosamine ketone (NNK). It has been proposed that NNK can be further metabolized and spontaneously degraded

Significance

E-cigarette smoke (ECS) delivers nicotine through aerosols without burning tobacco. ECS is promoted as noncarcinogenic. We found that ECS induces DNA damage in mouse lung, bladder, and heart and reduces DNA-repair functions and proteins in lung. Nicotine and its nitrosation product 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone can cause the same effects as ECS and enhance mutations and tumorigenic cell transformation in cultured human lung and bladder cells. These results indicate that nicotine nitrosation occurs in the lung, bladder, and heart, and that its products are further metabolized into DNA damaging agents. We propose that ECS, through damaging DNA and inhibiting DNA repair, might contribute to human lung and bladder cancer as well as to heart disease, although further studies are required to substantiate this proposal.

Author contributions: H.-W.L., S.-H.P., M.-w.W., H.-T.W., L.-C.C., and M.-s.T. designed research; H.-W.L., S.-H.P., M.-w.W., H.-T.W., and M.-s.T. performed research; M.-s.T. contributed new reagents/analytic tools; H.-W.L., S.-H.P., M.-w.W., W.C.H., H.L., X.-R.W., and M.-s.T. analyzed data; and H.-W.L., S.-H.P., M.-w.W., H.-T.W., W.C.H., H.L., X.-R.W., L.-C.C., and M.-s.T. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

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This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1718185115/-/DCSupplemental.

into methyldiazohydroxide (MDOH), pyridyl-butyl derivatives (PBDs), and formaldehyde, and that NNN degrade into hydroxyl or keto PBDs (20). While nicotine cannot bind to DNA directly, MDOH can methylate deoxyguanosines and thymidines in DNA (21). Although the fate of nitrosamine-induced formaldehyde and PBDs in vivo is less clear, both are capable of inducing DNA damage in vitro (22–25). Therefore, if ECS in fact is a carcinogen, it is likely that its carcinogenicity is derived from nitrosamines that are derived from the nitrosation of nicotine (5, 19, 21). Nitrosamines are potent carcinogens and it is generally believed that their carcinogenicity is via induction of methylation DNA damage (26, 27). As a step in examining the carcinogenicity of ECS, we determined whether ECS can induce O^6-methyl-deoxuguanosine (O^6-medG) adducts in lung, heart, liver, and bladder tissues of mice. Mice were exposed to ECS (10 mg/mL, 3 h/d, 5 d/wk) for 12 wk; the dose and duration equivalent in human terms to light E-cig smoking for 10 y. The results in Fig. 1 *A* and *B*, Fig. S1, and Table S1 show that ECS induced significant amounts of O^6-medG adducts in the lung, bladder, and heart and that the level of O^6-medG adducts in lung was three- to eightfold higher than in the bladder and heart. These results are consistent with the explanation that nicotine is metabolized into MDOH, which can methylate DNA (16, 20).

ECS Induces γ-OH-PdG in the Lung, Bladder, and Heart. Recently, we found that aldehyde-derived cyclic 1,N^2-propano-dG (PdG), including γ-OH-1,N^2-PdG (γ-OH-PdG) and α-methyl-γ-OH-1,N^2-PdG adducts, are the major DNA adducts in mouse models (28) induced by TS, which contains abundant nitrosamines and aldehydes (20). We therefore determined the extent of PdG formation in different organs of ECS-exposed mice using a PdG-specific antibody (28–30).

The results in Fig. 1 *C* and *D* show that ECS induced PdG adducts in the lung, bladder, and heart, and that the level of PdG in the lung is two- to threefold higher than in the bladder and heart. Moreover, the level of PdG is 25- to 60-fold higher than the level of O^6-medG in lung, bladder, and heart tissues, indicating that induction of PdG is more efficient than induction of O^6-medG by nicotine metabolic products and/or that O^6-medG is more efficiently repaired in these organs. ECS, however, did not induce either O^6-medG or PdG in liver DNA.

Due to the relatively minute amount of genomic DNA that is possible to isolate from mouse organs, in this case, specifically from bladder mucosa, which is only able to yield up to 2 μg of genomic DNA from each mouse, we used the sensitive ^{32}P-postlabeling thin layer chromatography (TLC)/HPLC method to identify the species of the PdG formed in lung and bladder tissues (13, 28, 31). The results in Fig. 1*E* show that the majority of PdG (>95%) formed in these tissues coelute with γ-OH-PdG adduct standards with a minor portion that coelute with α-OH-PdG standards.

Relationship of ECS-Induced PdG and O^6-medG Formation in Different Organs of Each Animal. We then determined the relationship of PdG and O^6-medG formation in different organs of each animal. The results in Fig. 2*A* show that the levels of PdG and O^6-medG in the same organs are positively related to each other. Thus, a lung tissue sample that had a high level of PdG also had a high level of O^6-medG. The same relationship between PdG and O^6-medG formation was found in the bladder and heart (Fig. 2*A* and Table S1). The results in Fig. 2*B* show that in the same mouse, the levels of PdG and O^6-medG formation in different organs also have a positive correlation: Mice with a high level of PdG and O^6-medG formation in the lung also had a high level of these DNA adducts in the bladder and heart (Fig. 2*B* and Table S1). Together, these results indicate that the formation of PdG and O^6-medG DNA adducts in the lung, bladder, and heart tissue are the result of DNA damaging agents derived from ECS exposure, and raising the possibility that the ability for nicotine absorption and metabolism and DNA-repair activity of different organs determine their susceptibility to ECS-induced DNA adduct formation.

ECS Reduces DNA-Repair Activity in the Lung. Recently, we have found that lung tissues of mice exposed to TS have lower DNA-repair activity and lower levels of DNA-repair proteins XPC and OGG1/2 and that aldehydes, such as acrolein, acetaldehyde, crotonaldehyde, and 4-hydroxy-2-nonenal, can modify DNA-repair proteins, causing the degradation of these repair proteins and impairing DNA-repair function (11, 12, 28). These findings raise the possibility that, via induction of aldehydes, ECS can impair DNA-repair functions. To test this possibility, we determined the effect of ECS on the activity of the two major DNA-repair mechanisms in mouse lung tissues: nucleotide excision repair (NER) and base excision repair (BER) (32). We adopted a well-established in vitro DNA damage-dependent repair synthesis assay, which requires only 10 μg of freshly prepared cell lysates (11, 13, 28). Since the amount of bladder mucosa collected from individual mice was minute, we were only able to determine DNA-repair activity in lung tissues (28). We used UV-irradiated DNA, which contains cyclobutane pyrimidine dimers as well as <6-4> photoproducts; Acr-modified DNA, which contains γ-OH-PdG; and H_2O_2-modified DNA, which contains 8-oxo-dG, as substrates (13, 28). It is well established that NER is the major mechanism that repairs cyclobutane pyrimidine dimers, <6-4> photoproducts, and γ-OH-PdG, and that BER is the major mechanism that repairs 8-oxo-dG (32, 33). Therefore, these two types of substrates allow us to determine the NER and BER activity in the cell lysates (11, 13). The results in Fig. 3 *A* and *B* and Fig. S2 show that both NER and BER activity in lung tissue of ECS-exposed mice are significantly lower than in lung tissue of filtered air (FA)-exposed mice.

ECS Causes a Reduction of Repair Protein XPC and OGG1/2. We then determined the level of XPC and OGG1/2, the two crucial proteins, respectively, for NER and BER (34, 35). The results in Fig. 3*C* show that the level of XPC and OGG1/2 in lung tissues of ECS-exposed mice was significantly lower than in control mice. We further determined the relationship between DNA adduct formation and DNA-repair activity in lung tissues of FA- and ECS-exposed mice. Since NER is the major repair mechanism for bulky DNA damage such as γ-OH-PdG and photodimers (11, 33) and BER is a major repair mechanism for base damage (32), we compared BER activity with the level of O^6-medG adducts and NER activity with the level of γ-OH-PdG adducts. The results in Fig. 3*D* show that NER and BER activity in lung tissue of different mice is inversely related to the level of γ-OH-PdG and O^6-medG adducts, respectively. These results indicate that in lung tissue, NER and BER activities are crucial factors in determining the level of ECS-induced γ-OH-PdG and O^6-medG DNA damage; mice that are more sensitive to ECS-induced DNA-repair inhibition accumulate more ECS-induced DNA damage in their lung and, perhaps, bladder and heart. It should be noted that in human cells, repair of O^6-medG adducts is mainly carried out by *O*^{6}-methylguanine DNA methyltransferase (MGMT) (36, 37). The positive relationship between BER activity and the O^6-medG level in lung tissues of mice implies that ECS impairs BER enzymes as well as MGMT, and/or O^6-medG is repaired by a BER mechanism in mice.

Nicotine Induces DNA Damage in Human Cells. Many tobacco-specific nitrosamines that result from the nitrosation of nicotine, such as NNN and NNK, are potent carcinogens and can induce cancer in different organs, including the lung (20, 21, 27). While NNK and NNN cannot covalently bind with DNA directly,

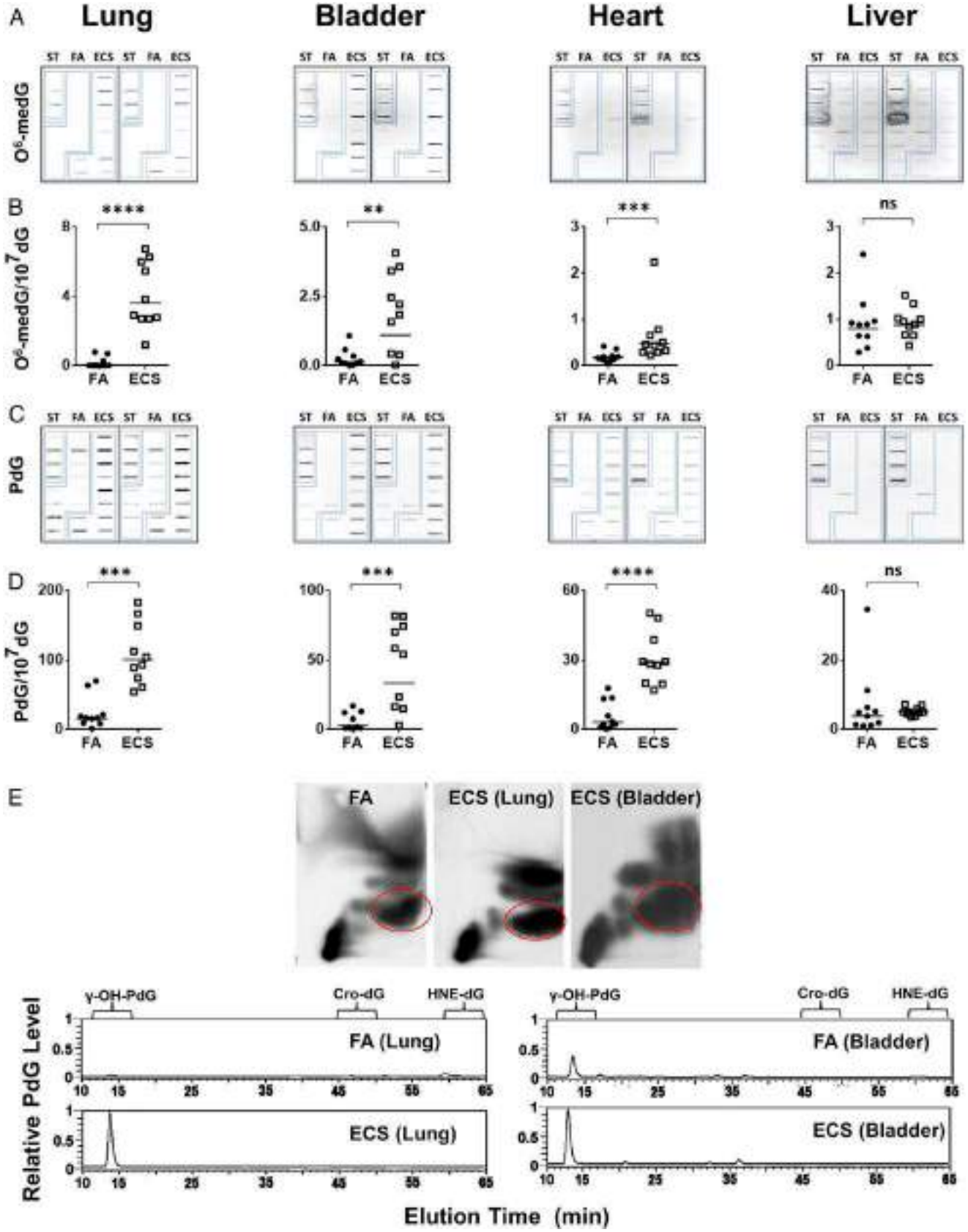

Fig. 1. ECS induces γ-OH-PdG and O^6-medG adducts in the lung, bladder and heart. Genomic DNA were isolated from different organs of mice exposed to FA or ECS as described in text. (*A*–*D*) O^6-medG and PdG formed in the genomic DNA were detected by immunochemical methods (28). (*A* and *C*) Slot blot. (*B* and *D*) Quantification results. The bar represents the mean value. (*E*) Identification of γ-OH-PdG adducts formed in the genomic DNA of lung and bladder by the 2D-TLC (*Upper*) and then HPLC (*Lower*) (28). ST, PdG, or O^6-medG standard DNA. ****$P < 0.0001$, ***$P < 0.001$, **$P < 0.01$, and *$P < 0.05$.

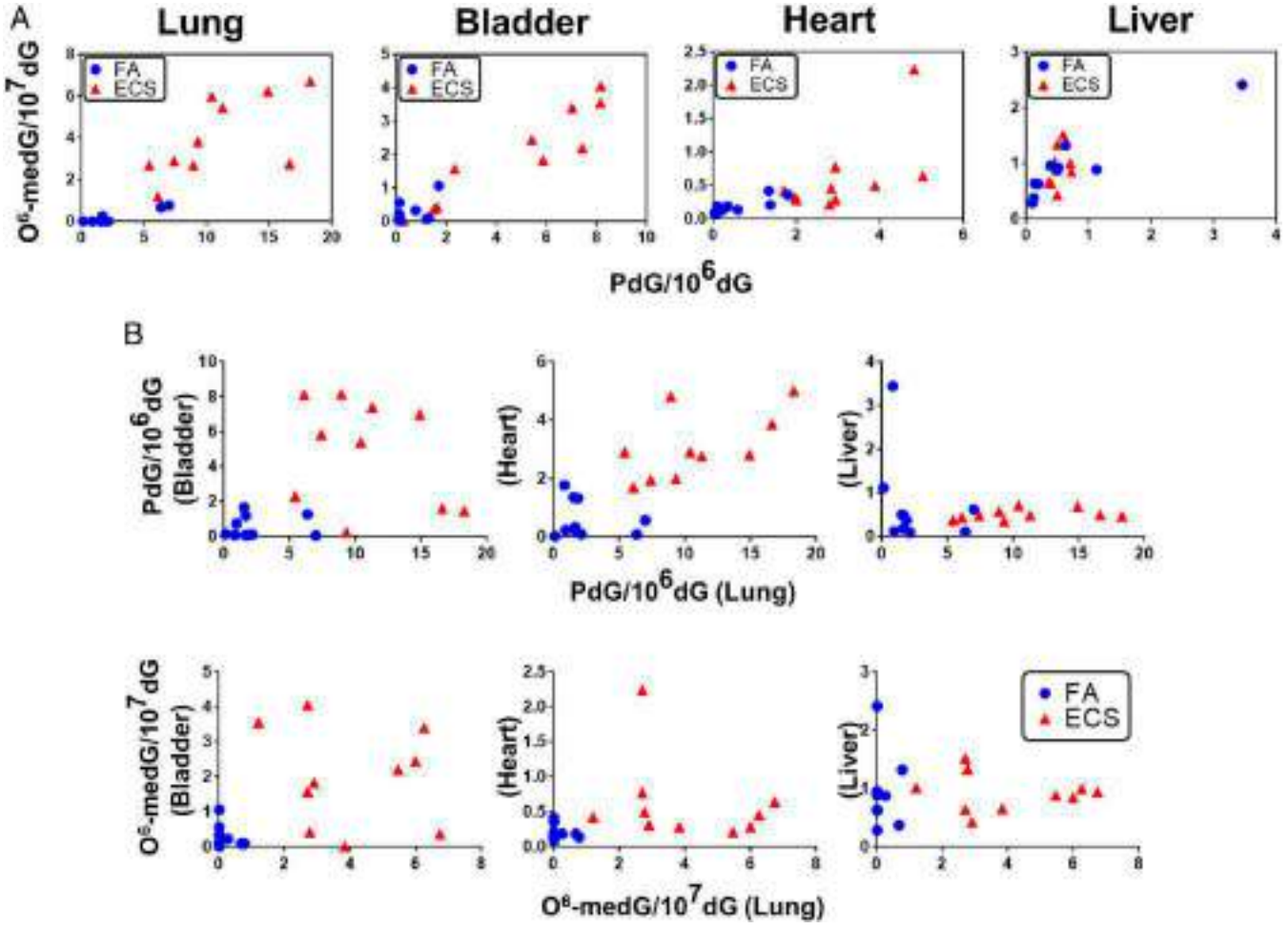

Fig. 2. Relationship of ECS-induced PdG versus O^6-medG formation in different organs of mice. The levels of PdG and O^6-medG detected in different organs from mice exposed to FA and ECS were determined in Fig. 1. In *A*, O^6-medG formation is plotted against PdG formation in each organ in mice exposed to ECS (red triangles) and FA (blue dots). In *B*, formation of PdG and O^6-medG in the bladder, heart, and liver is plotted against PdG and O^6-medG formation, respectively, in the lung of mice exposed to ECS and FA. Each symbol represents each individual mouse.

it has been proposed that one of NNK's metabolic products, MDOH, can interact with DNA to induce mutagenic O^6-medG adducts (20, 21, 27). These results raise the possibility that ECS-induced O^6-medG is due to the nitrosation of nicotine, and that NNK resulting from nicotine nitrosation then further transforms into MDOH in lung and bladder tissue (20). To test this possibility, we determined the DNA adducts induced by nicotine and NNK in cultured human bronchial epithelial and urothelial cells, and the effect of nicotine and NNK treatments on DNA repair, using the same methods indicated in Fig. 1. The results in Fig. 4 show that both nicotine and NNK can induce the same type of γ-OH-PdG adducts, and O^6-medG adducts. Since it is well established that many aldehydes can induce cyclic PdG in cells (38–40), these results suggest that aldehydes as well as MDOH are NNK metabolites, which induce γ-OH-PdG and O^6-medG.

Nicotine Reduces DNA Repair in Human Cells. We next determined the effects of nicotine and NNK treatment on DNA-repair activity and repair protein levels in human lung and bladder epithelial cells using the method described in Fig. 3. The results in Fig. 5 show that nicotine and NNK treatments not only inhibit NER and BER activities, they also reduce the protein levels of XPC and hOGG1/2. We found that these reductions of XPC and hOGG1/2 induced by nicotine and NNK can be prevented or attenuated by the proteasome and autophagosome inhibitors MG132, 3-methyladenine (3-MA), and lactacystin (Fig. S3) (13, 41–43). These results indicate that metabolites of nicotine and NNK can modify DNA-repair proteins and cause proteosomal and autophagosomal degradation of these proteins and that ECS's effect on the inhibition of DNA-repair activity is via modifications and degradation of DNA-repair proteins by its metabolites.

Together, these results indicate that human bronchial epithelial and urothelial cells as well as lung, heart, and bladder tissues in the mouse are able to nitrosate nicotine and metabolize nitrosated nicotine into NNK and then MDOH and aldehydes. Furthermore, whereas MDOH induces O^6-medG adducts, aldehydes not only can induce γ-OH-PdG, they also can inhibit DNA repair and cause repair protein degradation.

Nicotine Enhances Mutations and Cell Transformation. The aforementioned results demonstrate that ECS's major component nicotine, via its metabolites, MDOH, and aldehydes, not only can induce mutagenic DNA adducts, but that they also can inhibit DNA repair in human lung and bladder epithelial cells. These results raise the possibility that ECS and its metabolites can function not only as mutagens but also as comutagens to enhance DNA damage-induced mutagenesis. To test this possibility, we determined the effect of these agents on cell mutation susceptibility on UV- and H_2O_2-induced DNA damage

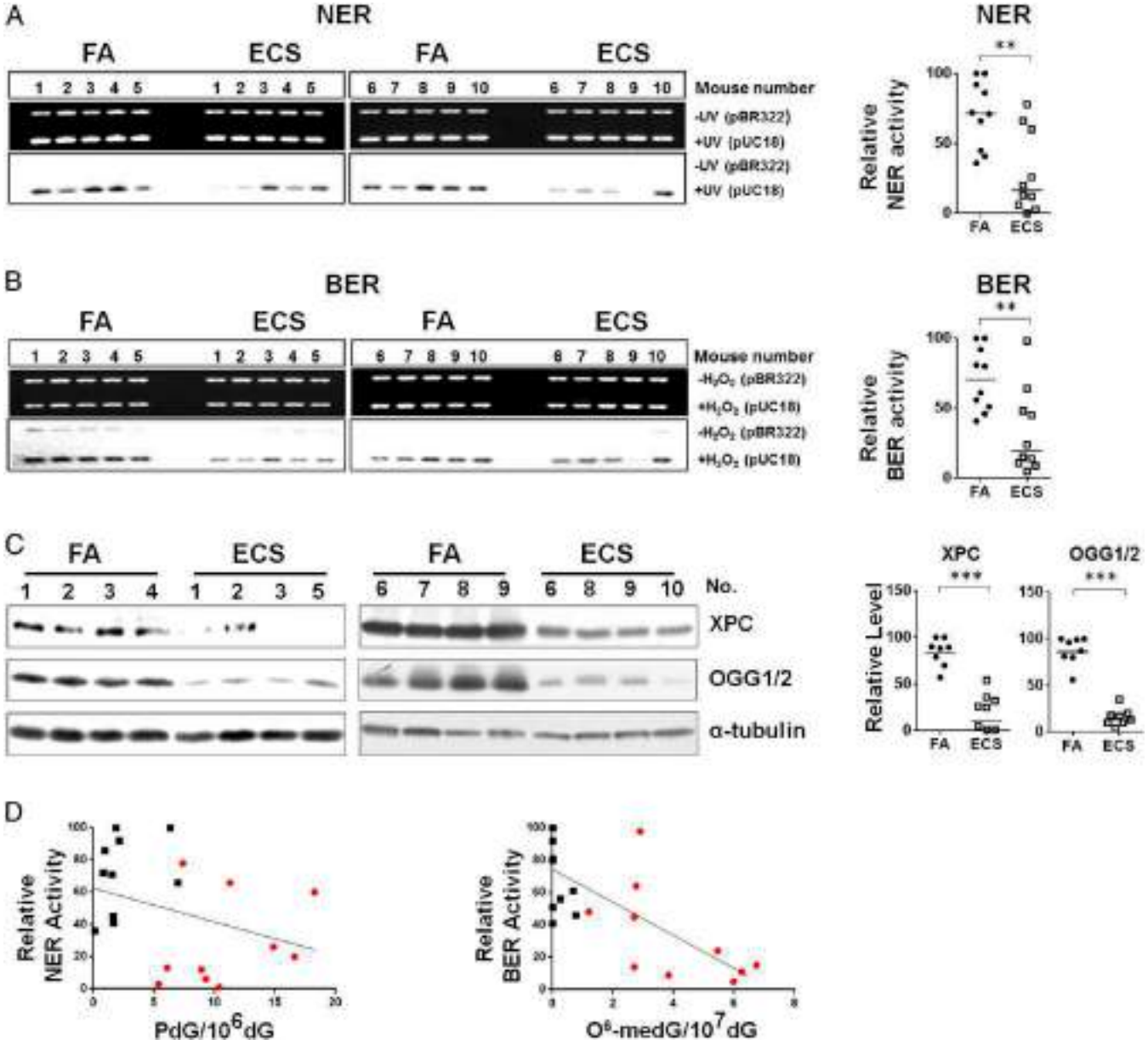

Fig. 3. ECS reduces DNA-repair activity and XPC and OGG1/2 in the lung. Cell lysates were isolated from lung tissues of mice exposed to FA ($n = 10$) or to ECS ($n = 10$) the same as in Fig. 1. The NER and the BER activity in the cell lysates were determined by the in vitro DNA damage-dependent repair synthesis assay as described (13, 28). (*A* and *B*) Ethidium bromide-stained gels (*Upper*) and autoradiograms (*Lower*) are shown in *Left*. In *Right*, the radioactive counts in the autoradiograms were normalized to input DNA. The relative repair activity was calculated using the highest band as 100%. (*C*) Detection of XPC and OGG1/2 protein in lung tissues ($n = 8$) by Western blot (*Left*). *Right* graphs are quantifications of ECS effect on the abundance of XPC and OGG1/2. The bar represents the mean value. (*D*) The relationship between the level of PdG and O^6-medG adduct and the NER and BER activity in lung tissues of FA- (black square) and ECS (red dot)-exposed mice.

using the well-established *supF* mutation system (13). The results in Fig. 6*A* show that nicotine and NNK treatment in both human lung and bladder epithelial cells enhances the spontaneous mutation frequency as well as UV- and H_2O_2-induced mutation frequency by two- to fourfold. These results indicate that nicotine and NNK treatment sensitize these human cells to the extent that they are more susceptible to mutagenesis. We further tested the effect of these agents on induction of tumorigenic transformation using the anchorage-independent soft-agar growth assay (44, 45). The results in Fig. 6 *B* and *C* show that nicotine and NNK greatly induce soft-agar anchorage-independent growth of human lung and bladder cells, a necessary ability for tumorigenic cells (46–49).

Discussion

The major purpose of E-cig smoking as well as tobacco smoking is to deliver the stimulant nicotine via aerosols, which allow smokers to obtain instant gratification. Unlike TS, which contains nitrosamines and numerous carcinogenic chemicals resulted from burning, ECS contains nicotine and relatively harmless organic solvents. Therefore, E-cig has been promoted as non-carcinogenic and a safer substitute for tobacco. In fact, recent studies show that E-cig smokers, similar to individuals on nicotine replacement therapy, have 97% less 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), an isoform form of NNK, a tobacco nitrosamine and lung carcinogen, in their body fluid

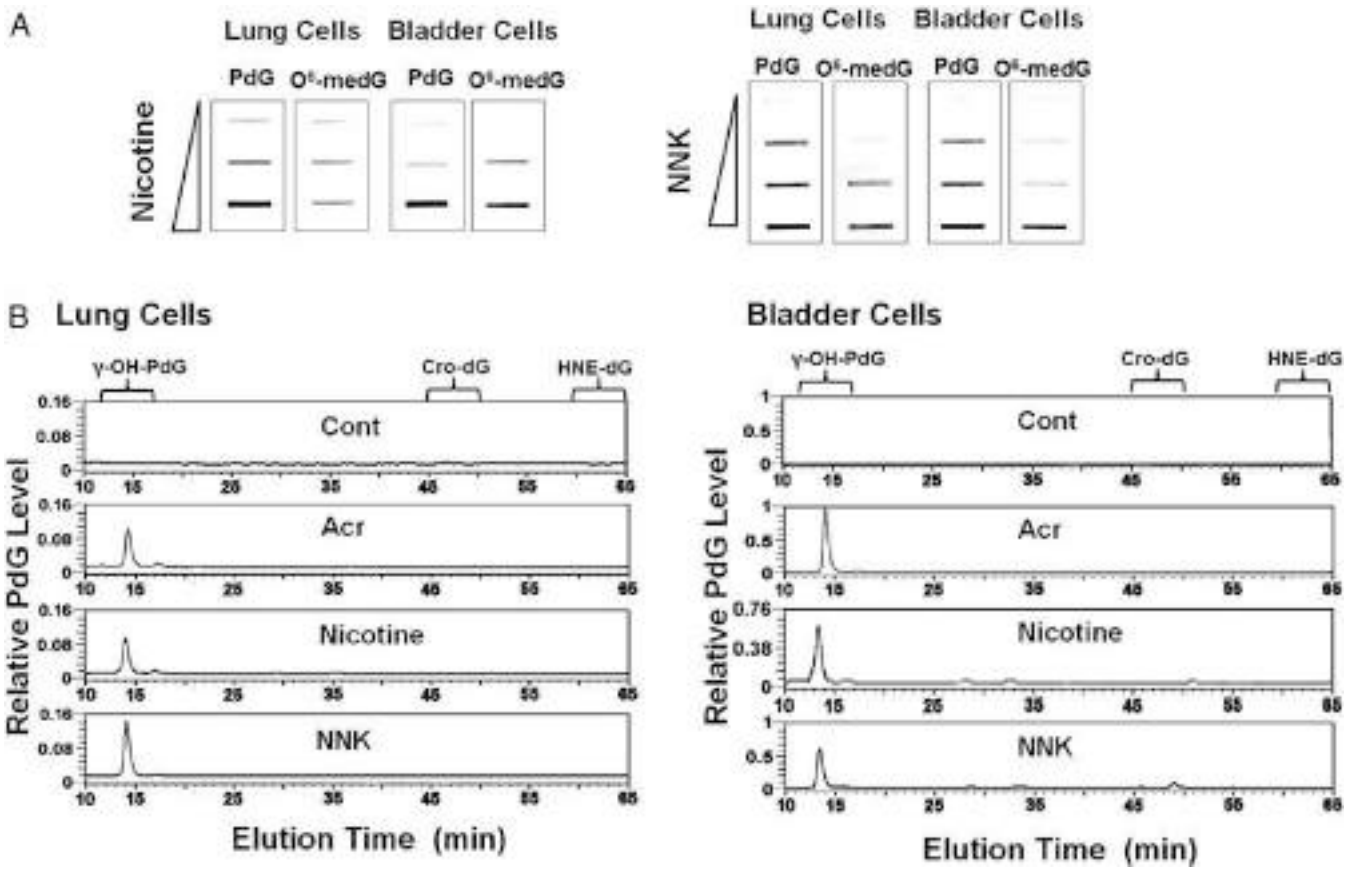

Fig. 4. Nicotine and NNK induce γ-OH-PdG and O^6-medG in cultured human lung and bladder epithelial cells. Human lung epithelial (BEAS-2B) cells and urothelial (UROtsa) cells were treated with different concentrations of nicotine and NNK as described in text. O^6-medG and PdG formed in the genomic DNA were determined as described in Fig. 1. (*A*) The DNA adducts were detected by immunochemical methods (13, 28). (*B*) The PdG adducts formed in the genomic DNA were further identified as γ-OH-PdG adducts by the ^{32}P postlabeling followed by 2D-TLC/HPLC method (13, 28).

than tobacco smokers (50). Based on these results, ECS has been recommended as a substitute for TS (50). However, E-cig smoking is gaining popularity rapidly particularly in young individuals and it is important to note that many of these E-cig smokers have taken up E-cig smoking habit are not necessary doing it for the purpose of quitting TS, rather, it is because they are assuming that E-cig smoking is safe. Currently, there are 18 million E-cig smokers in the United States and 16% of high school students smoke E-cig (51, 52). Understanding the carcinogenicity of ECS is an urgent public health issue. Since it takes decades for carcinogen exposure to induce cancer in humans, for decades to come there will be no meaningful epidemiological study to address the carcinogenicity of ECS. Therefore, animal models and cell culture models are the reasonable alternatives to address this question.

Nicotine has not been shown to be carcinogenic in animal models (7). However, during tobacco curing, substantial amounts of nicotine are transformed into tobacco-specific nitrosamines (TSA) via nitrosation, and many of these TSA, such as NNK and NNN, are carcinogenic in animal models (19, 53–55). Because of these findings, the occurrence and the level of nitrosamines in blood fluid have been used as the gold standard for determination of the potential carcinogenicity of smoking (56). While the NNAL level in E-cig smokers is 97% lower than in tobacco smokers, nonetheless, it is significant higher than in nonsmokers (50). This finding indicates that nitrosation of nicotine occurs in the human body and that ECS is potentially carcinogenic.

It is well established that cytochrome p450 enzymes in human and animal cells can metabolize and transform NNK, NNAL, and NNN into different products, which can modify DNA as well as proteins (20, 57, 58). This finding raises the possibility that the level of these nitrosamines detected in the blood stream of E-cig smokers at any given time may grossly underestimate the level of nicotine nitrosation. We undertake the approach of detecting DNA damage induced by nicotine rather than detecting nitrosamine level to address the potential mutagenic and carcinogenic effect of ECS. It should be noted that in vivo DNA damage can remain in genomic DNA for many hours and even days (13, 59, 60). Therefore, this approach not only is direct but also more sensitive in determining the carcinogenicity of ECS.

The level of γ-OH-PdG adducts induced by E-cig smoke in mice and by nicotine and NNK in cultured human cells is 10-fold higher than O^6-medG (Fig. 1). We have shown that γ-OH-PdG adducts are as mutagenic as BPDE-dG and UV photoproducts and induce G to T and G to A mutations similar to the mutations in the p53 gene in tobacco smoker lung cancer patients (11). Together, these results suggest that γ-OH-PdG adducts are the major cause of nitrosamine lung carcinogenicity.

The current understanding of NNK and NNN metabolism indicates that NNK metabolites are further transformed into PBDs, formaldehyde, and MDOH (20, 21, 61), while NNN metabolites are hydroxyl and keto forms of PBD (20, 21, 61). While MDOH can induce O^6-medG adducts, it is unclear what metabolites induce γ-OH-PdG adducts. It is well established that acrolein–DNA interaction generates γ-OH-PdG adducts (11, 13, 30) and that formaldehyde induces hydroxymethylated

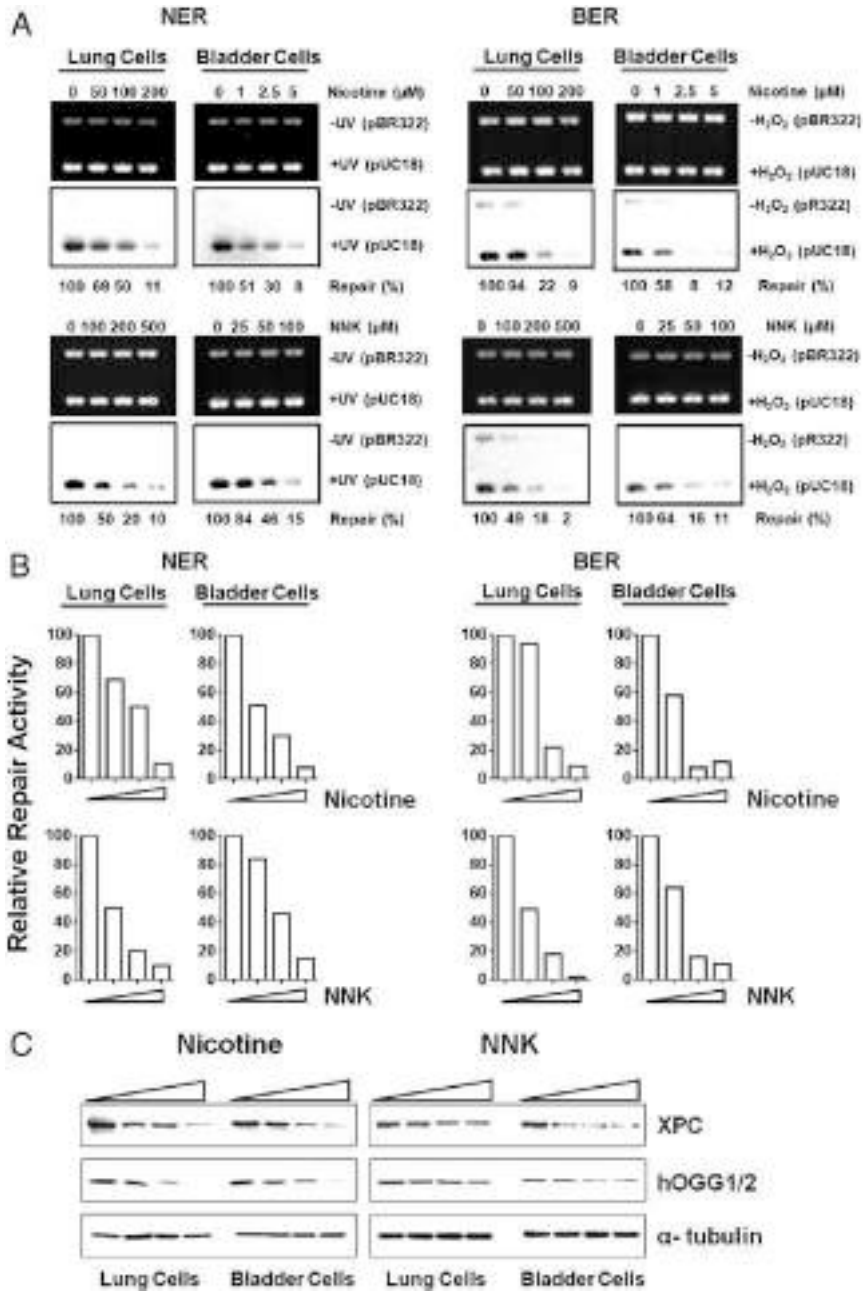

Fig. 5. Nicotine and NNK reduce DNA-repair activity and the level of repair proteins XPC and hOGG1/2 in cultured human lung and bladder epithelial cells. Cell-free cell lysates were isolated from human lung (BEAS-2B) and bladder epithelial (UROtsa) cells treated with different concentrations of nicotine and NNK 1 h at 37 °C. The NER and the BER activity in the cell lysates were determined by the in vitro DNA damage-dependent repair synthesis assay as described in Fig. 3. (*A*) Ethidium bromide-stained gels (*Upper*) and autoradiograms (*Lower*) are shown. (*B*) Quantifications results. The radioactive counts in the autoradiograms were normalized to input DNA. The relative repair activity was calculated using the control band as 100%. (*C*) The effect of nicotine and NNK treatment on abundance of XPC and hOGG1/2 in human lung and bladder urothelial cells were determined as described in Fig. 3.

nucleotides, mainly dG, in animal models (62). It has been found that in vitro formaldehyde combined with acetaldehyde can induce γ-OH-PdG (63). Therefore, it possible that ECS, nicotine, and NNK induce γ-OH-PdG via their metabolite formaldehyde, which triggers lipid peroxidation and produces acrolein and acetaldehyde byproducts; consequently, these byproducts induce γ-OH-PdG.

In summary, we found that ECS induces mutagenic γ-OH-PdG and O^6-medG adducts in lung, bladder, and heart tissues of exposed mice. ECS also causes reduction of DNA-repair activity and repair proteins XPC and OGG1/2 in lung tissue. Furthermore, nicotine and NNK induce the same effects in human lung and bladder epithelial cells. We propose that nicotine can be nitrosated, metabolized, and further transformed into aldehydes and MDOH in lung, bladder, and heart tissues of humans and mice. Whereas MDOH induced O^6-medG, aldehydes not only induce γ-OH-PdG, but also inhibit DNA repair and reduce XPC and OGG1 proteins (Fig. S3). We also found that nicotine and NNK can enhance mutational susceptibility and induced tumorigenic transformation of human lung and bladder epithelial cells. Based on these results, we propose that ECS is carcinogenic and that E-cig smokers have a higher risk

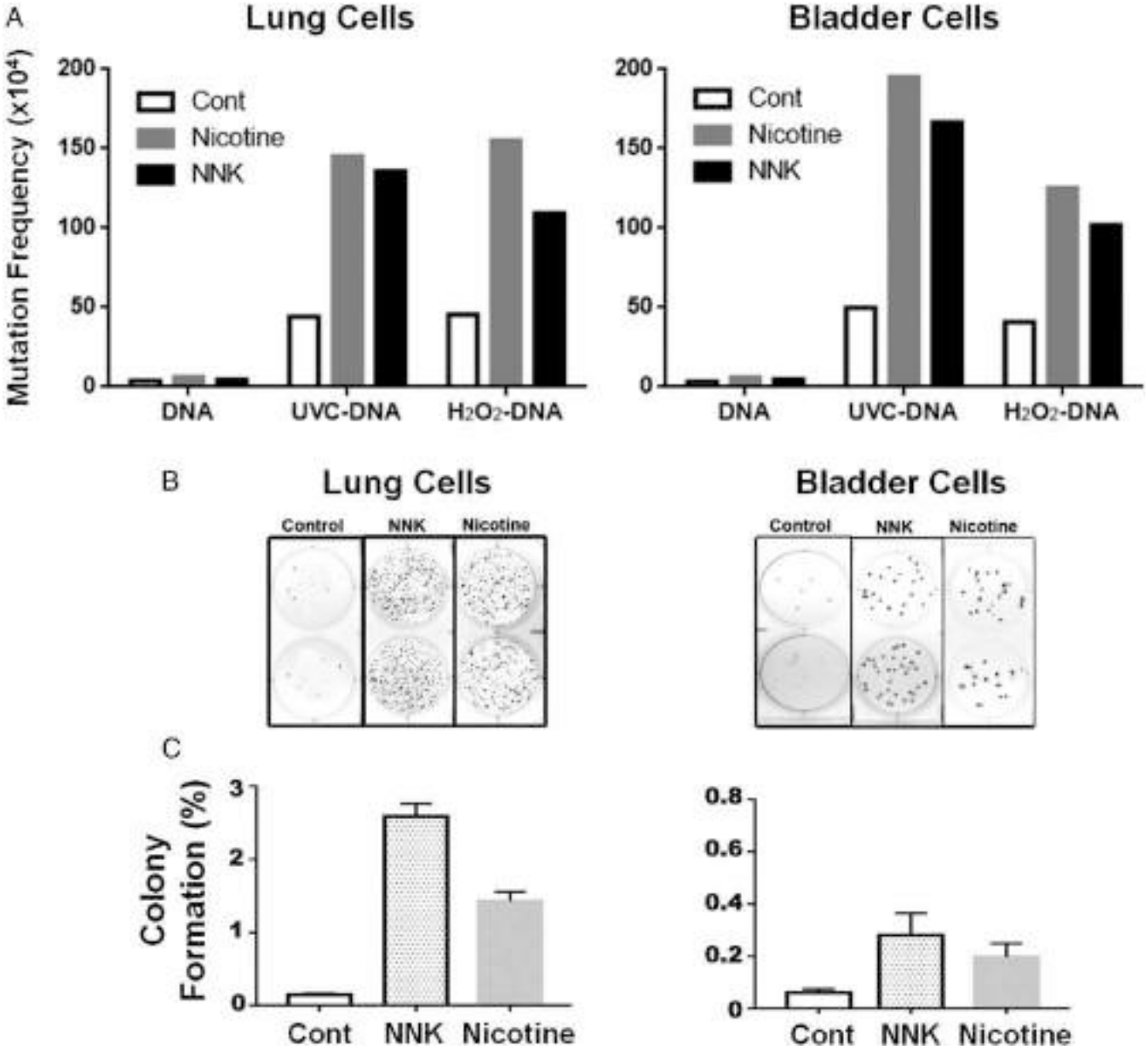

Fig. 6. Nicotine and NNK treatments enhance mutational susceptibility and cell transformation. Human lung and bladder epithelial cells (BEAS-2B and UROtsa) were treated with NNK (0.5 mM) and nicotine (25 mM for BEAS-2B cells, and 5 mM for UROtsa cells) for 1 h at 37 °C; these treatments render 50% cell killing. (*A*) UVC-irradiated (1,500 J/m^2) or H_2O_2 modified (100 mM, 1 h at 37 °C) plasmid DNAs containing the *supF* gene were transfected into these cells, and the mutations in control, and nicotine- and NNK- treated cells were detected and quantified as previously described (13, 28). (*B*) Detection of anchorage-independent soft-agar growth. A total of 5,000 treated cells were seeded in a soft-agar plate. The method for anchorage-independent soft-agar growth is the same as previously described (28). Typical soft-agar growth plates stained with crystal violet were shown. (*C*) Quantifications of percent of control, nicotine, and NNK-treated cells formed colonies in soft-agar plates.

than nonsmokers to develop lung and bladder cancer and heart diseases.

Materials and Methods

Materials. Acr-dG monoclonal antibodies and plasmid pSP189 were prepared, as described (13, 41). Acr-dG antibodies are specific for PdG adducts including Acr-, HNE-, and crotonaldehyde (Cro)-dG (29). Antibodies for XPC, hOGG1/2 (cross reacts with mouse OGG1/2), α-tubulin, and mouse/rabbit IgG; enzymes, T4 kinase, protease K, nuclease P, and RNase A; and chemicals, acrolein, nicotine, and NNK were commercially available. Immortalized human lung (BEAS-2B) and bladder epithelial (UROtsa) cells were obtained from American Type Culture Collection and J.R. Masters, University College London, London. All animal procedures were approved by the Institutional Animal Care and Use Committee, New York University School of Medicine.

ECS Generation and Mice Exposure. Twenty FVBN (Jackson Laboratory, Charles River) male mice were randomized into two groups, 10 each. Mice were exposed to ECS (10 mg/mL), 3 h/d, 5 d/wk, for 12 wk. ECS was generated by an E-cig machine, as previously described (64). An automated three-port E-cigarette aerosol generator (e~Aerosols) was used to produce E-cigarette aerosols from NJOY top fill tanks (NJOY, Inc.) filled with 1.6 mL of e-juice with 10 mg/mL nicotine in a propylene glycol/vegetable glycerin mixture (50/50 by volume; MtBakerVapor MESA). Each day the tanks were filled with fresh e-juice from a stock mixture, and the voltage was adjusted to produce a consistent wattage (~1.96 A at 4.2 V) for each tank. The puff aerosols were generated with charcoal and high-efficiency particulate filtered air using a

rotorless and brushless diaphragm pump and a puff regime consisting of 35-mL puff volumes of 4-s duration at 30-s intervals. Each puff was mixed with filtered air before entering the exposure chamber (1 m^3). Tanks were refilled with fresh e-juice at 1.5 h into the exposure period during the pause between puffs. Mass concentrations of the exposure atmospheres were monitored in real time using a DataRam4 (Thermo Fisher Scientific) and also determined gravimetrically by collecting particles on Teflon filters (Teflo, 2 mm pore size; Pall) weighed before and after sample collection using an electrobalance (MT-5; Metler).

Cell Cultures and Treatments of Nicotine and NNK. Exponentially growing BEAS-2B and UROtsa were treated with different concentrations of nicotine (BEAS-2B: 0, 100, 200 μM; UROtsa: 0, 1, 2.5 μM), and NNK (BEAS-2B: 0, 100, 300, 1,000 μM; UROtsa: 0, 50, 100, 200 μM) for determination of DNA adduct and DNA-repair activity. For XPC and hOGG1/2 detection, BEAS-2B were treated with nicotine (0, 50, 100, 200 μM), and NNK (0, 500, 750, 1,000 μM) and UROtsa were treated with nicotine (0, 1, 2.5, 5 μM) and NNK (0, 100, 200, 400 μM) for 1 h at 37 °C. Genomic DNA and cell lysate isolation from these cells was the same as described (28).

PdG and O^6-medG Adduct Detection. Cyclic PdG and O^6-medG adducts formed in the genomic DNA were determined by the immunochemical slot blot hybridization method using Acr-dG and O^6-medG antibodies and quantum dot labeled second antibody, as described (13, 28). PdG adducts formed in cultured human cells, and mouse lung tissue were further analyzed by the ^{32}P postlabeling-2D-TLC/HPLC method, as previously described (28).

In Vitro DNA-Damage-Dependent Repair Synthesis Assay. The DNA-repair activity was assessed by an in vitro DNA damage-dependent repair synthesis assay, as previously described (13).

DNA Repairs Proteins Detection. The levels of XPC and OGG1/2 proteins in lung tissues of mice with and without ECS exposure, and in BEAS-2B and UROtsa cells treated with nicotine and NNK, were determined, as described (13).

Mutation Susceptibility Determination. Shuttle vector pSP189 plasmids, which contain the tyrosine suppressor tRNA coding gene the *supF*, were UV (1,500 J/m^2) irradiated or modified with H_2O_2 (100 mM, 1 h at 37 °C), then transfected into cells with and without pretreated with nicotine and NNK for 1 h at 37 °C. Mutations in the *supF* mutations were detected, as previously described (13).

Anchorage-Independent Soft-Agar Growth. Lung (BEAS-2B) and bladder (UROtsa) epithelial cells were treated with NNK (0.5 mM) and nicotine (25 and 5 mM) for 1 h at 37 °C; these treatments rendered 50% cell killing. The method for anchorage-independent soft-agar growth is the same as previously described (28).

Statistical Analysis. Statistical analysis and graphs were performed with Prism 6 (GraphPad) software. Two group comparisons were conducted with the unpaired, two-tailed Mann–Whitney *u* test or the unpaired, two-tailed *t* test with Welsh's correction for unequal variances. A P value <0.05 was considered to be significant.

ACKNOWLEDGMENTS. We thank Drs. Frederic Beland and Catherine B. Klein for reviewing this manuscript and Ms. Mona I. Churchwell for technical assistance. This work was supported by National Institutes of Health Grants R01CA190678, 1P01CA165980, ES00260, and P30CA16087.

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Aldehydes are the predominant forces inducing DNA damage and inhibiting DNA repair in tobacco smoke carcinogenesis

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Edited by James E. Cleaver, University of California, San Francisco, CA, and approved May 23, 2018 (received for review March 20, 2018)

Tobacco smoke (TS) contains numerous cancer-causing agents, with polycyclic aromatic hydrocarbons (PAHs) and nitrosamines being most frequently cited as the major TS human cancer agents. Many lines of evidence seriously question this conclusion. To resolve this issue, we determined DNA adducts induced by the three major TS carcinogens: benzo(*a*)pyrene (BP), 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanoe (NNK), and aldehydes in humans and mice. In mice, TS induces abundant aldehyde-induced γ-hydroxy-propano-deoxyguanosine (γ-OH-PdG) and α-methyl-γ-OH-PdG adducts in the lung and bladder, but not in the heart and liver. TS does not induce the BP- and NNK-DNA adducts in lung, heart, liver, and bladder. TS also reduces DNA repair activity and the abundance of repair proteins, XPC and OGG1/2, in lung tissues. These TS effects were greatly reduced by diet with polyphenols. We found that γ-OH-PdG and α-methyl-γ-OH-PdG are the major adducts formed in tobacco smokers' buccal cells as well as the normal lung tissues of tobacco-smoking lung cancer patients, but not in lung tissues of non-smokers. However, the levels of BP- and NNK-DNA adducts are the same in lung tissues of smokers and nonsmokers. We found that while BP and NNK can induce BPDE-dG and O^6-methyl-dG adducts in human lung and bladder epithelial cells, these inductions can be inhibited by acrolein. Acrolein also can reduce DNA repair activity and repair proteins. We propose a TS carcinogenesis paradigm. Aldehydes are major TS carcinogens exerting dominant effect: Aldehydes induce mutagenic PdG adducts, impair DNA repair functions, and inhibit many procarcinogens in TS from becoming DNA-damaging agents.

tobacco smoke carcinogenesis | aldehydes | DNA damage | DNA repair | polyphenols

Tobacco smoke (TS) is the major cause of human cancer. More than 80% of lung cancers and 50% of bladder cancers are TS related (1). Recently, it has been found that both lung and bladder tumors carry numerous mutations, including those in oncogenes and tumor suppressor genes, indicating that TS induces mutagenic DNA damage in lung and bladder cells (2, 3). Indeed, it has been found that TS contains more than 60 documented cancer-causing agents that can induce DNA damage and mutations in human cells (4, 5). However, the identity of and cancer-causing mechanisms of the TS agents responsible for the induction of lung and bladder cancer remain controversial (6–8). Numerous studies have linked polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and nitrosamines to human cancers, including lung and bladder cancer, and indeed, many of the PAHs and nitrosamines in TS per cigarette (cig) are potent carcinogens in animal models (9–12). However, the amounts of PAHs (up to 2 μg) and nitrosamines (up to 0.2 μg) in TS are relatively minute (13, 14). The TS lung carcinogenicity of PAHs has also been seriously challenged by the findings that the so-called TS-induced DNA adducts detected in the thin-layer chromatography (TLC) diagonal zone are, in fact, aldehyde-induced DNA adducts, rather than PAHs-related adducts (15). It is worth noting that the amount of aldehydes including acrolein (Acr) in TS is more than a 1,000 times greater than those of PAHs and nitrosamines (15–17). Furthermore, it has been found that, in human bronchial epithelial cells, the distribution of DNA damage in the p53 gene induced by both the TS Acr and PAHs coincides with the p53 mutation spectrum in lung cancer (8).

Although TS nitrosamines such as 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone (NNK) and *N′*-nitrosonornicotine (NNN) are potent carcinogens in animal models that can induce cancer in different tissues including lung tissue, these nitrosamines induce mainly G-to-A transition mutations (18, 19), whereas the major mutations observed in TS-related human lung cancer are G-to-T mutations (20, 21).

These results raise the possibility that the role of various carcinogens in TS may be different from that of the individual carcinogens in isolation because of the effects of the over 6,000 TS chemicals on each other's absorption, metabolism, and deposition. It is also likely that components in TS may interact with each other, resulting in attenuating or enhancing their carcinogenic

Significance

Tobacco smoke (TS) contains numerous carcinogens. Intriguingly, while TS itself is a weak carcinogen in animal models, many of the TS components, such as 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone (NNK) and polycyclic aromatic hydrocarbons (PAHs), are strong carcinogens. We found that TS induces mainly aldehyde-DNA adducts in mice and humans. TS reduces DNA repair activity and repair proteins in mouse lung. All of these TS-induced effects can be reduced by diet polyphenols. Aldehydes prevent PAHs and NNK from inducing DNA damage in human cells. We propose that, because they act to damage DNA, reduce DNA repair activity, and inhibit NNK and PAHs from becoming DNA-damaging agents, aldehydes are the major TS carcinogens. These insights allow for better TS cancer risk assessment and the design of effective preventive measures.

Author contributions: M.-w.W., H.-W.L., S.-H.P., Y.H., H.-T.W., and M.-s.T. designed research; M.-w.W., H.-W.L., S.-H.P., Y.H., and H.-T.W. performed research; C.S.Y. contributed new reagents/analytic tools; M.-s.T. analyzed data; and L.-C.C., W.N.R., W.C.H., H.L., X.-R.W., and M.-s.T. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

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This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1804869115/-/DCSupplemental.

Published online June 18, 2018.

potentials. If this is the case, then, to understand the carcinogenic mechanisms of TS, assess cancer risk of TS, and design effective TS-related cancer prevention measures, investigations should be focused on the determination of DNA damage, mutagenicity, and carcinogenicity of total TS, rather than on the individual carcinogens found in TS.

To address these important questions, we have determined the major types of DNA adducts in different organs of mice exposed to mainstream TS (MTS). Specifically, we quantified cyclic 1,N^2-propano-dG (PdG), benzo(*a*)pyrene diol epoxide (BPDE)-dG, and O^6-methyl-dG (O^6-medG) adducts induced by three major DNA-damaging carcinogens in TS—namely, aldehydes, benzo(*a*)pyrene (BP), and NNK (22–24). We also determined the effects of MTS on DNA repair capacity and DNA repair protein expression in lung tissues. We found that Acr-derived γ-hydroxy-1,N^2-PdG (γ-OH-PdG) is the major type of adduct, and acetaldehyde (Acet)- and crotonaldehyde (Cro)-derived (6*R*,8*R*)-α-methyl-γ-hydroxy-PdG (α-meth-γ-OH-PdG) is the minor adduct in lung. Only γ-OH-PdG is formed in bladder, and these PdG adducts do not form in heart or liver. TS does not enhance BPDE-dG or O^6-medG DNA adduct formation in any of these organs, even though the amount of these compounds found in TS when isolated is sufficient to induce DNA damage in mice (25–28). MTS inhibits both nucleotide and base excision repair (NER and BER) and reduces the levels of the DNA repair proteins XPC and OGG1/2. We found that diet Polyphenon E (PPE) could prevent these TS effects: induction of aldehyde-DNA adducts, inhibition of DNA repair, and reduction of DNA repair proteins. Significantly, we found that γ-OH-PdG and α-meth-γ-OH-PdG, but not BPDE-dG and O^6-medG, are the two major adducts formed in buccal cells and lung tissues of tobacco smokers. We found that Acr can prevent BP and NNK from becoming DNA-damaging agents in human lung and bladder epithelial cells. Based on these results, we propose that aldehydes, rather than PAHs and nitrosamines, are the major TS carcinogens and that aldehyde carcinogenic effects can be effectively prevented by diet polyphenols.

Results

MTS Induces PdG in Lung and Bladder in Mice. The carcinogenicities of aldehydes, PAHs, and nitrosamines have been well established (28–30), and results from cultured cell studies clearly demonstrate that TS aldehydes, such as Acr, Acet, and Cro, as well as metabolically activated PAHs and nitrosamines, can induce mutagenic DNA damage (8, 31, 32). Therefore, a crucial factor determining the roles of these different carcinogens in TS-induced human cancer is their efficiency in inducing DNA damage in different tissues of animals and humans exposed to TS. To address this question, we measured PdG, BPDE-dG, and O^6-medG adducts in lung, bladder mucosa, heart, and liver tissues of mice exposed to TS. Mice were exposed to MTS at the level of ∼75 mg/m^3 for 12 wk, which is equivalent to the TS exposure of a habitual smoker with 40 pack-year history. PdG adducts were first measured by an immunochemical method, using a monoclonal antibody against PdG adducts (33–35). The results in Fig. 1 *A* and *B* show that MTS induced significant levels of PdG adducts in lung ($P < 0.0001$) and bladder ($P < 0.0001$) tissues, but not in heart or liver tissues. The PdG adducts formed in lung and bladder tissues were further analyzed by a ^{32}P-postlabeling and 2D-TLC/HPLC method (34, 35). The results in Fig. 1 *C* and *D* show that two types of PdG adducts, γ-OH-PdG and α-meth-γ-OH-PdG, were formed in lung tissue and that the level of γ-OH-PdG adducts was eightfold higher than the level of α-meth-γ-OH-PdG adducts. In contrast, only γ-OH-PdG adducts were formed in bladder tissue.

Since TS contains up to 500 μg per cig Acr, 40–50 μg per cig Cro, and up to 2,000 μg per cig Acet (16, 27), and while Acr induces γ-OH-PdG, both Acet and Cro can induce different isoforms of α-meth-γ-OH-PdG adducts (33, 36), it is puzzling as to why TS induces a higher level of γ-OH-PdG adducts than α-meth-γ-OH-PdG adducts in lung and only γ-OH-PdG in bladder. One possibility could be that, due to the volatility of Acet, with boiling point (16 °C) below ambient temperature, it is likely that the majority of Acet in MTS may not be inhaled as efficiently as Acr by mice during the whole-body exposure. We found that Acr is more efficient at inducing γ-OH-PdG adducts than Cro is in inducing α-meth-γ-OH-PdG adducts in lung epithelial cells (*SI Appendix*, Fig. S1). Taken together, these two factors may contribute to the lower levels of α-meth-γ-OH-PdG adducts than γ-OH-PdG adducts formed in lung tissues and bladder mucosa of mice exposed to TS.

MTS Exposure Does Not Significantly Induce BPDE-dG and O^6-medG in Lung and Bladder. We measured BPDE-dG adducts using an immunochemical method and the 3D-TLC method, and we quantified O^6-medG adducts through both an immunochemical method and HPLC analysis (33, 34, 37, 38). The results in Fig. 2 show that MTS does not induce BPDE-dG and O^6-medG significantly in lung, heart, liver, or bladder tissues. It is worth noting that the basal levels of BPDE-dG and O^6-medG adducts detected in lung, bladder, liver, and heart are 20- to 100-fold lower than the levels of PdG adducts in these organs (Fig. 1*B* vs. Fig. 2).

MTS Inhibits DNA Repair Function in Mouse Lung Tissue. Previously, we have found that Acr, Cro, and Acet not only can damage genomic DNA but also can modify repair proteins causing repair dysfunction in cultured lung and bladder epithelial cells (8, 33, 35). Since MTS contains an abundance of these aldehydes, it is possible that MTS may inhibit DNA repair function. To test this possibility, using the in vitro DNA-dependent repair synthesis assay, we measured the repair activity in cell-free cell lysates from lung and liver of mice exposed to MTS (8, 33, 35). The results in Fig. 3 *A* and *B* show that both NER and BER activity in lung tissues of MTS-exposed mice were much lower than in lung tissues of control mice. In contrast, the results in *SI Appendix*, Fig. S2 *A* and *B* show no significant differences in NER and BER repair activity in liver tissues between mice with and without MTS exposure. Due to limited amounts of tissue, we were unable to similarly determine DNA repair activity in bladder mucosa.

MTS Causes a Reduction of DNA Repair Proteins XPC and OGG1/2 in Mouse Lung Tissue. Previously, we have found that Acr, Cro, and Acet can modify DNA repair proteins such as XPC, hOGG1/2, MLH1, and PMS2, and that the modified DNA repair proteins are degraded via an autophagosome pathway in cultured lung and bladder epithelial cells (33, 35). These findings raised the possibility that the reduction of NER and BER activity in lung tissues of TS-exposed mice is due to reduction of repair proteins caused by TS aldehydes. To test this possibility, we measured XPC and OGG1/2 levels in lung tissues of mice with and without MTS exposure. XPC is a major NER protein for repair of bulky DNA adducts, such as UV-induced photodimers, BPDE-dG, and PdG adducts, in genomic DNA (39); OGG1/2 is a major enzyme for repair of 8-oxo-dG DNA damage (40). The results in Fig. 3*C* show that MTS exposure caused a significant reduction of XPC and OGG1/2 protein levels in lung tissues. However, MTS exposure did not affect XPC and OGG1/2 levels in liver tissues (*SI Appendix*, Fig. S2 *C* and *D*). These results indicate that either TS aldehydes do not enter into liver cells and/or liver cells have the capacity to inactivate MTS aldehydes.

PPE Prevents MTS-Induced PdG Formation and DNA Repair Inhibition in Lung and PdG Formation in Bladder Tissues. The results presented above indicate that aldehydes in MTS, mainly Acr, induce PdG adducts in lung and bladder tissues in vivo. MTS also inhibits NER and BER capacity in lung tissues, and this effect is most likely due to MTS aldehydes. We propose that these two outcomes of MTS exposure contribute to lung and bladder carcinogenesis. If

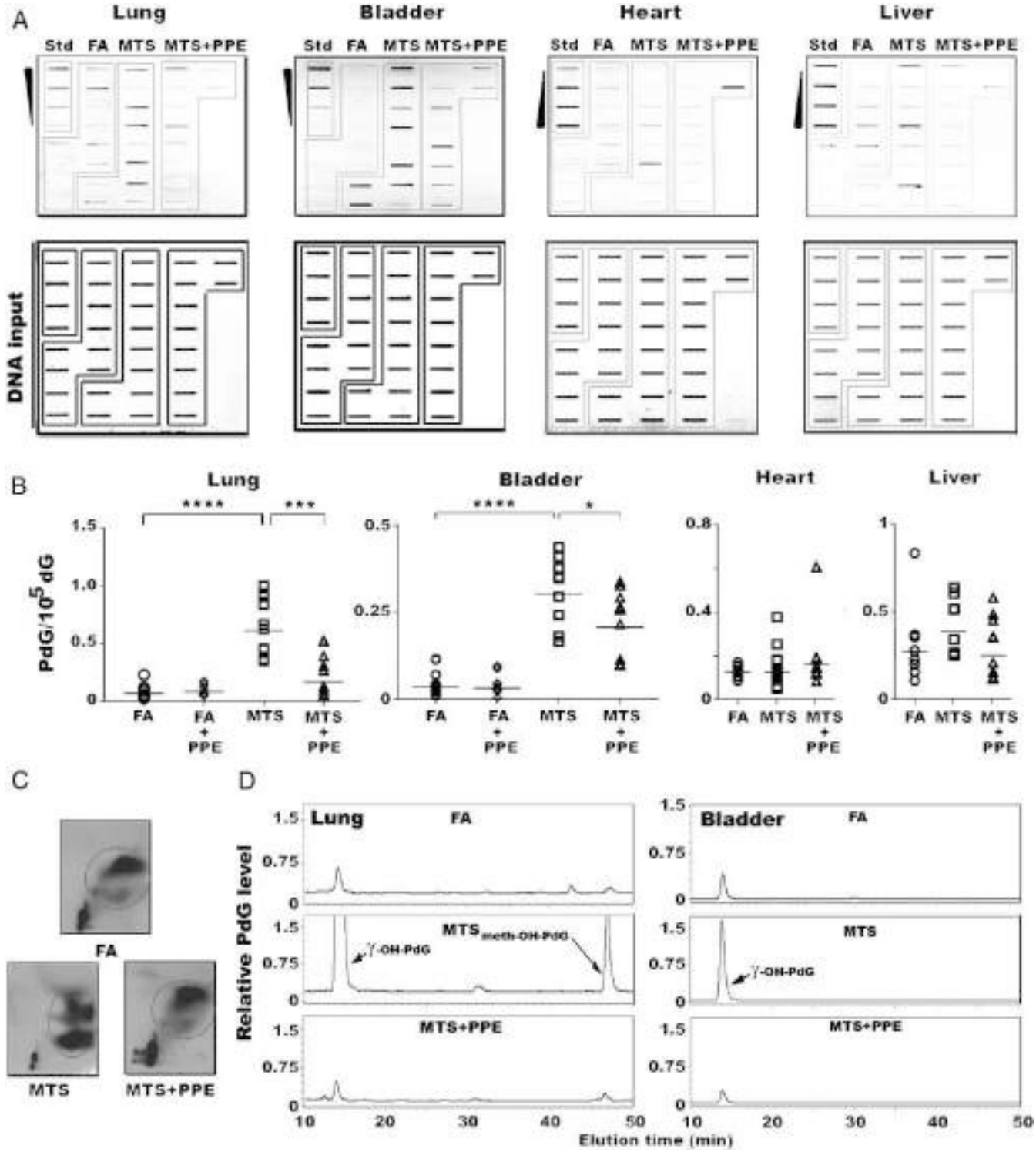

Fig. 1. Mainstream tobacco smoke (MTS) induces γ-OH-PdG and α-meth-γ-OH-PdG in lung and γ-OH-PdG in bladder, but not in heart and liver. Polyphenol E (PPE) can prevent this TS effect. Two groups of mice (20 mice per group) were fed a control diet or diet containing 0.1% PPE. Ten mice from each group were either exposed to filtered air (FA) or MTS for 12 wk, as described in the text. Genomic DNAs from lung, heart, liver, and bladder tissues were prepared as described (34). PdG formation in these tissues was analyzed by an immunochemical method using a monoclonal antibody against PdG and quantum dot-labeled secondary antibody, as previously described (33). Each sample was measured two to four times. Typical slot blot hybridization results (*Upper*, antibody reaction; *Lower*, input DNA) are shown in *A*, and the quantification results are shown in *B*. Lines represent the geometric average values. $^{****}P < 0.0001$, $^{***}P < 0.001$, and $^{*}P < 0.05$. PdG adduct formation in the lung and bladder tissues was further analyzed by a ^{32}P-postlabeling 2D-TLC/HPLC method, as previously described (34). (*C*) Typical 2D-TLC chromatographic autoradiograms. (*D*) The spots circled in *C* were extracted and further analyzed by an HPLC method (34). The elution positions of the standard γ-OH-PdG adduct and the α-meth-γ-OH-PdG adducts are indicated by the arrows. Note: MTS induced γ-OHPdG and α-meth-γ-OH-PdG in lung and γ-OH-PdG in bladder tissues, but not in heart and liver tissues. PPE prevented both types of DNA adduct formation in lung and bladder tissues in mice exposed to MTS, but PPE did not affect PdG adduct formation in lung and bladder tissues of the control mice. FA, mice exposed to FA; MTS, mice exposed to MTS; MTS + PPE, mice fed with diet with PPE and exposed to MTS; Std, standard DNA with different PdG levels.

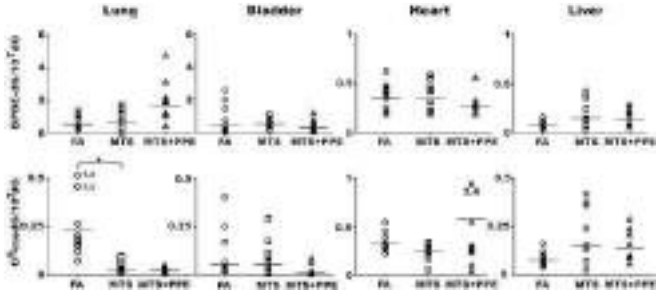

Fig. 2. Mainstream tobacco smoke (MTS) does not induce BPDE-dG and O^6-meth-dG formation in lung, bladder, heart, or liver tissues. The same genomic DNAs isolated from different organs of mice exposed to MTS and fed a diet with and without PPE, as described in Fig. 1, were used for BPDE-dG and O^6-medG adduct detection using an immunochemical method (35, 67). For simplicity, only the quantitation of DNA adduct levels is shown. Abbreviations are the same as in Fig. 1. The typical slot blot hybridization results are shown in *SI Appendix*, Fig. S4 *A* and *B*. Note: MTS did not induce a significant difference in BPDE-dG and O^6-medG adduct formation in lung, bladder, heart, or liver tissues of mice compared with the FA group. PPE did not affect BPDE-dG and O^6-medG adducts formation in these organs. MTS exposure significantly reduces the background O^6-medG level in lung (FA vs. MTS, $P = 0.044$).

this is correct, then it should be possible to prevent TS-induced lung and bladder cancer by neutralizing sufficient amount of TS aldehydes in vivo. It has long been recognized that the carbonyl group and the olefinic bond in Acr are the active moieties that can interact with DNA and proteins to form DNA and protein adducts (41, 42). These reactions can be prevented by numerous antioxidants and reducing agents with molecules that have sulfhydryl groups (43–45). We found that PPE and PP-60, polyphenols from tea extracts, which are potent antioxidants and appropriate for human consumption, can effectively prevent Acr-induced DNA adduct formation in cultured lung epithelial cells and bladder epithelial cells (*SI Appendix*, Fig. S3 *A*, *C*, *D*, and *F*). The results in *SI Appendix*, Fig. S3 *B*, *C*, *E*, and *F* show that PPE and PP-60 can also considerably reduce the inhibitory effects of Acr on DNA repair in cultured lung epithelial and urothelial cells.

Armed with these encouraging results, we then determined the effect of diet PPE on TS-induced PdG formation and DNA repair inhibition in mouse models. Four groups of mice, each with 10 mice, were fed with control diet (AIN93M) or diet containing 0.1% PPE (NIA93M). These mice were exposed to either MTS or filtered air (FA) for 12 wk, the same exposure protocol as described in Fig. 1. The PdG formation (Fig. 1) in lung and bladder tissue and DNA repair activity in lung tissue (Fig. 3 *A* and *B*) were determined. The results were compared with the groups that were fed the control diet without PPE but subjected to the same MTS exposure. The results in Fig. 1 show that PdG levels in lung tissues of MTS-exposed mice fed with PPE (MTS + PPE) were significantly lower than in MTS-exposed mice on control diets (MTS) ($P < 0.001$). PdG levels in bladder tissues of MTS-exposed mice fed with PPE were also significantly lower than in MTS-exposed mice on control diet ($P = 0.0423$). These results indicate that PPE can neutralize MTS effects on PdG induction in lung and bladder tissues. *SI Appendix*, Fig. S4*C* shows that there was no significant difference in PdG levels in lung tissue of mice fed with control diet and PPE-enriched diet without MTS exposure, indicating that PPE does not induce PdG adducts in lung and bladder tissues in mice.

We further tested whether or not PPE can prevent the MTS-caused reduction DNA repair activity and of XPC and OGG1/2 expression. The results in Fig. 3 *A* and *B* show that PPE can also prevent MTS-induced inhibition of both NER and BER activity in lung tissue. The results in Fig. 3*C* show that, whereas the levels of XPC and OGG1/2 are significantly lower in lung tissues of MTS-exposed mice than in FA mice (MTS vs. FA), the levels of these two proteins in the lung tissue of MTS-exposed mice fed with the diet containing PPE showed no significant difference compared with mice fed the control diet without MTS exposure [(MTS + PPE) vs. FA]. Together, these results indicate that the PPE prevention of TS-induced DNA repair inhibition is through neutralizing TS's effects on the reduction of XPC and OGG1/2, the two crucial factors for NER and BER.

α-Meth-γ-OH-PdG and γ-OH-PdG Adducts Are the Major DNA Damage Detected in Buccal Cells and Lung Tissues of Smokers. The aforementioned results demonstrate that, in a mouse model, aldehyde-derived γ-OH-PdG and α-meth-γ-OH-PdG adducts, rather than commonly believed PAH- and nitrosamine-derived DNA adducts such as BPDE-dG and O^6-medG, are the major MTS-induced DNA adducts in the lung and bladder in vivo, and that MTS also inhibits DNA repair and reduces the levels of DNA repair proteins. These results raise an important question: Does TS induce these effects in human lungs in the same manner as it does in the mouse model? Simply put, does TS induce PdG rather than BPDE-dG and O^6-medG adducts in human lung tissue? An insurmountable hurdle in addressing this question is the inability to obtain lung tissue, bronchoalveolar lavage, or bronchial brushing from smokers with different tobacco smoking consumption in a representative population with appropriate nonsmoking controls. We chose to use buccal cells and sputum as surrogates for lung cells. Buccal cells are the first line of cells to encounter TS exposure and have similar molecular responses to TS as airway epithelial cells and bronchial epithelial cells. Numerous studies have established a positive relationship between TS and cytological and molecular markers in lung cancer (46), and buccal cells have also been used for the early diagnosis of oral and lung cancer (47–49). Sputum consists of bronchial epithelial cells and macrophages in the lung (48). DNA adduct levels obtained from these two types of samples may thus reflect TS effects in different regions of the airway. Furthermore, a sufficient amount of buccal cells and sputum for analyzing DNA adduct formation is obtainable via oral brushing and sputum induction, which are both relatively minor procedures. Using the same immunochemical method and ^{32}P-postlabeling and 2D-TLC/HPLC method as described above, we determined the PdG and BPDE-dG formation in buccal cells of individuals with different smoking and nonsmoking histories. The results in Fig. 4 show that (*i*) the levels of BPDE-dG adducts in buccal cells from smokers (S) and nonsmokers (NS) show no significant differences (Fig. 4*C*); (*ii*) the levels of PdG adducts in buccal cells were significantly higher in smokers (S) than in nonsmokers (NS) (Fig. 4*A*, NS vs. S, $P < 0.0001$) and are related to 40 smoking pack-year (Fig. 4*B*, 0 vs. 30–40, $P < 0.0001$; 0 vs. 41–50, $P < 0.0001$; 0 vs. >50, $P = 0.0007$); and (*iii*) γ-OH-PdG and α-meth-γ-OH-PdG adducts were the two major types of PdG adducts detected in buccal cells from smokers (Fig. 4*E*). The results also show that the levels of PdG adducts in sputum were significantly higher in smokers than in nonsmokers (Fig. 4*D*, NS vs. S, $P = 0.0193$). In summary, these results indicate that aldehydes are the major TS agents that cause DNA damage in buccal cells and lung tissues of smokers.

We also determined the DNA adduct formed in noncancerous lung tissues obtained from lung lobectomy of lung cancer patients of tobacco smokers ($n = 41$) and lung tissues from nonsmokers ($n = 13$). The results in Fig. 5 show that the levels of γ-OH-PdG and α-meth-γ-OH-PdG adducts in lung tissues of smokers are significantly higher than in nonsmokers, and that the levels of α-meth-γ-OH-PdG are higher than γ-OH-PdG. However, the levels of BPDE-dG and O^6-medG are similar in the lung tissues of smokers and nonsmokers. It is worth noting that the basal levels of BPDE-dG and O^6-medG are significantly lower than the levels of γ-OH-PdG and α-meth-γ-OH-PdG in

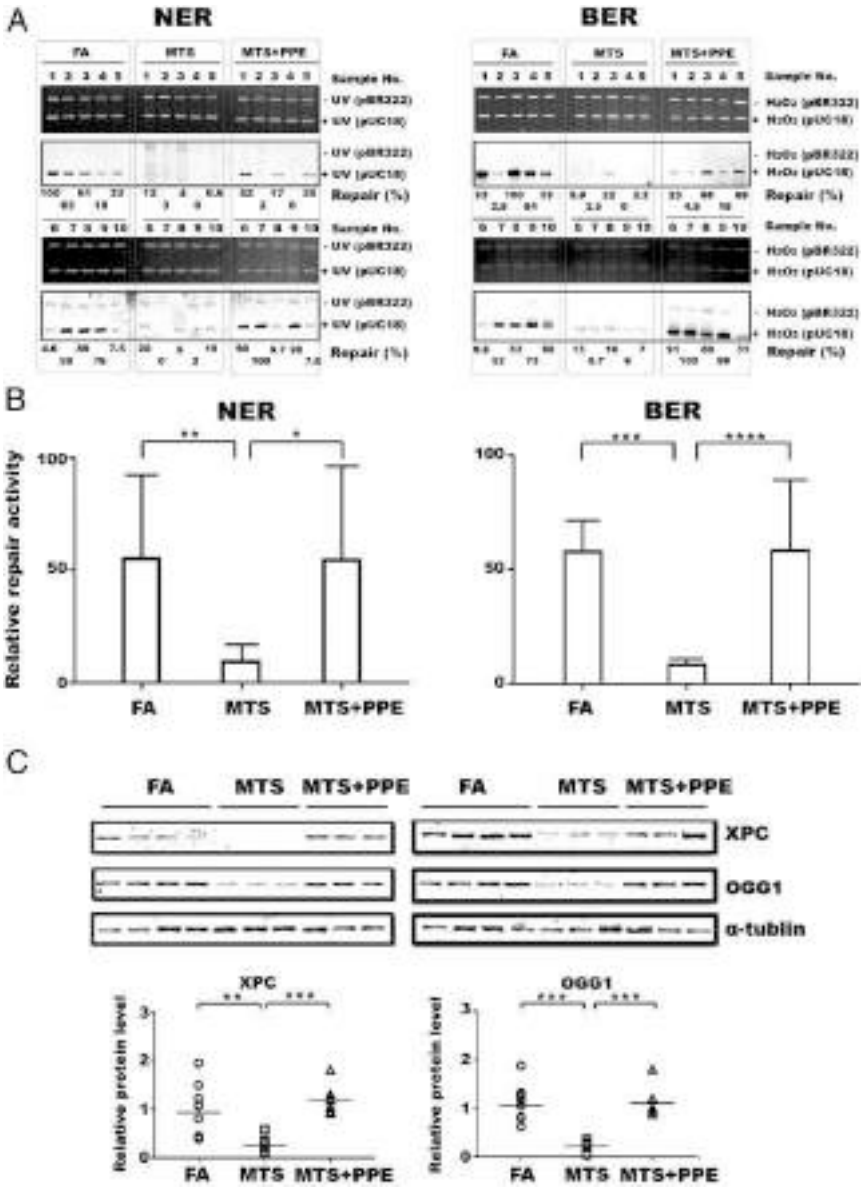

Fig. 3. Mainstream tobacco smoke (MTS) causes a reduction of DNA repair capacity and levels of repair proteins, XPC, and OGG1 in lung tissues. Polyphenon E (PPE) can prevent these TS effects. Mice fed control diet and diet with PPE were exposed to filtered air (FA) and MTS, as described in Fig. 1. Cell-free cell lysates of lung tissues from these mice were prepared. The nucleotide excision repair (NER) and base excision repair (BER) capacities of the cell lysates were determined by methods previously described (8, 34, 78). (*A*) Typical autoradiograms (*Lower* panels), DNA staining (*Upper* panels) of the electrophoresed gels, and relative repair capacity for individual mouse (*Bottom*). (*B*) Quantitation of relative NER and BER activity. (*C*) The XPC and OGG1 proteins were detected by Western blots (*Upper*), and the relative protein levels were quantified (*Lower*). Abbreviations are the same as in Figs. 1 and 2. $^{****}P < 0.0001$, $^{***}P < 0.001$, and $^{**}P < 0.01$.

lung tissues of both smokers and nonsmokers. Similar results were observed in TS-exposed mice (Figs. 1 and 2). These results indicate that TS induces mainly γ-OH-PdG and α-meth-γ-OH-PdG in smokers' lung tissues.

Acr Exerts Dominant and Inhibitory Effect on BP- and NNK-DNA Adduct Induction in Lung and Bladder Epithelial Cells. Lung and bladder epithelial cells contain a variety of cytochrome p450s (CYPs) that can metabolically activate PAHs, including BP, into epoxide forms that can effectively adduct DNA (11, 50–52). CYPs in lung and urothelial cells can also metabolize nitrosamines into metabolites that can spontaneously degrade into pyridyl-butanoic acid derivatives, formaldehyde, as well as methyldiazohydroxide, which can methylate DNA (11, 53). Why then did MTS not induce BPDE-dG and O^6-medG adducts in the lung tissue and bladder mucosa of mice and in human lung tissue? Aldehydes such as Acr, Cro, and Acet can cause protein dysfunction by modifying the proteins (50–52). Perhaps TS aldehydes inhibit the activation of BP and nitrosamines via modification of CYP proteins. To test this possibility, we determined the effect of Acr exposure on BP- and NNK-induced DNA adduct formation in human lung epithelial and urothelial cells. The results in Fig. 6 show that, by themselves, BP can induce BPDE-dG and NNK can induce PdG and O^6-medG adducts. However, in the presence of Acr, the ability of BP to induce BPDE-dG adducts and the ability of NNK to induce O^6-medG adducts were greatly reduced. In fact, only PdG adducts were observed in cells treated with the combination of BP and Acr (Fig. 6 *C*, *D*, *G*, and

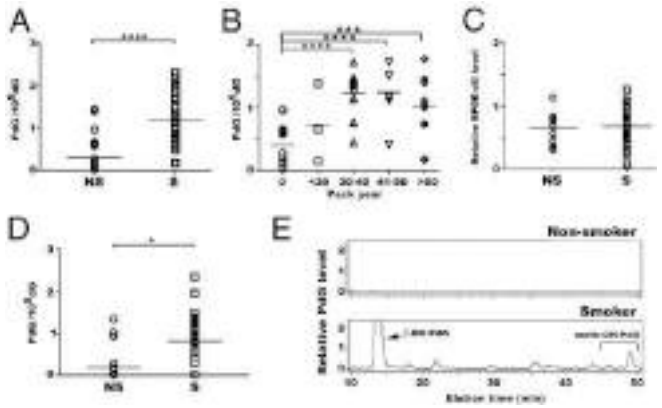

Fig. 4. The levels of γ-OH-PdG and α-meth- γ-OH-PdG adducts, but not BPDEdG, were higher in buccal cells of tobacco smokers than nonsmokers. γ-OHPdG, α-meth-γ-OH-PdG, and BPDE-dG in buccal cells of nonsmokers (NS) (n = 17) and smokers (S) (n = 33) with different smoking history (pack-year) were determined by methods described in Figs. 1 and 2. (*A*) The PdG adducts was detected by the immunochemical methods. (*B*) The PdG levels in individuals with different smoking history. (*C*) Relative levels of BPDE-dG in smokers vs. nonsmokers. The PdG adducts in sputum samples of nonsmokers (NS) (n = 8) and smokers (S) (n = 22) with different smoking history were detected by the immunochemical method as described in Fig. 1, and the results were shown in *D*. (*E*) HPLC profiles of PdG adduct formed in buccal cells. Genomic DNA from buccal cells of smokers and nonsmokers were pooled for ^{32}P-postlabeling and 2D-TLC/HPLC analysis as in Fig. 1. Note: (*i*) Due to the limited number of sputum samples collected, the PdG adducts were not analyzed by ^{32}P-postlabeling, 2D-TLC/HPLC. (*ii*) The ratio of γ-OH-PdG to α-meth-γ-OHPdG detected in buccal cells of smokers is similar to that detected in lung tissues of mice exposed to MTS (8-9:1). ****$P < 0.0001$, ***$P < 0.001$, and *$P < 0.05$.

H). These results indicate that Acr can inhibit BP and NNK from becoming DNA-damaging agents. Therefore, our results suggest that the most likely reason MTS does not induce BPDE-dG and O^6-medG adducts in lung and bladder tissues of exposed mice and in human lung tissues is that, in these tissues, Acr in MTS inhibits the CYP enzymes, which are necessary for the activation of PAHs and nitrosamines to become DNA-damaging agents.

Discussion

TS contains more than 60 known human carcinogens including PAHs, heterocyclic hydrocarbons, aromatic amines, and nitrosamines (12, 14). The mutagenicity, as well as carcinogenicity, in animal and cultured cell models of many TS carcinogens, particularly BP and NNK, are well established (12, 14). BP is a ubiquitous contaminant and a strong carcinogen in animal models (29, 30, 39). BPDE, a major electrophilic metabolite of BP, is a potent DNA-damaging agent and mutagen (29, 30, 39). It induces G-to-T transversion mutations similar to TS-induced mutations in the p53 gene (6, 54). BPDE, as well as other epoxide forms of PAHs, induce DNA damage in the p53 gene in human lung cells, preferentially at the TS-related lung cancer p53 mutational hot spots (55, 56). NNK by itself is a strong carcinogen in animal models; it induces tumors in different organs including the lungs (14). Hence, PAHs and nitrosamines, particularly BP and NNK, have been accepted as major causes for TS-related cancers (11–14, 24, 30, 50).

It is therefore puzzling that no BPDE-dG and O^6-medG adducts were found in the lung and bladder tissue of mice exposed to MTS (Figs. 1 and 2). Similar results have been found in mice exposed to side-stream TS, which is responsible for 20–30% of TS-related cancers and heart diseases (57–60). However, BPDE-dG and O^6-medG adducts were observed in lung tissues of mice exposed to BP or NNK alone exhibiting higher levels than those exposed to MTS (25, 61). We found that, indeed, BP and NNK can induce PdG and O^6-medG, respectively, in human lung and bladder epithelial cells. Therefore, induction of BPDE-dG and O^6-medG adducts are most likely a major carcinogenic mechanism in BP and NNK carcinogenesis. However, we also found that Acr can greatly inhibit this DNA damage induction effect of BP and NNK in human cells (Fig. 6). The total amount of TS aldehydes including Acr, Cro, Acet, and formaldehyde, is 10,000-fold more than PAHs and nitrosamines (14). We propose that aldehydes in TS, because of their abundance and capability to adduct proteins, inhibit CYP enzyme activities, which are necessary for the metabolism of PAHs and NNK to reactive forms that are able to adduct genomic DNA (Fig. 6). In fact, several reports have shown that Acr can inhibit the function of CYP enzymes (62–64).

It is well established that γ-OH-PdG and α-meth-γ-OH-PdG adducts are mutagenic, and that aldehydes can reduce DNA repair capacity (8, 34, 41). Furthermore, it has been found that Acet, Cro, and formaldehyde can induce tumors in animal models (65–67). Although the extremely high cardiopulmonary toxicity of Acr to mice has hampered the full evaluation of its lung carcinogenicity, it has been shown that, in combination with uracil, Acr also can induce bladder tumors in animals (68). Based on these results, we propose a paradigm for TS carcinogenesis: TS aldehydes such as Acr, Acet, formaldehyde, and Cro are the major TS lung and bladder carcinogens; their carcinogenicity is via induction of DNA damage, mainly γ-OH-PdG and α-meth-γ-OH-PdG adducts, and inhibition of DNA repair mechanisms including NER, BER, and mismatch repair. The abundance of aldehydes in TS also effectively prevents the metabolic activation process of the relatively small amount of TS procarcinogens such as PAHs, nitrosamines, aromatic amines, heterocycle hydrocarbons, and benzene, all of which require metabolic activation by CYPs to become carcinogenic DNA-damaging agents. Consequently, TS carcinogenicity is mainly a manifestation of aldehyde carcinogenicity, rather than an additive result of all TS carcinogens.

It is worth noting that the distribution of Acr-induced DNA damage in the p53 gene of human bronchial epithelial cells coincides with the p53 mutational spectrum of TS-related lung

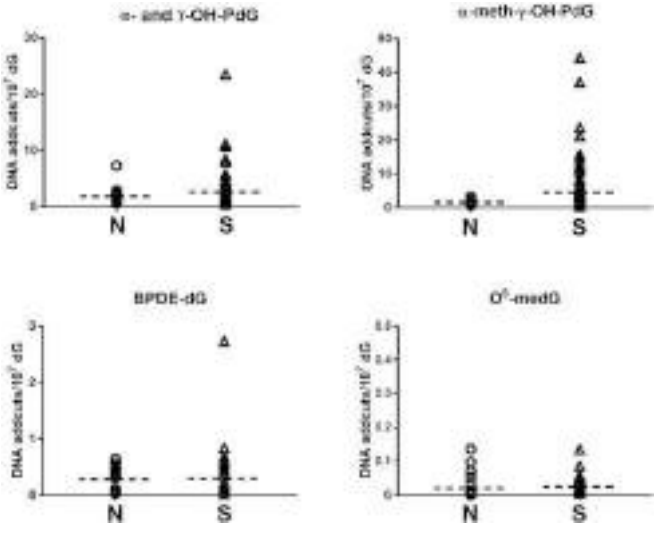

Fig. 5. Quantitations of α-OH-PdG, γ-OH-PdG, α-meth-γ-OH-PdG, BPDEdG, and O^6-medG adduct in human lung tissues. Lung tissue samples were obtained from 13 nonlung cancer patients of nonsmokers (N) and 41 lung cancer patients who were smokers (S). Only nontumor lung tissue samples from smoker lung patients were used for DNA adduct detection. Methods for DNA adduct detection are the same as described in Figs. 1, 2, and 4.

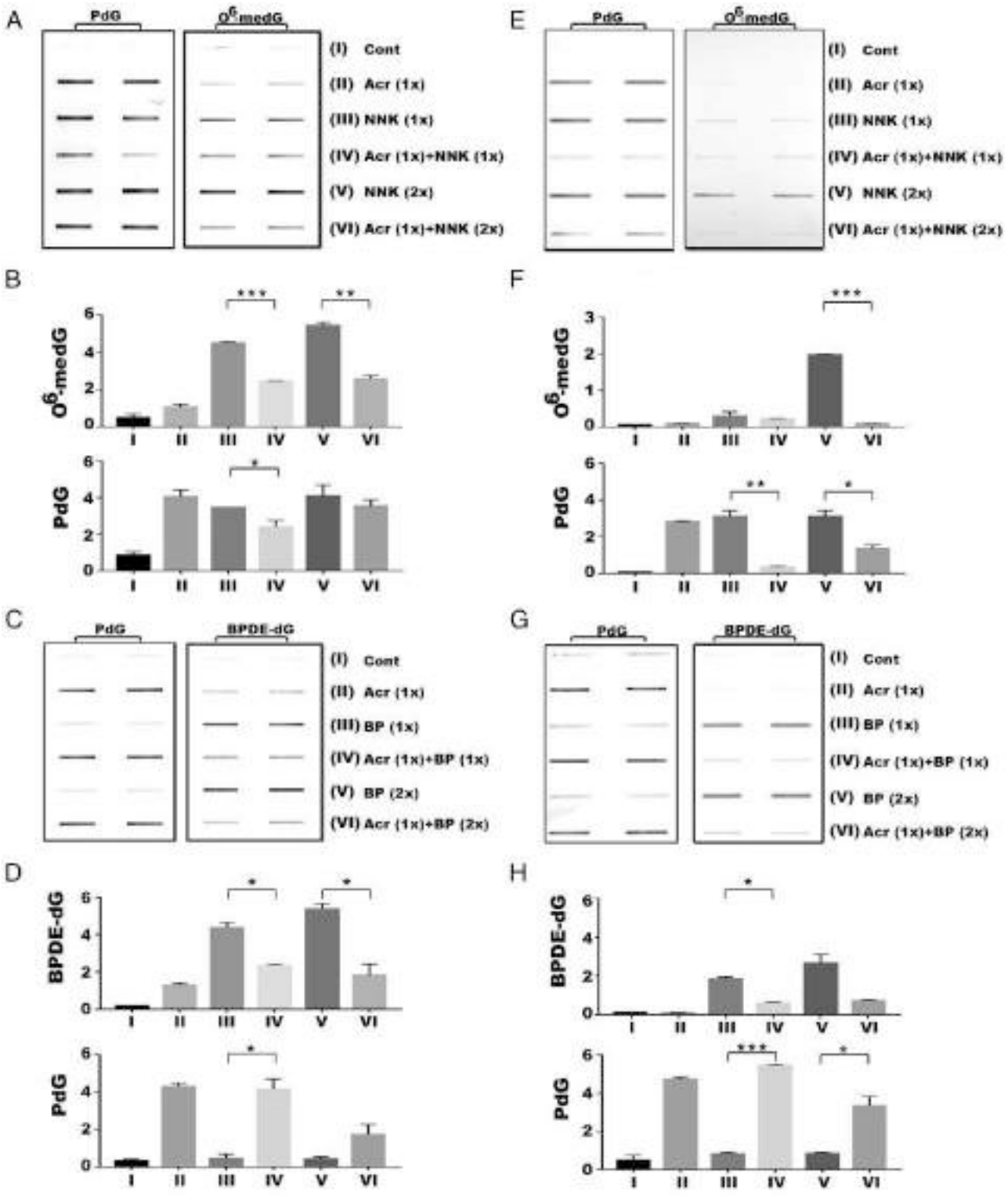

Fig. 6. Acr prevents BP and NNK from inducing DNA damage. Human lung epithelial BEAS-2B cells (*A–D*) and urothelial UROtsa cells (*E–H*) were treated with (*A* and *E*) NNK (1× = 75 μM and 2× = 150 μM) or (*C* and *G*) BP (1× = 25 μM and 2× = 50 μM) in the presence and absence of Acr (1× = 75 μM) for 1 h. (*A*, *C*, *E*, and *G*) The relative levels of BPDE-dG, O^6-medG, and PdG adducts were determined by the immunochemical method shown in Fig. 1. (*B*, *D*, *F*, and *H*) Quantification results. Symbols: (I), (II), (III), (IV), (V), and (VI) on the *x* axis of *B*, *D*, *F*, and *H* represent different treatments as shown in *A*, *C*, *E*, and *G*. Note: Acr significantly reduced BP- and NNK-induced BPDE-dG and O^6-medG adduct formation. ***$P < 0.001$, **$P < 0.01$, and *$P < 0.05$. NNK also reduced Acr-induced PdG formation (*SI Appendix*, Fig. S6).

cancer and that the percentage of G-to-T and G-to-A mutations induced by Acr is similar to those found in the p53 gene of human lung cancer patients (8, 41, 54). It has been found that the level of γ-OH-PdG adducts is 30–40 times higher than 4-aminobiphenyl-DNA adducts in normal human urothelial mucosa (35).

Our results raise the intriguing question of why the PdG adducts are not formed in heart and liver, but only in lung and bladder. The lung is the first major organ exposed to TS; therefore, lung cells are subjected to damage from all aldehydes in inhaled TS. Upon entering the bloodstream, we believe that the aldehydes are quickly conjugated with proteins in blood and that these protein-conjugated aldehydes are no longer able to enter cells in other organs such as the heart and liver. The protein-conjugated aldehydes in the bloodstream eventually are reversed into aldehydes and protein in the renal system and are then excreted in the urine. Therefore, bladder tissue is also exposed to the concentrated aldehydes in urine, which induce PdG in bladder cells. It should be noted that only γ-OH-PdG adducts are detected in human bladder mucosa (35). Why are only γ-OH-PdG adducts formed in bladder tissue? We found that the ability of Cro to induce PdG in urothelial cells in urine is less than one-third that in the Tris-buffer condition. In contrast, Acr's ability to induce PdG in urine is similar, if not identical, to its ability in Tris-buffer conditions (*SI Appendix*, Fig. S5).

Since MTS is inhaled directly into the aerodigestive system of smokers, human buccal cells and lung tissues are exposed to Acet and Cro, as well as Acr, which induce α-meth-γ-OH-PdG and γ-OH-PdG adducts, respectively (8, 32, 36). TS contains a fourfold higher amount of Acet and Cro than Acr (69). However, we found that the levels of γ-OH-PdG are eightfold to ninefold higher than the levels of α-meth-γ-OH-PdG in buccal cells of smokers, as well as in lung tissue of mice subjected to whole-body MTS exposure. We believe that since the boiling point of Acet is much lower than ambient temperature, a major portion of Acet in TS escapes from absorption by smokers, and that Cro is less efficient than Acr in inducing DNA adducts. We found that the levels of α-meth-γ-OH-PdG are slightly higher than the levels of γ-OH-PdG in lung tissues of smokers, although the reason is unclear. We found that the relative levels of these two types of PdG in buccal cells and lung tissues of smokers are different. The cause for this difference is unclear.

Our results that TS does not induce PdG, BPDE-dG, or O^6-medG adducts in liver tissue raise two important possibilities: First, TS-related liver cancer is not caused by aldehydes, BP, or NNK; and second, TS-related cancers in different organs may be caused by different carcinogens in TS. If these possibilities are correct, then it is necessary to determine the types of DNA damage induced by TS in different organs to design effective cancer preventive measures.

Last, but not least, our results indicate not only that PPE is effective in eliminating the effect of TS on inducing DNA damage in mouse lung and bladder tissues but also that it is effective in inhibiting DNA repair activity and reducing the abundance of repair protein in lung tissues. Similarly, polyphenols can greatly reduce the effect of Acr in DNA adduct induction and repair inhibition in cultured human lung and bladder epithelial cells. These results raise the possibility that polyphenols may be able to prevent TS-induced lung and bladder cancer. It is worth noting that epidemiology studies have suggested that tea consumption reduces lung cancer risk (70–72).

In 2015, there were 36.5 million tobacco smokers in the United States alone (73). Smokers are not the only people who are exposed to TS; innocent bystanders and family members of smokers are also exposed to TS. We found that side-stream TS also induces DNA damage and inhibition of DNA repair the same as MTS does (34). For the foreseeable future, TS will remain a major cause of human cancer. Our findings that aldehydes, rather than the PAHs and nitrosamines, are the major agents that induce DNA damage and inhibit DNA repair, the two carcinogenic mechanisms, provide crucial insights not only for cancer risk assessment but also for the design of clinically effective preventive measures for reducing TS-related cancers.

Similar to TS effects, we recently have found that electronic-cigarette smoke (ECS) induces γ-OH-PdG and O^6-medG in lung, heart, and bladder tissues, but not in liver tissue, and reduces DNA repair activity in lung tissue in the same mouse model with the same 12-wk exposure time (74). It should be noted that, whereas TS-induced DNA damage and repair inhibition are via the aldehydes in TS, which result from the incomplete combustion of tobacco leaves, ECS-induced DNA damage and repair inhibition are via aldehydes resulting from nitrosation, metabolism, and degradation of nicotine (74). These results indicate that the amount of TS and ECS consumption is most likely an important factor in determining the levels of DNA damage induction and DNA repair inhibition. These two effects, however, can serve as valuable parameters for assessing the relative harmful effects of TS and ECS.

Materials and Methods

Mice and Diet Supplement with PPE. Forty mice (male FVBN mice; 8 wk old; purchased from Charles River) were randomized into four groups (A, B, C, and D) with 10 mice in each group. Two groups (A and B) of mice were fed the AIN93M diet containing 0.1% PPE (NIA93M), and the other two groups (C and D) were fed the AIN93M diet as control. PPE was a gift from Dr. Yukihiko Hara (Mitsui Norin Company, Tokyo, Japan). The diet was prepared by Research Diets.

Exposure of Mice to MTS. The details of MTS and FA exposure method are as previously described (75–77). In brief, mice were exposed to MTS (groups A and D) or FA (groups B and C) 6 h/d, 5 d/wk for 12 wk. The MTS (~75 mg/m^3) was generated with an automated cigarette-smoking machine (CH Technologies), using 2R4F cigarettes (Kentucky Tobacco Research and Development Center). Three cigarettes were lit at a time, with an automatically regulated piston pump (2-s puff of 35-mL volume once per min) to produce MTS. The MTS produced from the cigarette was diluted by FA and introduced into a 1.3-m^3 stainless-steel chamber for animal exposure (75–77). Mice were killed 24 h after the last exposure. The lung, heart, liver, and bladder were collected from each animal and immediately frozen at −80 °C.

Genomic DNA Isolation and Cell Lysate Preparation. Genomic DNAs were isolated from lung, bladder, liver, and heart, as previously described (34). Cell-free cell lysates were prepared from lung tissues, as previously described (8, 33, 78).

DNA Damage and DNA Repair Function. The levels of DNA damage (PdG, BPDE-dG, and O^6-medG adducts) in lung, liver, heart, and bladder and the DNA repair capacity (NER and BER) in the lung tissues of all four groups of mice were determined. PdG adducts were determined by an immunochemical method and ^{32}P postlabeling, followed by 2D-TLC/HPLC analysis, as described (32–34) (*SI Appendix, Supplementary Methods*). BPDE-dG adducts were determined by an immunochemical method and a 3D-TLC method (33, 34) (*SI Appendix, Supplementary Methods*). O^6-medG adducts were determined by an immunochemical method and confirmed by an HPLC method (37, 38). The NER and BER capacity in cell lysates isolated from lung tissues was measured by their capacity to carry out DNA damage-dependent repair synthesis using ^{32}P-labeled dNTP as precursors and supercoiled DNA with UV- or H_2O_2-induced DNA damage as substrates as previously described (8, 33, 78).

Detection of DNA Repair Proteins. The effects of MTS exposure on the NER- and BER-related XPC and OGG1 protein levels in lung tissues were determined as previously described (33, 34).

Treatment of Human Bronchial Epithelial and Urothelial Cells with Acr and Polyphenols. Immortalized human bronchial epithelial cells BEAS-2B and urothelial cells UROtsa were pretreated with different concentrations of PPE (0, 20, 80, and 160 μg/mL) and PP-60 (0, 20, 40, and 80 μg/mL; Sigma) for 1 h at 37 °C. The medium was removed and replaced with fresh medium containing Acr (10 μM), and the cells were incubated for 1 h at 37 °C. The DNA repair activity and PdG formation in these cells were determined as described above (33–35, 78).

Effect of Acr on BP-Induced BPDE-dG Formation and on NNK-Induced O^6-medG Formation in Human Lung Epithelial Cells and Urothelial Cells. Human bronchial epithelial cells, BEAS-2B, and urothelial cells, UROtsa, with and without preincubation with Acr (75 μM) were incubated with BP (25 or 50 μM) or NNK

(75 or 150 μM) for 1 h. BPDE-dG, PdG, and O^6-medG adducts formed in the genomic DNA were detected by the immunochemical method as described (33–35).

Human Buccal Cells and Sputum. Buccal mucosa were collected using a cytologic brush, as described (79), per an approved IRB protocol. Sputum samples were collected by the method described (80). Collected buccal cells and sputum samples were immediately frozen at −80 °C. All subjects were free of lung cancer at the time of the initial screening. The smoking histories (pack-year) of these patients were based on patients' report. The method for purifying genomic DNA from buccal cells and sputum was the same as previously described (81).

Lung Tissues and Genomic DNA Isolation. The "normal lung tissue" samples from lung cancer patients of smokers (n = 41) were obtained from the marginal tissues that were free of tumors, as determined by surgeons, of surgical resected lung tumor. The lung tissue samples of non-lung cancer patients (n = 13) were obtained from the Lung Tissue Research Consortium of the National Heart Lung and Blood Institute under the National Institutes of Health (NIH). The lung tissues were dissected into small pieces on ice and used Dounce-type homogenizer with cell lysis buffer to loosen tissue cells. The method for purifying genomic DNA from these tissues was the same as previously described (34).

Effect of NNK on Acr-Induced PdG Formation. To determine the effect of NNK on Acr-induced PdG formation, different concentrations of NNK (0, 37.5, 75, 150, and 225 μM) were incubated with Acr (0.1 mM) in the presence of human genomic DNA in Tris buffer; the PdG adducts were detected by the immunochemical method, as described above (33).

Statistical Analysis. All statistical analyses were performed using Microsoft Excel and the statistical software GraphPad Prism 7. The geometric means were compared between different sample groups using two-sided Student's t tests.

ACKNOWLEDGMENTS. We thank Drs. Frederic Beland and Catherine B. Klein for reviewing this manuscript. This work was supported by NIH Grants 1P01CA165980, R01CA190678, P30CA16087, and ES00260.

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Effects similar to those seen in regular smokers and patients with chronic lung disease

E-cigarette vapour boosts the production of inflammatory chemicals and disables key protective cells in the lung that keep the air spaces clear of potentially harmful particles, reveals a small experimental study, published online in the journal *Thorax*.

The vapour impairs the activity of alveolar macrophages, which engulf and remove dust particles, bacteria, and allergens that have evaded the other mechanical defences of the respiratory tract.

The findings prompt the researchers to suggest that while further research is needed to better understand the long term health impact of vaping on people, e-cigarettes may be more harmful than we think, as some of the effects were similar to those seen in regular smokers and people with chronic lung disease.

Vaping is increasing in popularity, but most of the current body of research has focused on the chemical composition of e-cigarette liquid before it is vaped.

To find out how vaping might change this chemical soup, and what impact this might have, the researchers devised a mechanical procedure to mimic vaping and produce condensate from the vapour.

They extracted alveolar macrophages from lung tissue samples provided by eight non-smokers who had never had asthma or chronic obstructive pulmonary disease (COPD).

A third of the cells were exposed to plain e-cigarette fluid, a third to different strengths of the artificially vaped condensate with and without nicotine, and a third to nothing for 24 hours.

The results showed that the condensate was significantly more harmful to the cells than e-cigarette fluid and that these effects worsened as the 'dose' increased.

After 24 hours of exposure the total number of viable cells exposed to the vaped condensate was significantly reduced compared to the untreated cells, and condensate containing nicotine exaggerated this effect.

Exposure to the condensate increased cell death and boosted production of oxygen free radicals by a factor of 50, and it significantly increased the production of inflammatory chemicals -- more so when the condensate contained nicotine.

What's more, the ability of cells exposed to vaped condensate to engulf bacteria was significantly impaired, although treatment with an antioxidant restored this function and helped lessen some of the other harmful effects.

The researchers conclude that the vaping process itself can damage vital immune system cells, at least under laboratory conditions.

"Importantly, exposure of macrophages to [e-cigarette vapour condensate] induced many of the same cellular and functional changes in [alveolar macrophage] function seen in cigarette smokers and patients with COPD," they write.

In an accompanying podcast, lead author Professor David Thickett explains that many e-cigarette companies have been bought up by the tobacco giants, "and there's certainly an agenda to portray e-cigarettes as safe."

While e-cigarettes are safer than traditional cigarettes, they may still be harmful in the long term, he says, as the current body of research is in its infancy and not able to answer that question yet.

"In terms of cancer causing molecules in cigarette smoke, as opposed to cigarette vapour, there are certainly reduced numbers of carcinogens. They are safer in terms of cancer risk, but if you vape for 20 or 30 years and this can cause COPD, then that's something we need to know about," he states.

"I don't believe e-cigarettes are more harmful than ordinary cigarettes," he concludes. "But we should have a cautious scepticism that they are as safe as we are being led to believe."

Story Source:

Materials provided by **BMJ**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Aaron Scott, Sebastian T Lugg, Kerrie Aldridge, Keir E Lewis, Allen Bowden, Rahul Y Mahida, Frances Susanna Grudzinska, Davinder Dosanjh, Dhruv Parekh, Robert Foronjy, Elizabeth Sapey, Babu Naidu, David R Thickett. **Pro-inflammatory effects of e-cigarette vapour condensate on human alveolar macrophages**. *Thorax*, 2018; thoraxjnl-2018-211663 DOI: 10.1136/thoraxjnl-2018-211663

OPEN ACCESS

ORIGINAL ARTICLE

Pro-inflammatory effects of e-cigarette vapour condensate on human alveolar macrophages

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2018-211663).

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Received 8 February 2018
Revised 16 May 2018
Accepted 11 June 2018

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To cite: Scott A, Lugg ST, Aldridge K, *et al*. *Thorax* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/thoraxjnl-2018-211663

ABSTRACT

Objective Vaping may increase the cytotoxic effects of e-cigarette liquid (ECL). We compared the effect of unvaped ECL to e-cigarette vapour condensate (ECVC) on alveolar macrophage (AM) function.

Methods AMs were treated with ECVC and nicotine-free ECVC (nfECVC). AM viability, apoptosis, necrosis, cytokine, chemokine and protease release, reactive oxygen species (ROS) release and bacterial phagocytosis were assessed.

Results Macrophage culture with ECL or ECVC resulted in a dose-dependent reduction in cell viability. ECVC was cytotoxic at lower concentrations than ECL and resulted in increased apoptosis and necrosis. nfECVC resulted in less cytotoxicity and apoptosis. Exposure of AMs to a sub-lethal 0.5% ECVC/nfECVC increased ROS production approximately 50-fold and significantly inhibited phagocytosis. Pan and class one isoform phosphoinositide 3 kinase inhibitors partially inhibited the effects of ECVC/nfECVC on macrophage viability and apoptosis. Secretion of interleukin 6, tumour necrosis factor α, CXCL-8, monocyte chemoattractant protein 1 and matrix metalloproteinase 9 was significantly increased following ECVC challenge. Treatment with the anti-oxidant N-acetyl-cysteine (NAC) ameliorated the cytotoxic effects of ECVC/nfECVC to levels not significantly different from baseline and restored phagocytic function.

Conclusions ECVC is significantly more toxic to AMs than non-vaped ECL. Excessive production of ROS, inflammatory cytokines and chemokines induced by e-cigarette vapour may induce an inflammatory state in AMs within the lung that is partly dependent on nicotine. Inhibition of phagocytosis also suggests users may suffer from impaired bacterial clearance. While further research is needed to fully understand the effects of e-cigarette exposure in humans in vivo, we caution against the widely held opinion that e-cigarettes are safe.

Key messages

What is the key question?
► Do e-cigarettes have a negative impact on alveolar macrophage viability and function?

What is the bottom line?
► Vapourised e-cigarette fluid is cytotoxic, pro-inflammatory and inhibits phagocytosis in alveolar macrophages.

Why read on?
► This work demonstrates a nicotine dependent and independent effect and also examines how these effects may be abrogated.

INTRODUCTION

Electronic cigarettes, also known as electronic nicotine delivery systems (ENDS), were introduced over a decade ago and since 2010 the inhalation of e-cigarette vapour or 'vaping' has risen exponentially in both smokers and ex-smokers.[1] There is a significant body of published material on ENDS/e-cigarettes and despite varying opinions their main effects remain controversial. They may be a useful tool for reducing traditional cigarette smoking but for many they are simply a replacement nicotine delivery method. As such they may precipitate a new public health problem.[2] The public perception is that they are less of a health hazard than conventional cigarette smoking, yet the long-term effects of e-cigarettes remain to be elucidated.[2]

E-cigarettes have developed significantly in the last decade, increasing in complexity and capacity. They are now considered to be in the fourth generation, comprising highly modifiable devices capable of modulating the energy input used to generate vapour. Using ever increasing energy input, sub-ohm atomiser resistances and custom mixtures for electronic cigarette liquid (ECL), the effect of user exposure is becoming more uncertain and potentially a new health hazard.[3 4]

Prior to vaping, ECL is composed of humectants such as vegetable glycerin (VG) and propylene glycol (PG) with or without nicotine. Several potentially cytotoxic metal and silicate particles are present in e-cigarette vapour equal to or exceeding the levels found in traditional cigarette smoke.[5 6] Much of the current literature has focused on the effect of non-vapourised ECL or ECL condensate. However, such studies do not fully reflect the potential effect on an e-cigarette user as, importantly, the process of vaping itself causes changes in the chemical composition of ECL.[7–11] Recently, some studies have attempted a more physiological approach using aqueous extract systems similar to those used to create traditional cigarette smoke extract (CSE),[12] although this also results in considerable dilution. In vivo studies have also been carried out using whole animal aerosol exposure systems, without vaping, which have also predominantly focused

on the effects on the lungs-.[13 14] These studies showed exposure to unvaped fluid increased secretion of inflammatory markers, induced airway hyper-reactivity and caused lung tissue degradation in chronic exposure.[13 14] These studies demonstrated the potential negative impact of e-cigarette fluid exposure, however the proven change in composition caused by the vaping process has not been factored in these models.

For this study, we developed a novel system to generate e-cigarette vapour condensate (ECVC) to be a more physiological method of exposure. We hypothesised the change in chemical composition caused by vaping would increase cytotoxicity and moreover the presence of nicotine would exacerbate any cytotoxic and pro-inflammatory effects. Alveolar macrophages (AMs) are a unique lung cell population that eliminate airborne irritants and infectious agents, while also coordinating the initiation of resolution of lung inflammation.[15]

Disturbances in AM function could therefore increase the risk of infection and enhance susceptibility to chronic obstructive pulmonary disease (COPD). We also assessed the effects of our ECVC with and without nicotine on human AMs to determine if this is a key component and determine whether anti-oxidants abrogate any of the effects.

METHODS

Detailed methods are provided in the online supplement.

ECVC preparation

ECVC was prepared using a novel method employing six tracheal suction traps (Unomedical, Denmark) connected in series and cooled in a dry ice/methanol bath (see online supplementary figure E1a). We calculated the optimal puff duration of 3 s every 30 s based on published data.[16–21] This allows time for the vapour to condense between each puff and prevented overheating of the device; 1.4 mL of ECL/nicotine-free ECL (nfECL) was vaped from each device. On completion, suction traps were normalised to room temperature and spun at 1500g for 10 min to collect the condensate.

E-cigarette devices

We chose a second-generation END, popular in the UK, to produce condensate (Kanger Ltd, Shenzhen, China; see online supplementary figure E1b). The devices were fitted with a standard 650 mAh battery with a fresh 1.8 Ohm coil head (atomiser) for each preparation.

E-cigarette liquids

ECLs with and without pharmaceutical grade nicotine were obtained from American E-liquids Store (Milwaukee County Research Park, Wauwatosa, WI, USA), which adheres to US Food and Drug Administration (FDA) approved good manufacturing standards and has been used in previous animal exposure studies.[13] To avoid confounders, only flavourless liquids were used. Nicotine containing ECL was 36 mg/mL, nfECL was simply a 50:50 mixture of PG:VG.

Alveolar and THP-1 macrophages

AMs from eight never smokers, five men and three women, with normal spirometry and no history of asthma/COPD were obtained by repeated saline lavage from non-affected lung resection specimens (see online supplement for full extraction methods).

THP-1 human monocytic leukaemia cells (European Collection of Cell Cultures) were differentiated into macrophages by stimulation with 0.2 mM phorbol 12-myristate 13-acetate (PMA) for 24 hours. Adhered cells were rested in RPMI for 3 days before use.[22]

Gas chromatography–flame ionisation detector assessment of nicotine content

Gas chromatography–flame ionisation detector (GC-FID) assessment was performed by the University of Birmingham Chemistry Department to determine nicotine concentration. L-Nicotine standard (#10337220 Fisher Scientific, UK) was used as a reference standard for quantification.

Cellular methods

Viability was assessed using CellTiter 96 AQueous One Solution (Roche, UK). Apoptosis was assessed by flow cytometry using an Annexin V assay (BD Biosciences, UK) in combination with the vital dye propidium iodide (PI) (Sigma-Aldrich, UK). CXCL-8, interleukin (IL)-6, monocyte chemoattractant protein (MCP)-1, tumour necrosis factor (TNF)-α and matrix metalloproteinase (MMP)-9 levels in cell-free supernatants were quantified using commercially available ELISA kits (Biotechne, UK). Reactive oxygen species (ROS) were measured using DCFDA assay (Abcam ab113851) according to the manufacturer's instructions. Phagocytosis assay was carried out using pHrodo Red *Escherichia coli* or *Staphylococcus aureus* BioParticles (Invitrogen, UK) according to the manufacturer's instructions.

Statistical analyses

Statistical analyses were performed using GraphPad PRISM 6.0 software package (San Diego, California, USA). Results are expressed as the median with IQR, unless specified otherwise. All results are representative of at least eight independent experiments performed in duplicate. Differences between multiple treatments were compared by the Kruskal–Wallis test followed by Dunn's multiple comparison post-test correction. A P-value ≤ 0.05 was considered to represent a statistically significant difference.

RESULTS

Inter-batch variability of unvaped ECL

All condensates used in this study were generated from two batches of ECL. GC-FID data (table 1A) suggested actual nicotine content of ECL was 31.0 mg/mL and 30.7 mg/mL for batch 1 and 2 respectively. No nicotine was detected in nicotine-free liquids.

Validation of our model system of condensing vaped ECL

Detailed validation of our model of condensing vaped ECL is available in the online supplement (online supplementary figure E2). The model system proved both reliable and reproducible in terms of volume of recovery (60.8%), nicotine content (87%), as well as particulates (OD at 370 nm, table 1B). There was no significant variance in biological activity between each fresh preparation (online supplementary figure E2), however biological activity was lost over time with storage at −80°C (online supplementary figure E3, $P<0.0001$).

ECVC is significantly more cytotoxic to AM than ECL

AMs were exposed to ECL and ECVC for 24 hours, and produced a dos- dependent reduction in viability (figure 1). Unvaped ECL/nfECL effect on viability varied significantly compared with untreated control (UTC) following 2.5% (v/v) challenge (figure 1A, B): ECL: 78.8% viable (IQR 72.3%–87.6%, $P<0.001$), nfECL: 84.6% viable (IQR 83.9%–87.9%, $P<0.001$).

Table 1 Inter-batch variance. (A) Inter-batch variation between ECLs obtained from American e-liquids store was assessed by GC-FID to determine nicotine content. (B) Inter-batch variation between preparations of condensate was assessed by measurement of physical characteristics, including volume recovered, nicotine recovery, optical density and cytotoxic potential following a 24 hour challenge with each condensate. Preparations 1–3 were produced from ECL batch 1, preparations 4–6 were produced from ECL batch 2

	ECL batch	
(A)	1	2
Expected nicotine (mg/mL)	36.00	36.00
Observed nicotine (mg/mL)	31.00	30.70
Disparity	13.89	14.72
Mean OD 370 nm	0.22	0.21

	Condensate preparation								
(B)	1	2	3	4	5	6	Mean	SD	CV %
Input volume (µL)	1400	1400	1400	1400	1400	1400	1400	0	0
Volume recovered (µL)	850	870	830	860	810	890	851.7	28.6	3.4
Recovery (%)	60.7	62.1	59.3	61.4	57.9	63.6	60.8	2.0	3.4
Nicotine (mg/mL)	26	24.8	28	23.9	26.8	29.6	26.5	2.1	7.9
Recovery (%)	85.4	81.5	92.0	78.5	88.1	96.4	87.0	6.6	7.6
Mean OD 370 nm	0.47	0.51	0.52	0.50	0.56	0.55	0.52	0.2	6.7

ECL, e-cigarette liquid; GC-FID, gas chromatography-flame ionisation detector; OD, optical density.

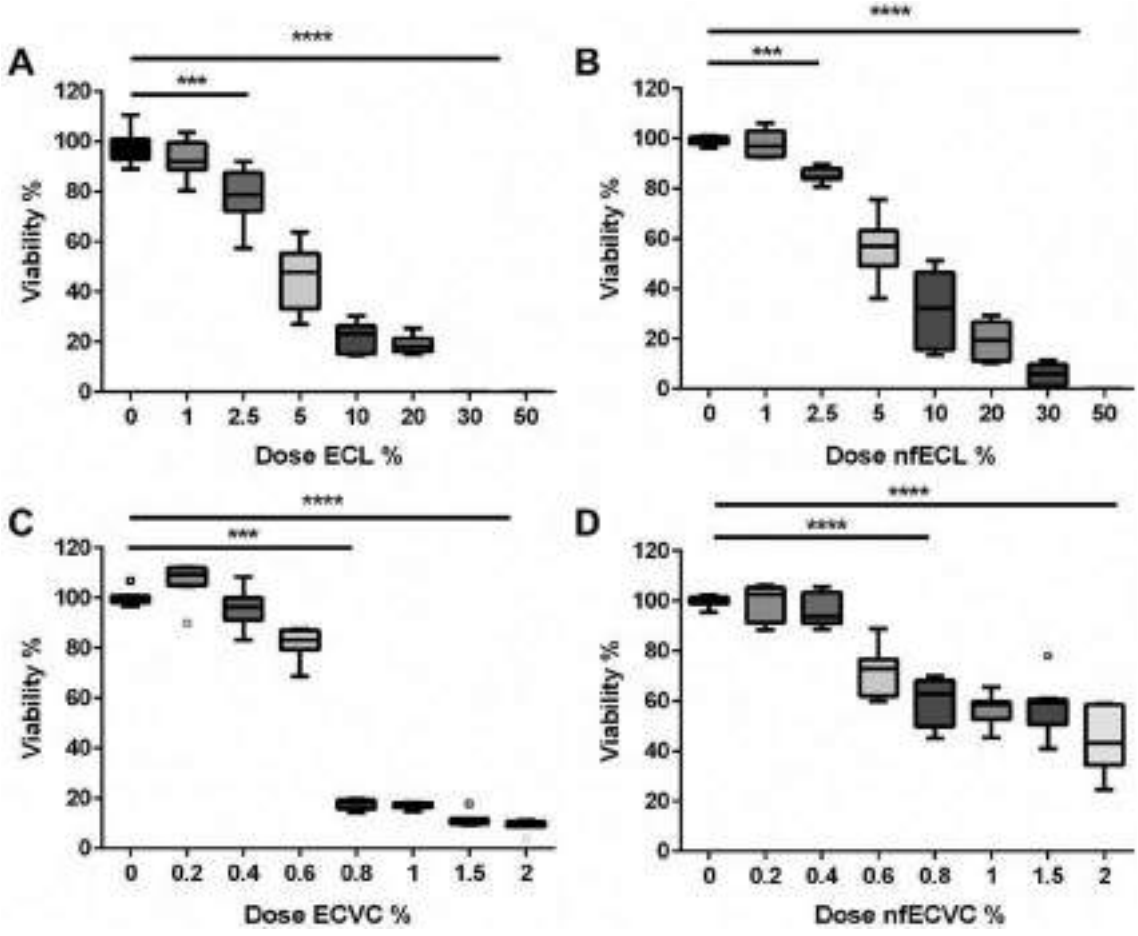

Figure 1 Effect of e-cigarette vapour condensate (ECVC) and -cigarette liquid (ECL) on alveolar macrophage viability. Viability was assessed by 4 hour incubation with cell titre aqueous assay following 24 hour exposure to a range of doses with (A) ECL, (B) nicotine-free ECL (nfECL), (C) ECVC, (D) nicotine-free ECVC (nfECVC). Graphs presented as median with IQR of eight independent experiments. The central horizontal line on each box plot represents the median, the upper and lower horizontal lines represent the first (Q1) and third (Q3) quartiles, respectively, and the vertical lines represent the range of values within the limits Q1–1.5 (Q3–Q1) and Q3–1.5 (Q3–Q1). n=8, *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

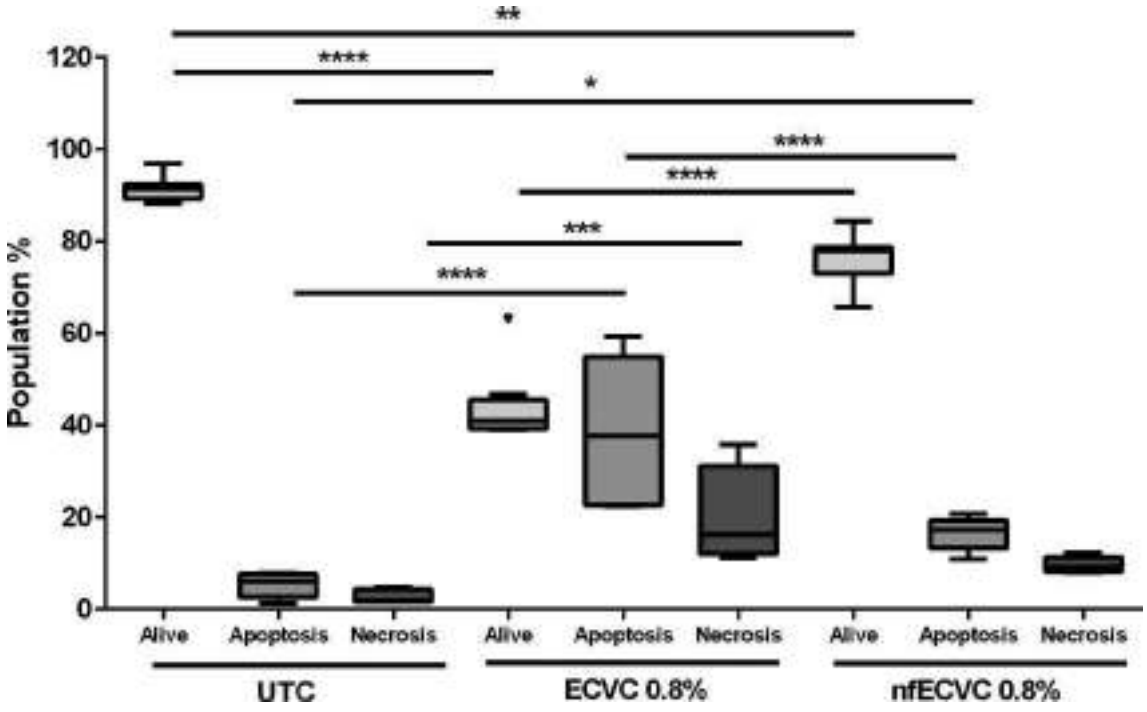

Figure 2 Effect of e-cigarette vapour condensate (ECVC)/nicotine-free ECVC (nfECVC) on alveolar macrophage (AM) apoptosis and necrosis. Induction of apoptosis and necrosis in AM following a 24 hour exposure to 0.8% ECVC/nfECVC. Graphs presented as median with IQR of eight independent experiments. The central horizontal line on each box plot represents the median, the upper and lower horizontal lines represent the first (Q1) and third (Q3) quartiles, respectively, and the vertical lines represent the range of values within the limits Q1–1.5 (Q3–Q1) and Q3–1.5 (Q3–Q1). n=8, *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. UTC, untreated control.

Contrastingly ECVC/nfECVC produced a greater reduction in viability following a 0.8% (v/v) challenge (figure 1C, D): ECVC: 18.2% viable (IQR 15.7%–19.5%, P<0.001), nfECVC 62.8% viable (IQR 49.9%–68.1% p<0.0001) compared with UTC. Viability of AMs was maintained better in the nicotine-free challenge (nfECL/nfECVC), than that containing nicotine (figure 1A/C vs B/D), suggesting that although vaping significantly increases the cytotoxic potential of ECL, much of the cytotoxic effect was nicotine dependent.

ECVC induces AM apoptosis and necrosis and is exaggerated by the presence of nicotine

AMs were exposed to 0.8% ECVC/nfECVC for 24 hours and compared with UTC. After 24 hours the majority of cells remained viable; median: 92.5% (IQR 91.5%–96.9%, (Annexin–/Pi-), with low levels of apoptosis (Annexin +cells): 6.17% (IQR 2.63%–7.77%), and necrosis (Annexin–/PI+): 1.9% (IQR 1.7%–4.4%) (figure 2).

After 24 hours, total viable cells were significantly reduced when treated with either ECVC (40.87% alive, IQR 39.29%–45.61%, P<0.0001) or nfECVC (77.94% alive, IQR 73.09%–78.69%, P<0.01) compared with UTC.

ECVC exposure significantly increased apoptosis (37.7%, IQR 22.7%–54.9%, P<0.0001) and necrosis (16.3%, IQR 12.1%–31.2%, P<0.001) compared with controls. Exposure to nfECVC also increased apoptosis significantly (17.36, IQR 13.28%–19.4%, P<0.05), but not necrosis (9.27%, IQR 8.3%–11.3%)

ECVC treatment induced significantly more apoptosis than nfECVC (17.4%, IQR 13.3%–19.4%, P<0.0001) and resulted in a greater total loss of viable cells after 24 hours of treatment (P<0.0001). These data confirm the cytotoxic effects of ECVC and support both a nicotine-dependent and nicotine-independent effect.

Effect of ECVC on macrophage function

The effects of sub-lethal ECVC exposure were assessed using measures of macrophage function important in the innate immune response, namely ROS production, cytokine, chemokine and protease release, as well as bacterial (*Escherichia coli* and *Staphylococcus aureus*) phagocytosis.

ROS are induced by ECVC treatment

ROS production was assessed following exposure of AMs to a sub-cytotoxic dose (0.5%) of ECVC/nfECVC for 4 hours. Untreated macrophages showed a low baseline level of ROS production (figure 3) (1085, IQR 863.7–1133 relative fluorescence units (RFUs)). Condensate challenge resulted in a 50-fold increase in ROS production for both ECVC (53 858, IQR 48 375–56 425 RFU, P<0.0001) and nfECVC (48 746, IQR 44 238–56 063 RFU, P<0.0001) compared with UTC.

Pro-inflammatory cytokines, chemokines and proteases are induced by 24 hour exposure to 0.5% ECVC

The effects on pro-inflammatory cytokines, chemokines and metalloprotease production is shown in figure 4. 0.5% ECVC significantly induced production of all analytes: IL-6 (P<000.1), TNF-α (P<0.001), CXCL8 (P<0.0001), MCP-1 (P<0.01) and matrix metalloprotease 9 (MMP-9) (P<0.0001) compared with UTC. The response to nfECVC was more variable, with a lower increase in IL-6 (P<0.001), CXCL-8 (P<0.0001) and MMP-9 (P<0.0001) compared with UTC. Non-significant changes were also seen for TNF-α and MCP-1.

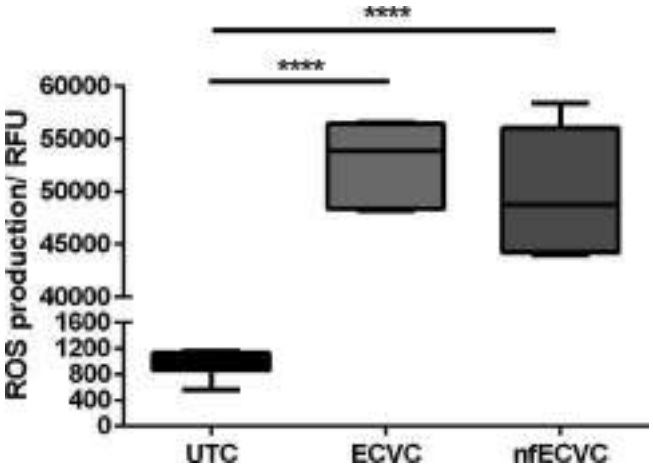

Figure 3 Functional effects of e-cigarette vapour condensate (ECVC)/ nicotine-free ECVC (nfECVC) exposure to alveloar macrophages (AMs) on reactive oxygen species (ROS). AMs were exposed to 0.5% ECVC/ nfECVC for 4 hours. Following this, production of ROS was assessed by DCFDA assay. Graphs presented as median with IQR of eight independent experiments. The central horizontal line on each box plot represents the median, the upper and lower horizontal lines represent the first (Q1) and third (Q3) quartiles, respectively, and the vertical lines represent the range of values within the limits Q1–1.5 (Q3–Q1) and Q3–1.5 (Q3–Q1). n=8, *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

ECVC significantly inhibits phagocytosis by AM and THP-1 macrophages

Incubation of AMs with ECVC and nfECVC reduced pHrodo *E. coli* BioParticle phagocytosis by 30% (P<0.0001) and 50.2% respectively (P<0.0001, figure 5A).

Incubation of THP-1 macrophages with ECVC and nfECVC reduced pHrodo *E. coli* BioParticle phagocytosis by 41.7% (P<0.0001) and 48.5% respectively (P<0.0001, figure 5B).

Incubation of THP-1 macrophages with ECVC and nfECVC reduced pHrodo *S. aureus* BioParticles phagocytosis by 60.9% (P<0.0001) and 62.9% respectively (P<0.0001, online supplementary figure E4).

The effect of N-acetyl cysteine treatment following ECVC challenge

ROS production in response to cigarette smoking (or smoke extract) has been implicated as a mediator of adverse effects,[23] therefore we examined the possible utility of N-acetyl cysteine (NAC) treatment in reducing the harmful effects of ECVC in THP-1 macrophages. Both AM and THP-1 macrophages were used for these experiments due to the large number of experimental conditions and numbers of cells required.

NAC can ameliorate the cytotoxic effects of ECVC on THP-1 derived macrophages

Similar to our observations in AMs, ECVC and nfECVC were cytotoxic to THP-1-derived macrophages (24.4%, IQR 21.8%–27.4%, P<0.0001; 62.8%, IQR 54.4%–68.4%, P<0.0001, respectively(. 1 mM NAC treatment given simultaneously with condensate challenge prevented the effects on viability of both ECVC and nfECVC compared with UTC (figure 6A).

NAC can ameliorate the pro-apoptotic effects of ECVC on THP-1-derived macrophages

ECVC challenge of THP-1 macrophages increased apoptosis to 36.1% (IQR 35.8%–39.8%, P<0.0001, figure 5B). Exposure to nfECVC increased apoptosis to a lesser degree (18.8%, IQR 13.8%–20.2%, P<0.0001, figure 6B). NAC treatment given simultaneously with condensate challenge significantly reduced apoptosis in both ECVC (5.9%, IQR 4.6%–7.4%, P<0.0001) and nfECVC (4.5%, IQR 2.4%–4.6%, P<0.0001) challenged cells (figure 5B).

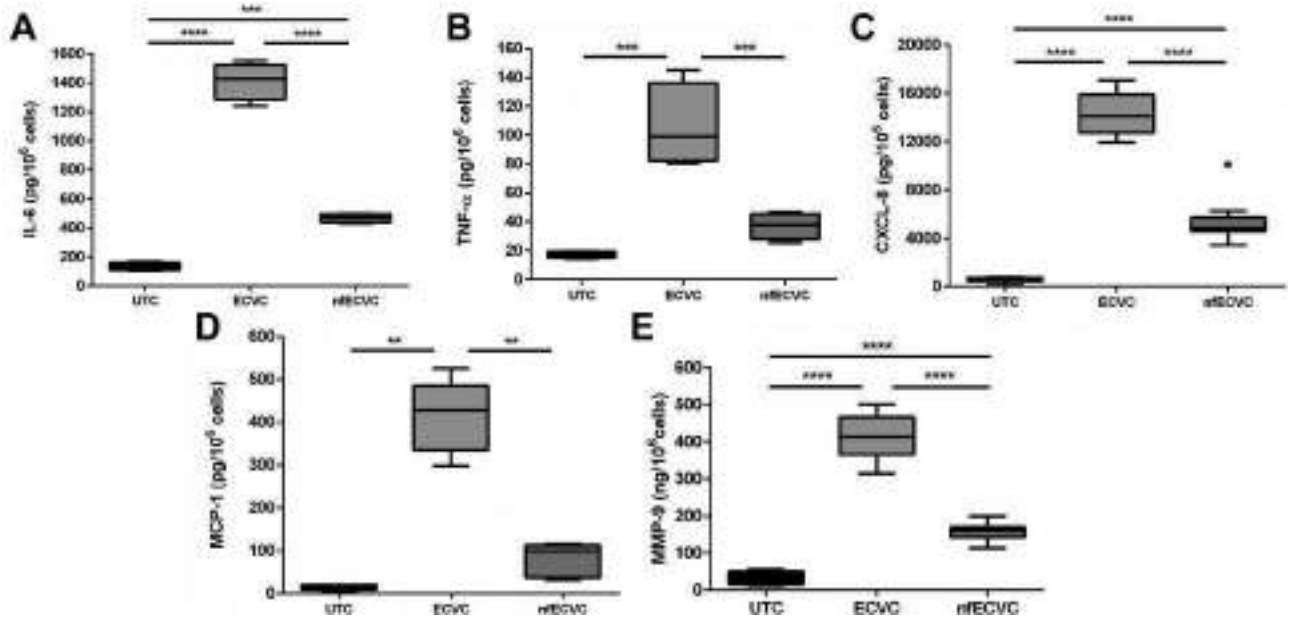

Figure 4 Functional effects of e-cigarette vapour conensate (ECVC)/nicotine-free ECVC (nfECVC) exposure to alveolar macrophages (AMs). Production of inflammatory cytokines (A, B), chemokines (C, D) and (E) matrix metalloproteinase (MMP-9). AMs following 24 hour exposure to ECVC (0.5%) as assessed by ELISA. Data are presented as pg/106 live cells at the end of the experiment to account for cell loss. n=8, *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

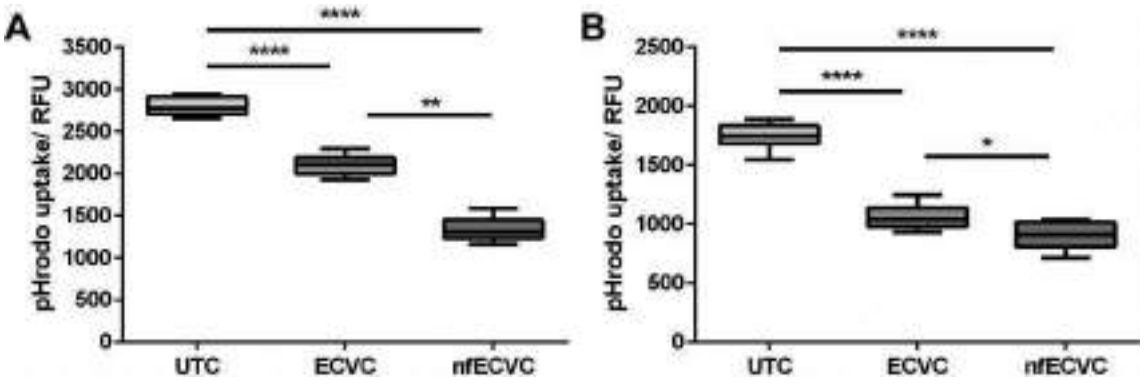

Figure 5 Functional effects of e-cigarette vapour condensate (ECVC)/nicotine-free ECVC (nfECVC) exposure to (A) alveolar macrophage (AM) and (B) THP-1 macrophage phagocytosis. Cells were exposed to 0.5% ECVC/nfECVC for 6 hours, following which uptake of pHrodo bioparticles was assessed. Graphs presented as median with IQR of eight independent experiments. The central horizontal line on each box plot represents the median, the upper and lower horizontal lines represent the first (Q1) and third (Q3) quartiles, respectively, and the vertical lines represent the range of values within the limits Q1–1.5 (Q3–Q1) and Q3–1.5 (Q3–Q1). n=8, *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. UTC, untreated control.

NAC can restore phagocytic function of ECVC-treated macrophages

Incubation of AMs with ECVC and nfECVC reduced pHrodo *E. coli* BioParticle phagocytosis (figure 6A). NAC (1 mM) given simultaneously with ECVC/nfECVC restored phagocytic function (P<0.001), although not to pretreatment levels (figure 7A).

Using THP-1 macrophages, an increased dose of NAC treatment was assessed to determine if a greater protective effect could be achieved. ECVC treatment reduced phagocytosis of *E. coli* pHrodo BioParticles by 41.9% (figure 6B, P<0.0001) and nfECVC by 48.4% (figure 7B, P<0.0001). Simultaneous treatment with NAC (5 mM) restored phagocytic function to levels comparable to the control (figure 6B, P<0.0001). Higher doses of NAC had an even greater restorative effect on cell function.

Phagocytosis of *S. aureus* pHrodo bioparticles was also significantly restored by simultaneous NAC treatment. (Online supplementary figure E4)

ECVC effects on THP-1 macrophage viability and apoptosis are attenuated by inhibitors of phosphopinositol 3 kinase

ROS-induced lung inflammation in COPD has been reported to be associated with phosphopinositol 3 kinase (PI3K) activation.[24] To explore a role for PI3K in ECVC-induced responses we used the pan- inhibitor LY294002 (5 nM) as well as an isoform selective inhibitor (PIK75 10 nM).

Both general PI3K inhibition (online supplementary figure E5a) and PI3K α isoform inhibitor (PIK-75, figure 8) attenuated the effects of ECVC (Ly294002; 37.4%, PIK75; 35% increase in viability compared with ECVC, P<0.0001). This protective effect was also evident when cells were challenged with nfECVC (Ly294002 25%, PIK75 29.2% increase in viability compared with nfECVC, P<0.0001). PI3K inhibition was also shown to partially restore phagocytic capacity (online supplementary figure E6), after challenge with sub-cytotoxic levels of both ECVC (Ly294002; 21.3%, PIK75; 23.2% restoration compared with ECVC alone, P<0.005) and nfECVC (Ly294002; 25.8%, PIK75; 20.9% compared with nfECVC alone, P<0.005).

DISCUSSION

We have validated a simple, cheap and effective system for condensing vaped ECL vapour to enable in vitro work. This is the first study to report human AM responses to ECVC and demonstrates dose-dependent cytotoxicity, inducing apoptosis with both nicotine dependent and independent responses

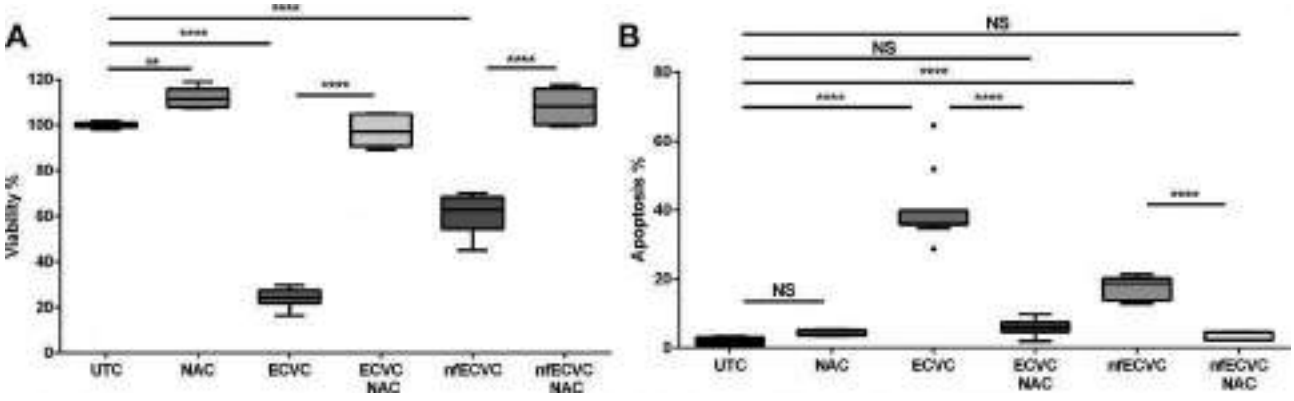

Figure 6 Effect of antioxidant treatment on macrophages. (A) Viability following 24 hour exposure to e-cigarette vapour condensate (ECVC)/nicotine-free vapour condensate (nfECVC) in the presence or absence of N-acetyl cysteine (NAC). Graphs presented as median with IQR of eight independent experiments. (B) Apoptosis following 24 hour exposure to ECVC/nfECVC, in the presence or absence of NAC. Graphs presented as median with IQR of six independent experiments. The central horizontal line on each box plot represents the median, the upper and lower horizontal lines represent the first (Q1) and third (Q3) quartiles, respectively, and the vertical lines represent the range of values within the limits Q1–1.5 (Q3–Q1) and Q3–1.5 (Q3–Q1). n=8, *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. UTC, untreated control.

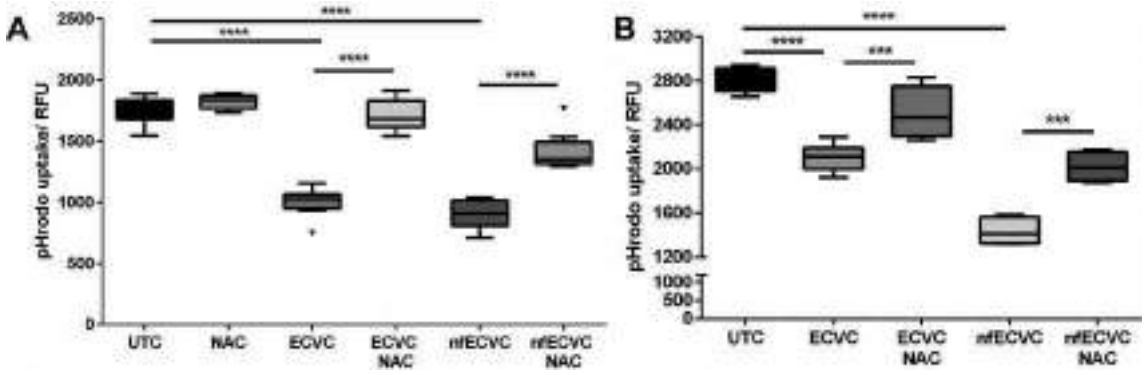

Figure 7 Functional effects of e-cigarette vapour condensate (ECVC)/nicotine-free vapour condensate (nfECVC) phagocytosis. (A) Alveolar macrophages (AMs) exposed to 0.5% ECVC/nfECVC for 6 hours in the presence or absence of 1 mM NAC treatment, following which uptake of pHrodo bioparticles was assessed. (B) THP-1 macrophages were exposed to 0.5% ECVC/nfECVC for 6 hours, in the presence or absence of 5 mM NAC treatment, following which uptake of pHrodo bioparticles was assessed. Graphs presented as median with IQR of eight independent experiments. The central horizontal line on each box plot represents the median, the upper and lower horizontal lines represent the first (Q1) and third (Q3) quartiles, respectively, and the vertical lines represent the range of values within the limits Q1–1.5 (Q3–Q1) and Q3–1.5 (Q3–Q1). n=8, *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. UTC, untreated control.

which the vaping process accentuates. At sub-cytotoxic doses, ECVC enhances production of ROS, inflammatory cytokines, chemokines and metalloproteinases, although the response is less pronounced with nfECVC. Bacterial phagocytosis by macrophages is inhibited acutely by ECVC and the effects are attenuated by the anti-oxidant NAC, suggesting ROS and reactive aldehydes play a role in the effects of ECVC/nfECVC. These effects appear to be partially PI3K dependent.

We have confirmed that vaping exaggerates the cytotoxic effects of ECL, inducing both cellular apoptosis and necrosis. These effects were seen when AMs were treated with both ECVC and nfECVC, suggesting both nicotine dependent and independent mechanisms.

Several studies have examined the change in composition of e-cigarette vapour,[2 3 7–11] and have identified many different chemicals that could be toxic, including free radicals, particulates, formaldehyde, nitrosamines, volatile organic compounds and polycyclic aromatic hydrocarbons.[3 8] Importantly, the levels of several of these toxicants have been reported to be increased after vapourisation, due to heat and/or voltage generated by the battery in e-cigarettes.[2 3 7–11] Many variables affect constituents of the vapour produced: the nicotine content, the ratio of humectants PG and VG present, the energy input used in the vapourising process, and the temperature achieved are all important factors.

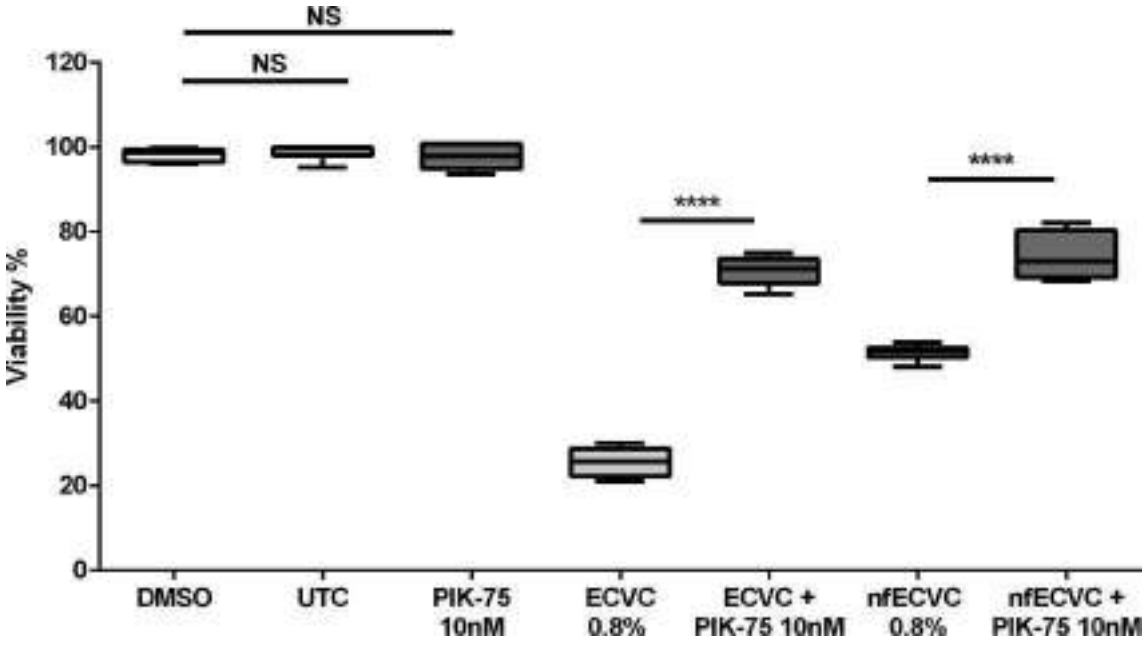

Figure 8 Effect of e-cigarette vapour condensate (ECVC)/nicotine-free ECVC (nfECVC) and phosphopinositol 3 kinase (PI3K) inhibitor PIK-75 on alveolar macrophage viability. Viability was assessed by 4 hour incubation with cell titre aqueous assay following 24 hour exposure to class one specific PI3K inhibitor PIK-75 and challenged with ECVC or nfECVC (0.8%). Graphs presented as median with IQR of six independent experiments. The central horizontal line on each box plot represents the median, the upper and lower horizontal lines represent the first (Q1) and third (Q3) quartiles, respectively, and the vertical lines represent the range of values within the limits Q1–1.5 (Q3–Q1) and Q3–1.5 (Q3–Q1). n=8, *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. UTC, untreated control.

E-cigarette vapour has been reported to contain up to 7×10^{11} free radicals per puff.[10] Both nicotine-free and nicotine-containing condensate induced a significant increase in ROS release from our AMs, which may explain the induction of apoptosis in nicotine-free liquid. There was significantly greater ROS production in AMs treated with nicotine-containing condensate than in nicotine-free condensate, once again suggesting both nicotine dependent and independent mechanisms at work. Consistent with our results, nicotine has been shown to increase ROS production in both epithelial cells[25] and macrophages.[26] A recent patient study by Reidel *et al* examined the protein content of induced sputum in e-cigarette users and smokers.[27] In support of our findings, proteomic analysis showed significant upregulation of oxidative stress-related proteins in both smokers and vapers, such as MMP-9, known to be implicated in inflammatory lung diseases such as COPD. The effects of ECVC with and without were ameliorated by NAC and PI3K inhibition.

Sub-lethal exposure of AMs to ECVC induced significantly more cytokine, chemokine and MMP-9 production than nfECVC. Others have similarly reported a significant induction of IL-6 and CXCL-8 in H292 cells following exposure to ECL but not following nfECL challenge.[28] The importance of nicotine in ECL is reflected in the lesser effect on cytokine release and was also recently confirmed in vivo in a murine aerosol model using unvaped fluid.[5]

Detection and phagocytosis of pathogens is key to macrophage function and in many cases is the first step in orchestrating an immune response to infection in the airways. Any effect of e-cigarette vapour on the phagocytic ability of AMs is therefore of potential significance to the innate immune response in vivo. At sub-cytotoxic levels both ECVC and nfECVC inhibited phagocytosis of *E. coli* and *S. aureus*, suggesting vaping might significantly impair bacterial clearance. Our data are supported by murine models in which mice exposed to e-cigarette vapour showed significantly impaired pulmonary bacterial clearance compared with air-exposed mice following an intranasal infection with *Streptococcus pneumoniae*. This defective bacterial clearance was due to reduced phagocytosis by AMs from e-cigarette vapour exposed mice.[29] A recent human volunteer study[30] found e-cigarette vapour significantly increased platelet-activating factor receptor (PAFR) expression, which aids pneumococcal adhesion to airway cells. In vitro PAFR is significantly upregulated by inducers of oxidative stress such as traditional cigarette smoke. Miyashita *et al* demonstrated increased PAFR leads to increased pneumococcal adhesion.[30] A broader study also found risk of bronchitic symptoms was increased by almost twofold among e-cigarette users.[31] These studies in human volunteers support our suggestion that e-cigarette usage may lead to increased or more serious respiratory tract infections, however further community-based studies will be required to fully assess the effect on lung health of e-cigarette users.

Interestingly, in these experiments nfECVC produced a greater inhibitory effect than ECVC on phagocytosis. Activation of nicotinic acetylcholine receptors (nAChR) has been shown to upregulate phagocytosis in tissue-resident macrophages.[32] Nicotine may therefore be offsetting some of the inhibitory effects in both ECVC and nfECVC, which are working through a nicotine-independent mechanism.

Cytotoxic compounds generated during the vaping process,[3 8] such as reactive aldehyde species—formaldehyde, acetyl aldehyde and acrolein—are known to induce apoptosis by lipid peroxidation.[33] Reactive aldehydes further cause the accumulation of 4-hydroxynonenal (4-HNE) which can induce apoptosis via the Fas-mediated and P53-dependent pathways. HNE formation can also be caused by inflammation-induced ROS.[34 35] With this in mind, we performed experiments using THP-1-derived macrophages challenged with a cytotoxic dose (0.8%) of ECVC/nfECVC in the presence and absence of NAC, a well characterised anti-oxidant and anti-aldehyde. NAC significantly attenuated both the cytotoxic activity and pro-apoptotic effects of condensate with or without nicotine. As shown with AMs, in THP-1 macrophages, ECVC caused significantly greater loss of viability and significantly more apoptosis than nfECVC, again suggesting a nicotine dependent and independent mechanism of action.

Traditional cigarette smoking is implicated as the cause of COPD in at least 20% of smokers, which is characterised by increased neutrophilic inflammation and oxidative stress within the lung.[24 36 37] The effects of oxidative stress in epithelial cells are mediated through micro-RNA34a via activation of PI3Kα.[24] Micro-RNA34a has been implicated in accelerated cellular senescence, inducing a proliferative, apoptotic phenotype. These effects were aborogated by use of PI3K inhibitors restoring the baseline phenotype.[24] Nicotine receptor seven is highly expressed on alveolar macrophages and its activation has also been shown to activate PI3K.[38 39] We therefore examined the effects of pan PI3K inhibitor Ly294002 and class one isoform selective inhibitor PIK-75 on THP-1-derived macrophages. There was a significant protective effect after PI3K inhibition with Ly294002. This effect was mostly conserved when class one isoform inhibitor PIK-75 was used. PIK-75 selectively inhibits the p110α subunit 200-fold more potently than p110β subunit, suggesting a large portion of the activity is moderated through the class one isoform. However, further work remains to be carried out to fully elucidate the mechanism(s) of action of ECVC/nfECVC on AMs.

This study has limitations. First, we have used an in vitro study on primary AMs with exposure levels which may not be physiological but are more reflective of the inhalant. In addition, the nicotine-containing ECL we selected has been shown to induce changes reflective of COPD in mice, suggesting the results have physiological plausibility. Second it is difficult to determine an optimal dose of nicotine exposure. In this study we have used 0.8% ECVC (containing 208 µg/mL nicotine) and 0.5% ECVC (containing 130 µg/mL nicotine). It is not possible to determine a standard nicotine dose for smoking experiments as each individual will titrate their nicotine intake to match their requirement. An average cigarette has 10–14 mg of nicotine,[40] and while the majority of this nicotine is not absorbed, intake is approximately 1–1.5 mg.[41] Puffing topography studies of e-cigarette users[16 20] have shown nicotine intake of approximately 1.2 mg in a 20 min vaping session, with users also titrating intake to maintain their specific plasma nicotine concentration. There is a lack of information about epithelial lining fluid levels of nicotine in smokers. AM exposure in vivo will also vary according to techniques used by users to modify their nicotine intake, such as depth and frequency of intake as well as breath-holding/expiration.[16 20 42]

Third, our model represents an acute exposure, rather than a chronic exposure system which is better suited to in vivo animal experiments. Fourth, there is currently a huge disparity in the literature regarding e-cigarettes. Many groups have championed the benign nature of ECL while others have shown the cytotoxic effects of ECL in vitro and in vivo. This disparity may reflect the lack of a standardised model of in vitro cellular exposure and interpretation. Therefore, until a gold standard is established, continued controversy is likely. However, our model seeks to replicate the actual exposure of the users' AMs post vaping. We believe this is an important step in establishing an in vitro system

by which to investigate the effects of e-cigarettes on the airways. Finally, we have not assessed the effects of flavours on cellular effects,[43] partly because this adds another layer of uncertainty and potential confounders. However, the data provide a background on which to study these other potential factors, with and without nicotine.

In conclusion, we sought to replicate the potential effects of exposure of the user in an acute in vitro system using our vaping-condensate technique. We show a significant increase in cytotoxicity caused by the vaping process itself. Importantly, exposure of macrophages to ECVC induced many of the same cellular and functional changes in AM function seen in cigarette smokers and patients with COPD. While further research is needed to fully understand the effects of e-cigarette exposure in humans in vivo, we suggest continued caution against the widely held opinion that e-cigarettes are safe.

Contributors Author Contributions: Concept and design: DRT, AS, STL, DD, KEL, BN, RF. Cell preparation, laboratory work and data analysis: AS, RM, STL, KA. GCFID-AB. Additional laboratory work: FSG. Patient recruitment: BN, DRT, DP, RM. Drafting manuscript: AS, DRT. ALL authors have read and approved the manuscript.

Funding DRT (G1100196/1), ES (MR/L008335/1), AS (MR/L002736/1) and RM (MR/N021185/1) were funded by the MRC. AS, STL and DD were supported by the British Lung Foundation (PPRG16-12).

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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PLOS ONE

RESEARCH ARTICLE

The association between electronic-cigarette use and self-reported oral symptoms including cracked or broken teeth and tongue and/or inside-cheek pain among adolescents: A cross-sectional study

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OPEN ACCESS

Citation: Cho JH (2017) The association between electronic-cigarette use and self-reported oral symptoms including cracked or broken teeth and tongue and/or inside-cheek pain among adolescents: A cross-sectional study. PLoS ONE 12 (7): e0180506. https://doi.org/10.1371/journal.pone.0180506

Editor: Yu Ru Kou, National Yang-Ming University, TAIWAN

Received: February 25, 2017

Accepted: June 18, 2017

Published: July 11, 2017

Data Availability Statement: Data are available from Figshare: https://figshare.com/articles/kyrbs2016_sav/5146498.

Funding: The study was supported by the 2016-2nd semester Hanyang Women's University Research Fund (2016-2-034). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Background

Little is known about oral health related to electronic-cigarette (EC) use, even though EC use is increasing rapidly. The aim of this study is to assess the relationship between EC use and oral health, including 'gingival pain and/or bleeding', 'tongue and/or inside-cheek pain', and 'cracked or broken teeth' among adolescents.

Methods

A total of 65,528 students in 2016 were included in this cross-sectional study.

Results

For EC use, 0.5% (n = 297) students were daily users, 1.9% (n = 1259) were '1 to 29 days past month users', and 5.9% (n = 3848) were former users. Overall, 18.5% students reported they had experienced 'gingival pain and/or bleeding', 11.0% reported 'tongue and/or inside-cheek pain', and 11.4% reported a 'cracked or broken tooth' within the past 12 months. When comparing 'daily EC users', '1 to 29 days past month EC users', and 'former EC users' with 'never EC users', the adjusted ORs for 'cracked or broken tooth' were 1.65 (95% CI: 1.19–2.27), 1.26 (95% CI: 1.06–1.51), and 1.16 (95% CI: 1.04–1.30), respectively. Comparing 'daily EC users' with 'never EC users', the adjusted OR for 'tongue and/or inside-cheek pain' was 1.54 (1.05–2.26). However, EC use among adolescents was not associated with 'gingival pain and/or bleeding' when adjusted for the potential confounders.

Conclusions

Based on the results, the odds of cracked or broken teeth among daily, '1 to 29 days past month', and former EC users were significantly higher than those among never EC users. The odds of tongue and/or inside-cheek pain among daily EC users were significantly higher

Competing interests: The authors have declared that no competing interests exist.

than those among never EC users. In conclusion, the results suggest that daily EC use among adolescents may be a risk factor for cracked or broken teeth and tongue and/or inside-cheek pain.

Introduction

Electronic cigarettes (EC) are battery-powered electronic devices, which aerosolize liquid that contains nicotine, humectants, and flavors [1]. EC use has increased rapidly and globally, particularly among smokers and adolescents [2]. During 2010–2013, ever EC use increased among current conventional cigarettes (CC) smokers (9.8%–36.5%) and among former CC smokers (2.5%–9.6%) in a study of US adults. Among Korean adolescents, ever EC use was 0.5% in 2008 and increased to 8.2% in 2014 [3]. In Poland, ever EC use among high school students increased from 16.8% in 2010/11 (n = 1,760) to 62.1% in 2013/14 (n = 1,970) [4]. The North Carolina Youth Tobacco Survey found that prevalence of use in the past 30 days increased from 1.7% in 2011 (n = 4,791) to 7.7% in 2013 (n = 4,092) [5]. The issues regarding their effectiveness as a smoking cessation aid and health risks due to EC use are still controversial [6]. So far, there is no strong evidence in regards to their safety, although there are reports that ECs may be less harmful to users and bystanders, than CCs [7]. It is known that the main reasons for using ECs are to quit CCs, as an alternative to CCs, curiosity, appealing flavors, and peer influences [8, 9].

Oral disease is one of the most common public health issues worldwide and constitutes a significant socio-economic burden [10]. Oral health is an important part of the quality of life among adolescents [11] and can influence school attendance [12]. Over 7% of American children have already lost at least one tooth in their lifetime because of cavities by the age of 17 [13]. Biology, lifestyle, and environment are important factors of oral health [14]. Tobacco products are one of the risk factors for oral health. For example, CC smoke impairs innate defenses against pathogens, modulates antigen presentation and immunity in the oral cavity, and promotes gingival and periodontal disease and oral cancer [15]. Additionally, the messenger RNA expression of dentin matrix acidic phosphoprotein-1, bone sialoprotein, and alkaline phosphatase activity significantly decreased in nicotine-treated human dental pulp cells, and mineralized nodule formation was also inhibited [16]. Namely, nicotine inhibits the cytodifferentiation and mineralization of human dental pulp cells, possibly via nicotinic acetylcholine receptors. Besides, a recent experimental research reported that EC aerosols caused cytotoxicity to oral epithelial cells, and the molecular mechanisms might be due to oxidative stress induced by toxic substances present in EC aerosols [17]. Moreover, ECs increased inflammatory and pro-senescence responses in oral epithelial cells and periodontal fibroblasts [18]. A previous report to dental professionals has recommended that all patients should be advised about the unknown dangers of ECs because there were no product standards that would control levels of dosing, chemicals, or carcinogens in the solution used in ECs or the aerosols [19].

Even though EC use is increasing rapidly, little is known about oral health related to EC use. There has never been a representative population study assessing the association of EC use with oral health among adolescents or among adults. Therefore, the aim of this study was to assess the association between EC use and oral symptoms that includes 'gingival pain and/or bleeding', 'tongue and/or inside-cheek pain', and 'cracked or broken teeth' among adolescents in South Korea.

Methods

Study population

The Twelfth Korean Youth Risk Behavior Web-based Survey (KYRBWS) was approved by an institutional review board of the Korean Center for disease Control and Prevention (2014-06EXP-02-P-A). This study was reviewed by the Institutional Review Board of Hanyang Women's University and complied with ethical requirements (AN01-201504-HR-010-01). Data used was from the Twelfth KYRBWS, 2016, Ministry of Education, Ministry of Health and Welfare, and Korean Center for Disease Control and Prevention [3, 20]. The understanding, reliability and validity of the questions were investigated by the Centers for Disease Control and Prevention of Korea (KCDC) [21]. The Eleventh KYRBWS provides a representative sample of all middle and high school students in Korea, ranging from 7^{th} to 12^{th} school grade students. The population was sampled from 400 middle and 400 high schools. Out of 67,983 students, 65,528 students responded, an overall response rate of 96.4% from 798 schools. Out of 33,251 middle school students, 32,219 students responded, an overall response rate of 96.9%. Out of 34,732 high school students, 33,309 students responded, an overall response rate of 95.9%.

Outcome definition

Oral symptoms were defined as an outcome on a student's self-report. Students were asked the question: "Within the past 12 months, have you experienced gingival pain and/or bleeding?" (yes/no). Students were also asked the question: "Within the past 12 months, have you experienced tongue and/or inside-cheek pain?" (yes/no). Students were lastly asked the question: "Within the past 12 months, have you experienced a cracked or broken tooth?" (yes/no).

EC use

EC use was defined by the question, "Have you ever used an EC in your life, even one or two puffs?" (yes/no). A no answer was categorized as 'never user.' Respondents who answered in the positive were asked the next question: "During the past 30 days, on how many days have you used ECs?" Respondents answering 'none' were categorized as a 'former user.' Positive responses were re-categorized into two groups: '1 to 29 days past month user: 1 to 29 days use' and 'daily user: all 30 days use.' A report of the Surgeon General on smoking assessed current CC smoking prevalence for youth and young adults based on having smoked all or part of at least one cigarette in the past 30 days [22]. Similarly, current EC users are usually defined as adolescents who indicated use in the past 30 days. In this study, however, in order to assess the daily EC use effects, we re-classified the 'past 30 day users' into two groups as above. First EC experience was defined by the question: "When did you experience ECs for the first time?" Response options were re-categorized into five groups: 'never EC users,' '10^{th}– 12^{th} grade', '7^{th} -9^{th} grade', '1^{st} - 6^{th} grade', and '$<1^{st}$ grade.' We also assessed the reasons for using ECs applying the questions "What is the main reason for using ECs?" The response options were 'it seems to be healthier than CCs', 'to quit smoking CCs', 'to use them indoors', 'it is easier to get ECs than CCs', 'good taste', 'good flavors', 'doesn't smell bad', 'curiosity', and 'other.' We assessed sources from which EC users acquire EC-liquids using the questions "How do you usually get EC-liquids?" The response options were 'from friends', 'purchase from an EC shop', 'purchase through the internet', 'other', and 'only purchase nicotine free EC-liquids.' The response options were also re-classified into two groups: 'nicotine-free EC user in the past 30 days' and 'nicotine-containing EC user in the past 30 days.' Unless explicitly specified, all EC fluids in Korea contain nicotine due to their popularity. Also, only ECs which contain

Characterization of Electronic Cigarette Aerosol and Its Induction of Oxidative Stress Response in Oral Keratinocytes

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Research Article

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- Published: May 25, 2016
- https://doi.org/10.1371/journal.pone.0154447

- Media Coverage
- Figures

Correction

29 Dec 2016: Ji EH, Sun B, Zhao T, Shu S, Chang CH, et al. (2016) Correction: Characterization of Electronic Cigarette Aerosol and Its Induction of Oxidative Stress Response in Oral Keratinocytes. PLOS ONE 11(12): e0169380. https://doi.org/10.1371/journal.pone.0169380 View correction

Abstract

In this study, we have generated and characterized Electronic Cigarette (EC) aerosols using a combination of advanced technologies. In the gas phase, the particle number concentration (PNC) of EC aerosols was found to be positively correlated with puff duration whereas the PNC and size distribution may vary with different flavors and nicotine strength. In the liquid phase (water or cell culture media), the size of EC nanoparticles appeared to be significantly larger than those in the gas phase, which might be due to aggregation of nanoparticles in the liquid phase. By using *in vitro* high-throughput cytotoxicity assays, we have demonstrated that EC aerosols significantly decrease intracellular levels of glutathione in NHOKs in a dose-dependent fashion resulting in cytotoxicity. These findings suggest that EC aerosols cause cytotoxicity to oral epithelial cells *in vitro*, and the underlying molecular mechanisms may be or at least partially due to oxidative stress induced by toxic substances (e.g., nanoparticles and chemicals) present in EC aerosols.

Citation: Ji EH, Sun B, Zhao T, Shu S, Chang CH, Messadi D, et al. (2016) Characterization of Electronic Cigarette Aerosol and Its Induction of Oxidative Stress Response in Oral Keratinocytes. PLoS ONE 11(5): e0154447. https://doi.org/10.1371/journal.pone.0154447

Editor: Muy-Teck Teh, Queen Mary University of London, UNITED KINGDOM

Received: September 8, 2015; **Accepted:** April 13, 2016; **Published:** May 25, 2016

Data Availability: All relevant data are within the paper.

Funding: The authors received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

Introduction

Electronic cigarettes (ECs) are battery-operated devices for a user to inhale an aerosol rather than cigarette smoke. ECs typically have a heating element that generates aerosols by atomizing a liquid solution known as E-

liquid, which usually contain a mixture of selected level of nicotine, propylene glycol or glycerin as solvent, and flavors additives. Awareness and use of ECs have greatly increased in the past few years, particularly among young people and women [1]. Although ECs have been proposed as long-term substitutes for traditional smoking or as a tool for smoking cessation, scarce experimental data are available on their safety and health related risks [2]. Most of the current studies are focused on understanding EC users' behavior or pathological symptoms through the use of approaches including questionnaires compiled by the EC users, surveys from online forums or systematic review of published literature [2–4]. While studies have suggested that the use of ECs substantially decreased cigarette consumption without causing significant side effects in smokers not intending to quit [5], others emphasized that the health effects caused by EC use are not well understood and there is a wide range of reported positive and negative health effects. While the use of the EC may help reduce the number of cigarettes smoked and withdrawal symptoms, the effects are mainly related to a short period of use, and data on long-term efficacy and safety of ECs is currently lacking, which will be of utmost importance to form the basis for guidelines and regulatory decisions on ECs [3, 4].

While the effects of conventional cigarette smoke on human health have been well documented through *in vitro* and *in vivo* model studies, little direct work has been done to understand the health risks of ECs, particularly those on the oral cavity. A recent study on E-liquids demonstrated that menthol additives of E-liquid show a harmful effect on human periodontal ligament fibroblasts. The incubation with menthol-flavored E-liquids led to a significant reduction of cell proliferation and viability, which might indicate that menthol additives should be avoided for ECs [6]. Although E-liquid itself is not the same as EC aerosol generated after heating, this study highlights the importance of investigating oral health-related effects of ECs. So far, studies of ECs at molecular levels have been performed on lung/airway epithelia cells. E-liquid has been found to increase inflammation and virus infection in primary human airway epithelial cells [7]. Exposure to ECs impairs pulmonary anti-bacterial and anti-viral defenses in a mouse model, and vapors produced by ECs and E-liquids with flavorings induce toxicity, oxidative stress, and inflammatory response in lung epithelial cells and in mouse lung [8, 9]. Nevertheless, to the best of our knowledge, there is essentially no data describing the effects of EC aerosols on oral epithelial cell function and mechanisms involved in inducing the effects.

In this study, we have generated and characterized EC nanoparticles in gas and liquid phases using a combination of advanced technologies. By using *in vitro* high-throughput cytotoxicity assays and quantitative PCR (qPCR), we have further demonstrated that EC aerosols significantly decrease intracellular levels of glutathione (GSH) in NHOKs in a dose-dependent fashion, induce the expression of heme oxygenase 1 (HO-1) and cause cytotoxicity to normal oral epithelial cells. This suggests that EC aerosols may induce oxidative stress response and toxicological outcomes in the oral cavity.

Materials and Methods

Cell culture

Normal human oral keratinocytes (NHOKs) were maintained in EpiLife culture media supplemented with the human keratinocyte growth supplement (Invitrogen, Carlsbad, CA, USA), as described previously [10]. The cell line was provided by Dr. Wei Chen at the University of California, Los Angeles. NHOKs were treated with the EC aerosol-impinged EpiLife culture media for 24 hours prior to harvesting of cells for the analysis. Generation of EC aerosols and EC aerosol-impinged cultured media are described below in details.

Generation of EC aerosols

E-liquid with different nicotine strength and flavors were used to generate EC aerosols. A homemade puffing machine composed of a compressed air source, a solenoid valve, and a Raspberry Pi (Raspberry Pi Foundation, UK), which serves as a timer and solenoid valve controller, was used to puff the ECs by pushing clean air through the EC from the front air hole. A piece of Python code running on the Raspberry Pi, which can be adjusted by changing the code, accurately controlled the puff duration and puff interval. The flow rate of the inlet air was calibrated by a flow meter DC-Lite (Drycal, Bios Inc., US). Particle number concentration (PNC) and size distribution of EC aerosols were measured as a function of puff duration from approximately 2 to 5 seconds inside a 320 L stainless-steel chamber. The chamber was tightly closed to avoid air exchange with ambient air. During the experimental period, the relative humidity and temperature inside the chamber were controlled at 30 ± 10% and 24 ± 1°C, respectively. Details of the experiment set up can be found elsewhere [11].

Measurement of particle number concentration and size distribution

The particle number concentration and size distribution of EC aerosols were measured by a Condensation Particle Counter (CPC 3785, TSI Inc., Shoreview, MN) and an Scanning Mobility Particle Sizer (SMPS 3080, TSI Inc., Shoreview, MN), respectively. The sampling flow rate of the SMPS was 0.6 L/min and the measurement range was 7–289 nm (100 s up scan, 20 s down scan). The SMPS starts to work right after each puff. The particle measurements were all repeated five times for each puff duration. After each measurement, the chamber was flushed by clean air until the total particle number concentration in the chamber was less than 1000 cm^{-3}.

Physicochemical characterization of EC particles in liquid

For the liquid phase particle size distribution, the EC aerosols were impinged into liquid (water or culture media) for 10 min, by using the same puffing system at the same flow rate, 1 L/min. High throughput dynamic light scattering (HT-DLS, Dynapro™ Plate Reader, Wyatt Technology) was performed to determine the particle size and size distribution of the EC aerosols in water and cell culture media. Transmission electron microscopy (TEM), using a JEOL 1200 EX (accelerating voltage 80 kV), was used to observe the morphology and to determine the primary size of EC aerosol nanoparticles. Elemental analysis of the EC aerosols were determined by energy-dispersive X-ray spectroscopy (EDX) using a FEI Titan 80/300 microscope. Quantitative elemental analysis of the EC aerosols was determined by inductively coupled plasma optical emission spectrometry (ICP-OES). 500 µL of the impinged EC sample was digested by 3 mL of concentrated nitric acid at 90°C for 3 h. The digested solution was dried by evaporation at 120°C, and 8 mL of 5% nitric acid was added for ICP-OES measurement.

Cytotoxicity assays

The cytotoxicity of EC aerosols in NHOK cells was determined by a ATP assay using the ATPliteTM firstep (Perkin-Elmer, Boston, MA) [12]. After 24 h exposure to EC aerosol-impinged culture medium in a 96-well plate, the culture medium was removed, and cells were washed three times with PBS and incubated with 100 µL of reconstituted ATPlite firstep reagent for 10 min. The luminescence intensity was recorded on a SpectraMax M5 microplate spectrophotometer (Molecular Devices, Sunnyvale, CA).

Determination of intracellular GSH

A GSH-Glo assay kit (Promega, Madison, WI) was used to determine the intracellular GSH levels after EC aerosol exposure in NHOKs [13]. The NHOKs were exposed to EC aerosol particles in a 96-well plate at 37°C and 5% CO_2 for 24 h. After exposure, the cellular supernatant was removed and 100 µL of GSH-Glo reaction buffer containing Luciferin-NT and glutathione S-transferase was added to each well in the plate and incubated at room temperature with constant shaking for 30 min. Then, 100 uL of Luciferin D detection reagent was added to each well and the plate was incubated at room temperature with constant shaking for another 15 min. The luminescent signal was quantified using a SpectraMax M5 microplate reader (Molecular Devices; Sunnyvale, CA).

Quantitative real time PCR

Total RNA was isolated from cultured cells using the RNeasy Mini Kit (Qiagen, Valencia, CA). With Superscript II reverse transcriptase (Invitrogen, #18064–022), 1.5µg of RNA per sample was converted into cDNA. The primers sequences were: HO-1-F, CAGGCAGAGAATGCTGAGTT; HO-1-R, GCTTCACATAGCGCTGCA; NRF-2-F, CGGTATGCAACAGGACATTG; NRF-2-R, ACTGGTTGGGGTCTTCTGTG; β-actin-F, GCGCGGCTACAGCTTCA; β-actin-R, CTTAATGTCACGCACGATTTCC. To quantify HO-1 and NRF-2 gene expression levels in untreated and EC aerosol-treated NHOK samples, 1µl of diluted cDNA solution (1:10) was mixed with primers, nucleotides and the SYBR Green I MasterMix (Roche, Indianapolis, IN) in a 96 well PCR plate and the reaction was performed on a CFX96 qPCR system (Bio-Rad, Hercules, CA).

Statistical analysis

Statistical significance was determined by two-tailed Student's t-test for two-group analysis. For all the Figs, the values shown represent mean ± SEM.

Results

Puff duration and particle number concentration (PNC) of EC aerosols

We have generated EC aerosols and measured PNC and size distribution as a function of puff duration from approximately 2 to 5 seconds. The results are presented in Fig 1, which shows a strong positive correlation (R^2 = 0.99) between puff duration and PNC.

Download:

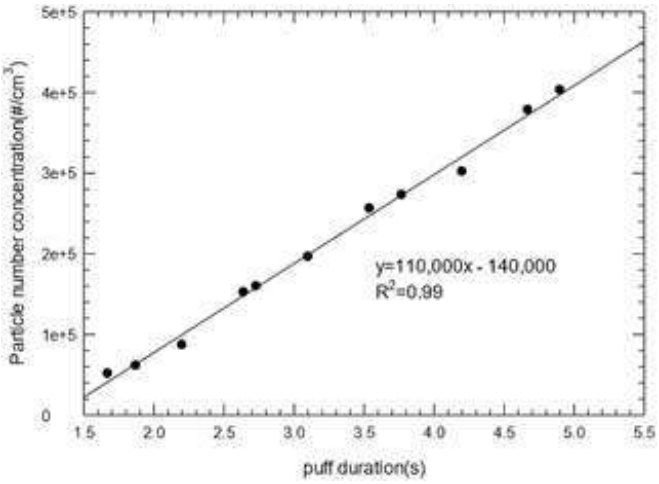


Fig 1. (a) Particle number concentration (PNC) as a function the puff duration.

Particle number was determined by Condensation Particle Counter (CPC).

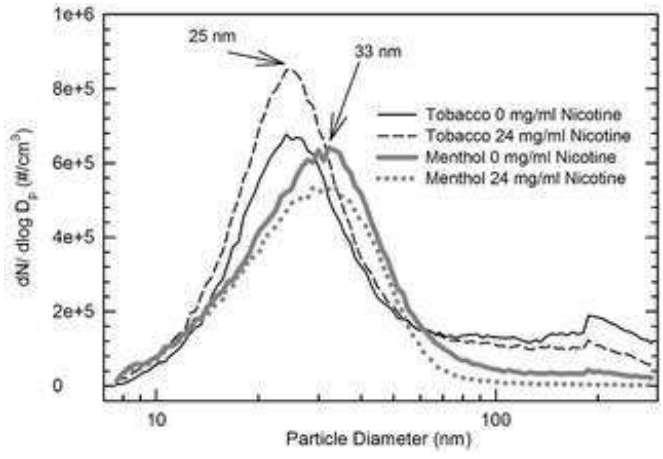
https://doi.org/10.1371/journal.pone.0154447.g001

PNC and size distribution of EC aerosols at different flavors and nicotine strength

The PNC and size distribution of EC aerosols of different flavors and nicotine strength were also compared (Fig 2). The menthol-flavored EC generates particles with larger sizes (33 nm) compared to the tobacco flavors (25 nm). It also appears to have generated fewer nanoparticles than the tobacco flavored by 13–35%. Compared to zero nicotine, at 24 mg/ml nicotine level, the tobacco flavored showed 9% increase in PNC, but the menthol flavored had approximately 20% decrease in PNC.

Download:

Fig 2. Comparison of particle size distribution of aerosol emissions from tobacco (0 and 24 mg/ml nicotine) and menthol (0 and 24 mg/ml nicotine) flavored ECs.



https://doi.org/10.1371/journal.pone.0154447.g002

Characterization of EC nanoparticles in liquid phase

To perform in vitro cellular studies with NHOKs, the EC aerosol was impinged into the culture medium for NHOK (KGM medium with human keratinocyte growth supplement) for 10 min. Since the suspension of the aerosol particles in aqueous solution will likely change their physicochemical properties, we compared the hydrodynamic size distribution of EC aerosols in NHOK culture medium, DMEM medium and water (different dispersion media) using high-throughput dynamic light scattering analysis (DLS) (Fig 3). Our data indicate that when the EC particles

were impinged in water, their hydrodynamic size is around 1181.1±340.1 nm. In contrast, when they were prepared in NHOK culture media, their hydrodynamic size is significantly reduced to 442.3 nm (Table 1), which reflects the dispersion effect of proteins including growth factors that are present in the culture media as a result of the formation of a protein corona on the particle surface that provides electrostatic hindrance preventing agglomeration. When the EC particles were impinged in DMEM medium containing fetal bovine serum, the hydrodynamic size is further reduced to 328.5±9.1 nm, due to dispersal effect of fetal bovine serum as a result of the formation of a protein corona on the particle surface, which contributes to the suspension stability [14]. Fig 4A shows the transmission electron microscope (TEM) image, revealing the flake-like morphology of EC aerosol nanoparticles in the water. Furthermore, energy-dispersive X-ray spectroscopy (EDX) was used to determine the elemental components of EC aerosols (Fig 4B). Silicon (Si), iron (Fe), and sodium (Na) were found in the EC particles. Copper (Cu) was also found but it came from the TEM grid, not the nanoparticles. Quantitative assessment of EC aerosols by inductively coupled plasma optical emission spectrometry (ICP-OES) further confirms the EDX analysis. Besides the elements identified by EDX, ICP-OES also shows the existence of calcium (Ca), magnesium (Mg), and sulfur (S) (Table 2).

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Fig 3. Hydrodynamic diameters of EC aerosols in different dispersing media (water or cell culture media).

Cell media 1: DMEM with fetal bovine serum. Cell media 2: EpiLife media with growth supplement. Hydrodynamic size of EC aerosols was determined using high throughput dynamic light scattering (HT-DLS).

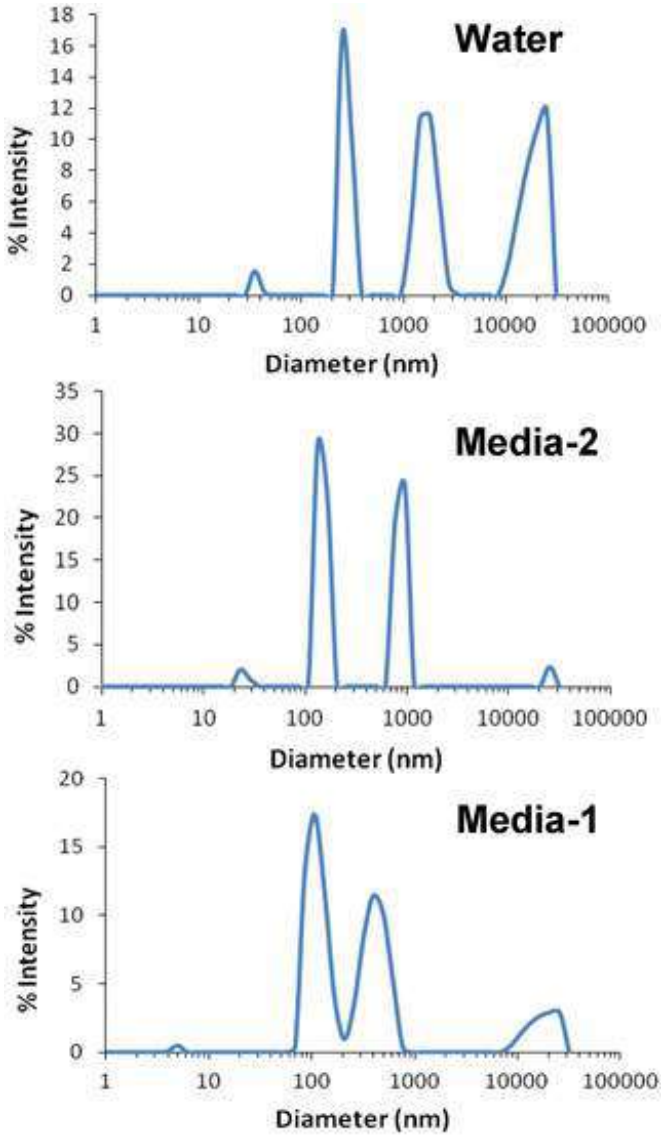

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Fig 4. Characterization of EC aerosols impinged in water.

(A) TEM analysis of EC aerosol nanoparticles in water. (B) EDX analysis of EC aerosols that identified elemental composition of EC nanoparticles.

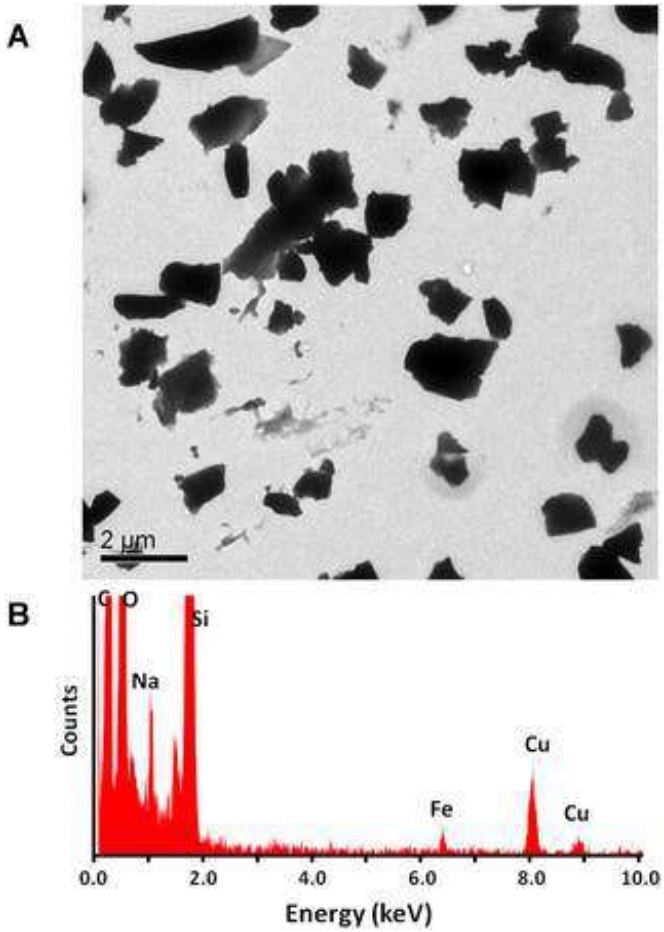

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Table 1. Hydrodynamic diameter of EC aerosols in different dispersing media analyzed by DLS.

Sample	Hydrodynamic diameter (nm)
EC in water	1181.1 ± 340.1
EC in culture media-1	442.3 ± 125.2
EC in culture media-2	328.5 ± 9.1

Note: Culture media-1: EpiLife with growth supplement for NHOKs. Culture media-2: DMEM with fetal bovine serum

doi:10.1371/journal.pone.0154447.t001

https://doi.org/10.1371/journal.pone.0154447.t001

Element	Concentration (mg/L)
Ca	0.121±0.001
Fe	0.828±0.005
Mg	0.042±0.000
Na	2.289±0.081
S	0.764±0.003
Si	0.117±0.002

doi:10.1371/journal.pone.0154447.t002

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Table 2. Elemental analysis of EC aerosols by ICP-OES.

https://doi.org/10.1371/journal.pone.0154447.t002

EC aerosol-induced oxidative stress response and cytotoxicity in oral epithelial cells

In vitro analysis of EC aerosol-treated NHOKs show that EC aerosols are capable of inducing oxidative stress as indicated by significant decrease of intracellular glutathione (GSH) levels (Fig 5A). Similar to previously published data [15], the use of fumed silica as a positive control demonstrated a significant decrease in cellular GSH in NHOKs. GSH level decrease is also dose-dependent (Fig 5B). Oxidative stress represents a dynamic equilibrium between antioxidant defense that acts to restore redox equilibrium and oxidant injury responses that can result in

toxicological outcomes. We found the injurious oxidative stress in NHOKs leads to significant cytotoxicity as indicated by the ATP assay (Fig 5C). As shown in Fig 5D, qPCR analysis demonstrated that EC aerosols induced the expression of HO-1 in NHOKs, but NRF-2 expression was not significantly altered (Fig 5E).

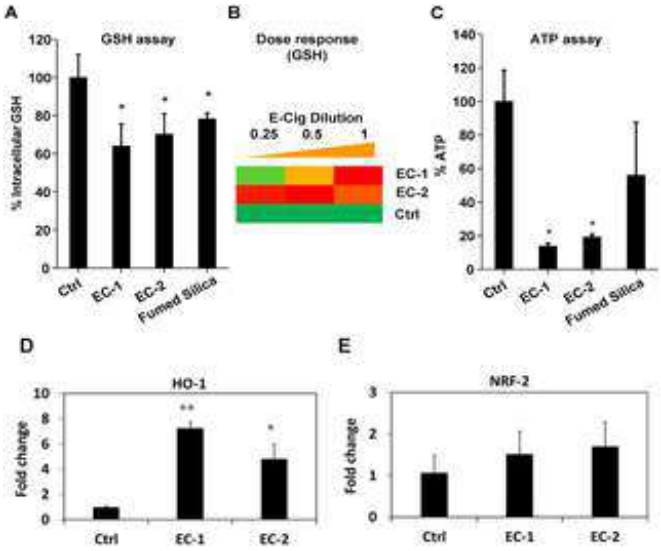

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Fig 5. Oxidative stress and cytotoxicity induced by EC aerosols in NHOKs.

(A) Intracellular GSH levels in NHOKs after exposure to EC aerosols. NHOKs were exposed to EC aerosols for 24 h and intracellular GSH levels were determined using a GSH-Glo assay. Fumed silica (100 μg/ml) was used as a positive control. *p<0.05 compared to untreated control cells. (B) Heat maps to show the dose-dependent increase in oxidative stress induced by EC in NHOKs. Conditions are the same as (A). (C) Cell viability of NHOKs after exposure to EC aerosols for 24 h was determined using ATP assay. The cell viability of the EC-treated cells was normalized to the value of non-treated control cells, for which the viability was regarded as 100%. Fumed silica (100 μg/ml) was used as a positive control. *p<0.05 compared to untreated control cells. (D&E) qPCR analysis of heme oxygenase 1 (HO-1) and nuclear factor (erythroid-derived 2)-like 2 (NRF-2) expression in NHOKs after exposure to EC aerosols. *p<0.05; ** p<0.01 compared to untreated control cells.

https://doi.org/10.1371/journal.pone.0154447.g005

Discussion

EC creates aerosols that consist of nanoparticles and contain small amount of chemicals that may cause toxicological outcome to human oral cavity. Smoking characteristics such as puffing topography or EC device voltage and physicochemical characteristics of vaporized nicotine and other chemical products in ECs are profoundly different when compared to conventional cigarettes. How these toxic substances/nanoparticles from EC aerosols and related smoking/physicochemical characteristics affect the oral cavity remains largely unknown. Considering the increasing popularity of ECs in the general population, there is an urgent need to characterize EC aerosols and assess their biological hazard on oral epithelial cells.

In this study, an impinging method was chosen because it minimizes EC aerosols loss due to evaporation, which is inevitable if filter collection method is used [16, 17]. In addition, impinging method allows EC aerosols to be directly captured in the medium and avoids intermediate steps such as extraction, which are necessary if a filter trapping is used.

Previous studies have shown significant amounts of nanoparticles are present in EC aerosols [16, 18–20]. These observed PNC in gas phase ranged from 1.8×10^9 cm^{-3} to 8.4×10^9 cm^{-3} and count median diameter (CMD) ranged from 14 nm to 458 nm. Puffing topography and device voltage of ECs have been found to affect EC aerosol characteristics. Fuoco *et al*. reported that longer puff duration was associated with higher PNC [20]. This has been confirmed by our studies (Fig 1). Ohta *et al*. [21] measured carbonyls emitted from ECs at voltages from 1.5 V to 7.5 V and found increased carbonyl levels when the voltage was above 3 V. In addition, our studies indicate that the PNC and size distribution of EC aerosol emissions may vary with different flavors and nicotine strength (Fig 2). The menthol flavored EC generated particles with larger sizes compared to the tobacco flavors. It also

produced fewer nanoparticles than the tobacco flavored EC. Nicotine levels appeared to affect the PNC differently from the menthol flavor. Compared to zero nicotine, the tobacco flavored EC showed a 9% increase in PNC at 24 mg/ml nicotine level, while the menthol flavored EC had approximately 20% decrease in PNC. In contrast, Fuoco and colleagues reported that flavors did not significantly change the PNC [22]. However, they did find that the PNC significantly increased when nicotine levels in E-liquid are higher, which agrees with our measurements for the tobacco flavor. These finding demonstrates the complexity and knowledge gap in EC aerosol characteristics and highlights the importance to systematically evaluate the impacts of puff duration, EC device voltage and E-liquid composition on EC aerosol characteristics. This information might be important to link the physicochemical properties of EC aerosols under controlled conditions to the biological/toxicological outcomes to the oral cavity.

We also measured the size of EC aerosol nanoparticles in liquid phase. EC aerosols were impinged into water or the cell culture medium for NHOKs and the nanoparticles present in the culture medium were measured with TEM. The EC nanoparticles in liquid phase appeared to be significantly larger than those in the gas phase (Fig 3), and this might be due to aggregation of nanoparticles in the liquid phase. The difference in EC aerosol size distribution and aggregation status between the air and aqueous solution needs to be investigated because it may generate differential toxicological outcomes to cells.

Small trace amount of toxic chemicals and metals were found in the E-liquid and EC aerosols in previously reported studies. For example, formaldehyde, which is assumed to be the product of thermal dehydration of the glycerin or glycols, was detected in EC aerosols [23–25]. However, another study suggested that the formaldehyde may come from exhaled breath rather than from the ECs [16]. Diethylene and ethylene glycol were detected as impurities in E-liquid [26] and in EC aerosols [27]. However, the prevalence of these impurities in E-liquid remains unclear. Kim and Shin [28] found substantial amounts of tobacco specific nitrosamines (TSNA) which are carcinogenic, while McAuley and colleagues [27] detected that TSNA in EC aerosols were at least six times lower than in tobacco smoke. In addition, heavy metal nanoparticles (i.e. Sn, Ag, Fe, Ni, Al, Cr) were found in EC aerosols which could be resulted from the oxidation of the heating coil [29]. We also examined the elemental components of the EC nanoparticles in the liquid phase and Fe, Si and Na were detected with the EDX analysis. Due to their unique physicochemical properties including high surface area, metal/metal oxide nanoparticles exhibit higher dissolution rate or surface reactivity compared to their bulk form. Our previous studies revealed that metal/metal oxide nanoparticles could cause oxidative stress and cytotoxicity *in vitro* and acute lung inflammation *in vivo* [12, 30]. The exact role of particles in EC-induced cytotoxicity needs to be determined in future studies.

There is a practical challenge when studying the physicochemical characteristics of EC aerosols. Due to the chemical complexity of EC aerosols, it appears to be very difficult to link a specific chemical component of EC aerosols to the toxicological outcomes. As reported earlier, cigarette smoke is a complex mixture consisting of more than 5600 identified chemical constituents of which approximately 150 have been identified so far as "tobacco smoke toxicants" [31, 32]. This can be partially solved by including well-characterized controls (*e.g.*, metal/metal oxide nanoparticles) [12]. Trace metals or chemicals identified by other instrumental analysis methods (e.g., ICP or LC/GC-MS) would provide useful information on the potential toxic components in EC aerosols, and by including reference standards for *in vitro* studies, we might be able to identify major toxic components in EC aerosols.

More importantly, our data suggest that EC aerosols may cause cytotoxicity to human oral keratinocytes via oxidative stress response. High-throughput cytotoxicity assays confirmed that EC aerosols are capable of inducing oxidative stress in NHOKs as indicated by significant dose-dependent decrease of intracellular GSH levels. We also found the injurious oxidative stress causes cytotoxicity of NHOKs as indicated by the ATP assay. In addition, similar to our previous studies on the toxicology of nanoparticles [12, 33], HO-1 expression was found to be induced in NHOKs by EC aerosols, which correlate well with the high-throughput cytoassay data on decreased intracellular GSH level and cytotoxicity.

As a summary, we have prepared and measured PNC and size distribution of EC aerosols in the gas phase and found that there is a strong positive correlation between puff duration and PNC. We have also characterized the hydrodynamic size of EC nanoparticles in liquid phase (water and cell cultured media) and determined their elemental composition. Because PNC, particle size and chemical content are highly relevant to the toxicity of EC aerosols, it is important to characterize these physiochemical parameters and understand the effect of smoking characteristics such as puff duration and device voltage on these physiochemical parameters. Our *in vitro* assays have shown that EC aerosols could cause oxidative stress responses and induce cytotoxicity in oral epithelial cells. These data suggest that EC aerosols damage human keratinocytes *in vitro*, and the underlying molecular

mechanisms may be or at least partially due to oxidative stress and inflammation responses induced by toxic substances (e.g., nanoparticles and chemicals) present in EC aerosols. Therefore, further safety assessment of toxicological and pathological effects of EC aerosols on human health is certainly important. In the future, our research focus is to investigate pathological effects and oxidative stress/inflammation responses in the animal models caused by EC aerosol exposure.

Author Contributions

Conceived and designed the experiments: TX YZ DM SH. Performed the experiments: EHJ BS TZ SS CHC. Analyzed the data: BS EHJ TX YZ SH. Contributed reagents/materials/analysis tools: BS EHJ TZ SS CHC. Wrote the paper: TX YZ SB SH.

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Written evidence submitted by Dr Robert D Combes and Professor Michael Balls (ECG0080)

1. Executive Summary

- As professional toxicologists interested in improving testing methods for assessing the safety to humans of chemicals, we starting collaborating with the tobacco industry, to help identify promising new methods, beginning with tobacco smoking harm reduction products and then e-cigarettes.
- We soon became perplexed over the FDA's tobacco deeming regulations and then became even more-concerned about the way in which the UK authorities were laying the foundations for using e-cigarettes in the fight against smoking-related disease. We are especially surprised by the lack of scholarship and scientific rigour that is being applied to the safety assessment of these products, and feel it important to exploit our independence by speaking out.
- The current stipulations regarding the regulatory control and authorisation of electronic cigarettes (ECs) and vaping in the UK are scientifically flawed, as they are based on little more than conjecture and value judgment, backed only by poor science.
- There has been over-reliance on chemical analysis, the use of incomplete data, and risk assessments confused with the perceived benefits of vaping versus smoking, all of which bear little resemblance to standard approaches in toxicological risk assessment.
- The authorities, and other stakeholders, have systematically ignored, or erroneously dismissed, basic principles of pharmacology and toxicology, and inconvenient scientific observations, while promoting vaping as a way of ceasing smoking, instead of discouraging the use of nicotine in any form.
- The research being overlooked includes evidence of the many pleiotropic adverse biological effects of nicotine, more of which continue to be revealed with increasing frequency, which are likely to be highly relevant to carcinogenicity and disease.
- We discuss this very serious situation, and offer some suggestions for a better way forward, for the benefit of individual humans, now and in the future.

2 Introduction

Electronic cigarettes (e-cigarettes; ECs) are handheld, electronic devices that vaporise a liquid (e-liquid) containing nicotine with a other additives (e.g. propylene glycol or glycerol, and flavouring agents), and deliver the vapour to the lungs via inspiration and inhalation (a process called vaping).

In August 2015, Public Health England (PHE) declared that, in principle, ECs should be made available on prescription to reduce tobacco smoking (https://www.theguardian.com/society/2015/aug/19/public-health-england-e-cigarettes-safer-than-smoking). It was also made clear that ECs will be regulated as new medicines by the Medicines and Healthcare products Regulatory Agency (MHRA). This was followed by the news of the first e-cigarette (Evoke) to receive marketing authorisation from the agency.

These announcements have proved to be highly controversial, especially since they were justified by an estimate of there being 95% less harm from vaping than from tobacco smoking (https://www.gov.uk/government/news/e-cigarettes-around-95-less-harmful-than-tobacco-estimates-landmark-review). This submission explains why we believe that the decision by PHE is, in the light of current knowledge, irresponsible and unacceptable. We

Comment [RD]: https://www.theguardian.com/society/2015/aug/19/public-health-england-e-cigarettes-safer-than-smoking

also propose some recommendations to avoiding the potentially very serious consequences, if this situation is allowed to continue.

3 Ignoring basic principles of toxicology

This is the most common characteristic exhibited by individuals, reports and publications discussing safety issues relating to ECs (Table 1; 1-3). The main consequences are: a) the belief that it is legitimate to base safety studies on analytical chemistry to determine the presence or absence of specific chemicals, and that data on their relative concentrations in e-liquids and emissions are sufficient to provide a quantitative measure of harm; b) the belief that the route of exposure has little effect on nicotine toxicity, and that, as few toxic effects have been observed since the times when various nicotine delivery devices were first introduced (ranging from 10 years for ECs to 30 years or more for nicotine replacement therapies {NRTs]), nicotine must be relatively inactive; and c) the belief that long-term toxicity can be predicted on the basis of acute effects.

The idea of deriving quantitative information on risk, while having only qualitative supporting data for ECs, originated from a Multiple-criteria decision analysis (MCDA) study (4). Our concerns about this are summarised in Table 2. Nutt *et al.* must have settled on 95% as a convenient comparative number, which PHE eventually simply expressed differently, ever since which the figure has been quoted *ad nauseam*, without any supporting data.

Overlooking the effect of route of administration is exemplified by a report of the Royal College of Physicians (4) which stated: *There are, however, no grounds to suspect that inhaled nicotine will have an appreciably different risk profile from nicotine delivered via other routes of absorption.* This statement is imprecise, and was not backed by any references. There are many reasons why toxicity can depend greatly on route, rather than merely on target organ(s). Another important factor is the possibility of drugs going into systemic circulation, once entering the body, usually by routes other than orally, before passing through the liver first - the organ which normally reduces systemic concentrations of parent compounds and which alters them to produce various metabolites, which can be more toxic or less toxic than the parent compound.

4. Superficial and inaccurate reporting of supporting evidence

A paper by Cheng (6), cited in a report commissioned by PHE, written by McNeill et al. (7), provides evidence of the presence in vapours of some potentially carcinogenic tobacco-specific nitrosamines (TSNAs) at widely different levels (RF), but McNiell et al. did not mention the evidence in relation to safety, even though they made some other statements on the issue. This contrasts with another PHE-Commissioned report focusing on safety, (8), authored by Britton and Bogdanovica. These authors did not mention the extensive analytical data for such chemicals, as Cheng's paper was omitted in favour of one by Goniewicz et al describing that only very low levels of these chemicals are associated with ECS (9).

In a highly critical editorial (10), *The Lancet* noted that the PHE report was evidence-based confusion rather than being a *"landmark review"*, as referred to by Kevin Fenton, PHE's Director of Health and Wellbeing. When commenting on a paper purporting to demonstrate a link between DNA damage in lung cells and exposure to EC vapour,

Comment [RD]: Nutt, D.J., Phillips, L.D., Balfour, D., Curran, H.V., Dockrell, J.M., Foulds, J., Fagerstrom, K., Letlape, K., Milton, A., Polosa, R., Ramsey, J. & Sweanor, D. (2014). Estimating the harms of nicotine-containing products using the MCDA approach. E. Addiction Research 20, 218–225.Nutt et al 2014

Comment [RD]:

Written evidence submitted by Dr Robert D Combes and Professor Michael Balls (ECG0080)

Fenton, replied that *Public Health England has always been clear that e-cigarettes are not 100 per cent safe and we will carefully consider this new study and continue to be vigilant. But our major world leading review, published recently, found that e-cigarettes carry a fraction of the risk of smoking' [underlining added].….'. (*http://www.telegraph.co.uk/science/2016/03/12/e-cigarettes-are-no-safer-than-smoking-tobacco-scientists-warn/*).* The so-called 'world-leading review' by PHE was nothing of the sort – it was essentially a very poor appraisal of the situation.

We also note that, while Nutt *et al.,* in 2014 (4), urged caution when interpreting their MCDA data, they supported PHE's 95% safer value in a letter published two years later (11). The MCDA paper (4) is also superficial, especially with respect to criteria for calculating maximum relative harm (MRH) and on how the inescapable problem of the huge bias in data for tobacco smoking compared with ECs was corrected for. This bias is due to the much shorter time for which ECs have been available for use and for testing, meaning that more subjectivity would have been required when assessing ECs to reach consensus at the decision conference, an even greater problem in 2013, when the discussions took place. This problem was also noted in a review on ECs, published in April 2014 (12), which concluded that *"Existing evidence suggests that these products [ECs] are by far a less harmful alternative …."*, although it was admitted that only a very few toxicological studies were available.

Despite searching background literature on the MCDA technique, some of it recommended by Nutt *et al.*, and after watching seminars (13-15) by the two leading authors, we have not found any convincing explanations for our concerns about MCDA. Other critics of the MCDA approach include: Kujawski (16), who commented that the specific MCDA model used can greatly influence the rankings of the alternatives for a given set of criteria; and Rolles and Measham (17), who were highly critical of the criteria and weighting used for ranking.

5. Nicotine - an inconvenient truth?

There is widespread agreement in the various reports supporting ECs that, apart from its addictivity, nicotine, is otherwise non-toxic at its in-use concentrations.
Nicotine is actually one of the most toxicologically and pharmacologically active substances known (see reviews cited in ref 1). Structural alerts for DNA and protein binding were identified (unpublished studies by us, by using Toxtree, a decision-tree expert system for structure-activity relationships [SAR]), explaining the observed genotoxicity in the literature, and raising questions about respiratory sensitization (mediatied by DNA binding), and other mechanistically-related diseases, such as Chronic Obstructive Pulmonary Disease (COPD). Of interest is the fact that propylene glycol and glycerine lacked these alerts, although they might be precursors for toxic carbonyl compounds, the generated amounts of which increased with heater settings in one study (18), but it is possible to generate them without the excessive levels causing dry puff.

The literature on nicotine carcinogenicity and reproductive toxicity, reviewed by us in ref 1 [18 references cited therein], at the very least, suggests that, if not a complete carcinogen (acting as an itiator and promoter, nicotine acts on a variety of key post-initiation stages of the multi-step process of carcinogenesis (Fig. 1), including inhibition of apoptosis and immune system suppression, tumour promotion, cell proliferation, progression, stimulation of specific cell activating factors, angiogenesis, and the induction of unique patterns of

Comment [RD]: Ther Adv Drug Saf. 2014 Apr; 5(2): 67–86.
doi: 10.1177/2042098614524430
PMCID: PMC4110871

Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review

Konstantinos E. Farsalinos and Riccardo Polosa

differential gene expression (see also 19). The drug also activates at least five mitogenic signaling pathways and cooperates with TSNAS toward the carcinogenic activity of tobacco smoke (20), and is also embryotoxic and modulates fertilization.

6. Cardiovascular disease (CVD) effects

Nicotine and ultra-fine fibres in the particulate matter in tobacco smoke have been implicated separately to be involved in smoking related CVD via their ability to induce inflammation in the endothelial layer in blood vessel walls, a first step in atherogenesis leading to CVD (21, 22). The fibres increase the surface area for reactive oxygen species (ROS), and possibly act also by causing some physical damage to the cells

It is possible that the two components have to interact synergistically for an effect. Such a model would explain the lack of association between NRT usage and CVD, and would suggest that EC use would also not be linked to NRT, unless some other component could mimic the effect of the fibres. Candidates for this role are the nanoparticles generated from the heating elements in e-liquid reservoirs. Some of the fibres have overlapping dimensions with NPs (23), but their surface chemistry needs to be characterised, and further work is needed to see if they interact with nicotine to induce atherosclerosis. Interestingly, Zhao *et al.* (24) recently demonstrated ROS generation by e-cigarettes, which was highly dependent on brand, flavour, puffing pattern, and voltage.

7. Basing the safety of nicotine on human studies of NRT users and snus takers

Often, the results from epidemiological studies of users of NRT, and of smokeless tobacco (e.g. 'snus', which is popular in Scandinavia, the device being a pouch of tobacco, maintained in the mouth for extended periods), without increases in the incidence of conditions like cancer, COPD or CVD, in device-users compared with matched non-users, are used to argue against nicotine being toxic. However, such arguments fail to explain all of the evidence and/or do not accord with all of the facts.

While the 30-year or so period during which NRT products have been available would seem to be a sufficiently long time for the lack of increased susceptibility to cancer to be attributed to the non-carcinogenicity of nicotine, it is a collective figure for all users, which should not be confused with individual treatment durations for a course of NRT (typically 8-12 weeks per patient) – too short a duration for assuming non-carcinogenicity.

With regard to snus, careful reading of the statistics in the annual Swedish Cancer Registry (http://www.socialstyrelsen.se/english) reveals a complex relationship between snus-taking, lung cancer and other cancers. Two key conclusions from the statistics, a) that the use of snus almost halved lung cancer incidence in males in Sweden, and b) that it is not associated with increases in the occurrence of a range of other 'common' cancers, do not agree with all the available evidence, some of which suggests that snus usage has had only a minimal effect on lung cancer incidence overall, in males, and that increases in a range of other cancers (including oral and pancreatic) can be linked to exposure to snus.

Therefore, the statistics on the change in cancer incidence in relation to snus-taking in Sweden need to be interpreted carefully. Some other published analyses of population studies, including that by Lee *et al.* (25), essentially giving snus the all-clear, were criticised by Tomar *et al.* (26). Finally, if nicotine were a tumour promoter, a long period

Comment [RD]:
Benowitz, N.L. & Burbank, A.D. (2016). Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. Trends k Cardiovasc. Med. 26, 515-523.

Comment [RD]:

Comment [RD]:
https://doi.org/10.1016/j.jhazmat.2017.10.057

between exposure to an initiator and promoter is just what would be expected to still potentially result in tumorigenesis.

8. An attempt to obtain long-term data on ECS

A so-called 'long-term' biomonitoring study, published in March 2017 (27), allegedly demonstrating the much greater safety of vaping compared with smoking, has been hailed as being the closest yet to endorsing the 95% less harmful value and PHE's policy on ECs.

Biomonitoring assesses internal exposure to, and the possible systemic effects of, a substance to which an individual is exposed, thereby strengthening the link between exposure and effect. The study in question analysed urine samples obtained from smokers, vapers and those on various types of other NRT devices, for the presence of biomarkers of exposure to several carcinogens found in tobacco smoke and linked to lung cancer. The key criterion for inclusion in the study was the daily use of the same broad category of device for at least six months prior to sampling. This allowed conventional NRT users to use devices with varying routes of administration, introducing a further source of variability. Levels of biomarkers were detected and quantified by using highly sensitive methods for chemical analysis.

The lowest concentrations of all the biomarkers were found in the samples from the EC-only users. As the differences were quoted as being between 90-100%, the authors interpreted this as vindication of the 95% figure.

However, the study was flawed in its rationale (it relied on chemical analysis), and its design (small numbers of volunteers and wide differences in gender ratios between some of the cohorts and only one timepoint). Conventional long-term toxicity testing involves repeat exposure studies and continual surveillance of laboratory animals, for at least several months. The tests are designed to detect chemicals that might not specifically exhibit acute effects. Therefore, this study, with only one sampling, should not be regarded as being equivalent to a repeat-dose toxicity study. There was also no control of fluid and nutrient intake on the day of sampling, let alone of the type of device, and no determination of the various e-liquid compositions. At best, the study could have provided only a snapshot of what was happening during the period involved.

9. A role for non-animal methods

Regulatory test batterIes for new drugs include subchronic and chronic tests that are specifically designed to predict repeat-dose toxicity (<90 days) and longer-term toxicity, some studies of which take some 2-3 years to complete. Long-term models of respiratory diseases also exist (2, 28). An example of one of these has recently been published (29), in which mice were exposed by inhalation to nicotine-containing EC fluids for one hour daily over four months. The exposures induced effects associated with the onset of COPD, including cytokine expression, airway hyper-reactivity, and lung tissue destruction. These effects were nicotine-dependent in the mouse lung, suggesting that inhaled nicotine contributes to airway and lung disease.

However, our suggestion of the need for more hazard data for ECs does not necessarily mean more animal testing, since many *in vitro* methods exist (see citations in refs 1-3)

These offer many advantages over their *in vivo* counterparts, ranging from more-precise dosimetry to advantages in data interpretation. This is especially true for inhalation testing (28).

Monolayer-cultures of cells from target airway sites can be used. For example, in the four-month COPD study mentioned above, the same results were obtained when normal human bronchial epithelial [NHBE] airway cells were cultured at an air-liquid interface (ALI) and exposed to EC vapours or nicotine solutions by using a Vitrocell smoke exposure robot.

It should be possible to obtain more-reliable and more-relevant data expeditiously through the application of integrated testing strategies involving advanced human cell-based tissue culture systems, in which their differentiated status is retained in culture, and which are representative of the major target sites in the airways for respiratory toxicity and disease, by using ALI exposure. Moreover, some of the toxicity endpoints (e.g. DNA damage) can be measured *in situ* in the tissue construct (several reviews have been published over the past year).

The tobacco industry has been active in this area, holding workshops and various integrated tiered testing strategies have emerged for improving and expediting hazard identification. We present a generalized strategy, based on this type of approach (Figure 2). The strategy also includes a repeat-dose toxicity testing stage involving the use of hollow fibre technology for maintaining the longevity of cells in culture by replacing spent culture medium with fresh medium.

It is also possible to develop *in vitro* micro-culture models of whole organs, in order to predict the effects of exposure at several different sites within the same organ, simultaneously. A pertinent example is a small 'airway-on-a-chip' device developed by Benam and coworkers (30). This system is lined by living human bronchiolar epithelium from normal or COPD patients. The device is connected to an instrument that delivers whole cigarette smoke in and out of the chips, to permit the study of smoke-induced pathophysiology *in vitro*.

10. Smoking cessation versus nicotine quitting

We also note that the rationale for NRT was originally geared toward the ultimate goal of detoxication from nicotine drug dependency. In other words, it was intended that treatment would progress from a phased withdrawal, from dual usage via exclusive NRT usage to no usage. The current emphasis ion smoking cessation is regrettable, since it would greatly prolong exposure to nicotine. While this might not increase drug dependency, it could result in many other adverse effects, including tumour promotion and progression of initiated cells already formed in smokers before they started to quit.

11. Discussion

The argument for encouraging the use of ECs is based on: a) the apparent lack of association between nicotine exposure and carcinogenesis, CVD and other respiratory diseases, interpreted as meaning that they can be regulated lightly by waiving the batteries of preclinical and clinical tests to which most new medicines are subjected; b) an estimate with no scientific basis that vaping is 95% less harmful than tobacco smoking; and c) the belief that the focus should be on achieving tobacco smoking cessation, rather than drug independence. Our investigations have encouraged us to conclude that all these assumptions are spurious when considered with respect to principles of toxicology involving hazard prediction and risk assessment.

The safety assessment of ECs should, in principle, be no different from that required for other new medicines. No good reasons for by-passing the risk assessment and risk-benefit procedures normally required for registering pharmaceuticals have been made public, and we also note that PHE mandated itself to publish its decision, without first having a public consultation stage.

We also consider that the use of panels of experts to decide, largely on the basis of opinion and value judgment, especially for ECS, about the 'relative harms' of nicotine-release devices, without relevant and reliable quantitative data about the harms resulting from exposure especially to EC vapour, was unwise and unnecesdsary, especially when non-animal testing strategies are available to generate meaningful hazard information and to fill data gaps, to be used, with other information, in a convincing weight-of-evidence assessment.

Finally, we stand by our belief, expressed in a letter published in *The Times* on 18 February 2016, that *"The human respiratory system is a delicate vehicle, on which the length and quality of our lives depend. For governments and companies to condone, or even suggest, the regular and repeated inhaling of a complex mixture of chemicals with addictive and toxic properties, but without comprehensive data, is irresponsible and could have serious consequences."*

12. Recommendations

1. Good Manufacturing Practice guidelines should specify device design, capability, construction, mode of nicotine delivery and permissible ingredients, and their maximum amounts.
2. The designs should avoid the potential for excessive customisation.
3. Professional toxicologists should be involved in advising on safety issues relating to regulation of the use of ECs.
4. The intrinsic risks from vaping should be investigated and calculated separately, before comparison with the risks from tobacco smoking.
5. ECs should be considered as NRT products, rather than for prolonged recreational usage, until more long-term safety data have become available.
6. The toxicity of nicotine should be investigated further, as should the ability of nanoparticles in EC emissions to mimic the effects on CVD of particulate matter in tobacco smoke.
7. Threshold values for nicotine toxicity should be identified.

8. The end-game should be total cessation of the use of nicotine, beginning with tobacco smoking, but proceeding to cessation of the use of NRTs and ECs.
9. POS (point of sale) literature should emphasise the importance of nicotine quitting.
10. The MHRA should be more transparent about how ECs will be regulated via a ‘light-touch” approach, especially by applican of the concept of bioequivalence.
11. We strongly urge that further *in vitro* methods for detecting long-term toxicity and chronic disease conditions as a result of inhalation, should be developed and validated and accepted for use as soon as possible.
12. Several prospective long-term epidemiological studies should be initiated in the near future, to assess the adverse clinical and toxic effects from vaping. These should involve biomarkers of exposure and effect, such as DNA adducts, chemically-modified bases, and genotoxicity of body fluids.

December 2017

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14. Tables and figures:

Written evidence submitted by Dr Robert D Combes and Professor Michael Balls (ECG0080)

Table 1
Ten principles of toxicology being ignored in the debate in the UK concerning electronic cigarettes

1. There can be synergistic or antagonistic effects between constituents of complex mixtures.
2. Non-linear dose-responses are often exhibited.
3. There can be lag periods of many years between exposure and effect, e.g. for some cancers.
4. Analytical chemistry is of limited value for predicting non-toxicity.
5. Some chemicals and endpoints lack thresholds of toxicological concern, and toxicity can occur at very low concentrations.
6. Long-term effects are just as important as acute ones.
7. Quantitative expressions of safety should *always* be based on numerical data.
8. Route of entry/administration can have a large effect on toxicity.
9. Acute toxicity data should be used with great care, when attempting to predict long-term effects.
10. When in doubt, adopt the precautionary approach.

Table 2

Ten problems with the MCDA study (Nutt et al., 2014)* on Maximum Relative Harms (MRHs) for nicotine devices, and its subsequent interpretation

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1. Insufficient information available to repeat study closely with a completely different panel of experts (e.g. criteria for MRH unclear).
2. Panel did not have on it a toxicologist experienced in risk assessment (the focus was not on comparison of hazard compared with exposure).
3. Huge bias of harm information available for tobacco smoking compared with vaping, (meaning much more conjecture in scoring the latter).
4. Therefore, although scoring in general based on opinion, this would have been less so for tobacco smoking.
5. Since 2013/4, much more safety data have become available for vaping, and such information should inform fresh new discussions.
6. No explanation as to how consensus was achieved between the panelists (no proceedings of face-face workshop).
7. No numerical hazard data to support the quantitative estimate made for relative harm of vaping versus tobacco smoking (resulting in a false impression of accuracy).
8. Insufficient focus on the toxicity of nicotine and its contribution to harms (leading to a possible under-estimation of harm from vaping).
9. Harms from smoking based on short-term and chronic effects, whereas, for vaping, no chronic data available (long-term safety cannot be accurately predicted from acute effects).
10. MRH values were based on wide range of criteria, other than safety *per se*,** meaning use of the term 'harm' in the paper is misleading ('harm' has been used to infer safety, when the terms are not synonymous).

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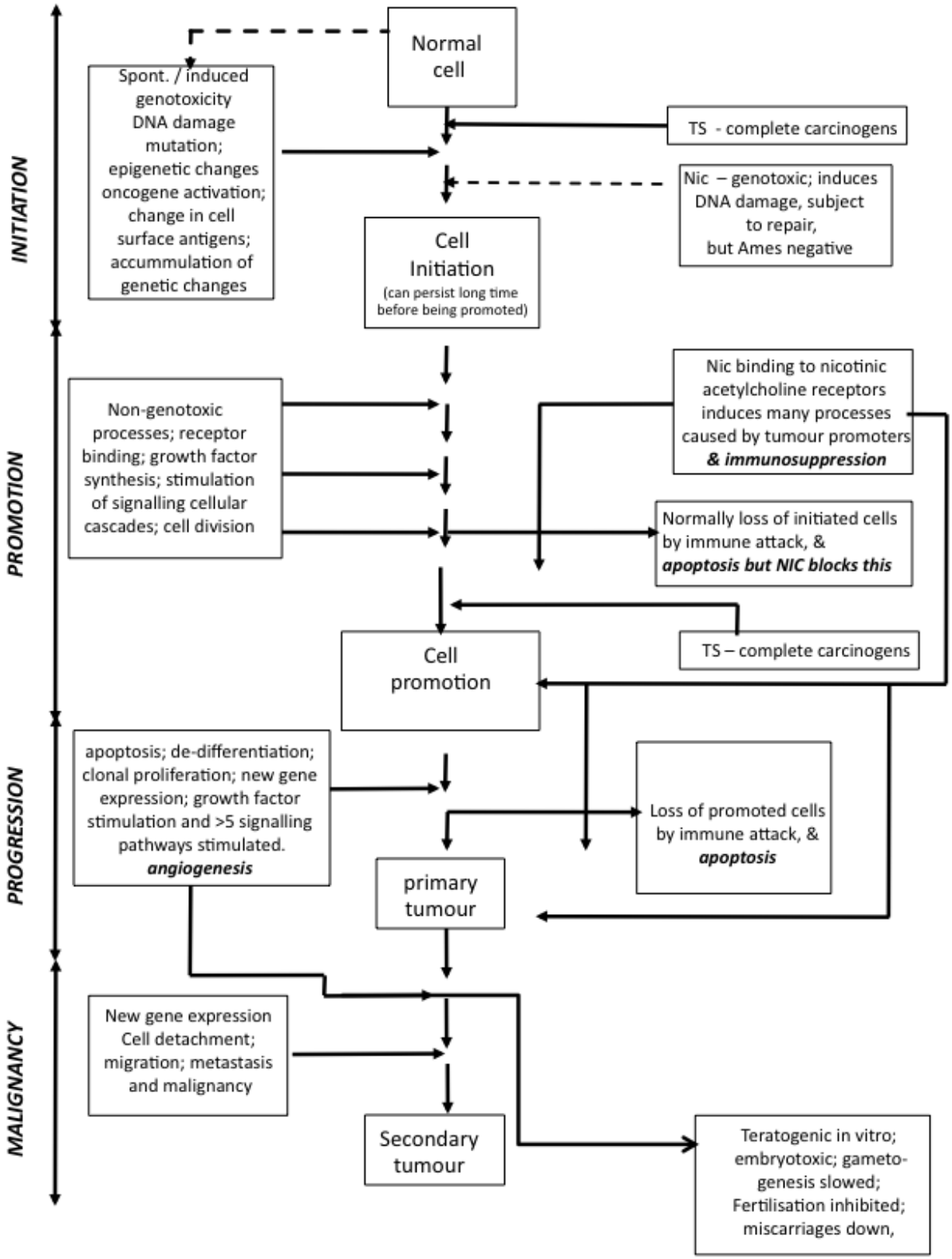
* reference 4 in References

**only 5/14 harm criteria were related to personal user adverse effects, and one of these was drug dependency;

Written evidence submitted by Dr Robert D Combes and Professor Michael Balls (ECG0080)

Figure: 1 Multi-stage carcinogenesis – effects of tobacco smoke (TS) & nicotine (NIC)



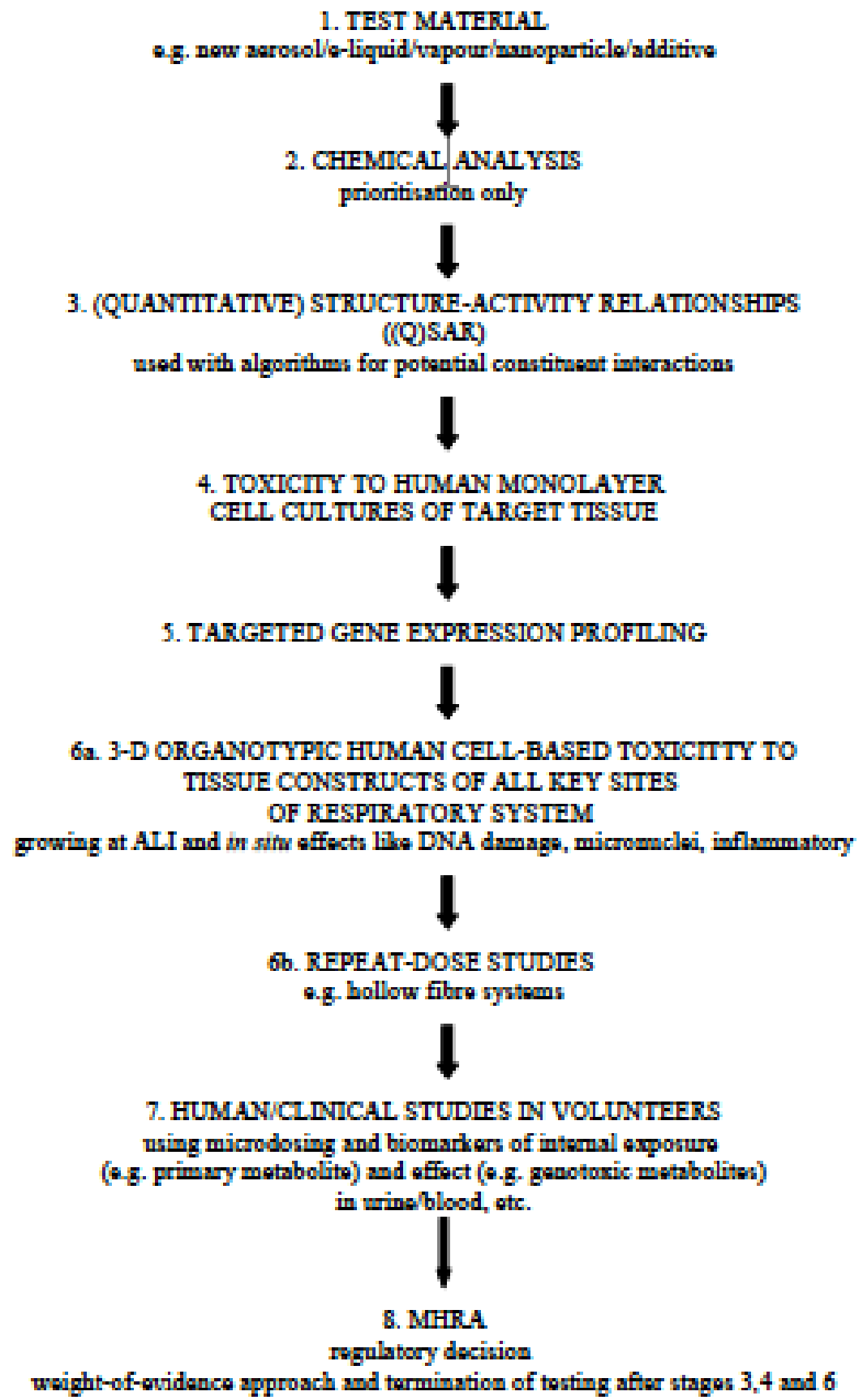


FIGURE 2 A GENERALISED INTEGATED TOXICITY TESTING STRATEGY FOR E-CIGARETTES

Written evidence - Dr Robert Combes and Professor Michael Balls

Written evidence submitted by Dr Robert D Combes and
Professor Michael Balls (ECG0080)

1. Executive Summary

- As professional toxicologists interested in improving testing methods for assessing the safety to humans of chemicals, we starting collaborating with the tobacco industry, to help identify promising new methods, beginning with tobacco smoking harm reduction products and then e-cigarettes.
- We soon became perplexed over the FDA's tobacco deeming regulations and then became even more-concerned about the way in which the UK authorities were laying the foundations for using e-cigarettes in the fight against smoking-related disease. We are especially surprised by the lack of scholarship and scientific rigour that is being applied to the safety assessment of these products, and feel it important to exploit our independence by speaking out.
- The current stipulations regarding the regulatory control and authorisation of electronic cigarettes (ECs) and vaping in the UK are scientifically flawed, as they are based on little more than conjecture and value judgment, backed only by poor science.
- There has been over-reliance on chemical analysis, the use of incomplete data, and risk assessments confused with the perceived benefits of vaping versus smoking, all of which bear little resemblance to standard approaches in toxicological risk assessment.
- The authorities, and other stakeholders, have systematically ignored, or erroneously dismissed, basic principles of pharmacology and toxicology, and inconvenient scientific observations, while promoting vaping as a way of ceasing smoking, instead of discouraging the use of nicotine in any form.
- The research being overlooked includes evidence of the many pleiotropic adverse biological effects of nicotine, more of which continue to be revealed with increasing frequency, which are likely to be highly relevant to carcinogenicity and disease.
- We discuss this very serious situation, and offer some suggestions for a better way forward, for the benefit of individual humans, now and in the future.

2 Introduction

Electronic cigarettes (e-cigarettes; ECs) are handheld, electronic devices that vaporise a liquid (e-liquid) containing nicotine with a other additives (e.g. propylene glycol or glycerol, and flavouring agents), and deliver the vapour to the lungs via inspiration and inhalation (a process called vaping).

In August 2015, Public Health England (PHE) declared that, in principle, ECs should be made available on prescription to reduce tobacco smoking (https://www.theguardian.com/society/2015/aug/19/public-health-england-e-cigarettes-safer-than-smoking). It was also made clear that ECs will be regulated as new medicines by the Medicines and Healthcare products Regulatory Agency (MHRA). This was followed by the news of the first e-cigarette (Evoke) to receive marketing authorisation from the agency.

These announcements have proved to be highly controversial, especially since they were justified by an estimate of there being 95% less harm from vaping than from tobacco smoking (https://www.gov.uk/government/news/e-cigarettes-around-95-less-harmful-than-tobacco-estimates-landmark-review). This submission explains why we believe that the decision by PHE is, in the light of current knowledge, irresponsible and unacceptable. We also propose some recommendations to avoiding the potentially very serious consequences, if this situation is allowed to continue.

3 Ignoring basic principles of toxicology

This is the most common characteristic exhibited by individuals, reports and publications discussing safety issues relating to ECs (Table 1; 1-3). The main consequences are: a) the belief that it is legitimate to base safety studies on analytical chemistry to determine the presence or absence of specific chemicals, and that data on their relative concentrations in e-liquids and emissions are sufficient to provide a quantitative measure of harm; b) the belief that the route of exposure has little effect on nicotine toxicity, and that, as few toxic effects have been observed since the times when various nicotine delivery devices were first introduced (ranging from 10 years for ECs to 30 years or more for nicotine replacement therapies {NRTs]), nicotine must be relatively inactive; and c) the belief that long-term toxicity can be predicted on the basis of acute effects.

The idea of deriving quantitative information on risk, while having only qualitative supporting data for ECs, originated from a Multiple-criteria decision analysis (MCDA) study (4). Our concerns about this are summarised in Table 2. Nutt et al. must have settled on 95% as a convenient comparative number, which PHE eventually simply expressed differently, ever since which the figure has been quoted ad nauseam, without any supporting data.

Overlooking the effect of route of administration is exemplified by a report of the Royal College of Physicians (4) which stated:There are, however, no grounds to suspect that inhaled nicotine will have an appreciably different risk profile from nicotine delivered via other routes of absorption. This statement is imprecise, and was not backed by any references. There are many reasons why toxicity can depend greatly on route, rather than merely on target organ(s). Another important factor is the possibility of drugs going into systemic circulation, once entering the body, usually by routes other than orally, before passing through the liver first - the organ which normally reduces systemic concentrations of parent compounds and which alters them to produce various metabolites, which can be more toxic or less toxic than the parent compound.

4. Superficial and inaccurate reporting of supporting evidence

A paper by Cheng (6), cited in a report commissioned by PHE, written by McNeill et al. (7), provides evidence of the presence in vapours of some potentially carcinogenic tobacco-specific nitrosamines (TSNAs) at widely different levels (RF), but McNiell et al. did not mention the evidence in relation to safety, even though they made some other statements on the issue. This contrasts with another PHE-Commissioned report focusing on safety, (8), authored by Britton and Bogdanovica. These authors did not mention the extensive analytical data for such chemicals, as Cheng's paper was omitted in favour of one by Goniewicz et al describing that only very low levels of these chemicals are associated with ECS (9).

In a highly critical editorial (10), The Lancet noted that the PHE report was evidence-based confusion rather than being a "landmark review", as referred to by Kevin Fenton, PHE's Director of Health and Wellbeing. When commenting on a paper purporting to demonstrate a link between DNA damage in lung cells and exposure to EC vapour, Fenton, replied that Public Health England has always been clear that e-cigarettes are not 100 per cent safe and we will carefully consider this new study and continue to be vigilant. But our major world leading review, published recently, found that e-cigarettes carry a fraction of the risk of smoking' [underlining added]…..'. (http://www.telegraph.co.uk/science/2016/03/12/e-cigarettes-are-no-safer-than-smoking-tobacco-scientists-warn/). The so-called 'world-leading review' by PHE was nothing of the sort – it was essentially a very poor appraisal of the situation.

We also note that, while Nutt et al., in 2014 (4), urged caution when interpreting their MCDA data, they supported PHE's 95% safer value in a letter published two years later (11). The MCDA paper (4) is also superficial, especially with respect to criteria for calculating maximum relative harm (MRH) and on how the inescapable problem of the huge bias in data for tobacco smoking compared with ECs was corrected for. This bias is due to the much shorter time for which ECs have been available for use and for testing, meaning that more subjectivity would have been required when assessing ECs to reach consensus at the decision conference, an even greater problem in 2013, when the discussions took place. This problem was also noted in a review on ECs, published in April 2014 (12), which concluded that "Existing evidence suggests that these products [ECs] are by far a less harmful alternative ….", although it was admitted that only a very few toxicological studies were available.

Despite searching background literature on the MCDA technique, some of it recommended by Nutt et al., and after watching seminars (13-15) by the two leading authors, we have not found any convincing explanations for our concerns about MCDA. Other critics of the MCDA approach include: Kujawski (16), who commented that the specific MCDA model used can greatly influence the rankings of the alternatives for a given set of criteria; and Rolles and Measham (17), who were highly critical of the criteria and weighting used for ranking.

5. Nicotine - an inconvenient truth?

There is widespread agreement in the various reports supporting ECs that, apart from its addictivity, nicotine, is otherwise non-toxic at its in-use concentrations.

Nicotine is actually one of the most toxicologically and pharmacologically active substances known (see reviews cited in ref 1). Structural alerts for DNA and protein binding were identified (unpublished studies by us, by using Toxtree, a decision-tree expert system for structure-activity relationships [SAR]), explaining the observed genotoxicity in the literature, and raising questions about respiratory sensitization (mediatied by DNA binding), and other mechanistically-related diseases, such as Chronic Obstructive Pulmonary Disease (COPD). Of interest is the fact that propylene glycol and glycerine lacked these alerts, although they might be precursors for toxic carbonyl compounds, the generated amounts of which increased with heater settings in one study (18), but it is possible to generate them without the excessive levels causing dry puff.

The literature on nicotine carcinogenicity and reproductive toxicity, reviewed by us in ref 1 [18 references cited therein], at the very least, suggests that, if not a complete carcinogen (acting as an itiator and promoter, nicotine acts on a variety of key post-initiation stages of the multi-step process of carcinogenesis (Fig. 1), including inhibition of apoptosis and immune system suppression, tumour promotion, cell

proliferation, progression, stimulation of specific cell activating factors, angiogenesis, and the induction of unique patterns of differential gene expression (see also 19). The drug also activates at least five mitogenic signaling pathways and cooperates with TSNAS toward the carcinogenic activity of tobacco smoke (20), and is also embryotoxic and modulates fertilization.

6. Cardiovascular disease (CVD) effects

Nicotine and ultra-fine fibres in the particulate matter in tobacco smoke have been implicated separately to be involved in smoking related CVD via their ability to induce inflammation in the endothelial layer in blood vessel walls, a first step in atherogenesis leading to CVD (21,22). The fibres increase the surface area for reactive oxygen species (ROS), and possibly act also by causing some physical damage to the cells

It is possible that the two components have to interact synergistically for an effect. Such a model would explain the lack of association between NRT usage and CVD, and would suggest that EC use would also not be linked to NRT, unless some other component could mimic the effect of the fibres. Candidates for this role are the nanoparticles generated from the heating elements in e-liquid reservoirs. Some of the fibres have overlapping dimensions with NPs (23), but their surface chemistry needs to be characterised, and further work is needed to see if they interact with nicotine to induce atherosclerosis. Interestingly, Zhao et al. (24) recently demonstrated ROS generation by e-cigarettes, which was highly dependent on brand, flavour, puffing pattern, and voltage.

7. Basing the safety of nicotine on human studies of NRT users and snus takers

Often, the results from epidemiological studies of users of NRT, and of smokeless tobacco (e.g. 'snus', which is popular in Scandinavia, the device being a pouch of tobacco, maintained in the mouth for extended periods), without increases in the incidence of conditions like cancer, COPD or CVD, in device-users compared with matched non-users, are used to argue against nicotine being toxic. However, such arguments fail to explain all of the evidence and/or do not accord with all of the facts.

While the 30-year or so period during which NRT products have been available would seem to be a sufficiently long time for the lack of increased susceptibility to cancer to be attributed to the non-carcinogenicity of nicotine, it is a collective figure for all users, which should not be confused with individual treatment durations for a course of NRT (typically 8-12 weeks per patient) – too short a duration for assuming non-carcinogenicity.

With regard to snus, careful reading of the statistics in the annual Swedish Cancer Registry (http://www.socialstyrelsen.se/english) reveals a complex relationship between snus-taking, lung cancer and other cancers. Two key conclusions from the statistics, a) that the use of snus almost halved lung cancer incidence in males in Sweden, and b) that it is not associated with increases in the occurrence of a range of other 'common' cancers, do not agree with all the available evidence, some of which suggests that snus usage has had only a minimal effect on lung cancer incidence overall, in males, and that increases in a range of other cancers (including oral and pancreatic) can be linked to exposure to snus.

Therefore, the statistics on the change in cancer incidence in relation to snus-taking in Sweden need to be interpreted carefully. Some other published analyses of population studies, including that by Lee et al. (25), essentially giving snus the all-clear, were criticised by Tomar et al. (26). Finally, if nicotine were a tumour promoter, a long period between exposure to an initiator and promoter is just what would be expected to still potentially result in tumorigenesis.

8. An attempt to obtain long-term data on ECS

A so-called 'long-term' biomonitoring study, published in March 2017 (27), allegedly demonstrating the much greater safety of vaping compared with smoking, has been hailed as being the closest yet to endorsing the 95% less harmful value and PHE's policy on ECs.

Biomonitoring assesses internal exposure to, and the possible systemic effects of, a substance to which an individual is exposed, thereby strengthening the link between exposure and effect. The study in question analysed urine samples obtained from smokers, vapers and those on various types of other NRT devices, for the presence of biomarkers of exposure to several carcinogens found in tobacco smoke and linked to lung cancer. The key criterion for inclusion in the study was the daily use of the same broad category of device for at least six months prior to sampling. This allowed conventional NRT users to use devices with varying routes of administration, introducing a further source of variability. Levels of biomarkers were detected and quantified by using highly sensitive methods for chemical analysis.

The lowest concentrations of all the biomarkers were found in the samples from the EC-only users. As the differences were quoted as being between 90-100%, the authors interpreted this as vindication of the 95% figure.

However, the study was flawed in its rationale (it relied on chemical analysis), and its design (small numbers of volunteers and wide differences in gender ratios between some of the cohorts and only one timepoint). Conventional long-term toxicity testing involves repeat exposure studies and continual surveillance of laboratory animals, for at least several months. The tests are designed to detect chemicals that might not specifically exhibit acute effects. Therefore, this study, with only one sampling, should not be regarded as being equivalent to a repeat-dose toxicity study. There was also no control of fluid and nutrient intake on the day of sampling, let alone of the type of device, and no determination of the various e-liquid compositions. At best, the study could have provided only a snapshot of what was happening during the period involved.

9. A role for non-animal methods

Regulatory test batterles for new drugs include subchronic and chronic tests that are specifically designed to predict repeat-dose toxicity (<90 days) and longer-term toxicity, some studies of which take some 2-3 years to complete. Long-term models of respiratory diseases also exist (2, 28). An example of one of these has recently been published (29), in which mice were exposed by inhalation to nicotine-containing EC fluids for one hour daily over four months. The exposures induced effects associated with the onset of COPD, including cytokine expression, airway hyper-reactivity, and lung tissue destruction. These effects were nicotine-dependent in the mouse lung, suggesting that inhaled nicotine contributes to airway and lung disease.

However, our suggestion of the need for more hazard data for ECs does not necessarily mean more animal testing, since many in vitro methods exist (see citations in refs 1-3) These offer many advantages over their in vivo counterparts, ranging from more-precise dosimetry to advantages in data interpretation. This is especially true for inhalation testing (28).

Monolayer-cultures of cells from target airway sites can be used. For example, in the four-month COPD study mentioned above, the same results were obtained when normal human bronchial epithelial [NHBE] airway cells were cultured at an air-liquid interface (ALI) and exposed to EC vapours or nicotine solutions by using a Vitrocell smoke exposure robot.

It should be possible to obtain more-reliable and more-relevant data expeditiously through the application of integrated testing strategies involving advanced human cell-based tissue culture systems, in which their differentiated status is retained in culture, and which are representative of the major target sites in the airways for respiratory toxicity and disease, by using ALI exposure. Moreover, some of the toxicity endpoints (e.g. DNA damage) can be measured in situ in the tissue construct (several reviews have been published over the past year).

The tobacco industry has been active in this area, holding workshops and various integrated tiered testing strategies have emerged for improving and expediting hazard identification. We present a generalized strategy, based on this type of approach (Figure 2). The strategy also includes a repeat-dose toxicity testing stage involving the use of hollow fibre technology for maintaining the longevity of cells in culture by replacing spent culture medium with fresh medium.

It is also possible to develop in vitro micro-culture models of whole organs, in order to predict the effects of exposure at several different sites within the same organ, simultaneously. A pertinent example is a small 'airway-on-a-chip' device developed by Benam and coworkers (30). This system is lined by living human bronchiolar epithelium from normal or COPD patients. The device is connected to an instrument that delivers whole cigarette smoke in and out of the chips, to permit the study of smoke-induced pathophysiology in vitro.

10. Smoking cessation versus nicotine quitting

We also note that the rationale for NRT was originally geared toward the ultimate goal of detoxication from nicotine drug dependency. In other words, it was intended that treatment would progress from a phased withdrawal, from dual usage via exclusive NRT usage to no usage. The current emphasis ion smoking cessation is regrettable, since it would greatly prolong exposure to nicotine. While this might not increase drug dependency, it could result in many other adverse effects, including tumour promotion and progression of initiated cells already formed in smokers before they started to quit.

11. Discussion

The argument for encouraging the use of ECs is based on: a) the apparent lack of association between nicotine exposure and carcinogenesis, CVD and other respiratory diseases, interpreted as meaning that they can be regulated lightly by waiving the batteries of preclinical and clinical tests to which most new medicines are subjected; b) an estimate with no scientific basis that vaping is 95% less harmful than tobacco smoking; and c) the belief that the focus should be on achieving tobacco smoking cessation, rather than drug independence. Our investigations have encouraged us to conclude that all these assumptions are spurious when considered with respect to principles of

toxicology involving hazard prediction and risk assessment.

The safety assessment of ECs should, in principle, be no different from that required for other new medicines. No good reasons for by-passing the risk assessment and risk-benefit procedures normally required for registering pharmaceuticals have been made public, and we also note that PHE mandated itself to publish its decision, without first having a public consultation stage.

We also consider that the use of panels of experts to decide, largely on the basis of opinion and value judgment, especially for ECS, about the 'relative harms' of nicotine-release devices, without relevant and reliable quantitative data about the harms resulting from exposure especially to EC vapour, was unwise and unnecesdsary, especially when non-animal testing strategies are available to generate meaningful hazard information and to fill data gaps, to be used, with other information, in a convincing weight-of-evidence assessment.

Finally, we stand by our belief, expressed in a letter published in The Times on 18 February 2016, that “The human respiratory system is a delicate vehicle, on which the length and quality of our lives depend. For governments and companies to condone, or even suggest, the regular and repeated inhaling of a complex mixture of chemicals with addictive and toxic properties, but without comprehensive data, is irresponsible and could have serious consequences.”

12. Recommendations

1. Good Manufacturing Practice guidelines should specify device design, capability, construction, mode of nicotine delivery and permissible ingredients, and their maximum amounts.

2. The designs should avoid the potential for excessive customisation.

3. Professional toxicologists should be involved in advising on safety issues relating to regulation of the use of ECs.

4. The intrinsic risks from vaping should be investigated and calculated separately, before comparison with the risks from tobacco smoking.

5. ECs should be considered as NRT products, rather than for prolonged recreational usage, until more long-term safety data have become available.

6. The toxicity of nicotine should be investigated further, as should the ability of nanoparticles in EC emissions to mimic the effects on CVD of particulate matter in tobacco smoke.

7. Threshold values for nicotine toxicity should be identified.

8. The end-game should be total cessation of the use of nicotine, beginning with tobacco smoking, but proceeding to cessation of the use of NRTs and ECs.

9. POS (point of sale) literature should emphasise the importance of nicotine quitting.

10. The MHRA should be more transparent about how ECs will be regulated via a ‘light-touch” approach, especially by applican of the concept of bioequivalence.

11. We strongly urge that further in vitro methods for detecting long-term toxicity and chronic disease conditions as a result of inhalation, should be developed and validated and accepted for use as soon as possible.

12. Several prospective long-term epidemiological studies should be initiated in the near future, to assess the adverse clinical and toxic effects from vaping. These should involve biomarkers of exposure and effect, such as DNA adducts, chemically-modified bases, and genotoxicity of body fluids.

December 2017

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14. Tables and figures:

Table 1

Ten principles of toxicology being ignored in the debate in the UK concerning electronic cigarettes

1. There can be synergistic or antagonistic effects between constituents of complex mixtures.
2. Non-linear dose-responses are often exhibited.
3. There can be lag periods of many years between exposure and effect, e.g. for some cancers.
4. Analytical chemistry is of limited value for predicting non-toxicity.
5. Some chemicals and endpoints lack thresholds of toxicological concern, and toxicity can occur at very low concentrations.
6. Long-term effects are just as important as acute ones.
7. Quantitative expressions of safety should always be based on numerical data.
8. Route of entry/administration can have a large effect on toxicity.
9. Acute toxicity data should be used with great care, when attempting to predict long-term effects.
10. When in doubt, adopt the precautionary approach.

Table 2

Ten problems with the MCDA study (Nutt et al., 2014)* on Maximum Relative Harms (MRHs) for nicotine devices, and its subsequent interpretation

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1. Insufficient information available to repeat study closely with a completely different panel of experts (e.g. criteria forMRH unclear).
2. Panel did not have on it a toxicologist experienced in risk assessment (the focus was not on comparison of hazard compared with exposure).
3. Huge bias of harm information available for tobacco smoking compared with vaping, (meaning much more conjecture in scoring the latter).
4. Therefore, although scoring in general based on opinion, this would have been less so for tobacco smoking
5. Since 2013/4, much more safety data have become available for vaping, and such information should inform fresh new discussions.
6. No explanation as to how consensus was achieved between the panelists (no proceedings of face-face workshop).
7. No numerical hazard data to support the quantitative estimate made for relative harmof vaping versus tobacco smoking (resulting in a false impression of accuracy).
8. Insufficient focus on the toxicity of nicotine and its contribution to harms (leading to a possible under-estimation of harm from vaping).
9. Harms from smoking based on short-term and chronic effects, whereas, for vaping, no chronic data available (long-term safety

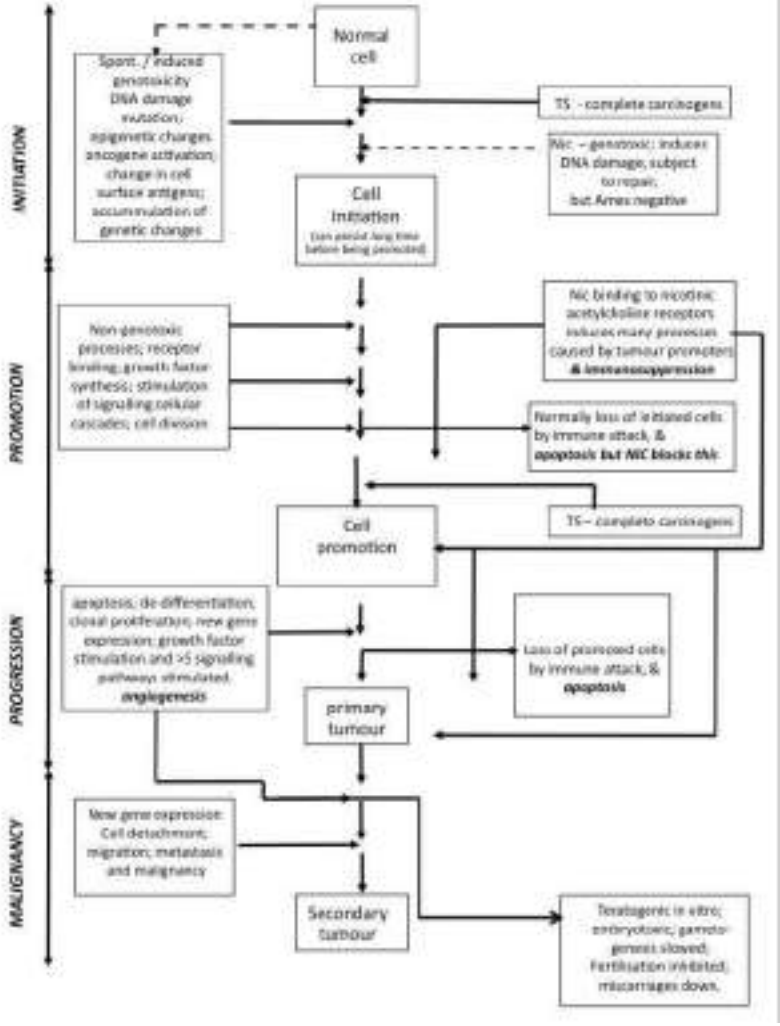
cannot be accurately predicted from acute effects).

10. MRH values were based on wide range of criteria, other than safety*per se*,** meaning use of the term 'harm' in the paper is misleading ('harm' has been used to infer safety, when the terms are not synonymous).

* reference 4 in References

**only 5/14 harm criteria were related to personal user adverse effects, and one of these was drug dependency;

Figure: 1 Multi-stage carcinogenesis – effects of tobacco smoke (TS) & nicotine (NIC)



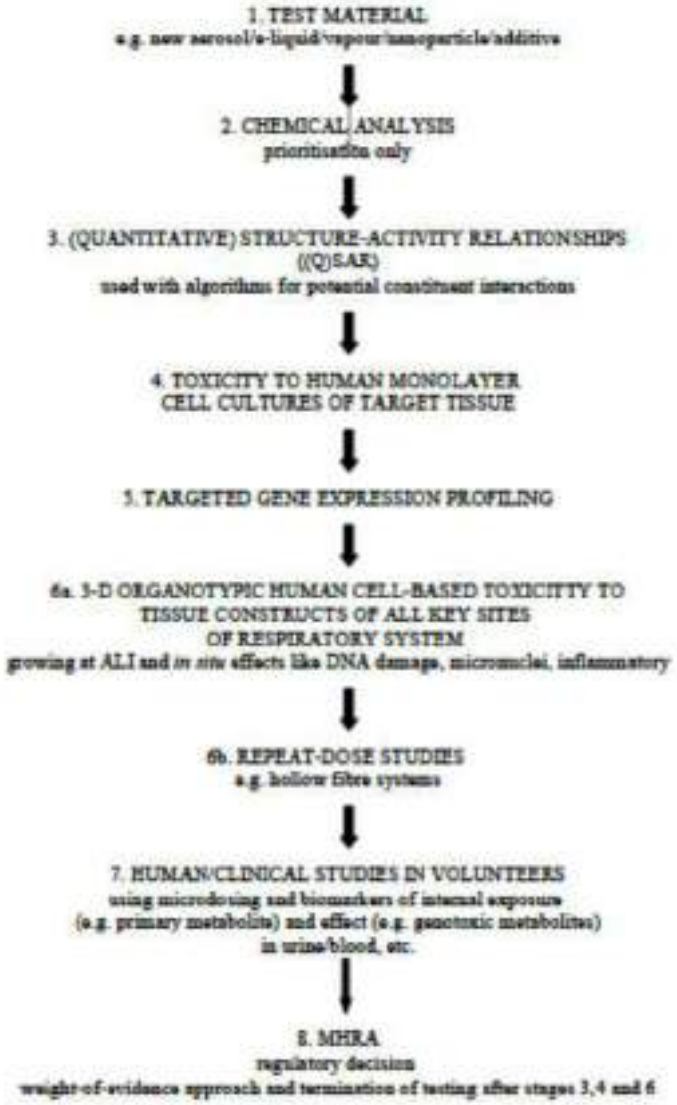


FIGURE 2 A GENERALISED INTEGATED TOXICITY TESTING STRATEGY FOR E-CIGARETTES

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ncbi.nlm.nih.gov/myncbi/robert.combes.1/comments/

ROBERT COMBES

Comments 1 to 2 of 2

- On the safety of e-cigarettes: "I can resist anything except temptation". Combes RD.Altern Lab Anim. 2015.2 commentsCoral Gartner also commented

  ROBERT COMBES2016 Sep 17 12:37 p.m.

  Professor Michael Balls and Dr Robert Combes respond to Dr Coral Gartner regarding concerns about possible conflicts of interest.

  We thank Dr Gartner for her comments, and for the opportunity to clarify potential conflicts of interest relating to our paper [1]. This was written by us as independent individuals, free of any commercial influence or funding, and after both of us had ceased having close ties with FRAME. FRAME is a scientific charity that has openly received financial support from the chemical, cosmetic, household product, pharmaceutical and tobacco industries, to enable it to undertake independent research into the development, validation and acceptance of alternatives to animal experiments.
  Some of this work included the development, characterisation and preliminary assessment of in vitro models of inhalation toxicology. While we are not in a position to say anything about FRAME'S current policy on industrial funding, we must stress that the tobacco industry funding enabled FRAME to investigate ways to replace highly invasive and complex animal experiments with urgently needed alternatives with the potential for producing more-relevant and more-reliable data for assessing human safety.

  As far as personal remuneration is concerned, RDC has acted as an external consultant for the tobacco industry since retiring in 2007 from FRAME. This work was conducted under standard contract research agreements, the last of which terminated over 12 months prior to the writing of our article. The work referred to by Dr Gartner, that was co-authored by RDC with a named individual as lead, relates to research undertaken when this individual and RDC were employed by Inveresk Research International (IRI, now Charles River Laboratories), a contract research establishment. This can be directly verified by opening the authors' affiliations in PubMed (http://9www.ncbi.nlm.nih.gov/pubmed)for each of the four respective abstracts (PMID: 9491389; PMID: 1600961; PMID: 1396612; and PMID: 7968569). This work was entirely funded by the US Government, as was acknowledged in each of the papers, and also by the inclusion of another co-author, then based at NIEHS

(the National Institute of Environmental Health Sciences, Research Triangle Park, USA), who acted as project leader. It should be noted that the lead author of the publications arising from the work conducted at IRI subsequently went to work at BAT, and this might have added to any confusion.

MB has never been a paid consultant for any industrial company. He was honorary Chairman of the FRAME Trustees from 1981 to 2013, and has been honorary Editor of FRAME's journal, Alternatives to Laboratory Animals, since 1983. He no longer has any influence on FRAME's policies on the tobacco industry or on any other issue. None of FRAME's industrial supporters ever attempted to dictate or limit FRAME's activities, or influence the circulation and/or publication of the results of any FRAME research. While MB was head of the FRAME Alternatives Laboratory at the University of Nottingham Medical School, no tobacco product, or chemical, other material or product of interest to the tobacco industry was involved in FRAME's research. He left the University of Nottingham in 1993, to become the first head of the European Commission's European Centre for the Validation of Alternative Methods, a position from which he retired in 2002. We consider that there is a distinction between the above situation, in which, despite previous links of various kinds with the tobacco industry, we wrote our critique [1](ref) without any form of external influence, and that which we referred to, involving alleged conflicts of interest in the MCDA study. However, while we acknowledge that conflicts of interest and their consequences are complex, we hope that we have taken into account as much relevant information as possible to permit a fair and balanced appraisal of the information on which PHE's policy on electronic cigarettes is based. We consider it crucial that scientific opinions, and the policies which result from them, are based on freely-available evidence of high quality, which has been openly conducted and independently assessed. We know of no such evidence to support PHE's claim that e-cigarettes are 95% safer than tobacco cigarettes.

We welcome Dr Gartner's comment, we hope that others will address the scientific arguments that we have used to justify our position, since, the validity, or otherwise, of these should be unaffected by any conflicts of interest. There is a great deal at stake, including the future well-being of those who have opted for vaping as an alternative to tobacco smoking. We stand by our belief, expressed in a letter published in The Times on 18 February 2016, that "The human respiratory system is a delicate vehicle, on the which the length and quality of our lives depend. For governments and companies to condone, or even suggest, the regular and repeated inhaling of a complex mixture of chemicals with addictive and toxic properties, but without comprehensive data, is irresponsible and could have serious consequences."

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  McKee M.N Engl J Med. 2016.9 commentsClive Bates, Gerry Stimson and 2 others also commented

ROBERT COMBES2016 Sep 09 8:08 p.m.

Robert Combes and Michael Balls

In a recent exchange of views, in PubMed Commons, with Simon Chapman on the effectiveness and safety of vaping for achieving the cessation of tobacco smoking, provoked by a paper published by Martin McKee [and comments therein], Clive Bates has criticised one of our publications. The paper in question urges caution concerning any further official endorsement of electronic cigarettes (ECs), at least until more safety data (including results from long-term tests) have become available. Bates questions why we should write on such issues, given our long-standing focus on 'animal rights', as he puts it, and from this mistaken assumption he makes the remarkably illogical deduction that our paper is without merit. Bates also implies that our views should not be taken seriously, because we published in Alternatives to Laboratory Animals (ATLA), a journal owned by FRAME (Fund for the Replacement of Animals in Medical Experiments), an organisation with which we have been closely associated in the past.

We have written a document to correct Bates' misconceptions about who we are, what our experience is, why we decided to write about this topic in the first place, what we actually said, and why we said it. In addition, we have elaborated on our views concerning the regulatory control of e-cigarettes, in which we explain in detail why we believe the current policy being implemented by PHE lacks a credible scientific basis. We make several suggestions to rectify the situation, based on our careers specialising in cellular toxicology: a) the safety of electronic cigarettes should be seen as a problem to be addressed, primarily by applying toxicological principles and methods, to derive relevant risk assessments, based on experimental observations and not opinions and guesswork; b) such assessments should not be confused with arguments in favour of vaping based on how harmful smoking is, and on the results of chemical analysis; c) it would be grossly negligent if the relevant national regulatory authorities were to continue to ignore the increasingly convincing evidence suggesting that exposure to nicotine can lead to serious long-term, as distinct from acute, effects, related to carcinogenicity, mutagenicity (manifested as DNA and chromosomal damage) and reproductive toxicity; and d) only once such information has been analysed, together with the results of other testing, should risks from vaping be weighed against risks from not vaping, to enable properly informed choice.

Due to space limitations, the pre-publication version of the complete document has to be downloaded from:
https://www.researchgate.net/publication/307958871_Draft_Response_regarding_comments_made_by_Clive_Bates_about_one_of_our_publications_on_the_safety_of_electronic_cigarettes_and_vaping and our original publication is available from:
https://www.researchgate.net/publication/289674033_On_the_Safety_of_E-cigarettes_I_can_resist_anything_except_temptation1

We hope that anyone wishing to respond will carefully read these two documents before doing so.

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Article *in* Alternatives to laboratory animals: ATLA · December 2015

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Comment

On the Safety of E-cigarettes: "I can resist anything except temptation"[1]

Robert D. Combes and Michael Balls

Strategic policy decisions are being made about e-cigarettes, based on the plausibility of their greater safety, rather than on essential scientific evidence which would permit a proper risk assessment. If e-cigarettes are *really 'safer', then their use should be recommended, but only after an intelligent analysis of their risk to human health, based on integrated* in silico, in vitro *and clinical studies for both scientific and logistical reasons*

Concern Raised by Public Health England's Proposal for ECs to be Available on the NHS

In a Comment article published in the September 2015 issue of *ATLA*,[2] we expressed our concern that, although we welcomed the prospect of new tobacco-related products aimed at reducing harmful exposures, it appeared that new regulations would require that their relatively greater 'safety' would have to be established via complex testing regimes which would be heavily reliant on traditional animal procedures of doubtful relevance and reliance. We argued that, instead, the focus should be on the intelligent and integrated use of non-animal *in silico*, *in vitro* and clinical studies.

Just before our article went to press for publication, Public Health England (PHE; a UK executive agency, sponsored by the Department of Health) proposed that electronic cigarettes (ECs), a non-tobacco alternative to smoking, should be made available via the NHS (National Health Service),[3] as a means of reducing the general incidence of disease and harm attributable to conventional smoking.

We found that there was an increasingly heated debate about the safety of ECs, between those that want their use encouraged and endorsed with little delay, and others who urge caution. The PHE proposal is a classic example of the temptation of short-term gain irrespective of the possibility of long-term pain.[4] It is dangerous, because the relatively greater safety of ECs has not been scientifically established — and regrettable, because it is likely that other authorities, notably those on the other side of the Atlantic, are likely to insist on the introduction of complex testing regimes which will require animal testing, as is the case for new smoking materials.[2]

Background

PHE's proposal is a matter of concern, mainly because of the lack of safety data and the resulting inability to perform any sort of risk assessment of the type normally undertaken for consumer products, as well as doubts concerning the relevance of the data on the impact of ECs on smoking habits. In addition, our review was not specifically on ECs, as a consequence of which there is other, relevant published information on usage and safety, which needs to be considered. We now take this opportunity to elaborate on our initial response, and on our reasons for urging caution, in the light of recent developments regarding ECs, both at home and in the USA.

This issue needs to be resolved urgently, since the popularity of ECs is rapidly gaining ground, especially with young people, at the expense of tobacco smoking, largely on the assumption that ECs either lack many of the toxic constituents, contaminants and by-products to which conventional smokers are exposed, or that these substances are encountered at sufficiently low concentrations so as to cause no health problems. Moreover, an update on the situation with ECs is timely since: a) the FDA is about to be charged with responsibility for regulating ECs in the USA (http://www.fda.gov/TobaccoProducts/ Labeling/ ucm388395.htm); b) as we write, the *Third Summit on Electronic Cigarettes* has just taken place in London (http://www.e-cigarette-summit.com/); and c) the UK (via the Department of Health and the Medicines and Healthcare Products Regulatory Agency [MHRA]) has a deadline of May 2016 to complete the process of transposing into its national legislation, the EU revised Tobacco Products Directive (http://ec.europa.eu/health/ tobacco/ docs/ dir_201440_en.pdf), which came into force in May 2014.

The situation regarding ECs is also highly relevant to the Three Rs, since we have the prospect of significant levels of safety testing, some of which could involve traditional animal tests, highly invasive procedures and the use of non-human primates, to satisfy new regulatory requirements in Europe and the USA.[2] Although, after careful consideration, we believe that more information is required before ECs become incorporated into strategies for tackling the burden of disease and ill-health due to tobacco smoking, we feel that most, if not all, of the required data could be obtained in a more-timely way by implementing a strategy focused on the coordinated use of chemical, *in vitro* and clinical methods. Moreover, because the information will have largely been obtained by using organotypic tissue culture systems comprised of cells from the target tissues and species, it will be of direct relevance to assessing risk levels arising from the use of ECs.

The Controversy

Understandably, PHE's suggestion has provoked considerable discussion and controversy, while being generally welcomed by those who see ECs as a quick solution to the smoking and health problem. To illustrate the type of approach being taken by some stakeholders to address the EC issue, we quote the opening sentence of what looks like an internal report on the burdens of regulating ECs, but dated September 2013,[5] which states that: *E-cigarettes are very low risk alternatives to cigarettes, used by smokers as a pleasurable way of taking the relatively harmless recreational drug, nicotine*. However, we were unable to find any evidence, or citations to original articles presenting toxicity data, in support of such a potentially far-reaching statement by the authors in their 26-page document, which, essentially, urges the UK Government to resist being overburdened with EU regulations for ECs — requirements which, in the authors' opinion, are unnecessary, because they could delay the take-up of ECs by the public. The authors qualify the risk level, by claiming it is 'very low', again without any reference to quantitative hazard data — most extraordinary!

In direct contradiction, and two years following publication of that statement, our in-depth appraisal[2] of the use, safety assessment and regulatory control of tobacco-related products in general, including ECs, leads us to believe that, whatever the long-term consequences of any such policy, or however worthy the ultimate objective of PHE may be, it is, *in the light of current knowledge*, a reckless and irresponsible suggestion.

Poor Reporting

PHE's justification for its proposal relies heavily on two reports which it commissioned, and which were not peer-reviewed.[6,7] It ignores the possibilities that users might be repeatedly exposed to hitherto undetected contaminants and by-products, as well as to carcinogenic chemicals, or their precursors (which have been detected in solvent extracts and vapours, and which are derived from tobacco during solvent extraction or generated during solvent heating), that can have effects at very low dose levels, following repeat exposures, which can occur without clear threshold doses, thus necessitating zero-dose extrapolation.[8] Also, the PHE report contains information on the likely adoption and use of e-cigarettes by existing and potential smokers that could be of questionable relevance to the UK. This is because this information is derived from experience in other countries, with differing attitudes to smoking, or it applies to other tobacco-related products that are used mainly elsewhere, or it is conflicting, or merely circumstantial.

On comparing our Comment[2] with the PHE document, as well as looking at data that were published before the document was released, we have found that some key references are missing from it, or have been selectively covered, with the omission of some important information. For example, we have previously discussed evidence of the presence in vapours of some tobacco-specific nitrosamines (TSNAs), but the PHE report, which included the same reference,[9] omitted any mention of the analytical data for such chemicals. There are several other reports of the detection of TSNAs in ECs,[10,11] but there is no discussion in the PHE report of the potential role of such contaminants, some of which are highly-potent genotoxins[12] in the aetiology of lung cancer. In fact, cancer is not specifically mentioned anywhere in relation to safety, and there is no record of published reports of exposure to additional substances, such as nanoparticles (NPs) derived from metals[13] (also see Combes and Balls[2]). NPs, together with certain other chemicals, have been linked to respiratory sensitisation and mechanistically-related diseases, such as chronic obstructive pulmonary disease. Sensitisation is another endpoint for which clear thresholds for induction doses are difficult to identify.[14] This might be because they do not exist, as with genotoxins, or because of technical deficiencies, but either way, this complicates risk assessment.

The omission by PHE of several key papers and information from a report that was intended to be used to determine public health policy on the basis of the evidence available, is completely inexcusable. This is especially the case, as the above facts combined suggest that there is a tangible, and, at

present, unquantifiable, risk that repeated and prolonged exposure to even low doses of such chemicals, as would be expected to occur as a result of using ECs, could be sufficient to trigger cellular changes eventually culminating in serious conditions, sometimes not manifested until some considerable time following the onset of exposure.

With regard to the possibility of the presence of undetected chemicals, some of which could be toxic, it is worth noting that very few of the analytical methods in use have been validated for the purpose in question, which could, in part, explain the relatively high levels of variation seen between EC brands, and which also could account for the variation experienced within experiments.

The PHE report also fails to mention one of the main findings of the earlier investigations into the safety of ECs, namely, that different brands can vary substantially in the levels of contaminants, by-products and active components (e.g. nicotine), such that there is an urgent need for more harmonisation of the different products available.[3]

A reminder of how difficult it can be to predict the adverse effects of complex mixtures, such as EC aerosols and liquids, is provided by a recent study[15] on the potential modulating influence of nicotyrine, a product present in tobacco which also arises in EC fluids as a result of slow oxidation of nicotine. This chemical is an inhibitor of cytochrome (CYP) isozymes (CYP P450 mixed function oxidases), which clear nicotine from the body and are active in both hepatic and extrahepatic systems. The authors noted that the metabolism of all of the substrates of the respective isozymes will be affected by nicotyrine. It so happens that one of these substrates is the TSNA, nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK),[12] one of the most potent of the known lung carcinogens in tobacco smoke. This substance is activated in airway cells, both *in vitro* and *in vivo*, by CYP2A13,[12] suggesting a potential anti-carcinogenic effect of nicotyrine, at least for this particular mechanistic pathway.

Neither our Comment,[2] nor the PHE report, referred to a review, published in April 2014, on the toxicity of ECs.[16] The authors of this review concluded that: *The available evidence suggests that these products are by far a less harmful alternative to smoking and significant health benefits are expected in smokers who switch from tobacco to electronic cigarettes.* However, while this seems to be good news, the authors admitted that only very few toxicological studies were available to them. Also missing from the PHE report is reference to an unpublished, but comprehensive 19-page document, available on the Internet,[17] which summarises various aspects of ECs, including safety issues.

The PHE report went considerably further than merely saying that ECs are safer than conventional smoking, by providing a quantitative estimate of the extent of this alleged greater safety. It claimed that ECs are up to 95% safer than conventional smoking, and that: *Best estimates show e-cigarettes are 95% less harmful to your health than normal cigarettes, and when supported by a smoking cessation service, help most smokers to quit tobacco altogether*. Later on, the report states that: *Acknowledging that the evidence base on overall and relative risks of EC in comparison with smoking was still developing, experts recently identified them as having around 4% of the relative harm of cigarettes overall (including social harm) and 5% of the harm to users.*

Misuse of Information

While these two statements are not referenced, it emerges later in the report that they are based on the outcome of a multi-criteria decision analysis (MCDA) study, in which a small group of experts considered the harms to human health and well-being posed by using a wide range of tobacco products.[18] Each product was ranked on a scale which put cigarette smoking top at almost 100% for several properties, including addiction and cancer. The authors stated that: *Within the tobacco products there was a gradual reduction in harm from water pipe, smokeless unrefined, smokeless refined to snus that has 5% of MRH. Among the purer non-tobacco vehicle products ENDS were rated to have only 4% of MRH and for the even purer NRTs the MRH was only rated at about 2%.* [where ENDS = electronic nicotine delivery systems; MRH = maximum relative harm; and NRTs = pharmacological replacement products.]

PHE then used the outcome of this study, as if it were equivalent to experimental data, to derive the 95% figure. Apart from being baffled by how any quantitative risk assessment can be made with the paucity of available hazard data, we are uncertain as to how to interpret the intended meaning of such a statement, other than by concluding that PHE believes that ECs are almost twice as safe as tobacco smoking. The quantification of risk in toxicology, although not a precise process by any means, implies some greater confidence in a particular prediction than is conveyed by a mere qualitative statement, and it has to be derived from detailed quantitative hazard data. However, in this case, the information was merely generated by an *ad hoc* group of experts, and was based on opinions, rather than being grounded in scientific observation.

Moreover, there are many difficulties with the MCDA approach in general, and in particular, with the above application of it.[2,19] This implies that the validity of its outcome is very questionable, being dependent on the amount and rele-

vance of pre-existing information, subject to much value judgement, and difficult to reproduce with a different set of experts, and with the same ill-defined criteria used to assess relative harm. We also noted one inescapable problem, which relates to the large bias in the overwhelming amount of available data on cigarette smoking compared to that on ECs. It is difficult to see how such an imbalance could be compensated for in practice, but it greatly complicates any comparison of the two types of products. The results from an MCDA study should be used only for what they are, that is, *predictions*, rather than as novel experimental data, which they certainly are not. MCDA is part of the analysis of evidence, rather than being an additional source of evidence *per se*.

Another UK study, investigating the perception of relative harm from the use of ECs,[20] involved recording the views of cohorts of smokers and ex-smokers given ECs, and involved standard statistical methods to estimate changes in perception over a three-year period. It was found that the proportion perceiving ECs to be less harmful than cigarettes decreased significantly over the period 2013 to 2014. Unsurprisingly, a major preliminary conclusion of the study was that: *Clear information on the relative harm of cigarettes and e-cigarettes is needed*. Another human study, a randomised controlled trial,[21] found that ECs, with or without nicotine, were only moderately good at assisting smokers to quit. The authors noted that: *Uncertainty exists about the place of e-cigarettes in tobacco control, and more research is urgently needed to clearly establish their overall benefits and harms.*

Like McKee and Capewell,[22] we doubt that the 95% figure can be given any scientific credibility, mainly due to the way in which it was derived. We go further, in saying that the statement is misguided and misleading. It is tempting to even suspect that the latter was used intentionally, as intimated by Kirby,[23] who summed up the situation well, if somewhat rather benevolently, thus: *While the PHE report contains many caveats, albeit subtle and largely missing from the media coverage, it has uniformly adopted the most favourable interpretation of the very limited evidence, rejecting the precautionary principle.*

In response to criticism of the 95% figure,[24] Professor John Britton (chair of the Royal College of Physicians Tobacco Advisory Group and co-chair of the PHE Tobacco Control Implementation Board, and also a co-author of one of the reports on ECs that was commissioned by PHE), suggested that, rather than dwell on an exact percentage figure, the real point is that ECs are substantially safer than tobacco smoking.[25] This begs the following question: If the 95% figure is not meant to be interpreted literally, why include it in the report, unless the aim was to have a headline for gaining publicity, with a view to persuading us all to accept the proposal without further questioning? However, in truth, as we have argued above, there is no *evidence* for the 95% estimate. Moreover, doubts have been expressed about the integrity and objectiveness of the MCDA study, due to the alleged conflicts of interest of some of its authors.[26] Unfortunately, little further information is available, and this fact, together with the other general drawbacks of implementing MCDA, discussed earlier, suggest that extreme caution should be exercised when considering the outcome. A similar issue with conflict of interest was encountered by Pisinger and Døssing,[27] when they found the problem to have arisen in some 34% of the 76 studies relating to EC safety that they reviewed. These authors could draw no firm conclusions from the information, due to high levels of data inconsistency, but they did state that: *Electronic cigarettes can hardly be considered harmless.* This study, incidentally, is yet another key publication missing from the PHE document.

What is Needed is a Role for Alternative Methods

Predictably, few, if any, of the small number of toxicity studies that have been published to date consist of medium-term to long-term investigations. The issue of chronic toxicity due to vaping has been noted by others, including, for example, Rowell and Tarran,[28] who recently discussed the lack of data relating to the ability of chronic exposures to ECs to induce serious lung disease. The need to take into account long-term consequences of EC use also applies to efficacy as well as safety, as Unger notes in a recent editorial: *Longitudinal studies are not yet available to assess the long term effects of e-cigarettes on health or their usefulness as a cessation tool*.[29] Some four years ago, Etter *et al.*[30] stated that ECs had not been adequately tested for safety or efficacy, and the situation has not altered very much since then. Until further studies of high quality and integrity are conducted, the marketing of ECs poses unknown health and safety concerns, particularly because the products available are extremely diverse, many of them on the market are not regulated, and no oversight of quality control is in operation.

While we understand that there is an urgent need to have more safety information, we believe that there is a better way of obtaining it than having several individuals sitting at a table trying to predict the harms of these products, when they have very little reliable information on which to base their decisions. Instead, we suggest the strategy which we have outlined previously,[2] involving an intelligent, integrated testing scheme, comprised mainly of chemical analysis, *in vitro*

methodologies and human/clinical studies. Such an approach would also expedite testing, particularly since traditional *in vivo* methods are often lengthy and their relevance and reliability are highly questionable.

The numbers of publications on *in vitro* studies with EC vapours are increasing (http://www.ashscotland.org.uk/what-we-do/supply-information-about-tobacco-and-health/tobacco-related-research/research-2015/e-cigarettes-2015/). In general, the data are promising, in that, for example, one paper[31] shows that several vapours exhibit substantially less activity in cytotoxicity testing and in a range of genotoxicity assays, compared with that exhibited by cigarette smoke. Other, more-recent studies, one involving the MatTek™ epithelial airway model, confirm the substantially lower cytotoxicity of vapours, and also demonstrate that this applies to airway cells in culture[32] (http://vaperanks.com/big-tobacco-study-claims-e-cigarette-vapor-is-as-harmless-to-human-airway-tissue-as-plain-air/).

However, while all this is encouraging, a glance at the Vape Ranks website (presenting news on ECs, rankings and reviews [www.http://vaperanks.com/]) shows that there is no shortage of other reports which raise legitimate safety concerns relating to ECs, that warrant further investigation. Among such reports are an increasing number of cases where ECs are being used to 'smoke' marijuana, a potentially worrying development (see, for example, Murphy[33]). Some of the investigations conducted *in vitro* also suggest that acute toxic effects could be caused by vaping. For example, a study in which cultures of human gingival fibroblasts were exposed to nicotine-containing or nicotine-free EC fluids, increased the production of reactive oxygen species (ROS) after 24 hours, along with an elevated expression of the *Bax* gene (an early indicator of apoptosis), followed by apoptosis itself, after 48 hours of exposure.[34] The authors concluded that such exposures could lead to periodontitis, but, in addition, the induction of such cellular changes could presage other, more-serious long-term toxicity.

An important part of the integrated testing strategy that we have proposed, involves human clinical studies, which have been undertaken for both efficacy and safety testing (the latter uniquely possible with tobacco and tobacco-related products, at an early stage), rather than following extensive preclinical testing, as with pharmaceuticals (see Combes and Balls[2]). Encouraging results were obtained in some of the first human studies (reviewed in Caponnetto *et al.*[35]), with high levels of tolerance and acceptance of the new products by existing smokers and non-smokers, as well as low incidences of side-effects or of overt signs of toxicity.

However, some subsequent studies have revealed several potential effects which cause concern. One example is an investigation[36] with smokers and non-smokers that involved monitoring changes in plasma nicotine and carbon monoxide (CO) concentration, and heart rate. One brand of ECs increased each of these parameters within the first five minutes of administration, an example of an acute adverse effect caused by vaping. Other evidence that ECs can exert acute effects on users, following brief exposures, was clearly demonstrated in a clinical study,[37] in which: a) non-smokers, using an EC for ten minutes, experienced elevated airway resistance; b) current regular smokers exhibited a significant rise in airway resistance after using an EC for ten minutes; and c) neither COPD nor asthma patients were affected (www.medicalnewstoday.com/articles/ 249784.php). In a blog, Phillips has questioned the relevance of these results.[38] However, although chemicals causing this effect may not elicit an immune response, the changes seen serve as biomarkers of lung exposure and of changes therein that could result in serious health consequences.

Another investigation, still ongoing, involves cohorts of smokers and non-smokers. At the 12-month stage, the results suggest that vaping has little effect on helping smokers to quit.[39] However, the trial is not scheduled to be completed until 2019. It is monitoring self-reported side-effects, and, hopefully, will include an assessment of biomarkers of disease and toxicity.

Nowhere are conflicting views regarding the safety of ECs more sharply delineated than by the different approaches to their use and regulation that are emerging in markets on either side of the Atlantic (reviewed in Combes and Balls[2]). On the one hand, in the UK, some Government agencies appear too ready to approve and promote the use of such products, without going through the necessary standard checks and balances, while, on the other hand, in the USA, the FDA is about to take over the regulation of ECs by subjecting them to a rigorous and formal assessment.

It was on 25 April 2014 that the FDA published a proposed rule, *Deeming Tobacco Products to be Subject to the Federal Food, Drug, and Cosmetic Act*. The period between then and now has been taken up by: a) a 75-day public comment period, which ended on 9 July 2014; b) an extension of the public comment period by 30 days, taking us to 8 August 2014; c) an unknown time delay for consideration and decision by the Agency of additional requests to extend the comment period a second time (which was not granted); and d) the analysis of comments (undisclosed time). Despite these delays, the question concerning the FDA's regulation of ECs is 'when', rather than 'if'. The latest information we can find is an entry in *The Hill* (the website presenting news of US Congress activities) in May 2015, where it is reported that Senator

Richard Blumenthal (D-Conn.) is giving the FDA until the end of the summer 2015 to finalise its deeming regulations for all tobacco products, including ECs and cigars (http://thehill.com/regulation/242125-fda-has-summer-to-finalize-tobacco-deeming-regs-sen-dem-says).

Once the FDA assumes responsibility for ECs for recreational use (it already regulates such products intended for therapeutic purposes), its approach to ECs would appear to be clear from its website (http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm172906.htm). This states that: *E-cigarettes have not been fully studied, so consumers currently don't know: the potential risks of e-cigarettes when used as intended; how much nicotine or other potentially harmful chemicals are being inhaled during use, or whether there are any benefits associated with using these products. Additionally, it is not known whether e-cigarettes may lead young people to try other tobacco products, including conventional cigarettes, which are known to cause disease and lead to premature death.*

This viewpoint is essentially one that we share, and, although we are not in favour of testing just for the sake of it, we fervently believe that it is very simplistic and premature, at this time, to base important public health decisions of the sort currently being proposed by PHE, on inadequate evidence of safety and/or potentially irrelevant and unreliable extrapolation. On the other hand, while we concur with FDA's overall assessment of the situation regarding ECs, we take issue with the way in which the Agency intends to regulate tobacco-related products, especially via the use of the substantial equivalence concept.[2] In addition, our views on the availability of data are shared by other organisations, notably the American Association for Cancer Research and the American Society of Clinical Oncology,[40] and the BMA.[41]

The official EU position on ECs is not clear at this time. The revised EU Directive on the marketing and use of tobacco products merely requires that manufacturers take responsibility for the safety of such products. However, we understand that, in the UK, once the Directive has been transposed into UK legislation, a process that will be facilitated by the Department of Health, the MHRA will become the competent authority (Dr Ian Hudson, personal communication, 2015) for ECs intended for medicinal purposes, which include quitting smoking. Accordingly, the MHRA will regulate such products in the same way that it does medicines. Indeed, the MHRA website has now documented data requirements for ECs (http://www.mhra.gov.uk/home/groups/commsic/documents/websiteresources/con454361.pdf), where it is stated (for preclinical studies) that: *The potential transformation of the formulation on thermal decomposition, and the potential for the heating element and associated components (including adhesives and solder) to shed metallic and other particles on heating, would warrant further investigation by the applicant to assess the inhalation safety risks and to limit exposure where necessary. In addition, the applicant should provide a detailed safety review of all the components in the formulation from the available literature; in particular a review of the safety following inhalation exposure (including long-term exposure) would be relevant. A comprehensive evaluation of the potential extractables and leachables originating from all components of the electronic cigarette should also be provided, with associated toxicological review.* For clinical studies, for some unaccountable reason, the focus is on the levels of nicotine in the body and its pharmacodynamics, to ensure that endogenous levels do not exceed maximum safe levels. We feel that this represents a missed great opportunity for undertaking biomarker and biomonitoring safety studies on vapours in the clinical setting, as we have explained in more detail elsewhere.[2]

How these regulations are going to be applied in practice after the various stakeholders and pressure groups, including the tobacco industry, have argued their various standpoints remains to be seen. However, if the MHRA sticks to its procedures and requirements for new medicines, it should be the case that: a) if the supporting toxicological data are deemed relevant and suitable, there will be no need for further testing and/or review; and b) where this is not so, or where data are missing, such information would have to be obtained by toxicity testing, according to International Conference on Harmonisation (ICH)-approved regulatory test methods for new medicinal products. Whether any products currently on the market will receive exemption is a matter of conjecture at this time. Therefore, we are now confronted by a ludicrous situation, whereby two UK Government authorities, the MHRA and PHE, both with the responsibility for safeguarding public health, are giving out different messages — the former has the remit of controlling the sale of the ECs according to international regulatory requirements, while the latter endorses the use of ECs now. Furthermore, the PHE report and its associated documents can be downloaded from the MHRA website — no wonder there is so much confusion!

Some notes on the presentations given at the Third E-Cigarette Summit, have been posted on the web (http://www.ecigarettedirect.co.uk/ashtray-blog/wp-content/uploads/2015/11/E-Cig-Summit-3-PDF.pdf). The notes provide a preliminary impression that the debate shows no signs of letting up, although it would appear that there is a growing admission among the protagonists that ECs are not harmless, and, among those looking at health

effects, that they are probably safer than smoking, but by how much it is difficult to tell. Perhaps we could be heading in the right direction, after all. We should get a better idea once the presentations have been uploaded to the resources section of the summit's website.

Concluding Comments

We are puzzled by: a) why there is such a gulf between the UK and the USA in approaches to regulating ECs; and, more importantly, b) why the fundamentals of toxicology, underpinning public health and safety, involving hazard identification and risk assessment,[42] seem to have been ignored by PHE, and are being overlooked in the ongoing debate by a growing number of stakeholders and so-called experts, when the same are usually so rigorously applied to other consumer products.

Calls endorsing the wider usage of ECs are being driven by two main factors, both of which cannot be supported on scientific grounds: a) an understandable, but misguided, wish for having a quick fix for the major health problems associated with smoking; and b) a mistaken belief that there is no need to test complex mixtures, such as EC liquids and vapours, when the levels of ingredients, whose presence and contribution to toxicity are known, are at very low concentrations. If this were possible, most of toxicology would now merely consist of chemical analysis of test samples, except in rare cases where the threshold of regulation concept[43] can legitimately be applied — for example, when synergistic or antagonistic effects between constituents can be accommodated.

One way in which risk assessment can be approached is to derive likely exposure levels from analytical data on the constituents of vapours and compare them with recommended maximum allowable daily intake figures for humans, obtained from safety tests. However, since most of the information relates to data obtained under laboratory conditions, mainly with rodents, sometimes involving different routes of exposure, it has to be extrapolated and scaled up to be relevant to human populations, and adjusted to provide for an extra margin of safety. Moreover, predicting exposure levels is confounded by individual differences in the way in which ECs are used, the extent to which they are used, the differences in design and composition of ECs, the degree of vapour inhalation, and variation in the biotransformation of inhaled constituents, and also by the possible endogenous generation of more TSNAs from vaped nicotine.[44]

It has been noted elsewhere (http://www.tobacco.ucsf.edu/9-chemicals-identified-so-far-e-cig-vapor-are-california-prop-65-list-carcinogens-and-reproductive-t) that nine constituents variously found in EC fluids and/or aerosols, are listed by the Environmental Protection Agency (EPA) of the US State of California as being of concern with regard to human safety, as part of the Agency's drive to improve and simplify the regulation of environmental chemicals. These chemicals are: acetaldehyde, cadmium, formaldehyde, isoprene, lead, nickel, nicotine, N-nitrosonornicotine (NNN) and toluene. NNN is widely considered to be a carcinogen in tobacco smoke. As a worse-case scenario, we have taken the threshold value of concern for this chemical (which the EPA has identified from rodent carcinogenicity studies, after adjustments for species and test system extrapolation), to have a NSRL (non-significant risk level) of 0.5μg/day (NSRL is the level of exposure that would result in no more than one excess case of cancer in 100,000 individuals exposed to the chemical). We have compared this figure with the amount of NNN that different ECs users might be expected to be exposed to, based on the maximum levels of chemical reported in Gureckis and Love,[4] which is 4.3μg/150 puffs (equivalent to 14.3μg/day for a user taking 500 puffs/day). As the respective NSRL value is 0.5μg/day, the expected exposure under these conditions exceeds the level of concern by almost 30-fold. Presumably, such a result would raise the possibility that ECs with similar constituent profiles could prompt the EPA in California to require appropriate product labelling as a precondition for marketing approval. We stress, however, that these are preliminary data, subject to several uncertainties, not the least of which are vaping behaviour and individual susceptibility, and we plan to investigate risk assessment in more detail for more ECs, and also for other risk assessment methods, such as the Margin of Exposure (see Hahn *et al.*[45]).

The more and more we read, the more convinced we are that the whole debate about ECs is premature, and would not be happening with other, equally dangerous consumer products, in the absence of powerful lobbying on behalf of industry. The title of the PHE report includes the phrase *...foundation for evidence-based policy and practice.* This sounds great, until one realises that the foundation is very weak indeed, having been built on sand, in the words of McKee and Capewell,[22] and that the evidence used was incomplete, conflicting, and used selectively. It is crucial that these new types of products are labelled appropriately and accurately, not only with regard to their benefits, but also with appropriate and proportionate warnings of any hazards to which users may be exposed. This will only be possible after there has been a full and scientifically-sound investigation of the toxicity of these products.

We seem to be living in a world now where the term *evidence-based* increasingly seems to be being used to imply some new revelatory approach to

scientific activity that guarantees high quality. We have 'evidence-based medicine' and, more-recently, 'evidence-based toxicology', and now: 'evidence-based public health' and 'evidence-based regulation'. But, in truth, of course, *evidence-based* is not a new concept, nor is it a panacea for quality — any thorough scientific piece of work is only as good as the evidence on which it is based. What does appear to be new is the attempt to use the phrase as a smokescreen for sub-standard scientific investigation, otherwise there would be no need to use it at all!

We leave the last word to the British Heart Foundation (BHF), by quoting from a booklet entitled *10 Minutes to Change Your Life — Time to Quit*, which is available in its high-street charity shops or from its website (https://www.bhf.org.uk/~/media/files/publications/smoking/g925_time_to_quit_01_14_booklet_chart.pdf). This states that: *E-cigarettes allow you to breathe in nicotine vapour. Unlike tobacco smoke, this nicotine [vapour] doesn't contain many of the chemicals that cause cancer and heart disease. But scientists don't know yet if e-cigarettes can help you quit or if they cause any long-term damage to your health.*

Simple, clear, informative and correct — this is where the debate needs to start and it is why the temptation for a quick fix to the smoking issue must be resisted!

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Draft Response regarding comments made by Clive Bates about one of our publications on the safety of electronic cigarettes…

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Draft Response regarding comments made by Clive Bates about one of our publications on the safety of electronic cigarettes and vaping.

(To be published; uploaded onto Researchgate 10.09.16)

Robert Combes (Independent Consultant, Norwich, UK) & *Michael Balls* (Emeritus Professor of Medical Cell Biology, University of Nottingham) write....

In a recent exchange of views with Simon Chapman on the effectiveness and safety of vaping for achieving the cessation of tobacco smoking, provoked by a paper published by Martin McKee [1 and comments therein - see: http://www.ncbi.nlm.nih.gov/pubmed/27518691/#comments], Clive Bates has criticised one of our publications [2]. Our paper urges caution concerning any further official endorsement of electronic cigarettes (ECs), at least until more safety data (including results from long-term tests) have become available [see also 3].

Bates questions why we should write on such issues, given our long-standing focus on 'animal rights', as he puts it, and from this mistaken assumption he makes the remarkably illogical deduction that our paper is without merit. Bates also implies that our views should not be taken seriously, because we published in *Alternatives to Laboratory Animals (ATLA)*, a journal owned by FRAME (Fund for the Replacement of Animals in Medical Experiments), an organisation with which we have been closely associated in the past. We feel it important to correct his misconceptions about who we are, what our experience is, why we decided to write about this topic in the first place, what we actually said, and why we said it.

First, when the paper was written, neither of us was closely affiliated to FRAME, which, incidentally, and contrary to Bates' impression, is not an animal rights organisation (see www.frame.org.uk), but is, instead, a scientific charity rooted in the principles of the Three Rs (Refinement, Reduction, and Replacement) as applied to animal experimentation. These concepts, first proposed by Russell and Burch in 1959 [4], are now the basis of laboratory animal protection legislation world-wide. We published in *ATLA*, because: a) it is the leading research forum for several key issues that we raised; and b) papers are very closely scrutinised and subjected to detailed peer review before acceptance. We wonder if this second criterion applies to articles Bates writes for his blog, called 'Counterfactual'. Lastly, both of us are experienced toxicologists, and have approached the safety of vaping from a strictly scientific point of view.

We explain in the paper [2] why we have taken a great interest in vaping, the relevant text (references omitted) of which reads: *'The situation regarding ECs is also highly relevant to the Three Rs, since we have the prospect of significant levels of safety testing, some of which could involve traditional animal tests, highly invasive procedures and the use of non-human primates.'* Also, we have become increasingly aware that there are several key principles of toxicology, which have been, and are being, ignored or misused, such that far-reaching government policy on ECs is being driven without an appropriate scientific basis.

The main principles at stake are: a) the need to fully characterise complex mixtures in terms of their constituents, possible interactions between them, and their contribution to causing the overall toxicity of the mixture; meaning that analytical chemistry on its own is inadequate to be confident of lack of toxicity; b) quantitative expressions of safety should always be based on numerical data relating to hazard and exposure; c) it is usually not possible to predict long-term toxicity from short-term test data, or from anecdotal, or other information of an acute nature, due to the operation of complex and different mechanisms of action; d) route of exposure can greatly affect toxicity; e) some chemicals can be toxic at very low doses, especially under chronic exposure conditions; f) long-term effects are just as important as acute ones, and their investigation should not be delayed, due to the possibility of induction of irreversible intracellular changes early during exposure history; and g) where doubt exists, the precautionary approach [5] should be adopted, to maximise human well-being and safety. The limitations of analytical chemistry (point (a) above) are illustrated by using cardiovascular disease (CVD), as an example. T As the identity of the causative

agent responsible for CVD is obscure, it is practicably impossible to predict the ability of vapour from ECs to induce the same endpoint, solely on the basis of its chemical composition.

Bates alleges that our work adds nothing of substance to the controversy, particularly about Public Health England (PHE) and its decision to endorse vaping for therapeutic purposes, and the evidence on which its decision was based [6], which led to its announcement that vaping is about 95% safer than smoking. This evidence primarily consists of two 'independent' government-commissioned reports [7, 8], on the effectiveness and safety of ECs, respectively, and only *one* peer-reviewed publication [9]. The latter describes a multi-criteria decision analysis (MCDA) of relative harms of various nicotine delivery systems, including smoking and vaping. We discussed this information in our publication, noting many shortcomings, including selective and incomplete coverage of the literature, lack of a rigorous scientific foundation, and the use of questionable methods.

Bates mentions a Royal College of Physicians (RCP) report [10], which appeared after our paper was published. This report is, indeed, quite detailed and useful, much more so than the previous advisory documents cited above. However: a) it was published *after* PHE had made up its mind about vaping, when it should have been available *beforehand*, so that PHE could have been better informed; and b) it is deficient in several areas, two of which we shall briefly refer to here.

First, the RCP accepts the highly controversial 95% figure for the amount by which PHE claimed that vaping is (roughly) safer than smoking. The MCDA study, on which this was based concluded with a simple statement of opinion agreed by experts (however well-informed) [9] at a workshop, rather than on any calculations based on numerical observations (e.g. minimally-effective dose levels versus daily exposure levels [11]). Nutt *et al.* [9] did not provide any data, but somehow transformed a qualitative expression of relative harm into a quantitative one. PHE accepted this and merely expressed it differently. This ploy has occurred again and again, particularly by the authors of the advisory reports, when using misleading phrases, such as: *'my reading of the evidence is….'* and *'the current best estimate is…*', simply following suit, repeating the mantra in the hope that eventually we, and other 'sceptics', will believe it to be fact [see e.g. 12-14]. Also, it has been reported, and endorsed almost as if it were a fact, by other bodies and individuals, including the BBC, Members of Parliament, and newspaper medical correspondents. McNeill *et al.* [15] argued that: *'Cigarette smoke constituents that harm health are either absent in e-cigarette vapour or, if present, are mostly at levels much below 5% of smoking doses; and second, the main chemicals present in e-cigarettes only have not been associated with any serious risk*.' and: *'the estimate of relative risk is a matter of logic'*. However, these statement are invalid, because: a) they rely solely on chemical analysis (see above); and b) nicotine exerts effects with potentially serious long-term effects (see below).

Bates follows in the same tradition, in his responses to points raised by Martin McKee and Simon Chapman. McKee is quite correct in saying that there is only one source for the 95% figure [1]. Bates misuses the word 'source', since he obviously believes that whenever the mantra is repeated, it automatically qualifies as a new source. This would only be true, if new data were presented each time, which independently gave the same results. Since there are no scientific facts presented in the original MCDA paper to agree with or reject, all that Bates and the rest are doing is to repeat an opinion without being able to explain why they support it. This is not corroboration; it is merely hearsay! Instead, Bates (and everyone else who has used the figure) should: a) provide the empirical and quantitative data to support it; and b) demonstrate why those, like us, are wrong, in our rejection of it and of the MCDA study itself for being flawed, for reasons we have detailed elsewhere [2, 16].

The second issue about which the RCP report is deficient is the toxicity and biological activity of nicotine itself, despite providing much information on the subject. Contrary to popular belief, which is based primarily on low levels of *acute* toxicity [e.g. 17], nicotine is, in fact, a highly versatile, pharmacologically and toxicologically active chemical, and the recent literature suggests that it could, at worst, act as a CMR chemical. Such chemicals induce carcinogenicity, mutagenicity and reproductive toxicity. Nicotine carcinogenicity is reviewed in references 18-24,

and, at the very least, if not a complete carcinogen, nicotine acts on a variety of key post-initiation stages of the multi-step process of carcinogenesis, including promotion, cell proliferation, progression, stimulation of specific cell activating factors, angiogenesis, induction of unique patterns of differential gene activation and anti-apoptosis [see e.g. 25-31]. CMR chemicals also induce mutagenicity, or, more correctly, genotoxicity in the case of nicotine, which causes DNA and chromosomal damage [reviewed in 32-34]. Several reports on nicotine genotoxicity describe effects in cultured airway cells and tissues obtained from healthy volunteer donors [e.g. 31, 35, 36]. There is also evidence that nicotine induces effects related to reproductive toxicity [see 37-39, and the earlier review citations]. In addition, McKee et al. [40] noted some of the effects, related to carcinogenesis, that are listed above, and which have been recently attributed to nicotine. The experience of several decades of exposure to nicotine during nicotine replacement therapy (NRT), without serious adverse consequences, does not negate the relevance of the toxicity findings, as this is a cumulative figure, and because most NRT patients will have *each* been exposed typically only for 8-12 weeks, some perhaps for as much as 18 months, before complete cessation. As it is the individual exposure duration that matters, the shorter durations should be used instead, and these durations represent insufficient time to be confident about lack of long-term effects. A very recent and comprehensive review [41] concludes that the available animal and epidemiological carcinogenicity data do not permit a definitive conclusion regarding human effects of nicotine to be made, either way.

The relevance of the above observations, specifically in relation to ECs, needs more consideration (regarding routes of administration and minimally effective doses, compared with those encountered during vaping), rather than being swept under the carpet as part of any attempt to downplay the importance of nicotine's toxic properties [42], which would mislead consumers even more about the relative risks of vaping [43]. To ignore these reports on nicotine, however, would be foolhardy in the extreme. This is particularly so, as many of its alleged cellular effects depend on binding to nicotinic acetylcholine receptors, the numbers of which could well increase if patients developed greater nicotine dependency [44, 45]. Such a phenomenon would also be likely to increase the overall activity of the above nicotine-provoked cellular changes, working in a vicious circle..

In conclusion, we strongly believe that the safety of ECs should be seen as a problem to be addressed, primarily by applying toxicological principles and methods. We cannot find evidence to suggest that any of the documents used by PHE to underpin its decision to endorse the use of ECs involved much, if any, input from a toxicologist *experienced in risk assessment*.

We are in the process of reviewing the whole area of vaping, explaining in more detail the ideas previously discussed, together with new information that suggests to us that the entire discipline of NRT, especially the use of ECs, needs to be re-examined. It is also apparent, from the Laypersons Assessment Reports (LARs on the MHRA website) for a range of different NRT devices, including an EC (Evoke) [see e.g. 46] that, although ECs are nominally regulated by the MHRA, as if they are new medicines, in practice, they are being treated more-leniently. This is revealed by the waiving of preclinical safety testing, based on an erroneous assumption of the bioequivalence of NRT products with each other, and with nicotine itself. Yet, such testing includes the very studies that would, if used, have provided the quantitative data for proper risk assessment!

We also find it ironic that, when vaping is being promoted, the focus is on short-term effects, whereas, when smoking is being denigrated, interest switches to long-term effects. A good deal of the justification for vaping is being based on how damaging to health tobacco smoking is, rather than on vaping's own intrinsic benefits and drawbacks. It seems premature to be undertaking such a risk-benefit analysis in the absence of accurate and relevant safety information, an alternative approach that is being implemented in the USA (47). When a more-accurate assessment of relative safety, compared with smoking, becomes available, it should be possible for the risks of vaping to be more-objectively weighed against the risks of not vaping, for all potential exposure scenarios and smoking histories of would-be users of ECs. This will then enable consumers to make more-

informed choices about how best to approach the difficult process of cessation of smoking and nicotine detoxication.

We are disappointed that Bates chose rhetoric and prejudice to state merely that our work '*can be dismissed on its merits'*. This is not helpful to anybody, nor does it do justice to our integrity. Had he used reasoned debate instead, we might have had a useful, worthwhile and mutually beneficial dialogue!

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How shaky are the twin pillars of the case for e-cigarettes?

theconversation.com/how-shaky-are-the-twin-pillars-of-the-case-for-e-cigarettes-53153

Simon Chapman

The central arguments made for the importance of electronic cigarettes (e-cigarettes) are that they are an exceptionally good way to quit smoking and that they represent trivial risk to health compared to the stratospheric risks of smoking. (Australian data published last year from the very large 45 and Up cohort study found that up to two in three long-term smokers were likely to die from a smoking-caused disease.)

Two just-released papers promise to further ignite debate about these two central pillars of the case being made for these putative harm-reduction products.

A systematic review of all studies examining whether smokers who use e-cigarettes quit smoking at a different rate to those who don't has been published today in Lancet Respiratory Medicine. The review identified 38 studies, with 20 having control groups.

Pooling these, they found that the odds of quitting cigarettes were 28% lower in those who used e-cigarettes compared with those who didn't.

Of course, not all vapers are using e-cigarettes to quit. Many use them to just cut down, often in the erroneous belief that reducing the number of cigarettes smoked daily will reduce harm. I summarised and linked to four cohort studies that demonstrate this folly in a recent lengthy Conversation piece.

So if many smokers are not even trying to quit with e-cigs, some might argue that that there should be no expectation that they would.

The problem with that assumption is that we have an increasing understanding that many smokers do not plan to try to quit, but rather do it quite spontaneously.

For example, in this 2006 paper on a national sample of English smokers, 48.6% of smokers reported that:

> their most recent quit attempt was put into effect immediately the decision to quit was made. Unplanned quit attempts were more likely to succeed for at least six months: among respondents who had made a quit attempt between six months and five years previously the odds of success were 2.6 times higher (95% confidence interval 1.9 to 3.6) in unplanned attempts than in planned attempts.

In this new review, the authors consider both smokers who were trying to quit by using e-cigs and those who were not. They found that:

> the association of e-cigarette use with quitting did not significantly differ among studies of all smokers using e-cigarettes (irrespective of interest in quitting cigarettes) compared with studies of only smokers interested in cigarette cessation.

In other words, regardless of whether a smoker using e-cigarettes was planning to quit or not, there was no difference in whether they did.

The authors note that pooled estimates in previous reviews of e-cigarettes' usefulness in smoking cessation did not include a comparison to other means of stopping besides e-cigarette use, so they cannot be used to determine whether e-cigarettes are associated with greater cigarette abstinence than quit rates being obtained in current practice.

They speculate that the poorer performance of e-cigs across all studies when pooled may mirror the changing situation of nicotine replacement therapy:

> Data from the large population-based California Tobacco Surveys, showed that nicotine replacement therapy (NRT) was associated with long-term success in quitting cigarettes when available by prescription only, but this association was lost when NRT became available over-the-counter.

This view should challenge those calling for the greatest possible ease of obtaining e-cigarettes.

In a second paper, globally renowned toxicologists Robert Combes and Michael Balls have written a critical commentary stimulated by the 2015 publication of Public Health England's (PHE) report on e-cigarettes.

The PHE report has already attracted critical commentary in both the Lancet and the BMJ about the provenance of a key and globally telegraphed statement in the report that e-cigarettes were about "95% less harmful" than cigarettes.

This figure was conjured as a "best estimate" by a heavily criticised consensus meeting of 12 people. Six of these were subsequent signatories to the 53 signature letter to Dr Margaret Chan at the World Health Organization calling for minimal regulation. Six had no research track record or experience in tobacco control whatsoever. Two had financial ties to the tobacco or e-cigarette industries (see here and here). There was no transparency about how this group had been selected and questions remain about the role of the tobacco industry in its funding.

Combes and Balls describe a recommendation from the PHE report that e-cigarettes be made available to smokers through the UK's National Health Service as:

> a classic example of the temptation of short-term gain irrespective of the possibility of long-term pain.

Pulling no punches, they argue that "lack of safety data and the resulting inability to perform any sort of risk assessment of the type normally undertaken for consumer products" makes the PHE's recommendation "in the light of current knowledge [about e-cigarette safety] a reckless and irresponsible suggestion."

Their commentary details numerous examples of significant absences of potential safety concerns in the PHE report, which appear to have been bypassed in light of what they call a well-meaning but misguided effort to propose a quick fix.

It is a paper that should be read by anyone who believes that the science is already settled on e-cigarettes.

Many e-cigarettes advocates are utterly convinced that vaping is highly effective at getting people off smoking, and of negligible health risk. It would be wonderful if they were right on both counts. These two papers should serve as a major amber light to such unbridled enthusiasm.

The very latest update of the Smoking in England project provides data that show that 68.2% of people who vape in England still continue to smoke (dual use):

And very worryingly, the percentage of smokers in England making a quit attempt in the last year is at the lowest point since 2007:

As these Conversation authors discussed, vaping may be holding many smokers back from quitting. At the population level, such an effect needs to balanced against the impact e-cigarettes may be having cessation so that we get an understanding of the net costs and benefits of e-cigarettes.

Some vaping advocates valiantly insist that their mission of “saving a billion lives” this century from tobacco deaths is so important that e-cigarettes should be able to by-pass all of the regulatory oversights that sensibly apply to chemicals and pharmaceuticals everywhere but in chaotic nations where anything goes and where consumers are unprotected from exploitation by manufacturers making misleading claims for useless and often dangerous products.

No one heroically claiming an AIDS or cancer cure on the same level of flimsy evidence of safety and efficacy that Combes and Balls point to with the current evidence base would get even a toe in the door to be allowed to sell and advertise such products.

If e-cigarettes are as safe and effective as their enthusiasts claim for them, let us all see the high quality data. We all want that, surely?

Editor’s note: please ensure your comments are courteous and on-topic.

Surprise! Lorillard Tobacco publishes two papers finding e-cigs pose no hazard

Submitted by sglantz on Tue, 2014-11-11 08:57

The *International Journal of Enviromental Research and Public Health* just published two papers by authors from Lorillard Tobacco reporting that "neither the e-cig liquids and collected aerosols, nor the extracts of the SLT or NRT products produce any meaningful toxic effects in four widely-applied *in vitro* test systems, in which the conventional cigarette smoke preparations, at comparable exposures, are markedly cyotoxic and genotoxic," and "exhaled e-cigarette areosol does not increase bystander exposure for phenolics and carbonyls above the levels observed in exhaled breaths of air." The second paper also reports virtually no nicotine in the exhaled e-cig aerosol.

The first paper avoided considering cell systems that are most sensitive to e-cigarette aerosol (example 1, example 2, example 3, example 4). Indeed, designing experiments and reporting results in a way that minimizes or obscures toxic effects is a common tobacco industry trick (for example, see industry papers on additives, endotoxins in tobacco smoke, indoor air pollution, and smoking on airplanes).

The study on exhaled e-cig aerosol reminds me of many earlier cigarette company-inspired studies that concluded that it was toxicologically impossible for secondhand to cause any disease. These studies did, of course, ignore the fact that there was a large literature (not yet well-developed for e-cigarettes) secondhand smoke *does* cause disease. We already know that bystanders to e-cigarette use absorb similar levels of nicotine as passive smokers in real world envionments.

Both papers say that the authors, who are employees of Lorillard, have "no conflict of interest." This seems odd, given that their employer has a strong interest in the outcome of these studies. It is also concerning that the *IJREPH* used Konstantinos Farsalinos, a person with a long history of funding from e-cigarette companies, as the external editor for both papers. If this journal wants to keep a reputation for independence and fair assessment of papers they need to pay more attention to conflicts of interest of both their authors and external editors. Indeed, this journal is looking more and more like the go-to place to publish papers supporting the e-cigarette industry.

- sglantz's blog

The irresponsible promotion of e-cigarettes and Swaptober

thelancet.com/journals/lanres/article/PIIS2213-2600(17)30473-3/fulltext

The House of Commons Science and Technology Select Committee have launched an inquiry into e-cigarette impact, implications, and regulation.[1] National guidance for improving health should be evidence based, with a complete understanding of what is disseminated and encouraged. However, despite substantial gaps in research, e-cigarettes are promoted as part of smoking cessation efforts, including in the Public Health England (PHE) campaign, One You. Should the suggestion of e-cigarettes as a lesser evil be promoted when evidence of their long-term effect is insufficient?

Stoptober is a 28-day PHE initiative that occurs annually in October, with the aim of supporting smokers to quit the habit. In 2017, the campaign began promoting e-cigarettes, which, as stated by the National Institute of Clinical Excellence (NICE), are devices that are not understood in terms of the long-term health benefits or harms.[2] The promotion of e-cigarettes also features in the One You campaign. However, the addition of e-cigarettes to the 2017 mass-media promotion of Stoptober is even more surprising given that the evidence that e-cigarettes aid smoking cessation or reduction is of very low quality,[3] and data are insufficient for a confident estimation of their effectiveness.[4] Hence, the presentation of e-cigarettes alongside evidence-based medicinal products (licensed nicotine-replacement therapy) seems premature, and their portrayal as quitting aids under the Stoptober message of “if you can stop smoking for 28-days, you are five times more likely to quit” is misleading.[5] The Independent British Vape Trade Association sponsors Stoptober, which, among other activities, promotes the vape industry and thus presents a potential conflict of interest. A further concern is the evidence of e-cigarette use by UK children.[6] Preliminary evidence also suggests that e-cigarette use could have deleterious effects in relevant patient groups (eg, those with chronic obstructive pulmonary disease). Given that further understanding of the health implications of e-cigarettes is needed, promotion to the public, including young people and vulnerable populations at risk of shorter-term effects, is not an appropriate implementation strategy.

An emerging concern is Swaptober, another annual October initiative. Launched in 2016, Swaptober aims to convert smokers from traditional cigarettes to e-cigarettes, and is promoted in support of Stoptober. E-cigarettes are promoted as a healthier alternative to smoking, particularly as a first step towards smoking cessation for those finding it difficult to stop. However, e-cigarette companies do not encourage smoking cessation, but rather encourage a long-term swap. Thus, Swaptober, which occurs at the same time as Stoptober, could overshadow and reduce the effectiveness of Stoptober. In line with NICE guidance,[2] smoking cessation should be encouraged, not the swapping to an alternative that is not fully understood. PHE have reported and subsequently been key in publicising the expert opinion that e-cigarettes are 95% safer than tobacco.[7] The credibility of this estimate has been questioned, and has been referred to as a premature conclusion about devices that warrant rigorous safety assessment.[8]

NICE called for caution regarding recommendations for e-cigarettes as a suitable alternative because of the paucity of evidence regarding the long-term health effects.[2] This stance contradicts the views of PHE and the Royal College of Physicians,[7, 9] both of whom advocate the wide promotion of e-cigarettes as a substitute for smoking. The contradictory stance of the UK's expert health organisations is likely to confuse public understanding. The inclusion of e-cigarettes in mass-media campaigns to help quit smoking is an example of short-term gain irrespective of the possible long-term consequences. Despite the divide in e-cigarette opinion, all health organisations should accept the need for a balanced approach to e-cigarette regulation. The House of Commons Science and Technology Select Committee inquiry[1] will probably highlight key gaps in the evidence regarding the health benefits or harms of e-cigarettes, which need to be addressed before any further public promotion of e-cigarettes. Until substantial evidence has been gathered on the health implications of e-cigarettes, the promotion of e-cigarettes by health organisations is irresponsible, unethical, and potentially harmful.

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We declare no competing interests.

Editorial

Do E-cigarettes Pose a Risk to Human Health?

Gerry Kenna

The claim by Public Health England that e-cigarettes have no concerning adverse health effects is flawed, because it is not evidence based

In a Comment featured in this issue of *ATLA*,[1] Robert Combes and Michael Balls challenge the recent assertions by Public Health England that "*…e-cigarette use is around 95% less harmful to health than smoking*" and that "*…e-cigarettes have the potential to help smokers quit smoking*".[2] They point out that the position adopted by Public Health England on e-cigarette safety is not evidence based, mainly because it is not supported by a scientifically rigorous risk assessment. This matters, because e-cigarette use is increasing rapidly in the UK and in many developed countries, whilst the smoking of tobacco has decreased.[1] The use of e-cigarettes will raise no concern if it is truly safe. However, were e-cigarette smoking to be unsafe, the adverse health consequences could prove to be substantial. Furthermore, Combes and Balls propose that human risk assessment of e-cigarettes should be undertaken by using a novel approach that does not require toxicity studies in experimental animals, which they have described in detail previously.[3]

Not too long ago, cigarette smoking was common across the populations of many countries. This was because tobacco-based products are highly addictive, the products themselves were relatively cheap, access to them was poorly regulated, and their role in initiating human diseases was complex and so was difficult to establish. The first clear evidence linking tobacco smoking to human ill-health was uncovered by Sir Richard Doll in 1950, following a methodical case study of possible explanations for the recent massive increase in the frequency of lung cancer in the UK population.[4] His pioneering work was not immediately accepted and acted upon, but was followed by further long-term prospective epidemiological studies. These confirmed an unequivocal causal relationship between smoking and lung cancer, and also revealed strong associations between smoking and chronic obstructive pulmonary disease, ischaemic heart disease and markedly reduced life expectancy.[5]

Subsequently, Doll's original findings were confirmed by others, and led to the recognition that cigarette smoking is the single largest avoidable cause of ill-health and fatality in developed nations. Eventually, governmental actions were taken in the UK and many other developed countries, which were intended to limit and reduce cigarette consumption and ensure it is restricted only to consenting adults. Hence, the prominent labelling of health risks on packs of cigarettes and other tobacco-based products, restrictions on advertising, high taxation, restrictions on vendors, and, most recently, the banning of cigarette smoking in public spaces. Bans on smoking in public places enable all of the population to breathe cleaner air, which is not polluted by tobacco smoke. The bans have also yielded valuable additional insight into the impact of smoking on health, by enabling comparisons to be made before and after their implementation. The results are striking: One meta-analysis of the health impact of 33 smoke-free laws, with a median follow up of 24 months, revealed that comprehensive smoking bans were associated with markedly reduced rates of hospital admissions or deaths due to coronary events (relative risk: 0.848), other heart diseases (relative risk: 0.610), cerebrovascular accidents (relative risk: 0.840) or respiratory diseases (relative risk: 0.760).[6]

A major problem confronting those wishing to achieve still further reductions in cigarette smoking-related human ill-health, is the highly addictive nature of the habit, which means that many smokers try to quit, but fail. The cause of the addiction is nicotine[7] and e-cigarettes are designed to provide convenient inhalational delivery of nicotine vapour without exposing the user to very many of the thousands of other chemicals present in tobacco smoke, some of which are highly toxic.[8] Based on scientific first principles, it is reasonable to presume that e-cigarette use could well be safer than cigarette smoking. However, it is unreasonable at the present time to assume that e-cigarette use is safe and therefore should be pro-

moted to help current smokers to reduce and ideally stop smoking, as has been proposed by Public Health England.[2] The relatively high levels of nicotine present in e-cigarette vapour cause concern, since nicotine exerts potent pharmacological effects on the cardiovascular system and other systems and also has many additional adverse biological effects, as do the other hazardous chemicals to which users of e-cigarettes will be exposed. Therefore an evidence-based assessment of the human health risk posed by e-cigarettes is needed.[1,3]

But which data are most suitable for this purpose? Combes and Balls propose that an integrated scheme, which includes chemical analyses, physiologically-relevant organotypic human *in vitro* models, physiologically-based *in vitro–in vivo* exposure scaling, and human *in vivo* clinical investigations, should be used to quantify *in vitro* hazards posed by chemicals present in e-cigarettes and to assess their risk to humans.[1,3] These could be complemented by prospective phase 1-type clinical studies involving biomarkers of exposure and effect, which could be augmented by prospective investigations on the health of e-cigarette users, cigarette smokers and non-smokers, of the type pioneered by Sir Richard Doll.[5]

When compared with the more classical toxicological strategy of long-term toxicity studies in animals, followed by human safety assessment via physiologically-based cross-species *in vivo* exposure modelling, the mechanistic approach set out by Combes and Balls has many scientific and pragmatic advantages. Also, it is aligned fully with the Three Rs principles. Let us hope that it is adopted by the scientific community and gains regulatory and governmental support, so that we can be informed of whether e-cigarettes really are as safe and useful as some would have us believe.[2]

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BMJ 2015;351:h4863 doi: 10.1136/bmj.h4863 (Published 15 September 2015)

ANALYSIS

Evidence about electronic cigarettes: a foundation built on rock or sand?

Public Health England recently endorsed the use of e-cigarettes as an aid to quitting smoking. **Martin McKee** and **Simon Capewell** question the evidence on safety and efficacy underpinning the recommendations

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Those responsible for safeguarding the health of the public must often tackle complex and controversial issues. Public Health England (PHE) has been courageous in entering the debate on the role of electronic cigarettes in tobacco control. In a new report it concludes that e-cigarettes are much safer than conventional cigarettes,[1] and one of its author is quoted as describing them as a potential "game changer" in tobacco control.[2] Media coverage suggests that the debate is now over, with a BBC correspondent describing the evidence as "unequivocal."[2] However, although British organisations such as the Royal College of Physicians of London[3] and ASH UK,[4] have endorsed some of the report's conclusions, albeit with caveats, many others have come to the opposite opinion. These include the British Medical Association, the UK Faculty of Public Health, the US Centers for Disease Control and Prevention, the American Lung Association, the World Health Organization,[5] the European Commission,[6] and other leading international health bodies.[7] The available evidence about e-cigarettes suggests that the debate is far from over and questions remain about their benefits and harms.

Defining the role of e-cigarettes

Fundamental divisions seem to exist between those engaged in this debate. Supporters of e-cigarettes focus narrowly on existing smokers, comparing the devices' effects with those of smoking conventional cigarettes. As well as being an aid to quitting, e-cigarettes are seen as having a role for people who do not want to quit, offering a safer substitute for some of the cigarettes they would otherwise smoke.

Meanwhile, those on the other side of the debate express concern about uptake of e-cigarettes among people, especially children and adolescents, who would not otherwise smoke and about their long term health effects. They argue that although e-cigarettes do not contain some of the most harmful substances found in conventional cigarettes, such as tar, they do contain other substances such as formaldehyde (a carcinogen) and diverse flavourings. Thus, it is equally important to include non-smoking as a comparator. They also draw attention to important epidemiological evidence that contrary to what is widely believed, reduced smoking (as opposed to quitting) may not reduce overall risk of death.[8] The expression "dual use," which acknowledges that two thirds of e-cigarette users also smoke, rarely occurs in the PHE report. Although some dual use is inevitable during the quitting process, if this persists long term health concerns remain. A recent cohort study by McNeill and colleagues showed that dual use among daily "vapers" apparently remained above 80% after 12 months follow-up, which is worrying.[9]

Quality of the evidence

A fundamental principle of public health is that policies should be based on evidence of effectiveness. So does the available evidence show clearly that e-cigarettes are as effective as established quitting aids? Unfortunately not. The recent Cochrane review is widely cited,[10] but it included only two randomised controlled trials, both with important limitations, and concluded that the evidence was of "low or very low quality by GRADE standards." The PHE report authors concede the weakness of the evidence, noting how a single observational study with substantial limitations offers "some of the best evidence to date on the effectiveness of e-cigarettes for use in quit attempts."

Where there is uncertainty about risks, the precautionary principle should apply. Thus, in the absence of scientific consensus that the substance is not harmful to the public, the burden of proof that it is not harmful falls on those taking an action. The quality of the evidence cited by PHE therefore becomes crucial. The headline message from the PHE report, widely quoted in the media, is that "best estimates show

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e-cigarettes are 95% less harmful to your health than normal cigarettes," seemingly leaving little room for uncertainty about long term risks. Yet a recent systematic review,[11] which the PHE report surprisingly fails to cite, came to a different conclusion. It found serious methodological problems in many of the 76 studies it reviewed, and one third of the studies (34%) were published by authors with conflicts of interest. The systematic review also expressed concern about the effects of various substances in e-cigarettes, some but not all of which are also found in conventional cigarettes. It concluded that "due to many methodological problems, severe conflicts of interest, the relatively few and often small studies, the inconsistencies and contradictions in results, and the lack of long-term follow-up no firm conclusions can be drawn on the safety of e-cigarettes. However, they can hardly be considered harmless."

We might also expect that the prominently featured "95% less harmful" figure was based on a detailed review of evidence, supplemented by modelling. In fact, it comes from a single meeting of 12 people convened to develop a multicriteria decision analysis (MCDA) model to synthesise their opinions on the harms associated with different nicotine containing products; the results of the meeting were summarised in a research paper.[12] The authors state: "The sponsor of the study had no role in any stage of the MCDA process or in the writing of this article, and was not present at the workshop." However, given the importance of complete transparency in an area as controversial as this, it is legitimate to ask about the sponsors. One is a company called EuroSwiss Health.[13] An internet search reveals little about its activities other than that it funded the meeting, but it is one of several companies registered at the same address in a village outside Geneva with the same chief executive. He is reported to have previously received funding from British American Tobacco (BAT)[14] for writing a book on nicotine as a means of harm reduction,[15] although the book states that "the statements, findings, conclusions and recommendations contained in the book were developed independently of BAT." He also endorsed BAT's public health credentials in its 2013 sustainability report.[16]

The paper also acknowledges support from Lega Italiana Anti Fumo (Italian Anti-Smoking League), whose chief scientific adviser was one of the 12 people attending the meeting. He declares funding from an e-cigarette manufacturer but not the funding he is reported elsewhere to have received previously from tobacco company Philip Morris International.[17] The rationale for selecting the members of the panel is not provided, but they include several known e-cigarette champions, some of whom also declare industry funding in the paper.[12] Some others present at the meeting are not known for their expertise in tobacco control. The meeting was also attended by the tobacco lead at PHE. Furthermore, their paper tellingly concedes that "A limitation of this study is the lack of hard evidence for the harms of most products on most of the criteria." However, none of these links or limitations are discussed in the PHE report.

Uncertainty around harms

The PHE report asserts that the available evidence suggests that e-cigarettes are not currently re-normalising smoking among children and young people in the UK. However, this remains a major concern for health professionals and parents. In England, experimentation with e-cigarettes among young people is worrying high, with over one fifth of 11-15 year olds having ever used e-cigarettes[18]; 73% of the young people surveyed who had tried e-cigarettes were non-smokers. Uptake of e-cigarettes among young non-smokers is a particular concern, given that nicotine use in young people may disrupt brain development with long term, irreversible consequences for brain function.[19] The authors categorically dismiss the possibility that e-cigarettes may be a gateway to smoking, arguing that even the concept of a children's gateway should be rejected. This view seems premature, particularly given recently emerging evidence[20] such as an American study, published after the PHE report, which concluded that "those who had ever used e-cigarettes at baseline compared with nonusers were more likely to report initiation of combustible tobacco use over the next year."[21] Furthermore, none of the research so far can be considered conclusive, and longer term studies are needed.

Evidence on the risk of e-cigarette aerosol to bystanders in enclosed public spaces is sparse. However, the PHE report seems to equate lack of evidence with evidence of lack of effect. It claims that there is "no identified risk to bystanders," a view that may be premature.

The report has many other omissions, such as concerns about product safety, including forged safety certificates reported by a BBC *Fake Britain* documentary in December 2014, and the lack of evidence of risks from long term dual use with conventional cigarettes.[22] Yet perhaps its most striking feature is its consistent adoption of the most optimistic position on the limited evidence available. To take one example, the report offers reassurance that e-cigarettes when "used as intended pose no risk of nicotine poisoning to users." This is true, but it is equally true of all poisons. The report rightly calls for nicotine to be in child-proof containers given the attraction of colourful packaging. However, it quotes a report of over 2400 poisoning cases in the United States up to February 2014[23] as saying "none resulted in any serious harm," although the US report included reference to a death attributed to suicide. Nor does it cite the report's conclusion that "the public should be aware that e-cigarettes have the potential to cause acute adverse health effects and represent an emerging public health concern."

The PHE authors also fail to consider the practical consequences of their recommendations. If e-cigarettes are so safe, presumably there will be no restriction on using them in cars. This will make the forthcoming ban on smoking in cars with children virtually unenforceable because it will be extremely difficult to determine what is causing a cloud of smoke or vapour in a moving car.

Finally, the PHE summary states, "The accuracy of nicotine content labelling currently raises no major concerns." Surely, England's leading public health agency cannot be indifferent to a situation where consumer product information is known to be wildly inaccurate?[6 24]

Where next for policy on e-cigarettes?

In 2016, the European Union Tobacco Products Directive[25] will come into force despite some of the most intensive tobacco industry lobbying ever seen.[26] Most of the lobbying effort concerned packaging of conventional cigarettes. However, there was also a powerful attack on the directive's substantial restrictions on e-cigarettes. These restrictions will hopefully limit the negative effect of this flawed PHE report. Meanwhile, directors of public health and the wider community desperately need advice on e-cigarettes that is evidence based and free from any suspicion of influence by vested interests.

Happily, a consensus may be emerging. The English chief medical officer (CMO) recently said that, if e-cigarettes have a role in smoking cessation that should be as "licensed medicines. This would provide assurance on the safety, quality, and efficacy to consumers who want to use these products as quitting aids."[27] That would, of course, require data to show that they were both

safe and effective because, as the CMO also notes, "there continues to be a lack of evidence on the long-term use of e-cigarettes." We agree with this view.

Competing interests: We have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Cite this as: *BMJ* 2015;351:h4863

Key messages

- Public Health England's endorsement of the safety and efficacy of e-cigarettes is based on uncertain evidence
- The quality of evidence that e-cigarettes help smokers to quit is weak
- Recent evidence questions the conclusion that e-cigarettes are not a gateway to smoking
- Until better evidence is available public health strategies should follow the precautionary principle

Teen Use of Non-Cigarette Tobacco Products Increases Smoking Risk

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Salynn Boyles,

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Action Points

- Note that this survey-based observational study found that the use of e-cigarettes in teens was strongly associated with future cigarette use.
- Be aware that this study does not provide proof of causality. Underlying risk factors may predispose teens to both e-cigarette and cigarette use.

Teens who used e-cigarettes, hookahs, cigars and smokeless tobacco products were twice as likely to begin smoking cigarettes within a year of use in a newly published analysis of data from the Population Assessment of Tobacco and Health (PATH) study.

The cigarette uptake rate at one-year follow-up was four times higher among adolescents who used more than one non-cigarette tobacco product, researchers from the University of California, San Francisco's Center for Tobacco Control Research and Education wrote in *JAMA Pediatrics*, published online Jan. 2.

More than a dozen recent studies have linked teen use of electronic cigarettes and other non-cigarette tobacco products with cigarette smoking uptake, and UCSF researcher Shannon Lea Watkins, PhD, said the evidence that they raise the risk for adolescent smoking is now indisputable.

"If our overall goal is to reduce cigarette use and the burden of disease from tobacco, we have to recognize that these products are encouraging young people to move on to cigarette use," Watkins told *MedPage Today.*

Watkins noted that the vast majority of adult cigarette smokers - approximately 90% - had smoked their first cigarette by the age of 18 years.

A 2017 meta-analysis of nine studies, also published in *JAMA Pediatrics*, found e-cigarette use by never-smoking adolescents to be associated with a roughly fourfold greater odds of future cigarette uptake.

The newly reported analysis of the PATH data was unique because of its large size and the inclusion of both e-cigarette and non-e-cigarette tobacco products in the assessment of smoking risk.

"To our knowledge, no prospective study has simultaneously estimated the associations of e-cigarette, cigar, hookah, and smokeless tobacco product use with subsequent cigarette smoking initiation," the researchers wrote.

They also examined whether poly-use of the products was associated with a greater risk for future smoking, compared to use of one product alone.

The analysis was based on the 10,384 PATH youth respondents who reported never having smoked a cigarette in wave 1 and whose ever smoking or past 30-day use was reported in wave 2. Mean age was 14.3; about half were female and half were white.

At one-year follow-up, 4.6% of all baseline never-smoking youths had tried a cigarette and 2.1% had smoked a cigarette within the past 30 days.

Cigarette ever use at follow-up ranged from 18.8% to 19.2% for youths who, at wave 1, had used e-cigarettes, hookah, non-cigarette combustible tobacco, or smokeless tobacco at baseline. In contrast, only about 4% of participants who had not used these tobacco products at baseline reported subsequent cigarette use at follow-up.

After adjusting for sociodemographic, environmental, and behavioral smoking risk factors and for baseline ever use of other tobacco products, the odds of past 30-day cigarette use at follow-up were approximately twice as high among baseline ever users of e-cigarettes (OR 1.87; 95% CI 1.15-3.05), hookah (OR 1.92; 95% CI 1.17-3.17), non-cigarette combustible tobacco (OR 1.78; 95% CI 1.00-3.19), and smokeless tobacco (OR 2.07; 95% CI 1.10-3.87).

Teens who had tried more than one type of tobacco product at baseline had an adjusted odds ratio of 3.81 (95% CI 2.22-6.54) for past 30-day cigarette smoking at follow-up than did baseline never-users of tobacco products.

"Although e-cigarettes are the most common form of non-cigarette tobacco used by youths (exceeding cigarette use), any use of all forms of non-cigarette tobacco was independently associated with greater risk of future cigarette smoking; risk was greatest with use of multiple products, a use pattern that is increasing among youths," the researchers wrote.

They added that the study has direct implications for regulatory policy aimed at preventing youth smoking.

"In policy terms, the findings provide a rationale to treat alternative cigarette products as a group and potentially extend policies that work for one product to others (such as a ban on flavorings)," they wrote. "Even if youths do not progress to smoking cigarettes, any tobacco use is harmful. The estimated health risks of non-cigarette tobacco products should include the addition health consequences of future cigarette use."

Smoking cessation researcher Scott McIntosh, PhD, of University of Rochester Medical Center, New York, told *MedPage Today* that the data examining the usefulness of e-cigarettes for smoking cessation are mixed.

He added that the clear potential of e-cigarettes and other emerging non-combustible tobacco products to addict teens to nicotine has to be part of the regulatory debate, noting

that once teens are addicted, smoking cigarettes may appeal to them as a cheaper, more convenient and more effective method for delivering nicotine.

"I think the FDA needs to be very careful about how they move forward with the message that these products might be useful for cessation," said McIntosh, who was not involved in the current study.

He added that the smoking cessation community is split among people who say it is good that these products are less harmful than conventional cigarettes and those who prefer to focus on the harms that non-cigarette tobacco products do cause.

"If hitting yourself on the head with a 4-pound hammer is bad, do we really want to be sending the message that it's better to hit yourself on the head with a 2-pound hammer?" he asked. "There are FDA approved products proven to be successful for reducing dependency, and that is where we should focus our attention."

Funding for this research was provided by the U.S. National Cancer Institute and FDA Center for Tobacco Products, the National Institute on Drug Abuse, and the National Center for Advancing Translational Sciences.

The researchers reported no relevant relationships with industry related to this study.

- Reviewed by F. Perry Wilson, MD, MSCE Assistant Professor, Section of Nephrology, Yale School of Medicine and Dorothy Caputo, MA, BSN, RN, Nurse Planner
- Primary Source

  JAMA Pediatrics

  Source Reference: Watkins SL, et al. "Association of noncigarette tobacco product use with future cigarette smoking among youth in the Population Assessment of Tobacco and Health (PATH) study, 2013-2015" *JAMA Pediatr* 2018; DOI:10.1001/jamapediatrics.2017.4173.

Another perspective on the Foundation for a Smoke-Free World

thelancet.com/journals/lancet/article/PIIS0140-6736(17)33312-3/fulltext

Much has, and is, being said about the Foundation for a Smoke-Free World,[1] an independent foundation funded by Philip Morris International, but one elemental point has been overlooked. A principal focus of the foundation, as stated on its website, is on treatment of addicted smokers to decrease mortality, including promoting the switch to reduced-risk products, such as e-cigarettes. Geoffrey Rose, in his masterful monograph *The Strategy of Preventive Medicine*, pointed to the so-called risk paradox, giving the example "whereby it was seen that many people exposed to a small risk may generate more disease than a few exposed to a conspicuous risk. Applied in reverse to prevention, this means that when many people each receive a little benefit, the total benefit may be large."[2] As a theoretical example, a 5% lowering of mean blood pressure across a population could achieve a 30% reduction in stroke, compared with a 15% reduction if all cases of hypertension were treated.

In Rose's bell curve, a wholesale shift to the left of the entire curve will achieve more than will a focus on the right-hand tail. When applied to public health measures—such as bans on public smoking, which address smoking-related mortality—this approach will shift the curve of tobacco-use prevalence, and thus mortality, to the left, which should in turn yield a greater effect than will treating cigarette smokers who are struggling to quit. A prime example of this is the reduction in the number of heart attacks witnessed in many parts of the world after bans on public smoking were introduced.[3] More recently, results from various meta-analyses also show reductions in perinatal and childhood respiratory diseases.[4] Although some individual patients in a clinical setting might benefit from e-cigarettes and other novel products, this does not mean that these electronic nicotine delivery systems (ENDS) should be promoted, marketed, or sold to the general population.

In light of these findings, the goals of the Foundation for a Smoke-Free World seem far less benign, even before considering the involvement of the tobacco industry. Unlike standard nicotine replacement therapy, counselling, and quitting cold turkey, e-cigarettes and heat-not-burn tobacco products maintain nicotine addiction. And unlike methadone, which is the cheapest manufactured drug in the USA and used as an example by ENDS advocates,[5] there is a huge profit to be made by the tobacco industry in prolonging nicotine addiction. Decades ago, an industry executive said bluntly, "Nicotine is addictive. We are, then, in the business of selling nicotine."[6] Whatever reduction in mortality is possibly achieved by ENDS would be offset to some degree by continued nicotine use, by non-smoking adolescents becoming addicted and switching to regular cigarettes (which is already occurring), and by any long-term toxicity associated with the ENDS products.

There are far better and more thoroughly tested ways to spend US$1 billion if the goal is to reduce smoking morbidity and mortality. To cite Geoffrey Rose again: "Mass diseases and mass exposures require mass remedies. A targeted approach may assist but it cannot be sufficient."[2] It is possible that the Foundation for a Smoke-Free World will come up with

some grand strategy other than to offer a platform for its sponsor's latest products; this remains to be shown.

I declare no competing interests.

» E-Cigarette Flavorings, Additives Increase Inflammation and Impair Lung Function

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E-Cigarette Flavorings, Additives Increase Inflammation and Impair Lung Function, Study Finds

Short-term e-cigarette use causes as much or more damage as conventional cigarettes

Rockville, Md. (October 11, 2018)—Flavoring and additive ingredients in e-cigarettes may increase inflammation and impair lung function, according to new research. **The study**, published ahead of print in the *American Journal of Physiology—Lung Cellular and Molecular Physiology*, also found that short-term exposure to e-cigarettes was enough to cause lung inflammation similar or worse than that seen in traditional cigarette use. The research was chosen as an **APS*select***article for October.

E-cigarettes, popular battery-powered devices that simulate the act of smoking a traditional cigarette, dispense a vapor derived from liquid chemicals in a refillable cartridge. The refills typically contain propylene glycol, nicotine and often flavorings. Propylene glycol—a colorless, odorless food additive—is found in numerous processed food and beverages; it is also used as a solvent in a number pharmaceuticals. E-cigarette devices and refills are not well regulated, and the long-term health effects of e-cigarette use are not widely known.

Researchers studied several groups of mice that received whole-body exposure to varying chemical combinations four times each day. Each exposure session was separated by 30-minute smoke-free intervals.

- One group was exposed to cigarette smoke (“cigarette”);
- One group was exposed to e-cigarette vapor containing propylene glycol and vegetable glycerol, an odorless liquid derived from plant oils (“propylene”);
- One group was exposed to e-cigarette vapor containing propylene glycol and nicotine (“propylene + nicotine”) and
- One group was exposed to e-cigarette vapor containing propylene glycol, nicotine and tobacco flavoring (“flavoring”).

The cigarette and e-cigarette groups were compared with a control group that was exposed to medical-grade air. Some of the animals in each group were exposed to short-term cigarette smoke or e-cigarette vapor (three days), while others were exposed for a longer term (four weeks).

The research team found an increase in markers of inflammation, mucus production and altered lung function in the propylene, propylene + nicotine and flavoring groups after three days. However, the propylene group showed fewer negative effects with long-term exposure, suggesting the additive alone elicits only a temporary irritation

that eventually subsides with continued use. In addition, two inflammation-producing proteins became elevated only in the flavoring group, suggesting that some of the many flavoring components on the market may not be safe for even short-term use.

The condition of the e-cigarette groups in comparison with the cigarette group surprised the researchers. The level of oxidative stress—stress at a cellular level—in the flavoring group was equal to or higher than that of the cigarette group. However, respiratory mechanics were adversely affected only in mice exposed to cigarette smoke and not to e-cigarette vapor after prolonged treatment. "The observed detrimental effects in the lung upon [e-cigarette] vapor exposure in animal models highlight the need for further investigation of safety and toxicity of these rapidly expanding devices worldwide," the researchers wrote.

Read the full article, "**Comparison of the effects of e-cigarette vapor with cigarette smoke on lung function and inflammation in mice**," published ahead of print in the***American Journal of Physiology—Lung Cellular and Molecular Physiology***. It is highlighted as one of this month's "best of the best" as part of the American Physiological Society's APS*select* program. Read all of **this month's selected research articles**.

NOTE TO JOURNALISTS: To schedule an interview with a member of the research team, please contact the **APS Communications Office** or 301-634-7314. Find more research highlights in the **APS Press Room**.

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RelatedItems

E-Cigarette Vapor—Even when Nicotine-Free—Found to Damage Lung Cells

Released May 26, 2015 - With the use of e-cigarettes on the rise, especially among young people, research to uncover the health effects of e-cigs is becoming increasingly important. In a new study published ahead of print in AJP-Lung, researchers find that e-cig solution and vapors—even those that are nicotine-free—damage lung health.

Older Adults' Lungs Remain Strong during Exercise

Released June 20, 2017 - Highly active older adults experience no limitations in the lungs' capacity to exchange gases (lung-diffusing capacity) during physical activity, researchers have found. The study is published in the *Journal of Applied Physiology*.

E-Cigarette Use Accelerates Effects of Cardiovascular Aging

Released August 12, 2017 - A new study suggests that a single exposure to e-cigarette (e-cig) vapor may be enough to impair vascular function. Researchers from West Virginia University will present findings today at the Cardiovascular Aging: New Frontiers and Old Friends meeting in Westminster, Colo.

Do electronic cigarettes increase cigarette smoking in UK adolescents? Evidence from a 12-month prospective study

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Received 17 November 2016
Revised 2 June 2017
Accepted 9 June 2017
Published Online First 17 August 2017

ABSTRACT

Background In cross-sectional surveys, increasing numbers of adolescents report using both electronic cigarettes (e-cigarettes) and cigarettes. This study assessed whether adolescent e-cigarette use was associated prospectively with initiation or escalation of cigarette use.

Methods Data were from 2836 adolescents (aged 13–14 years at baseline) in 20 schools in England. At baseline, breath carbon monoxide levels, self-reported e-cigarette and cigarette use, sex, age, friends and family smoking, beliefs about cigarette use and percentage receiving free school meals (measure of socioeconomic status) were assessed. At 12-month follow-up, self-reported cigarette use was assessed and validated by breath carbon monoxide levels.

Results At baseline, 34.2% of adolescents reported ever using e-cigarettes (16.0% used only e-cigarettes). Baseline ever use of e-cigarettes was strongly associated with subsequent initiation (n=1726; OR 5.38, 95% CI 4.02 to 7.22; controlling for covariates, OR 4.06, 95% CI 2.94 to 5.60) and escalation (n=318; OR 1.91, 95% CI 1.14 to 3.21; controlling for covariates, this effect became non-significant, OR 1.39, 95% CI 0.97 to 1.82) of cigarette use.

Conclusions This is the first study to report prospective relationships between ever use of e-cigarettes and initiation and escalation of cigarette use among UK adolescents. Ever use of e-cigarettes was robustly associated with initiation but more modestly related to escalation of cigarette use. Further research with longer follow-up in a broader age range of adolescents is required.

Longitudinal data on e-cigarette use and subsequent cigarette use are currently limited to US samples based on unverified self-reported measures.[16–18] For example, two US studies reported baseline e-cigarette use to be positively associated with the initiation of cigarette use 12 months later in 14-year olds controlling for various predictors of smoking (OR 1.75, 95% CI 1.10 to 2.77; OR 2.87, 95% CI 2.03 to 4.05).[17 18] Barrington-Trimis *et al*[16] reported similar findings over 16 months in 17-year-olds (OR 6.17, 95% CI 3.30 to 11.6), whereas Wills *et al*[19] reported that e-cigarette use was linked to initiation (OR 2.87, 95% CI 2.03 to 4.05) but not to escalation of smoking over 12 months in a sample of adolescents aged 14–15 years.

This study is novel in assessing these relationships between e-cigarette use and subsequent cigarette use in a sample of UK adolescents and in exploring a number of previously unexamined smoking risk factors as covariates and moderators. In particular, we investigated the extent to which baseline ever use of e-cigarettes was associated with the initiation or escalation of cigarette use (objectively validated) 12 months later in a sample of UK adolescents aged 13–14 years. The impact of controlling for various smoking risk factors such as friends and family smoking and their moderating effects was also explored.

METHODS

Participants and procedures

Data were collected as part of a 4-year cluster randomised controlled trial of a school-based smoking initiation intervention[20 21] based on

PREVENTING CHRONIC DISEASE
PUBLIC HEALTH RESEARCH, PRACTICE, AND POLICY
Volume 14, E32 APRIL 2017

RESEARCH BRIEF

Quit Methods Used by US Adult Cigarette Smokers, 2014–2016

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the weighted mean. We estimated 1) the prevalence of any quit method used (alone or in combination with any of the other 9 quit methods) and 2) the prevalence of using a single quit method among respondents who used only one method. All analyses were conducted using Stata version 13 (StataCorp LP).

Results

Among participants who were invited and eligible to participate in this study, 50.2% completed the follow-up surveys. Most respondents in the study were male (51.3%) and non-Hispanic white (59.9%). The greatest proportion, by age, was aged 35 to 54 years (36.9%); by education, had graduated from high school (37.3%), and by income, had an annual household income of $20,000 to $49,999 (32.8%).

Overall, 74.7% of adult current cigarette smokers used multiple quit methods during their most recent quit attempt (Table 1). Giving up cigarettes all at once (65.3%) and gradually cutting back on cigarettes (62.0%) were the most commonly used methods to try to quit, followed by substituting some cigarettes with e-cigarettes (35.3%), using a nicotine patch or gum (25.4%), switching completely from cigarettes to e-cigarettes (24.7%), and switching from "regular" cigarettes to "mild" cigarettes (20.4%). Quit methods used less often were getting help from a doctor or other health professional (15.2%), using smoking cessation medications approved by the US Food and Drug Administration (FDA) (12.2%), and getting help from a website (7.1%) or a telephone quitline (5.4%).

Among those who tried to quit in the previous 3 months, 25.3% reported using only one method to quit cigarettes during their most recent quit attempt (Table 2). The single most common quit method used alone was giving up cigarettes all at once (14.7%), followed by gradually cutting back on cigarettes (6.6%). Substituting some cigarettes with e-cigarettes or switching completely from cigarettes to e-cigarettes was each used by 1.1% of smokers. All other quit methods were used as a single quit method by less than 1% of smokers.

Discussion

Our study showed that most (74.7%) US adult smokers who tried to quit did so by using multiple quit methods as part of their most recent quit attempt. Giving up cigarettes all at once ("cold turkey") and gradually cutting back on cigarettes continue to be the most commonly used methods (4,5). Before this study, we knew that some cigarette smokers were using e-cigarettes to attempt to quit (6–8), but we did not know how the rise in e-cigarette use, particularly among current adult cigarette smokers, may have affected quitting behaviors. We found that substituting some cigarettes with e-cigarettes was used by a greater percentage of smokers than the nicotine patch, nicotine gum, or other FDA-approved cessation aids. There is no conclusive scientific evidence that e-cigarettes are effective for long-term cessation of cigarette smoking (6). E-cigarettes are not approved by the FDA as a smoking cessation aid (9,10). FDA-approved medications have helped smokers to quit, in many instances doubling the likelihood of success (11). Finally, we found that most smokers who are switching to e-cigarettes or "mild" cigarettes are not switching completely. These smokers are not stopping their cigarette smoking.

This study has some limitations. Respondents to our online survey may have systematically different quitting habits than smokers nationally. However, the potential for bias was reduced through probability-based sampling, lack of opt-in to the panel, and weighting the sample to the US smoker population. Second, respondents were asked only to self-report the quit methods used as part of the most recent quit attempt in the previous 3 months; therefore, our estimates could be subject to recall bias and may not reflect the full breadth of quit methods used as part of a quit attempt during the study period.

Given that our data show that e-cigarettes are more commonly used for quit attempts than FDA-approved medications, further research is warranted on the safety and effectiveness of using e-cigarettes to quit smoking.

Acknowledgments

Sources of funding were from the Affordable Care Act Prevention of Chronic Disease and Improving Public Health funds (OMB 0920-1083). The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, RTI International, or the University of North Carolina at Chapel Hill. The authors have no conflicts of interests.

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ORIGINAL ARTICLE

Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2015-208039).

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Received 6 November 2015
Revised 12 July 2016
Accepted 27 July 2016
Published Online First
24 August 2016

ABSTRACT

Background The use of electronic (e)-cigarettes is increasing rapidly, but their lung health effects are not established. Clinical studies examining the potential long-term impact of e-cigarette use on lung health will take decades. To address this gap in knowledge, this study investigated the effects of exposure to aerosolised nicotine-free and nicotine-containing e-cigarette fluid on mouse lungs and normal human airway epithelial cells.

Methods Mice were exposed to aerosolised phosphate-buffered saline, nicotine-free or nicotine-containing e-cigarette solution, 1-hour daily for 4 months. Normal human bronchial epithelial (NHBE) cells cultured at an air-liquid interface were exposed to e-cigarette vapours or nicotine solutions using a Vitrocell smoke exposure robot.

Results Inhalation of nicotine-containing e-cigarettes increased airway hyper-reactivity, distal airspace enlargement, mucin production, cytokine and protease expression. Exposure to nicotine-free e-cigarettes did not affect these lung parameters. NHBE cells exposed to nicotine-containing e-cigarette vapour showed impaired ciliary beat frequency, airway surface liquid volume, cystic fibrosis transmembrane regulator and ATP-stimulated K+ ion conductance and decreased expression of FOXJ1 and KCNMA1. Exposure of NHBE cells to nicotine for 5 days increased interleukin (IL)-6 and IL-8 secretion.

Conclusions Exposure to inhaled nicotine-containing e-cigarette fluids triggered effects normally associated with the development of COPD including cytokine expression, airway hyper-reactivity and lung tissue destruction. These effects were nicotine-dependent both in the mouse lung and in human airway cells, suggesting that inhaled nicotine contributes to airway and lung disease in addition to its addictive properties. Thus, these findings highlight the potential dangers of nicotine inhalation during e-cigarette use.

Key messages

What is the key question?
- What are the pulmonary consequences of electronic (e)-cigarette inhalation?

What is the bottom line?
- These findings show that the inhalation of nicotine present in e-cigarettes alters inflammation, ion conductance and mucociliary function in human bronchial epithelial cells and induces airway hyper-reactivity and air space enlargement in exposed mice.

Why read on?
- This study provides insights into the lung health effects of e-cigarettes and also implicates nicotine as a causative factor at the onset and progression of COPD.

INTRODUCTION

19% of the population continues to smoke.[1] Though nicotine replacement therapy (NRT) helps, nearly 93% of smokers will relapse despite NRT within 6 months of quitting.[2] Given these difficulties with smoking cessation and the enormous public health burden imposed by COPD, some healthcare advocates have argued that electronic (e)-cigarettes are a safer alternative for those individuals who cannot quit.[3]

e-Cigarettes are devices that effectively deliver vaporised liquid nicotine to the lungs. The user can choose the nicotine concentration of e-cigarette liquid (e-liquid) that is loaded into the device's cartridge. When the user inhales, the e-liquid, primarily nicotine in propylene glycol (PG) or vegetable glycerine (VG), is heated to produce a vapour that is inhaled into the lungs. Despite the many flavours and varieties available, almost all consumers

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JAMA Pediatrics | Original Investigation

Association of Noncigarette Tobacco Product Use With Future Cigarette Smoking Among Youth in the Population Assessment of Tobacco and Health (PATH) Study, 2013-2015

Shannon Lea Watkins, PhD; Stanton A. Glantz, PhD; Benjamin W. Chaffee, DDS, PhD

IMPORTANCE Approximately 90% of adult smokers first tried a cigarette by 18 years of age, and even infrequent smoking in adolescence is associated with established adult smoking. Noncigarette tobacco use is increasing and could stimulate subsequent conventional cigarette smoking in youths.

OBJECTIVE To estimate the longitudinal association between noncigarette tobacco use and subsequent cigarette smoking initiation among US youth.

DESIGN, SETTING, AND PARTICIPANTS In this prospective cohort study of the Population Assessment of Tobacco and Health (PATH) waves 1 (September 12, 2013, to December 14, 2014) and 2 (October 23, 2014, to October 30, 2015), a nationally representative sample of youths who never smoked a conventional cigarette at baseline and completed wave 2 follow-up (N = 10 384) was studied. PATH retention at follow-up was 87.9%.

EXPOSURES Ever use and past 30-day use of electronic cigarettes (e-cigarettes), hookah, noncigarette combustible tobacco, or smokeless tobacco at baseline.

MAIN OUTCOMES AND MEASURES Ever use and past 30-day use of cigarettes at follow-up.

RESULTS The present analysis was based on the 10 384 PATH youth respondents who reported never having smoked a cigarette in wave 1 and whose cigarette ever or past 30-day use was reported in wave 2 (mean [SD] age, 14.3 [1.7] years; age range, 12-17 years; 5087 [49.1%] female; 4829 [52.5%] white). At 1-year follow-up, 469 (4.6%) of all baseline never-smoking youths had tried a cigarette and 219 (2.1%) had smoked a cigarette within the past 30 days. Cigarette ever use at follow-up was higher among youths who had ever used e-cigarettes (78 [19.1%]), hookah (60 [18.3%]), noncigarette combustible tobacco (45 [19.2%]), or smokeless tobacco (29 [18.8%]) at baseline. After adjusting for sociodemographic, environmental, and behavioral smoking risk factors and for baseline ever use of other tobacco products, the odds of past 30-day cigarette use at follow-up were approximately twice as high among baseline ever users of e-cigarettes (odds ratio [OR], 1.87; 95% CI, 1.15-3.05), hookah (OR, 1.92; 95% CI, 1.17-3.17), noncigarette combustible tobacco (OR, 1.78; 95% CI, 1.00-3.19), and smokeless tobacco (OR, 2.07; 95% CI, 1.10-3.87). Youths who had tried more than 1 type of tobacco product at baseline had 3.81 (95% CI, 2.22-6.54) greater adjusted odds of past 30-day cigarette smoking at follow-up than did baseline never tobacco users.

CONCLUSIONS AND RELEVANCE Any use of e-cigarettes, hookah, noncigarette combustible tobacco, or smokeless tobacco was independently associated with cigarette smoking 1 year later. Use of more than 1 product increased the odds of progressing to cigarette use.

JAMA Pediatr. doi:10.1001/jamapediatrics.2017.4173
Published online January 2, 2018.

Supplemental content

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» E-Cigarette Flavorings, Additives Increase Inflammation and Impair Lung Function

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E-Cigarette Flavorings, Additives Increase Inflammation and Impair Lung Function, Study Finds

Short-term e-cigarette use causes as much or more damage as conventional cigarettes

Rockville, Md. (October 11, 2018)—Flavoring and additive ingredients in e-cigarettes may increase inflammation and impair lung function, according to new research. The study, published ahead of print in the *American Journal of Physiology—Lung Cellular and Molecular Physiology*, also found that short-term exposure to e-cigarettes was enough to cause lung inflammation similar or worse than that seen in traditional cigarette use. The research was chosen as an APSselectarticle for October.

E-cigarettes, popular battery-powered devices that simulate the act of smoking a traditional cigarette, dispense a vapor derived from liquid chemicals in a refillable cartridge. The refills typically contain propylene glycol, nicotine and often flavorings. Propylene glycol—a colorless, odorless food additive—is found in numerous processed food and beverages; it is also used as a solvent in a number pharmaceuticals. E-cigarette devices and refills are not well regulated, and the long-term health effects of e-cigarette use are not widely known.

Researchers studied several groups of mice that received whole-body exposure to varying chemical combinations four times each day. Each exposure session was separated by 30-minute smoke-free intervals.

- One group was exposed to cigarette smoke ("cigarette");
- One group was exposed to e-cigarette vapor containing propylene glycol and vegetable glycerol, an odorless liquid derived from plant oils ("propylene");
- One group was exposed to e-cigarette vapor containing propylene glycol and nicotine ("propylene + nicotine") and
- One group was exposed to e-cigarette vapor containing propylene glycol, nicotine and tobacco flavoring ("flavoring").

The cigarette and e-cigarette groups were compared with a control group that was exposed to medical-grade air. Some of the animals in each group were exposed to short-term cigarette smoke or e-cigarette vapor (three days), while others were exposed for a longer term (four weeks).

The research team found an increase in markers of inflammation, mucus production and altered lung function in the propylene, propylene + nicotine and flavoring groups after three days. However, the propylene group showed fewer negative effects with long-term exposure, suggesting the additive alone elicits only a temporary irritation

that eventually subsides with continued use. In addition, two inflammation-producing proteins became elevated only in the flavoring group, suggesting that some of the many flavoring components on the market may not be safe for even short-term use.

The condition of the e-cigarette groups in comparison with the cigarette group surprised the researchers. The level of oxidative stress—stress at a cellular level—in the flavoring group was equal to or higher than that of the cigarette group. However, respiratory mechanics were adversely affected only in mice exposed to cigarette smoke and not to e-cigarette vapor after prolonged treatment. "The observed detrimental effects in the lung upon [e-cigarette] vapor exposure in animal models highlight the need for further investigation of safety and toxicity of these rapidly expanding devices worldwide," the researchers wrote.

Read the full article, "**Comparison of the effects of e-cigarette vapor with cigarette smoke on lung function and inflammation in mice**," published ahead of print in the***American Journal of Physiology—Lung Cellular and Molecular Physiology***. It is highlighted as one of this month's "best of the best" as part of the American Physiological Society's APS*select* program. Read all of **this month's selected research articles**.

NOTE TO JOURNALISTS: To schedule an interview with a member of the research team, please contact the **APS Communications Office** or 301-634-7314. Find more research highlights in the **APS Press Room**.

Physiology is the study of how molecules, cells, tissues and organs function in health and disease.Established in 1887, the American Physiological Society (APS) was the first U.S. society in the biomedical sciences field. The Society represents more than 10,500 members and publishes 15 peer-reviewed journals with a worldwide readership.

RelatedItems

E-Cigarette Vapor—Even when Nicotine-Free—Found to Damage Lung Cells

Released May 26, 2015 - With the use of e-cigarettes on the rise, especially among young people, research to uncover the health effects of e-cigs is becoming increasingly important. In a new study published ahead of print in AJP-Lung, researchers find that e-cig solution and vapors—even those that are nicotine-free—damage lung health.

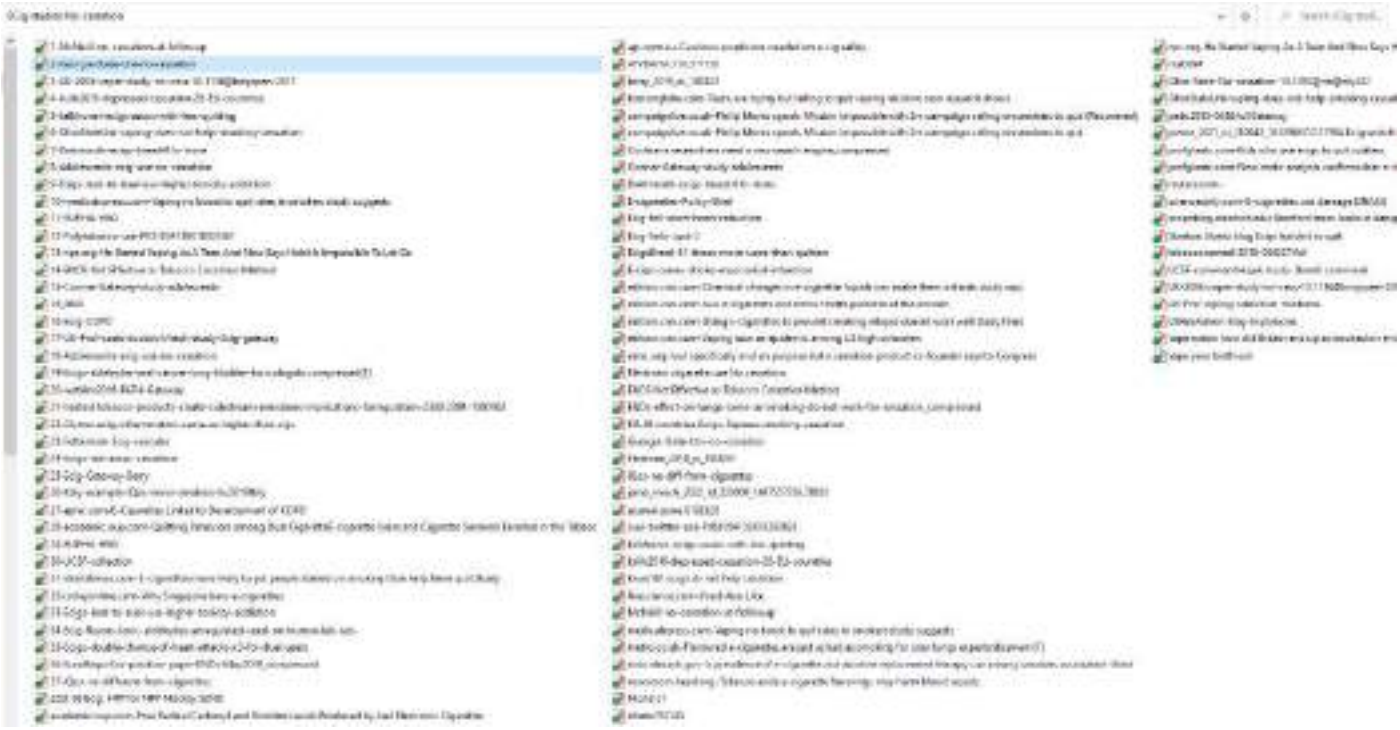
Older Adults' Lungs Remain Strong during Exercise

Released June 20, 2017 - Highly active older adults experience no limitations in the lungs' capacity to exchange gases (lung-diffusing capacity) during physical activity, researchers have found. The study is published in the *Journal of Applied Physiology*.

E-Cigarette Use Accelerates Effects of Cardiovascular Aging

Released August 12, 2017 - A new study suggests that a single exposure to e-cigarette (e-cig) vapor may be enough to impair vascular function. Researchers from West Virginia University will present findings today at the Cardiovascular Aging: New Frontiers and Old Friends meeting in Westminster, Colo.

ECIG studies and articles – they do not work for cessation at one year or more followup



Vaping product access and use among 14–17-year-olds in New South Wales: a cross-sectional study

Christina Watts,[1] Sam Egger,[1] Anita Dessaix,[2] Alecia Brooks,[2] Emily Jenkinson,[2] Paul Grogan,[1] Becky Freeman[3]

Abstract

Objectives: We assessed access to vaping products and types of products used and the factors associated with vaping and smoking among young people in the state of New South Wales (NSW), Australia.

Methods: A cross-sectional survey was conducted with a sample of 721 young people aged 14 to 17 years from NSW recruited through online panels. Poisson regression with robust variance was used to estimate relative risks of ever-vaping and ever-smoking.

Results: Almost one-third of the sample (32%, n=233) reported being an ever-vaper, of which more than half (54%) had never smoked prior to starting vaping. Ever-vaping was independently associated with age and being Aboriginal or Torres Strait Islander, and ever-smoking was independently associated with being male. Ever-smokers were seven times more likely to be ever-vapers than those who had never smoked, and ever-vapers were 18 times more likely to be ever-smokers than those who had never vaped. Among ever-vapers who reported which type of device they were using, 86% reported the use of disposable products. "Flavourings and taste" was rated as the most important characteristic of vapes. More than half of ever-vapers reported getting the last vape they used from their friends (55%, n=130). More than half of ever-vapers had used a vape that they knew contained nicotine (53%, n=123).

Conclusions: Vaping was the strongest risk factor for smoking, and vice versa, suggesting there is not a straightforward, unidirectional relationship between vaping and smoking in young people. Young people appear to be readily accessing nicotine vaping products, which are often disposable and flavoured, through both social and commercial channels.

Implications for public health: Stronger enforcement of federal and state policies designed to protect young people from vaping products is urgently needed.

Key words: electronic cigarettes, public health, tobacco control

The use of vaping products, also known as electronic cigarettes or e-cigarettes, is a rapidly evolving area of public health research and policy development. Compared to other nations with a similar track record of successful tobacco control, Australia has adopted strict measures to control access to nicotine vaping products. Despite nicotine vaping products being positioned as an important cessation aid,[1] including by the tobacco industry,[2] there is limited evidence of effectiveness.[3] To date, the Australian Therapeutic Goods Administration (TGA) has not approved any nicotine vaping product as a safe and effective smoking cessation aid.[4] As of 1 October 2021, Australians require a prescription to legally access nicotine vaping products as an unapproved medicine. The scheduling change closes a regulatory gap between Commonwealth and state and territory laws and is intended to enable current smokers to receive health advice on the use and risks associated with vaping and prevent uptake by non-smokers, especially young people.[4] In New South Wales, and all other states and territories except Western Australia, the retail sale, purchase and use of non-nicotine vaping products by adults, provided no therapeutic claims are made, is legal.[5]

With limited evidence available on the long-term health effects of vaping product use, there are concerns about product safety,[6] and the rapid growth in use by young people.[7] Vaping products contain a number of harmful substances including carcinogens such as formaldehyde, nitrosamines, and metals (e.g. nickel and chromium) and vaping products may increase the risk of cardiovascular diseases and lung disorders.[6,8] Nicotine use by young people is harmful to their developing brains and has adverse effects on the part of the brain that controls attention, learning, mood and impulse control.[9] An Australian study of 18–25-year-old never smokers found

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Submitted: February 2022; Revision requested: July 2022; Accepted: August 2022
The authors have stated the following conflicts of interest: CW, SE, AD, AB, EJ and PG report being employed by Cancer Council New South Wales during the conduct of the study and/or in the 36 months prior to submission of this manuscript. BF reports being a member of the Australian National Health and Medical Research Council Electronic Cigarettes Working Committee (May 2020), receiving consultancy payment for e-cigarette policy review for the NSW National Heart Foundation (December 2019), receiving reimbursement for travel expenses to attend the Oceania Tobacco Control Conference (2017) to present on e-cigarettes and cessation and the National Taiwan University for presenting on e-cigarette regulation (2016), providing opinion (unpaid) at the Australian Parliament's Standing Committee on Health, Aged Care and Sport public hearing into the Use and Marketing of Electronic Cigarettes and Personal Vaporisers (8 September 2017) and leading a contract on e-cigarette regulation in Australia for the Commonwealth Department of Health (2016).

Aust NZ J Public Health. 2022; 46:814-20; doi: 10.1111/1753-6405.13316

that e-cigarette users were significantly more curious about trying cigarettes and reported significantly higher intention to smoke within the next six months compared to those who had never used an e-cigarette.[10]

Australian population surveillance shows increasing rates of e-cigarette use.[11] In 2019, one in five (19.6%) non-smokers aged 18–24 years had tried an e-cigarette, up from 13.6% in 2016, and 7.8% of non-smokers aged 14–17 years had ever used an e-cigarette in 2019, with "curiosity" being the most common reason for using an e-cigarette (73.2%).[12] Population data from NSW found that 32.7% of persons aged 16–24 had ever used an e-cigarette in 2021 – the highest rate of all population groups.[13] Media, school and community reports suggest that vaping among young people in NSW has proliferated in recent years.[14,15] This seeming growth in vaping is corroborated by NSW compliance data showing that 54,556 illegal nicotine products were seized from retailers in the first half of 2021, up from 4,667 in the same period of 2020.[16]

Considering the evolving vaping product regulatory environment, the potential health concerns and growing rates of use in Australia, it is critical to understand the extent of current use and access among young people. To date, no Australian study has explored how young people are accessing vaping products, the type of devices they are using or their motivations for use. Such insights are necessary to ensure young people are protected from accessing and using vaping products. This study aims to assess access to vaping products and types of products used, and to explore the relationships between vaping, smoking and various socio-demographic factors among young people aged 14 to 17 years in New South Wales, Australia, prior to the October 2021 nicotine scheduling change.

Methods

Study design

This study is part of a larger ongoing study of vaping among Australian young people called *Generation Vape*. The *Generation Vape* project involves data collection activities (qualitative and quantitative) with four population groups (including 14–17-year-olds, 18–24-year-olds, parents of 14–17-year-olds and secondary school educators) at multiple time points during a three-year period. This paper reports on the first wave of quantitative data collection, involving an online cross-sectional survey of 14–17-year-old young people residing in New South Wales. Data collection was conducted in September 2021, prior to the national implementation of nicotine scheduling changes. It was designed to examine vaping product use and related awareness, perceptions, attitudes, and knowledge among young people. The questionnaire (see Supplementary File 1) was pre-tested for clarity with young people before the administration of the survey.

Procedure

Eligible participants were those who self-reported being aged between 14 and 17 years inclusive and were living in NSW at the time of the survey. We aimed for a minimum sample size of 700 participants, who were identified and recruited through multiple online panels via a third-party research provider. Recruitment through multiple online panels allowed us to extend the reach of the survey beyond the scope and size of one panel, as well as reducing skews and biases that may be present in individual panels. Young people who were members of these panels were recruited either directly through email invitation or indirectly through parents of 14–17-year-olds. All respondents were required to complete three screening questions to ensure they met the eligibility criteria: "What is your postcode?", "How old are you?" and "Have you ever seen or heard of vapes or e-cigarettes?", with the definition of a vape/e-cigarette provided. The latter question was deemed necessary to ensure only respondents who had prior knowledge of vaping products could participate. To ensure the sample was closely representative of the population, key demographic characteristics, including age, gender, location (metropolitan and non-metropolitan areas of NSW) and education (school grade), were monitored throughout data collection. To prevent the data from being skewed, pre-established caps were placed on gender and age. Parental consent was required of all participants before they started the survey. Respondents were also required to consent to participation in the study after receiving a Participant Information Statement. Ethics approval for the survey was granted by the University of Sydney Human Research Ethics Committee (Project number: 2021/442) in July 2021.

Measures

Sociodemographic variables

Demographic characteristics recorded included gender, age, current education level, remoteness (metro vs. non-metro areas of NSW), language spoken at home (English and/or another language) and Aboriginal and/or Torres Strait Islander status.

Vaping and smoking status

All teenage participants aged 14–17 years were asked: "Have you ever used a vape? How many times?" with response options "No, I've never vaped", "Yes just a few puffs", "Yes, I have vaped on fewer than 10 occasions in my life", "Yes, I have vaped on more than 10 but fewer than 100 occasions in my life" and "Yes, I have vaped more than 100 times in my life". Those who indicated that they had ever vaped were further asked: "Before you first tried vaping, how many tobacco cigarettes had you smoked in your lifetime?" with response options "None", "Just a few puffs", "Less than 10 tobacco cigarettes" and "Ten or more tobacco cigarettes". Responses to the above two questions were used to determine which participants were vapers and smokers, and whether smoking or vaping was tried first. Ever-vapers were also asked how many days they had vaped in the last 30 days, and during a typical month with no COVID-19 restrictions in place, since NSW was under COVID-19 lockdown restrictions, including home learning, at the time of data collection.

Vape products used and access

Participants who reported ever using a vape were asked: "Can you please describe the vape you use? For example, what kind of device is it? How does it work?". Open-ended responses to the question were manually coded into the following categories: "Disposable vape"; "Refillable vape"; "Pod vape"; "Heated tobacco product"; "Unsure" and "Not specified". Ever-vapers were also asked to rate the importance of various characteristics of vapes and vaping behaviour, such as "Flavouring and taste", "Price" and "Being able to make big vapour clouds" on a five-point scale from "Not at all important" to "Very important", as well as whether they had ever used a vape that they knew contained nicotine (Yes/No or Don't know).

Ever-vapers were also asked a series of questions relating to the last time they vaped, including if they had purchased the vape themselves (Yes/No), and how they got the

vape. There were different response options for those who purchased the vape (such as "From a friend or someone selling them"; "At a petrol station"; "At a tobacconist"; "Through a website"; "Through Facebook"), and for those who did not purchase the vape (such as "Friends gave/shared it with me"; "My parents or legal guardians gave/shared it with me"; "My brother or sister gave/shared it with me"). Ever-vapers were also asked how easy or hard it is to get a vape, with a 7-point response scale from "Very hard" to "Very easy".

Statistical methods

Poisson regression with robust variance was used to estimate the associations between the dichotomous dependent variable ever-vaping (vs. never-vaping) and various independent variables (with relative risks [RRs] as a measure of effect). The same regression technique was also used to estimate the associations between the dichotomous dependent variable ever-smoking (vs. never smoking) and independent variables. In these analyses, ever-vaping and ever-smoking were defined as ever having a few puffs or more of vapes or cigarettes, respectively. We selected the set of independent variables derived from the questionnaire that we hypothesised to be independently associated with the dependent variables or potential confounders of the effects of other selected independent variables, or that were associated with the dependent variables in bivariate analyses. In this paper, we report the estimates from the bivariate analyses and fully adjusted models containing all of the selected independent variables. For each independent variable, we report a *p*-value corresponding to a test of the null that all RRs equal one.

Results

Participant characteristics

A total of 721 young people aged 14 to 17 years participated in the survey, which comprised 359 males, 359 females and 3 non-binary and other participants (Table 1). Female participants tended to be older than male participants, with females more likely to be aged 16–17 than males (63% vs. 49% respectively). Five per cent of participants were Aboriginal or Torres Strait Islanders, 88% lived in a metropolitan area and 79% spoke English only.

Vaping patterns

Sixty-five per cent of participants had never smoked or vaped and 23% had both smoked and vaped (Table 2). Close to one-third of the sample (32%, *n*=233) reported being an ever-vaper (defined as having at least a few puffs of a vape), 16% (*n*=114) reported vaping in the last 30 days (49% of ever-vapers) and 5% (*n*=35) reported vaping between 10 and 30 days of the last 30 (15% of ever-vapers). However, in a typical month without COVID-19 restrictions in place, 62% (*n*=145) of ever-vapers reported vaping at least once and 19% (*n*=44), 10–30 times. Of the 233 ever-vapers, 125 (54%) had never smoked before they first tried vaping

Associations between ever-vaping, ever-smoking and socio-demographic factors

Ever-vaping was independently associated with age (p=0.010), being Aboriginal or Torres Strait Islander (p=0.010), smoking status (p<0.001) and lifetime quantity smoked (p<0.001); see Table 3. Specifically, after adjustment for participant characteristics (specified below in Table 3), 17-year-olds were 51% more likely to be ever-vapers than 14-year-olds (RR=1.51, 95%CI[1.15, 2.00]), and Aboriginal or Torres Strait Islander peoples were 35% more likely to be ever-vapers than non-Indigenous young people (RR=1.35, 95%CI[1.10, 1.66]). Participants who were ever-smokers were seven times more likely to be ever-vapers than those who had never smoked (RR=7.01, 95%CI[5.51, 8.92]). Also of note, 100% of ever-smokers who had smoked more than a few puffs in their lifetime were ever-vapers.

Ever-smoking was independently associated with gender (p=0.014), vape status (p<0.001) and lifetime vape quantity (p<0.001); see Table 4. Specifically, females were 22% less likely to be ever-smokers than males (R=0.78, 95%CI[0.66, 0.93]) and ever-vapers were 18 times more likely to be ever-smokers than

Table 1: Demographic characteristics of the 721 teenage study participants.

Characteristic	Male (n=359)	Female (n=359)	Non-binary and other (n=3)	Total (n=721)
Age (years)				
14	86 (24%)	55 (15%)	1 (33%)	142 (20%)
15	98 (27%)	77 (21%)	1 (33%)	176 (24%)
16	90 (25%)	126 (35%)	1 (33%)	217 (30%)
17	85 (24%)	101 (28%)	0 (0%)	186 (26%)
Current education level				
Year 7-8	49 (14%)	29 (8%)	0 (0%)	78 (11%)
Year 9	79 (22%)	52 (14%)	1 (33%)	132 (18%)
Year 10	92 (26%)	96 (27%)	1 (33%)	189 (26%)
Year 11	81 (23%)	91 (25%)	1 (33%)	173 (24%)
Year 12	46 (13%)	73 (20%)	0 (0%)	119 (17%)
Not in school	12 (3%)	18 (5%)	0 (0%)	30 (4%)
Aboriginal or Torres Strait Islander				
No	341 (95%)	337 (94%)	3 (100%)	681 (94%)
Yes	17 (5%)	21 (6%)	0 (0%)	38 (5%)
Prefer not to say	1 (0%)	1 (0%)	0 (0%)	2 (0%)
Remoteness of residence				
Metropolitan area	314 (87%)	320 (89%)	3 (100%)	637 (88%)
Non-metropolitan area	45 (13%)	39 (11%)	0 (0%)	84 (12%)
SES of residence area				
1 - Lowest SES	56 (16%)	36 (10%)	0 (0%)	92 (13%)
2	47 (13%)	65 (18%)	1 (33%)	113 (16%)
3	47 (13%)	50 (14%)	0 (0%)	97 (13%)
4	58 (16%)	69 (19%)	0 (0%)	127 (18%)
5 - Highest SES	151 (42%)	139 (39%)	2 (67%)	292 (40%)
Language				
English only	293 (82%)	274 (76%)	3 (100%)	570 (79%)
Another language only	13 (4%)	17 (5%)	0 (0%)	30 (4%)
English and another language	53 (15%)	68 (19%)	0 (0%)	121 (17%)

Note:
Numbers are frequencies and column percentages

those who had never vaped (RR=17.96, 95%CI[11.47, 28.12]).

Vaping products

When asked to describe the vaping product they used, 52% of ever-vapers described a disposable vape device (*n*=121), 3% described a vape that could be refilled with e-liquid (*n*=8), 3% described a vape that would be refilled with pods (*n*=8) and 1% described a heated tobacco product (*n*=3). More than one-third of ever-vapers did not specify details of the type of vape they used (34%, *n*=80). For example, some responses noted that the device was electric and contained a flavour, but did not say whether it was disposable, refillable or a heated tobacco product: "You breathe in the smoke from the device and it tastes like mangoes". Some ever-vapers also noted they were unsure of what product they had used (6%, *n*=13). Hence, among ever-vapers who reported which type of device they were using, 86% reported the use of disposable products.

More than half of ever-vapers had used a vape that they knew contained nicotine (53%, *n*=123), while 20% (*n*=47) said they had not used a nicotine-containing vape and 27% (*n*=63) did not know whether they had used a vape containing nicotine or not. When asked to consider the importance of various characteristics of vapes and vaping behaviour on a scale of 1 to 5, with a score of 5 being "very important" and a score of 1 being "not at all important", "Flavourings and taste" was rated the most important (mean importance score 3.9, 95%CI[3.7, 4.0]), followed by "Price", (mean importance score 3.6, 95%CI[3.4, 3.8]), and "Being able to hide the vape and vapour" (mean importance score 3.4, 95%CI[3.2, 3.6]). The reported importance of five other vaping characteristics among ever-vapers can be found in Supplementary File 2.

Table 2: Smoking and vaping usage characteristics of the 721 teenage study participants.

Characteristic	Male (n=231)	Female (n=236)	Non-binary and other (n=2)	Total (n=469)
Smoking/vaping status				
Never smoked or vaped	231 (64%)	236 (66%)	2 (67%)	469 (65%)
Smoked but never vaped	12 (3%)	7 (2%)	0 (0%)	19 (3%)
Vaped but never smoked	24 (7%)	41 (11%)	0 (0%)	65 (9%)
Smoked and vaped:	92 (26%)	75 (21%)	1 (33%)	168 (23%)
Smoked and vaped, tried vaping first (subtotal)	28 (8%)	32 (9%)	0 (0%)	60 (8%)
Smoked and vaped, tried smoking first (subtotal)	64 (18%)	43 (12%)	1 (33%)	108 (15%)
Lifetime vape quantity				
Never-vaper	243 (68%)	243 (68%)	2 (67%)	488 (68%)
A few puffs	57 (16%)	52 (14%)	0 (0%)	109 (15%)
More than a few puffs but <10 occasions	23 (6%)	24 (7%)	0 (0%)	47 (7%)
10 to <100 occasions	15 (4%)	23 (6%)	0 (0%)	38 (5%)
100+ occasions	21 (6%)	17 (5%)	1 (33%)	39 (5%)
Lifetime smoke quantity				
Never-smoker	255 (71%)	277 (77%)	2 (67%)	534 (74%)
A few puffs	70 (19%)	49 (14%)	1 (33%)	120 (17%)
More than a few puffs but <10 cigarettes	15 (4%)	15 (4%)	0 (0%)	30 (4%)
10 to <100 cigarettes	12 (3%)	9 (3%)	0 (0%)	21 (3%)
100+ cigarettes	7 (2%)	9 (3%)	0 (0%)	16 (2%)
Days of vaping in last 30 days (during Covid restrictions)				
Never vaper	243 (68%)	243 (68%)	2 (67%)	488 (68%)
0 days	55 (15%)	64 (18%)	0 (0%)	119 (17%)
1-2 days	24 (7%)	22 (6%)	0 (0%)	46 (6%)
3-5 days	15 (4%)	9 (3%)	0 (0%)	24 (3%)
6-9 days	5 (1%)	4 (1%)	0 (0%)	9 (1%)
10-19 days	7 (2%)	3 (1%)	0 (0%)	10 (1%)
20-30 days	10 (3%)	14 (4%)	1 (33%)	25 (3%)
Days of vaping during an average month (no COVID-19 restrictions)				
Never vaper	243 (68%)	243 (68%)	2 (67%)	488 (68%)
0 days	39 (11%)	49 (14%)	0 (0%)	88 (12%)
1-2 days	30 (8%)	31 (9%)	0 (0%)	61 (8%)
3-5 days	12 (3%)	10 (3%)	0 (0%)	22 (3%)
6-9 days	13 (4%)	5 (1%)	0 (0%)	18 (2%)
10-19 days	7 (2%)	5 (1%)	0 (0%)	12 (2%)
20-30 days	15 (4%)	16 (4%)	1 (33%)	32 (4%)

Note:
Numbers are frequencies and column percentages

Access to vapes

Of ever-vapers who did not purchase their last vape (70%, *n*=163), 80% (*n*=130) reported getting it from friends. A further 8% (*n*=13) reported that a sibling shared it, 7% (*n*=11) got someone to buy it for them, 3% (*n*=5) took it from home without parental permission and 2% reported that their parents or legal guardians gave or shared it with them (*n*=3). One person did not answer the question. Of ever-vapers who did purchase their last vape (30%, *n*=70), 49% (*n*=34) reported buying it from a friend or someone selling them, 31% (*n*=22) purchased it from a retailer such as a petrol station, tobacconist or convenience store, 9% (*n*=6) from social media such as Snapchat, Instagram or Facebook, 7% (*n*=5) from a website, 1% (*n*=1) from a vape store and 3% (*n*=2) from another source. Nearly 80% of ever-vapers found it very easy, easy or quite easy to access vapes (*n*=179) while less than 10% of ever-vapers found it quite hard, hard or very hard (*n*=20). Tables outlining the results relating to young people's access to vapes (where 14–17-year-olds obtained or purchased the last vape they used and reported ease of access to vaping products) can be found in online Supplementary File 2.

Discussion

Our study findings indicate that young people in New South Wales can readily access vaping products through both social and commercial channels. Flavoured, disposable vaping products that contain nicotine are commonly used, however, a number of respondents were unsure what type of device they used or whether or not it contains nicotine. These flavoured, disposable devices are marketed as easy for beginners to use, do not require liquid refilling and are simply activated by inhaling on the mouthpiece. Each device can contain hundreds of puffs and can cost as little as $5.00, making them highly affordable.[15] These products often contain nicotine salts which have a lower pH than free-base nicotine, allowing high levels of nicotine inhalation with less throat

irritation.[17] Non-nicotine vaping products sold at retail outlets in NSW have been tested and found to illegally contain nicotine;[18] our study confirms young people readily acquire these products.

Despite being positioned as cessation products that are only marketed to and used by older, adult smokers who have struggled to quit by other means, flavoured, disposable products appear to be highly appealing to NSW young people. This echoes data from the US where the disposal vaping product JUUL is the preferred product of young people[19] and has driven the explosive rise in youth vaping rates.[20]

In our study, vaping was the strongest risk factor for smoking, and vice versa. Young people who were classified as ever-vapers were 18 times more likely to be ever-smokers than those who had never vaped. However, among participants who were ever-vapers, more than half had never smoked before they started vaping. This suggests there is not a straightforward, unidirectional relationship between vaping and smoking in young people, that vaping does not necessarily preclude subsequent smoking initiation and that the dual use of cigarettes and vaping products is common.[21] Vaping may also be considered a separate behaviour from smoking among young people.[22] Vaping is not displacing smoking in young people in NSW, as evidenced by low smoking rates and low social acceptability of smoking by young people prior to vaping gaining popularity in Australia.[23]

Table 3: Relative risk of ever-vaping (vs never vaping) among the 721 teenage study participants.

Characteristic	Ever vaper n/N (%)	RR for ever-vaping (vs never-vaping) Unadjusted RR	Adjusted RR^
Total:	233/721 (32%)		
Gender			
Male	116/359 (32%)	ref.	ref.
Female	116/359 (32%)	1.00 (0.81, 1.24)	1.14 (0.99, 1.32)
Non-binary and other	1/3 (33%)	1.03 (0.21, 5.15)	0.96 (0.55, 1.68)
p-value		0.999	0.190
Age (years)			
14	27/142 (19%)	ref.	ref.
15	55/176 (31%)	1.64 (1.10, 2.46)	1.23 (0.90, 1.67)
16	73/217 (34%)	1.77 (1.20, 2.61)	1.18 (0.90, 1.56)
17	78/186 (42%)	2.21 (1.51, 3.22)	1.51 (1.15, 2.00)
p-value		0.001	0.010
Aboriginal or Torres Strait Islander			
No	206/681 (30%)	ref.	ref.
Yes	26/38 (68%)	2.26 (1.77, 2.89)	1.35 (1.10, 1.66)
Prefer not to say	1/2 (50%)	1.65 (0.41, 6.65)	1.43 (0.81, 2.53)
p-value		<0.001	0.010
Remoteness			
Metro	207/637 (32%)	ref.	ref.
Non-metro	26/84 (31%)	0.95 (0.68, 1.34)	0.79 (0.60, 1.02)
p-value		0.778	0.070
SES of residence area			
1 - Lowest SES	27/92 (29%)	ref.	ref.
2	41/113 (36%)	1.24 (0.83, 1.85)	1.07 (0.83, 1.39)
3	28/97 (29%)	0.98 (0.63, 1.54)	1.07 (0.77, 1.49)
4	34/127 (27%)	0.91 (0.59, 1.40)	0.95 (0.70, 1.28)
5 - Highest SES	103/292 (35%)	1.20 (0.84, 1.71)	1.17 (0.91, 1.50)
p-value		0.340	0.450
Language			
English only	199/570 (35%)	ref.	ref.
Another language only	8/30 (27%)	0.76 (0.42, 1.40)	0.96 (0.55, 1.67)
English and another language	26/121 (21%)	0.62 (0.43, 0.88)	0.90 (0.69, 1.18)
p-value		0.023	0.750
Smoke status			
Never-smoker	65/534 (12%)	ref.	ref.
Ever-smoker	168/187 (90%)	7.38 (5.85, 9.32)	7.01 (5.51, 8.92)
p-value		<0.001	<0.001
Lifetime smoke quantity			
Never-smoker	65/534 (12%)	ref.	ref.
A few puffs	101/120 (84%)	6.91 (5.43, 8.80)	6.72 (5.26, 8.59)
More than a few puffs but <10 cigarettes	30/30 (100%)	8.22 (6.54, 10.32)	7.61 (5.90, 9.83)
10 to <100 cigarettes	21/21 (100%)	8.22 (6.54, 10.32)	7.72 (5.93, 10.04)
100+ cigarettes	16/16 (100%)	8.22 (6.54, 10.32)	7.52 (5.79, 9.76)
p-value		<0.001	<0.001

Note:

^ Adjusted effect estimates for gender, age, Aboriginal or Torres Strait Islander, remoteness, language and smoke status were obtained from model containing all of these variables. Adjusted effect estimates for lifetime smoke quantity were obtained from model containing gender, age, Aboriginal or Torres Strait Islander, remoteness, language and lifetime smoke quantity.

Ever-vaping is defined as ever having a few puffs or more of vapes.

Potential limitations

First, while every effort was made to recruit participants that represented the demographic characteristics of New South Wales young people aged 14–17, our study was not designed to measure the prevalence of vaping among this population. However, random sampling is not required for reliable adjusted effects estimates based on internal comparisons within study populations.[24] Second, to ensure that we didn't recruit participants guessing their way through the survey on a topic they knew nothing about, participants were only included if they answered "Yes" to the screening question "Have you ever seen or heard of vapes or e-cigarettes?". While this screening requirement may have introduced some bias into our never-vaper results, we anticipate that very few young people have never seen or heard of vapes or e-cigarettes given the widespread use of vaping among young people.[13] Third, our study also highlights the need for Aboriginal and Torres Strait Islander-specific research, led by Aboriginal and Torres Strait Islander research partners, to assess vaping product use among Indigenous young people.

Policy and research implications

Assessing whether the October 2021 prescription-only scheduling change impacts young people's access to and preference for nicotine vaping products is a crucial next step. Removing non-nicotine vaping products from the market and prohibiting their sale,

particularly as product content is unregulated and they have no proven therapeutic value, would help control commercial access. While education approaches are often a default first action to address health behaviours, unless supportive policy action underpins an approach to reducing youth vaping, health education is unlikely to have any measurable impact. Increasing our understanding of any key differences between young vapers and non-vapers and what risk factors lead to regular, long-term vaping is required to assist with the implementation of effective interventions. Recognising the complex relationship between vaping and smoking among young people is essential, and comprehensive tobacco control, including policy, education, monitoring, and enforcement, must remain a public health priority.

Table 4: Relative risk of ever-smoking (vs never smoking) among the 721 teenage study participants.

Characteristic	Ever smoking n/N (%)	RR for ever-smoking (vs never-smoking) Unadjusted RR	Adjusted RR^
Total:	187/721 (26%)		
Gender			
Male	104/359 (29%)	ref.	ref.
Female	82/359 (23%)	0.79 (0.61, 1.01)	0.78 (0.66, 0.93)
Non-binary and other	1/3 (33%)	1.15 (0.23, 5.75)	1.04 (0.75, 1.44)
p-value		0.169	0.014
Age (years)			
14	22/142 (15%)	ref.	ref.
15	46/176 (26%)	1.69 (1.07, 2.67)	1.18 (0.83, 1.68)
16	63/217 (29%)	1.87 (1.21, 2.90)	1.31 (0.95, 1.79)
17	56/186 (30%)	1.94 (1.25, 3.02)	1.08 (0.80, 1.47)
p-value		0.023	0.218
Aboriginal or Torres Strait Islander			
No	165/681 (24%)	ref.	ref.
Yes	21/38 (55%)	2.28 (1.66, 3.13)	0.99 (0.78, 1.25)
Prefer not to say	1/2 (50%)	2.06 (0.51, 8.31)	0.77 (0.55, 1.07)
p-value		<0.001	0.262
Remoteness			
Metro	159/637 (25%)	ref.	ref.
Non-metro	28/84 (33%)	1.34 (0.96, 1.86)	1.31 (0.98, 1.74)
p-value		0.087	0.071
SES of residence area			
1 - Lowest SES	24/92 (26%)	ref.	ref.
2	35/113 (31%)	1.19 (0.76, 1.85)	0.99 (0.75, 1.32)
3	23/97 (24%)	0.91 (0.55, 1.49)	0.94 (0.64, 1.37)
4	28/127 (22%)	0.85 (0.53, 1.36)	0.95 (0.67, 1.33)
5 - Highest SES	77/292 (26%)	1.01 (0.68, 1.50)	0.89 (0.67, 1.19)
p-value		0.593	0.919
Language			
English only	165/570 (29%)	ref.	ref.
Another language only	6/30 (20%)	0.69 (0.33, 1.43)	0.89 (0.45, 1.76)
English and another language	16/121 (13%)	0.46 (0.28, 0.73)	0.70 (0.50, 0.96)
p-value		0.004	0.089
Vape status			
Never-vaper	19/488 (4%)	ref.	ref.
Ever-vaper	168/233 (72%)	18.52 (11.83, 28.99)	17.96 (11.47, 28.12)
p-value		<0.001	<0.001
Lifetime vape quantity			
Never-vaper	19/488 (4%)	ref.	ref.
A few puffs	71/109 (65%)	16.73 (10.54, 26.56)	16.74 (10.59, 26.48)
More than a few puffs but <10 occasions	38/47 (81%)	20.77 (13.08, 32.98)	19.93 (12.39, 32.05)
10 to <100 occasions	27/38 (71%)	18.25 (11.23, 29.66)	17.37 (10.66, 28.31)
100+ occasions	32/39 (82%)	21.07 (13.24, 33.55)	20.81 (13.03, 33.23)
p-value		<0.001	<0.001

Note:

^ Adjusted effect estimates for gender, age, Aboriginal or Torres Strait Islander, remoteness, language and vape were obtained from model containing all of these variables. Adjusted effect estimates for lifetime vape quantity were obtained from model containing gender, age, Aboriginal or Torres Strait Islander, remoteness, language and lifetime vape quantity.

Ever-smoking is defined as ever having a few puffs or more of cigarettes.

Acknowledgements

The authors would like to acknowledge and thank the members of the Generation Vape Research Project Advisory Committee for their advice, support and guidance on the development and implementation of this research

Ethics approval

Ethical approval for the study was provided by The University of Sydney Human Research Ethics Committee. Project number: 2021/442

Funding

This work was conducted with funding from the NSW Ministry of Health and the Minderoo Foundation. The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NSW Ministry of Health and the Minderoo Foundation.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Supplementary File 1: Cancer Council NSW E-cigarette use among young people in NSW Survey Questionnaire Wave 1 (14-17 year olds).

Supplementary File 2: Table: Reported importance of vaping characteristics among ever-vapers; Table: How young people obtained the vape they last used (for those who did not purchase it); Table: How young people bought the vape they last used (for those who reported purchasing it). Table: Reported ease of access to vaping products (ever-vapers only)

Study provides new insights on teen vaping behaviour in Australia

A new study tracking Australian teenager beliefs and behaviours using vapes (e-cigarettes) has found many are readily accessing and using illegal vaping products, writes A/Prof Becky Freeman, Dr Christina Watts and Sam Egger.

Teen vaping has been in the news, with reports of rapidly increasing use and illegal sales of e-cigarettes.

As a Four Corners documentary on ABC TV earlier this year showed, parents and schools are struggling to manage this swift rise in vaping, with fears children are addicted and harming their health.

In contrast, very limited research about Australian teen vaping has been published, until today.

We have published in the Australian and New Zealand Journal of Public Health the first results from the Generation Vape study. The study aims to track teenagers' knowledge, attitudes, beliefs and behaviours about using vapes (e-cigarettes).

Here's what we found about where teenagers were accessing vapes and what types of products they use.

Vaping common, especially in non-smokers

We surveyed more than 700 teenagers 14-17 years old from New South Wales. The sample was closely representative of the population, with key characteristics such as age, gender, location and education monitored throughout data collection.

We found teenagers are readily accessing and using illegal, flavoured, disposable vaping products that contain nicotine.

Among the teens surveyed, 32% had ever vaped, at least a few puffs. Of these, more than half (54%) had never previously smoked.

Where are teens getting vapes from?

We found most teens (70%) didn't directly buy the last vape they used. The vast majority (80%) of these got it from their friends.

However, for the 30% who did buy their own vape, close to half (49%) bought it from a friend or another individual, and 31% bought it from a retailer such as a petrol station, tobacconist or convenience store.

Teens also said they bought vapes through social media, at vape stores and via websites.

What products are teens using, and why?

Of the teens who had ever vaped and reported the type of device they used, 86% had used a disposable vape. This confirms anecdotal reports.

These devices appeal to young people and are easy to use. They do not require refilling (unlike tank-style vaping products) and are activated by inhaling on the mouthpiece.

Disposable vapes can contain hundreds, or even thousands of puffs, and are inexpensive, with illicit vapes from retail stores costing between $20-$30, or as little as $5 online.

There is an enormous range of vape flavours likely to appeal to children – from chewing gum to fruit and soft drink, even desserts. So it is unsurprising teens rated “flavourings and taste” as the most important characteristic of vapes they used.

Disposable vapes often contain very high concentrations of nicotine, even those claiming to be nicotine-free. The way these products are made (using nicotine salts rather than the free-base nicotine you’d find in cigarettes) allows manufacturers to increase the nicotine concentration without causing throat irritation.

In our study, over half (53%) of the teens who had ever vaped said they had used a vape containing nicotine. Many, however, were unsure whether they had used a vape containing nicotine (27%).

All vaping products, irrespective of nicotine content, are illegal to sell to under 18s in Australia.

Today, disposable vapes containing nicotine can only be legally sold in Australia by pharmacies to adult users with a valid prescription.

We need to end illegal imports and sales

Our results emphasise that teen vaping is increasingly normalised, and the most popular devices are designed to be highly appealing to young people. This is despite product manufacturers and proponents claiming they are smoking cessation aids only for adult smokers who are struggling to quit.

Turning the tide on teen vaping requires strong and immediate policy action, including ending the illicit importation and sale of vaping products.

Education is often the default first action to address unhealthy behaviours in young people. However, unless this is coupled with strong, supportive policy action, this approach is unlikely to have any measurable impact. Education campaigns cannot protect young people from an industry that so freely disregards laws meant to protect health.

We have strong evidence that vaping leads to harms such as poisoning, injuries, burns, toxicity, addiction and lung injury. The odds of becoming a smoker is more than three times higher for never-smokers who vape than for never-smokers who don’t vape.

What’s next?

This study uses data from the first wave of the Generation Vape research project, a three-year study with Australian teenagers, young adults, parents and guardians of teenagers, and secondary school teachers.

It is funded by the Cancer Council NSW, federal Department of Health and Ageing, NSW Ministry of Health, Cancer Institute NSW and the Minderoo Foundation.

Future waves of this repeat cross-sectional study, coupled with in-depth interviews, will allow us to track and monitor changes to adolescent, young adult, teacher, and parent attitudes, perceptions, and knowledge of vaping over time.

Vaping is a rapidly evolving public health crisis in Australia. Our research provides evidence for concerted policy action to prevent young people from accessing harmful and addictive products.

Failure to act will see a whole new generation of Australians addicted to dangerous products.

This article was first published in The Conversation and was written by Associate Professor Becky Freeman at the School of Public Health , Dr Christina Watts, and Sam Egger at the University of Sydney.

Calls for total elimination of direct sales of vaping products

All sales of vaping products other than those prescribed by a doctor to aid in quitting smoking should be stopped to curb skyrocketing uptake of e-cigarettes in young people, according to a leading tobacco control expert.

In a perspective published in *Public Health Research & Practice,* a peer-reviewed journal of the Sax Institute, Associate Professor Becky Freeman says predatory retailers, manufacturers and importers of vaping products have exploited loopholes in regulations to flood the market with illicit products that appeal to young people.

In theory, Australia's regulatory model should be effective in protecting young people from taking up vaping since a prescription from a medical practitioner is now required to access nicotine-containing products, which must only be used as an aid to quit smoking.

However, Associate Professor Freeman of the University of Sydney's School of Public Health and Charles Perkins Centre says in practice manufacturers continue to import and sell vaping products that contain nicotine by simply failing to label them as containing nicotine or falsely claiming they are nicotine-free.

Associate Professor Becky Freeman

“Distinguishing between a legal non-nicotine vaping product and an illegal nicotine-containing device requires laboratory testing, which hamstrings effective enforcement of the regulations,” she writes.

“Stopping the importation of all vaping products into Australia, regardless of nicotine content, unless bound for a pharmacy, would simplify and increase the effectiveness of enforcement and stop the flood of illicit products. This would also end young people’s easy access to vaping products.”

“ Stopping the importation of all vaping products into Australia, regardless of nicotine content, unless bound for a pharmacy, would simplify and increase the effectiveness of enforcement and stop the flood of illicit products. ”

Associate Professor Becky Freeman

A recent survey showed that about one-third of Australian teens aged 14-17 have vaped at some time, while previous research has found that vaping can cause harms such as poisoning, burns, addiction and lung injury.

Dr Freeman writes that Australia has fallen behind in tobacco control since the landmark plain packaging reforms of over a decade ago. Public health action has been understandably focused on the COVID-19 pandemic in recent years, which has led to stalled momentum in chronic disease prevention. Tobacco, alcohol, gambling and fast food industry players have been quick to seize the opportunity to exploit this lack of focus, she says.

“The Australian Government has been caught off guard by an aggressive industry that seeks to undo decades of effective tobacco control,” she writes.

But she also acknowledges the good news that “after 10 years of minimal action”, new measures and initiatives are in the pipeline to reduce smoking, which remains the single most important preventable cause of ill health and death in Australia.

In November 2022, the Federal Government announced it would reignite the fight against tobacco addiction with a package of new measures. Although these have yet to be put to the Australian Parliament, they are expected to include updated graphic warnings on tobacco products; prevention of

the use of additives such as flavours and menthol; and a requirement for tobacco companies to be transparent about their sales volumes, pricing, product ingredients and emissions, as well as their advertising, promotion and sponsorship activities.

A new National Tobacco Strategy with ambitious targets for reducing smoking rates was recently endorsed by health ministers, while the Therapeutic Goods Administration recently launched a consultation on potential reforms to prevent children and adolescents from accessing vaping products.

Declaration: Associate Professor Freeman is an Expert Advisor to the Cancer Council Tobacco Issues Committee and a member of the Cancer Institute Vaping Communications Advisory Panel. These are unpaid roles. She has received relevant research grant funding from the National Health and Medical Research Council, Healthway, and the Medical Research Future Fund. She is a PHRP Editorial Board member and Associate Editor but had no involvement in the review process for the manuscript.

www.phrp.com.au /issues/march-2023-volume-33-issue-1/reigniting-tobacco-control/

Reigniting tobacco control: returning Australia to the front of the pack

Megan Howe ⋮⋮ 14/3/2023

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Competing interests

BF has received consulting fees from the World Health Organization, Heart Foundation NSW, Cancer Council NSW, Cancer Council Australia, Cancer Institute NSW, and NSW Health and payments or honoraria for lectures/presentations to the Department of Health, The Government of Hong Kong Special Administrative Region, the US Food and Drug Administration and BMJ Tobacco Control. She reports support to attend the Oceania Tobacco Control conference and the Australian Public Health Association conference. She was an Expert Member of the National Health and Medical Research Council Electronic Cigarettes Working Committee (paid for time).

Author contributions

BF conceived of and drafted the manuscript.

Abstract

Australia has long been heralded as a leader in tobacco control, but more than 10 years have passed since the country implemented the world's first tobacco plain packaging reforms. In late 2022, the Australian Federal Government announced it would be "reigniting the fight against tobacco addiction". The forthcoming reforms package will help modernise and re-energise Australian tobacco control. The Government has signalled that preliminary reforms will include updating graphic health warnings, standardising tobacco pack sizes and filters, and banning menthol and flavours. The recently endorsed *National Tobacco Strategy 2023–2030* also opens the door to further supply-side reforms. Ten years ago, when Australia fought multiple legal challenges from the tobacco industry and established plain packaging as a best practice standard, e-cigarette or vaping products were a fringe issue with little presence in Australia. Today, vaping product use by young Australians has dramatically and rapidly increased. Easy access and marketing of cheap, flavoured, disposable, nicotine-containing vaping products are driving use. Recognising that the current approach to e-cigarette regulation is not achieving its aim of preventing children and adolescents from accessing vaping products, the Australian Therapeutic Goods Administration (TGA) launched a consultation on possible reforms in late 2022. Currently, vaping importers and retailers are exploiting an exemption for non-nicotine products in regulations, and nicotine-containing products are masquerading as non-nicotine products. The ideal public health solution would see the elimination of all vaping product sales, nicotine and non-nicotine alike, that fall outside of the TGA prescription-only access pathway. After 10 years of minimal action, it is invigorating to have three key initiatives in play to fully "reignite" tobacco control – the tobacco legislation renewal and update, the imminent national strategy release, and the TGA consultation on vaping products. Re-establishing Australia as a tobacco control leader is welcome news for public health.

Full text

Key points

- Australia, a leader in global tobacco control, has fallen behind in the 10 years since plain packaging reforms were adopted and lost focus during the COVID-19 pandemic
- The Australian Government has announced a package of reforms that will modernise and re-energise tobacco control
- There is a need for urgent action on e-cigarettes, to end the illicit supply of products to young people
- Reforms that disrupt the sale and supply tobacco products are needed

Falling to the back of the pack

Understandably, the last few years of public health action – globally and in Australia –have been overwhelmingly focused on the coronavirus disease 2019 (COVID-19) pandemic. The costs of this singular focus include stalled momentum in chronic disease prevention policy innovation. Modernising our approach to preventive health and ensuring that policies, practices, research, and funding match the actual determinants of health is crucial. Not only have governments been asleep on chronic disease, but commercial actors – alcohol, tobacco, gambling, fast food – have seized the opportunity to exploit this lack of focus at the expense of public health.[1]

Australia has long been heralded as a leader in tobacco control, but more than 10 years have passed since we implemented the world's first tobacco plain packaging reforms.[2] A sense of complacency had already set in well before the outbreak of COVID-19.[3] Tobacco control was in the dangerous territory of being considered "done" – despite 14% of the population aged over 14 years still currently smoking in 2019, and smoking remains the single most important preventable cause of ill health and death in Australia.[4] While tobacco taxes continued to increase during this 10-year pause, very little other national activity occurred. While some musicians can dine out on a greatest hits album for decades, most fade into obscurity without new material.

Reignited action

In late November 2022, the Australian Federal Government announced it would be "reigniting the fight against tobacco addiction with new measures."[5] Currently, Australian tobacco control measures are spread across a confusing number of laws, regulations, and voluntary agreements. The announced reforms aim to bring these disparate pieces of legislation together under one Act of Parliament. In much more exciting news, this reform package proposes introducing 11 new tobacco control measures. While the details of all 11 areas of reform have not yet been publicly released, the announcement included a snapshot of some of the approaches we can expect to see, including:[5]

- Updating graphic warnings on tobacco products (these have not been refreshed since 2012)
- Requiring individual cigarettes to be manufactured in unattractive colours or with printed warnings such as "smoking kills"
- Standardising the size of tobacco packets and products
- Preventing the use of specified additives, including flavours and menthol
- Mandating the design and look of filters
- Limiting the use of appealing names on products that falsely imply these products are less harmful, such as "organic" or "light"
- Requiring health promotion inserts inside packs
- Updating advertising regulations to capture e-cigarettes
- Requiring tobacco companies to be transparent about their sales volumes and pricing, product ingredients and emissions, as well as their advertising, promotion and sponsorship activities.

An overarching theme of these expected reforms is that they further limit the ability of the tobacco industry to manufacture and promote products that are attractive and appealing to young people. For example, manufacturers will likely no longer be able to insert flavour beads in filters that increase cigarette novelty and palatability. The reforms will also introduce a higher degree of mandated tobacco industry transparency and reporting that has the potential to make further reforms faster and more responsive.[6] Public health is always lagging behind tobacco industry marketing and sales innovations. Requiring the industry to fully report its marketing activities, rather than spending time and resources trying to track these activities, is far more efficient. Ensuring that laws regulating tobacco and e-cigarette, advertising, sponsorship, and promotion are up to date with modern marketing methods, including industry use of social media channels, must also be part of these changes.[7]

While the Government announcement did not specifically mention limiting where and how and to whom tobacco products are sold, the door to include reforms targeting these “supply-side initiatives, remains open. In addition to this legislative review, the *National Tobacco Strategy 2023–2030* was endorsed by Health Ministers in February 2023, and includes targets to reduce daily smoking prevalence in Australia below 10% by 2025 and to 5% or less by 2030. [8] Strengthening regulations to reduce the supply, availability and accessibility of tobacco products was included as one of 11 key priority areas in the draft strategy.[9] While the endorsement of the Strategy is important, the Government will need to fully fund it to successfully achieve its goals. Bold tobacco supply-side reforms, including increasing the legal age for purchasing tobacco products and dramatically reducing tobacco retail outlets, are currently being implemented in New Zealand.[10] A bit of healthy competition across the Tasman to see just how quickly smoking rates can be cut when multiple, comprehensive, bold measures are enacted is very welcome.

Vaping disruption

Ten years ago, when Australia fought multiple legal challenges from the tobacco industry and established plain packaging as a standard in effective public health action[11], e-cigarettes were a fringe issue with little presence in Australia. This is not the case today. The use of e-cigarettes or vaping by young people has skyrocketed during the COVID-19 pandemic.[12] Predatory retailers, manufacturers, and importers have exploited loopholes in e-cigarette regulation and flooded the market with illicit products that appeal to young users. Young people can easily access and prefer flavoured, disposable, inexpensive vaping products that contain nicotine.[13]

When taken at face value, Australia should have one of the most effective regulatory models for protecting young people from taking up vaping. To legally access nicotine-containing vaping products in Australia, users must have a valid prescription from an Australian medical practitioner and use the product to quit smoking. However, because non-nicotine-containing vaping products fall outside the prescription access requirements, they can be freely imported and sold online or at retail outlets. Users have continued to obtain nicotine-containing products because manufacturers either simply fail to label them as containing nicotine or falsely claim they are nicotine-free. Distinguishing between a legal non-nicotine vaping product and an illegal nicotine-containing device requires laboratory testing, which hamstrings effective enforcement of the regulations.

Recognising that the current approach to e-cigarette regulation is not achieving its aim of preventing children and adolescents from accessing vaping products, the Australian Therapeutic Goods Administration (TGA) also launched a consultation on potential reforms in late November 2022.[14] This consultation closed on 16 January 2023, and is reported to have received more than 4000 submissions.[15] Australia’s Health Ministers also agreed in February 2023 to establish a national E-cigarette Working Group, to review and advise on measures to protect young people from the harms of increasingly available e-cigarettes. [8]

The ideal public health solution would see the elimination of all vaping product sales, nicotine-containing and non-nicotine alike, that fall outside of the TGA prescription pathway.[16] Stopping the importation of all vaping products into Australia, regardless of nicotine content, unless bound for a pharmacy, would

simplify and increase the effectiveness of enforcement and stop the flood of illicit products. This would also end young people's easy access to vaping products and enhance the prescription model to ensure all smokers who use e-cigarettes to quit also receive smoking cessation support from health professionals.

Conclusion

After 10 years of minimal action, it is invigorating to have three key initiatives in play to fully "reignite" tobacco control – the tobacco legislation renewal and update, the national strategy release, and the TGA consultation on the regulation of vaping products. No doubt, the tobacco industry and its allies will continue to interfere in public health policy-making to block, water down, and delay these reforms. The Australian Government must be vigilant in upholding its obligations to protect public health from the tobacco industry's vested interests, as required under Article 5.3 of the WHO Framework Convention on Tobacco Control.[17] Addressing the commercial determinants of health has taken a back seat during the COVID-19 pandemic, and the Australian Government has been caught off guard by an aggressive industry that seeks to undo decades of effective tobacco control. It is time to return to the front of the pack.

Acknowledgements

BF is an Expert Advisor to the Cancer Council Tobacco Issues Committee and a member of the Cancer Institute Vaping Communications Advisory Panel. These are unpaid roles. She has received relevant research grant funding from the National Health and Medical Research Council, Healthway, and the Medical Research Future Fund. BF is a PHRP Editorial Board member and Associate Editor but had no involvement in the review process for the manuscript.

Peer review and provenance

Externally peer reviewed, not commissioned.

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OPEN ACCESS

Projections of smoking-related cancer mortality in Australia to 2044

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jech-2021-218252).

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Received 20 October 2021
Accepted 12 June 2022
Published Online First 24 June 2022

To cite: Luo Q, Steinberg J, Yu XQ, *et al*. *J Epidemiol Community Health* 2022;**76**:792–799.

ABSTRACT

Background While many high-income countries including Australia have successfully implemented a range of tobacco control policies, smoking remains the leading preventable cause of cancer death in Australia. We have projected Australian mortality rates for cancer types, which have been shown to have an established relationship with cigarette smoking and estimated numbers of cancer deaths attributable to smoking to 2044.

Methods Cancer types were grouped according to the proportion of cases currently caused by smoking: 8%–30% and >30%. For each group, an age–period–cohort model or generalised linear model with cigarette smoking exposure as a covariate was selected based on the model fit statistics and validation using observed data. The smoking-attributable fraction (SAF) was calculated for each smoking-related cancer using Australian smoking prevalence data and published relative risks.

Results Despite the decreasing mortality rates projected for the period 2015–2019 to 2040–2044 for both men and women, the overall number of smoking-related cancer deaths is estimated to increase by 28.7% for men and 35.8% for women: from 138 707 (77 839 men and 60 868 women) in 2015–2019 to 182 819 (100 153 men and 82 666 women) in 2040–2044. Over the period 2020–2044, there will be 254 583 cancer deaths (173 943 men and 80 640 women) directly attributable to smoking, with lung, larynx, oesophagus and oral (comprising lip, oral cavity and pharynx) cancers having the largest SAFs.

Interpretation Cigarette smoking will cause over 250 000 cancer deaths in Australia from 2020 to 2044. Continued efforts in tobacco control remain a public health priority, even in countries where smoking prevalence has substantially declined.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A range of tobacco control interventions have reduced smoking prevalence over time in Australia. Prior analyses have estimated the associated past and future reductions in lung cancer mortality.

⇒ There are limited data on long-term projections of mortality rates for all smoking-related cancer types or the estimated all-cancer deaths directly attributable to cigarette smoking.

WHAT THIS STUDY ADDS

⇒ Taking into account historical smoking patterns, this study estimated mortality rates for all smoking-related cancers to 2044 in Australia. The findings predict that there will be more than 250 000 cancer deaths directly attributable to smoking in the period 2020–2044.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These projections can serve as benchmarks against which to measure the impact of future cancer control initiatives.

⇒ This study highlights the ongoing and future impact of smoking on the cancer burden. Continued efforts in tobacco control remain an urgent public health priority, even in countries such as Australia, where smoking prevalence has substantially declined.

INTRODUCTION

Decreasing trends in cigarette smoking and tobacco consumption have been observed in many high-income countries that have successfully implemented tobacco control initiatives, including Australia. However, globally over one-third of men and approximately 1 in 10 women were current smokers in 2015,[1] and estimates from the most recent Global Burden of Disease study suggest that tobacco smoking killed more than 8.7 million people in 2019.[2] Australia has successfully implemented many tobacco control interventions, which have resulted in a marked decline in the prevalence of smoking in Australian men since the 1950s and in women since the 1980s. There has been a subsequent reduction in lung cancer mortality,[3] although projections indicate that the number of lung cancer deaths will continue to be substantial in 2040.[3] Over many years, from early studies establishing the association with lung cancer[4 5] through the International Agency for Research on Cancer (IARC) monograph[6] to a systematic review in 2013,[7] smoking has become causally associated with an increasing number of cancers, including lung, larynx, liver, oesophagus, bladder, pancreas, lip, oral cavity, pharynx, stomach, colorectum, kidney, cervix, uterus, myeloid leukaemia, gallbladder and biliary tract. These cancers at least in part attributable to smoking are hereafter referred to as 'smoking-related cancers'. However, little is known about past and future trends in mortality rates for cancers other than lung cancer in relation to smoking.

A number of different statistical models have been developed and used to project future cancer

mortality rates, ranging from a simple assumption of a constant cancer mortality rate to more complex methods such as age-period-cohort (APC) models, and extended methods that account for changes in exposure to risk factors.[8] To project lung cancer mortality rates, we have previously validated a generalised linear model (GLM), which included tobacco consumption as a covariate.[3] This method may also be applied to other cancers with an established association with cigarette smoking. We previously developed statistical models for the projections of all cancers combined and 21 individual cancer types.[9] However, to our knowledge, there have not yet been any published studies that report long-term projections of mortality rates for all smoking-related cancers in relation to past smoking behaviour, nor have there been estimates of the future number of cancer deaths directly attributable to smoking in Australia.

In this study, we have projected Australian mortality rates for all smoking-related cancers combined by taking into account historical smoking patterns, and also estimated the number of deaths from these cancers directly attributable to cigarette smoking for the period 2020–2044.

METHODS

Data sources

We obtained national tabulated data on the numbers of deaths from cancer in Australia from 1955 to 2019 by sex, age and calendar year from the WHO's Mortality Database[10] sourced from the Australian Institute of Health and Welfare (online supplemental material 1).[11] Australian population data by sex, 5-year age group and calendar year from 1955 to 2044 (Series B, based on medium population growth) were obtained from the Australian Bureau of Statistics.[12 13] Smoking data for 1945–2004 were obtained from the International Smoking Statistics Web Edition[14] and the National Drug Strategy Household Survey (NDSHS) data for 2007–2019.[15] Sex–age–period-specific smoking prevalence and cigarette tar exposure per capita in Australia were reconstructed backwards to 1920 and forwards to 2044.[3] For the purposes of our analyses, all data were aggregated into 5-year age groups and 5-year calendar periods. All age-standardised rates were standardised to the 2001 Australian population. Here, we use the terms men and women to denote males and females, given that the majority of deaths occur in people over the age of 18 years.

Selected cancer types and grouping of smoking-related cancers

We included all cancers listed by the IARC as causally related to smoking,[6] and also included gallbladder and biliary tract cancer based on more recent evidence.[7] We grouped cancer types into two groups according to the current proportion of cases caused by smoking. These groups were cancer types with >30% of cases currently caused by smoking, including lung, bladder, larynx, oesophagus and oral (comprising lip, oral cavity and pharynx) cancers and cancer types with 8%–30% of cases currently caused by smoking, including liver, stomach, gallbladder and biliary tract, pancreas, colorectal, kidney and ureter, myeloid leukaemia, uterus, cervix and ovarian cancers (online supplemental table S1).[6]

Statistical methods used for mortality rate projections

The outcomes of interest were the mortality rate and the number of deaths attributable to smoking for all smoking-related cancers. The selection of the most appropriate statistical projection model for each cancer group was based on the Bayesian Information Criterion and model validation using observed mortality rates (online supplemental material 2). For the group of cancer types with >30% of cases currently caused by smoking, GLMs including age, cohort and cigarette tar exposure (lagged 27 years for men and 29 years for women) were used to project mortality rates (online supplemental figure S1).[3] For the group of cancer types with 8%–30% of cases currently caused by smoking, APC models incorporating cigarette smoking exposure (lagged 32 years for men and 33 years for women)[16] were used to project mortality rates (online supplemental figure S2). The estimated numbers of deaths for these two cancer groups were then combined to estimate the overall projected mortality rate for all smoking-related cancers. To project the mortality rate for lung cancer, we used previously validated GLMs including age, cohort and cigarette smoking exposure.[3] A standard APC model was used to project the mortality rate for each remaining cancer types (online supplemental table S2).

Number of cancer deaths directly attributable to smoking

The smoking-attributable fraction (SAF) is the proportion of deaths that are directly attributable to smoking.[17] The total number of cancer deaths directly attributable to smoking for people aged 35 years and above was calculated by multiplying the SAF and the corresponding numbers of cancer deaths for each cancer type, age group and sex category and then aggregating these.

The SAF is calculated using the standard formula:

$$\mathrm{SAF} = \frac{P_1 \times (RR_1 - 1) + P_2 \times (RR_2 - 1)}{1 + P_1 \times (RR_1 - 1) + P_2 \times (RR_2 - 1)}$$

where P_1 is the prevalence of current smokers and P_2 is the prevalence of former smokers (both available from the NDSHS data), RR_1 and RR_2 are the relative risks of death from cancer for current and former smokers compared with never smokers, respectively. Sex-specific relative risks for each cancer type were derived from the American Cancer Society's Cancer Prevention Study II (CPS-II).[17 18] Due to the lack of reliable relative risk data, we did not calculate the numbers of smoking-attributable deaths for ovarian, gallbladder and biliary tract cancers. Due to the limited data on the past prevalence of current and former smokers in the population, smoking-attributable deaths were only calculated from 2000 onwards. All statistical analyses were performed using Stata (V.17, Stata Corporation, College Station, Texas).

RESULTS

Projections of mortality rates for cancers related to smoking

For both men and women, the age-standardised mortality rates for all smoking-related cancers combined are projected to decline continuously over the period 2015–2019 to 2040–2044, from 114.1 to 84.8 per 100 000 men and 76.5 to 57.8 per 100 000 women (figure 1 and table 1). For both men and women, the mortality rates are consistently lowest (<15 per 100 000) for those aged less than 55 years. The mortality rates for men in the older age groups showed a steady decline from the mid-1980s. Different patterns were observed for women, with lower rates overall and the decline occurring at a slower pace and starting later than was observed for men (figure 1). The decline in the mortality rate for women aged 55–64 years began in the 1990s, but for women in the older age groups (65 years and above) the decline began 5–20 years later.

Despite the decreasing mortality rates, due to population growth and ageing, the overall number of smoking-related cancer deaths is projected to increase by 31.8% (28.7% for men and 35.8% for women) from 138 707 (77 839 men and 60 868 women) in 2015–2019 to 182 819 (100 153 men and 82 666 women) in 2040–2044 (table 1).

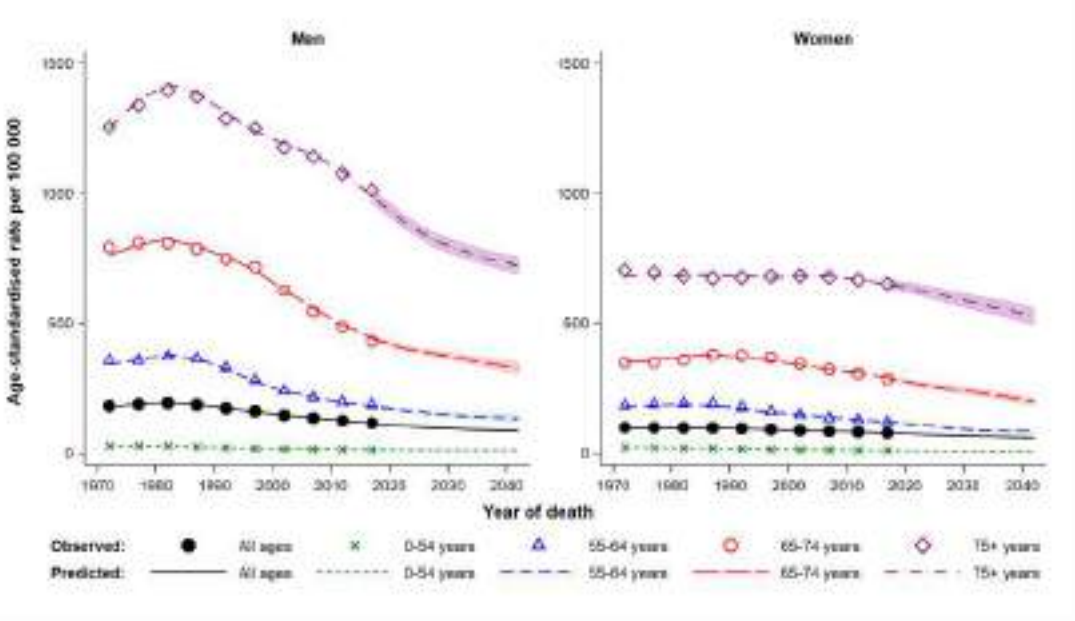

Figure 1 Observed and projected age-standardised mortality rates for smoking-related cancers by age group and sex in Australia, 1970–2044. All rates are age-standardised to 2001 Australian population. The shaded area represents the 95% confidence interval.

Estimated number of cancer deaths directly attributable to smoking

Figure 2 shows the total estimated numbers of cancer deaths directly attributable to smoking by age group and sex for people aged 35 years and above in Australia in 2000–2044. For both men and women, the numbers of cancer deaths directly attributable to smoking for the youngest age group (35–54 years) are consistently low (≤11% of the total), and the numbers of cancer deaths directly attributable to smoking for the 55–64 and 65–74 year age groups showed a steady decline over the projection period 2020–2044. In contrast to the younger age groups, the numbers of cancer deaths directly attributable to smoking for those aged

Table 1 Observed and predicted age-standardised mortality rates and numbers of deaths (with 95% confidence intervals) from all smoking-related cancers combined by sex and 5 year period, 2015–2044

	Observed	Projected					%
	2015–2019	2020–2024	2025–2029	2030–2034	2035–2039	2040–2044	Change*
Age standardised rate per 100 000†							
Men	114.1	104.1 (100.2–108.3)	97.0 (92.7–101.5)	92.0 (87.3–97.2)	88.0 (82.8–93.8)	84.8 (79.0–91.2)	−26.3
<55 years	12.9	12.0 (11.0–13.1)	11.5 (10.4–12.9)	11.2 (10.0–12.6)	11.2 (10.4–12.2)	11.1 (10.3–12.1)	−14.6
55–64 years	178.9	165.3 (158.1–172.9)	153.1 (144.0–162.8)	143.8 (132.7–155.9)	137.3 (121.9–155.7)	133.2 (118.3–151.3)	−28.2
65–74 years	432.3	405.5 (393.4–418.1)	384.7 (371.1–398.9)	364.4 (347.8–381.8)	343.8 (322.9–366.1)	325.7 (300.5–353.4)	−24.3
75+ years	1005.5	898.8 (870.3–928.4)	824.6 (796.8–853.5)	782.7 (753.7–812.8)	747.5 (717.3–779.1)	720.6 (685.9–757.1)	−28.8
Women	76.5	71.8 (68.6–75.2)	67.5 (63.9–71.4)	64.0 (60.1–68.3)	60.9 (56.7–65.4)	57.8 (53.6–62.5)	−24.5
<55 years	10.7	9.4 (8.7–10.2)	8.8 (8.1–9.6)	8.7 (7.9–9.6)	8.5 (7.8–9.2)	8.4 (7.8–9.1)	−22.9
55–64 years	117.7	108.8 (102.6–115.5)	96.9 (90.5–103.7)	87.5 (80.8–94.7)	83.0 (75.0–92.1)	83.0 (73.9–93.7)	−30.3
65–74 years	292.5	265.9 (254.7–277.6)	248.8 (234.6–263.8)	234.1 (218.2–251.1)	215.2 (199.8–231.9)	196.0 (180.4–213.1)	−31.3
75+ years	646.7	629.0 (606.6–652.2)	603.0 (577.4–629.7)	576.2 (548.8–605.1)	553.6 (522.5–586.6)	524.5 (492.6–558.6)	−19.5
Number of deaths from all smoking-related cancers							
Total	138 707	146 716 (140 952–152 815)	157 046 (149 822–164 760)	167 784 (158 964–177 296)	176 497 (166 011–187 918)	182 819 (170 702–196 155)	31.8
Men	77 839	81 572 (78 611–84 700)	86 808 (83 161–90 695)	92 232 (87 756–97 066)	96 639 (91 212–102 569)	100 153 (93 748–107 239)	28.7
<55 years	5730	5557 (5107–6082)	5617 (5079–6259)	5902 (5319–6611)	6424 (5925–6999)	6799 (6294–7375)	18.7
55–64 years	13 008	12 315 (11 779–12 878)	11 790 (11 093–12 531)	11 433 (10 542–12 420)	11 346 (10 134–12 783)	11 971 (10 689–13 514)	−8.0
65–74 years	22 370	23 639 (22 932–24 369)	24 268 (23 391–25 181)	24 415 (23 290–25 602)	23 842 (22 389–25 400)	23 383 (21 521–25 451)	4.5
75+ years	36 732	40 061 (38 793–41 371)	45 133 (43 598–46 724)	50 482 (48 605–52 433)	55 027 (52 764–57 387)	58 000 (55 244–60 899)	57.9
Women	60 868	65 144 (62 341–68 115)	70 238 (66 661–74 065)	75 552 (71 208–80 230)	79 858 (74 799–85 349)	82 666 (76 954–88 916)	35.8
<55 years	4934	4471 (4146–4846)	4419 (4060–4844)	4685 (4270–5180)	4990 (4593–5456)	5216 (4840–5656)	5.7
55–64 years	8711	8511 (8028–9028)	7921 (7402–8479)	7424 (6852–8049)	7230 (6548–8008)	7813 (6989–8768)	−10.3
65–74 years	15 358	16 484 (15 778–17 226)	17 059 (16 091–18 091)	17 134 (15 988–18 369)	16 427 (15 240–17 709)	15 549 (14 288–16 933)	1.2
75+ years	31 865	35 678 (34 389–37 015)	40 839 (39 108–42 651)	46 309 (44 098–48 632)	51 211 (48 418–54 176)	54 088 (50 837–57 559)	69.7

*Overall percentage change in the age standardised rates and numbers of deaths projected for 2040–2044 compared with the age standardised rates and numbers of deaths in 2015–2019.
†Age-standardised to 2001 Australian population.

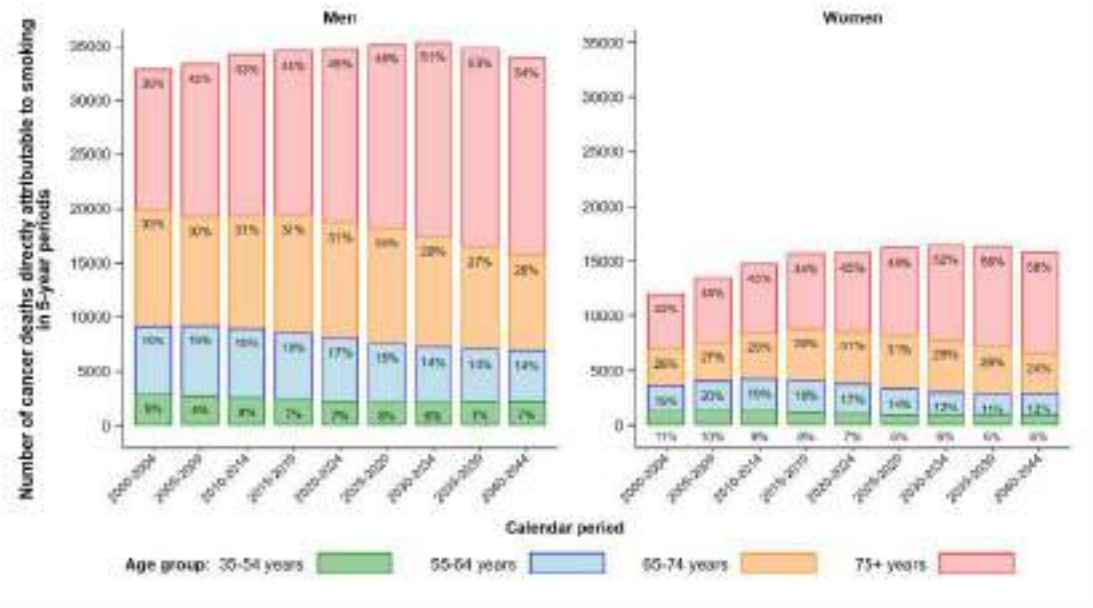

Figure 2 Total numbers of cancer deaths directly attributable to smoking by age group and sex in Australia, 2000–2044.

75 years and above are expected to continue to increase to 2044. We estimate that in Australia over the period 2020–2044, there will be 254 583 cancer deaths (173 943 men and 80 640 women) directly attributable to smoking, representing 32.3% (37.2% for men and 25.2% for women) of the total deaths from cancers, which are known to be related to smoking (table 2). Lung cancer is estimated to remain the cancer type with the largest number of deaths directly attributable to smoking, accounting for 61.7% of the total cancer deaths directly attributable to smoking in 2020–2044 (figure 3 and table 2). For every smoking-related cancer type, the SAF decreased over the period 2000–2044 (table 2). Cancer types with the largest SAFs for the period 2020–2044 are cancers of the lung, larynx, oesophagus and oral cancers (comprising lip, oral cavity and pharynx).

Discussion

Using Australia as an example of a high-income country with successfully implemented tobacco control initiatives, resulting in declining cigarette smoking and tobacco consumption, we have projected the future national burden of cancer deaths from smoking-related cancers. Our projections indicate that mortality rates for smoking-related cancers for both men and women in Australia are expected to continuously and gradually decline to 2044, to a large extent reflecting the success and velocity of past and current tobacco control measures. Despite these declining mortality rates, our results project that the overall number of deaths from smoking-related cancers are likely to increase by 32% over the period 2015–2019 to 2020–2044, as a result of the ageing population and increasing population size.

We estimate that there will be more than 250 000 cancer deaths directly attributable to smoking between 2020 and 2044, accounting for one-third of the total number of deaths from smoking-related cancers. Fortunately, the number of cancer deaths directly attributable to smoking for people aged less than 75 years is expected to decrease over the 25 years to 2044. A decline in the proportion of deaths directly attributable to smoking was apparent overall and for each individual cancer type, although the SAFs were still high for cancers of the lung, larynx, oesophagus and oral cancers. Lung cancer is estimated to remain the leading cause of smoking-related cancer death in Australia and will account for 61.7% of the total estimated number of cancer deaths directly attributable to smoking over the period 2020–2044. Notably, cancer is only one of many health problems associated with tobacco smoking.[17 19] The Australian Burden of Disease study estimated that cancer was responsible for ~56% of all deaths directly attributable to smoking in Australia in 2018,[20] thus the total number of deaths directly attributable to smoking in Australia will be substantially greater than estimated in this work for cancer alone.

Given the strong association between smoking and lung cancer mortality,[21] there has been increasing interest in incorporating information on smoking in lung cancer mortality projections.[3 8] However, these methods have not been used for projecting mortality rates for all smoking-related cancer types. By grouping smoking-related cancer types together based on the proportion of cases currently attributable to smoking, we were able to include historical and current smoking patterns in the projection models for cancer types, which could not be individually fitted using such a model due to the small numbers of deaths.[9] We confirmed that the models were reliable by providing validation of the 20-year projections using observed data. As there is a 26–33 year lag between changes in smoking behaviour and any subsequent impact on cancer mortality rates,[3] our projections to 2044 are likely to be robust as they are based on past tobacco consumption up to 2019.

The successful implementation of a range of tobacco control programmes has been crucial in the reduction in smoking prevalence and cigarette consumption evident in many high-income countries, including Australia.[22 23] The findings from this study confirmed that historical patterns in tobacco smoking are a strong predictor of mortality rates for smoking-related cancers.[3] The earliest research that revealed the link between smoking and cancer was published in the 1950s[4 5] and eventually initiated the introduction of tobacco control interventions internationally.[3 4] In Australia, mandatory health warnings on all cigarette packs were first implemented in 1973, and all cigarette advertising on radio and television was banned in 1976 with more comprehensive advertising and promotion bans in subsequent decades.[24]

Table 2 Observed and projected numbers of cancer deaths directly attributable to smoking and smoking attributable fraction by cancer type for people aged 35 years and above in 2015–2044 in Australia, ranked by the total number of cancer deaths directly attributable to smoking in 2015–2019

	Number of cancer deaths directly attributable to smoking						Smoking attributable fraction (%)				
	2015–2019	2020–2024	2030–2034	2040–2044	% change*	Total in 2020–2044	2015–2019	2020–2024	2030–2034	2040–2044	2020–2044
Total†	50 467	50 500	51 828	49 726	−1.5	254 583	39.5	36.8	32.5	28.6	32.3
Men	34 809	34 732	35 336	33 919	−2.6	173 943	45.3	42.2	37.3	33.1	37.2
Lung	21 092	20 586	20 276	18 760	−11.1	99 698	84.0	82.5	79.5	76.2	79.4
Oesophagus	3261	3435	3812	4028	23.5	18 851	66.9	64.5	60.1	55.6	59.7
Lip, oral cavity and pharynx	2180	2311	2545	2687	23.3	12 608	66.8	64.4	59.8	55.2	59.4
Bladder	1439	1369	1406	1458	1.3	7043	38.5	36.5	32.3	28.3	32.0
Colon and rectum	1251	1180	1101	992	−20.7	5460	8.8	8.0	6.7	5.7	6.7
Pancreas	1228	1277	1326	1275	3.8	6502	15.7	14.2	11.8	9.9	11.7
Liver	1219	1450	1736	1714	40.6	8290	18.6	17.1	14.5	12.4	14.3
Kidney and ureter	993	990	1019	1028	3.5	5068	31.9	29.7	25.9	22.4	25.7
Stomach	802	786	782	762	−5.0	3887	22.3	20.5	17.6	15.0	17.5
Larynx	696	654	596	559	−19.7	3005	77.8	75.8	72.2	68.6	72.3
Myeloid leukaemia	650	694	738	656	0.9	3529	17.6	16.0	13.5	11.4	13.4
Women	15 658	15 768	16 492	15 807	1.0	80 640	30.7	28.7	25.4	22.1	25.2
Lung	10 903	11 200	11 798	11 229	3.0	57 479	62.6	58.6	52.8	47.3	52.6
Pancreas	1284	1311	1414	1394	8.6	6914	17.9	15.8	13.4	11.4	13.3
Colon and rectum	900	795	736	680	−24.4	3681	7.4	6.6	5.6	4.7	5.6
Oesophagus	798	747	756	752	−5.8	3762	45.1	41.3	36.5	32.0	36.3
Lip, oral cavity and pharynx	483	478	505	507	5.0	2494	37.2	34.1	29.6	25.7	29.4
Liver	402	453	537	546	35.8	2591	12.2	10.6	9.0	7.8	8.9
Bladder	325	272	245	225	−30.8	1232	21.4	19.0	16.6	14.6	16.6
Myeloid leukaemia	237	218	218	195	−17.7	1062	9.6	8.3	7.1	6.1	7.1
Stomach	198	182	185	191	−3.5	930	9.6	8.5	7.2	6.1	7.1
Larynx	79	70	61	55	−30.4	307	63.7	60.3	56.0	51.4	55.9
Kidney and ureter	49	43	37	33	−32.7	188	2.9	2.6	2.1	1.7	2.1

*Overall percentage change in the numbers of deaths projected for 2040–2044 compared with the numbers of deaths in 2015–2019.
†The numbers of deaths directly attributable to smoking were not estimated for cancers of ovary, uterus, cervix, gallbladder and biliary tract. Only certain subtypes of ovarian cancer are associated with smoking, and the relative risks for cancers of uterus, gallbladder and biliary tract were not available. Individual projections for cervical cancer mortality were not available due to lack of data on the new protocol and screening technology introduced in 2017 and the human papilloma virus vaccination programme.

More recent tobacco control measures in Australia include media campaigns, plain packaging, a 25% increase in tobacco excise in 2010 and an annual 12.5% increase in tobacco excise implemented from 2013 to 2020.[24] All these measures have resulted in decreases in the prevalence of smoking, beginning in the 1950s for Australian men and in the 1980s for Australian women.[3]

Despite the success of tobacco control in Australia, the most recently published estimates of smoking prevalence in Australia show that over 11% of Australians aged 18 years and over are daily smokers and that an additional 1% smoke less frequently (noting that these data have been collected during the COVID-19 pandemic and may not be directly comparable to previous estimates).[25] Data have also shown considerable differences in smoking behaviour across sociodemographic groups in Australia, with higher smoking rates observed for those of lower socioeconomic status or with a lower level of education[26] and also among Aboriginal and Torres Strait Islander peoples and other priority populations.[27–29] The estimates presented demonstrate the effects of 'business as usual' and show that continuing current tobacco control efforts are likely to result in relatively slow declines in cancer rates and in increasing deaths over time. Without accelerated action, supported by adequate resources, it is expected that the positive effects of existing tobacco control measures will lessen over time.[30] There are also concerns regarding the impacts of online promotion,[22 31] and that electronic cigarettes (e-cigarettes) and other novel tobacco products may have an adverse impact on smoking initiation rates.[32] It is, therefore, important to strengthen and implement even more effective tobacco control programmes as soon as possible. A comprehensive time series analysis of the effectiveness of tobacco control measures in Australia in 2008 concluded that the most effective population level interventions were price control through excise and hard-hitting mass media antismoking campaigns, with a synergistic benefit when used in tandem.[33] Over the past decade, while excise has reached best-practice levels, there has been little or no commensurate investment in antismoking campaigns, other than targeted campaigns to tackle smoking by Aboriginal and Torres Strait Islander peoples.[34]

In this study, only cancer types which have been shown to have an established relationship with cigarette smoking were

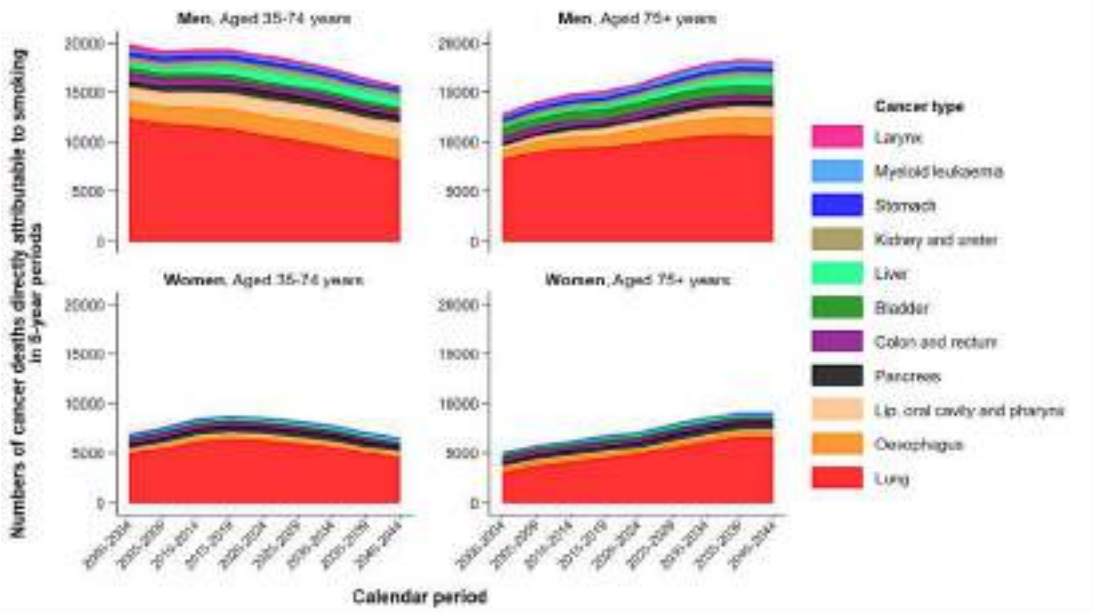

Figure 3 Numbers of cancer deaths directly attributable to smoking by cancer type, sex and age group to 2044 in Australia, ranked by the number of cancer deaths directly attributable to smoking in 2015–2019.

included,[6] but it should be acknowledged that smoking may also increase mortality from cancers for which there is limited evidence that smoking is a risk factor.[35] For example, previous studies reported that smokers diagnosed with prostate cancer have poorer survival outcomes than non-smokers,[17] and it has also been reported that women who were smokers at the time of breast cancer diagnosis are more likely to develop systemic recurrence after surgery.[36] In addition, smoking can decrease the effectiveness of many cancer treatments, so quitting smoking is likely to have a range of benefits for smokers who are diagnosed with cancer.[37] Furthermore, as tobacco smoking is also known to increase the risk of developing many non-cancer diseases,[38] which are not included in this study, the wider benefits from tobacco control on all deaths directly attributable to smoking will be even greater than we have estimated here.

While this study focused on the impact of changing patterns in smoking behaviour on cancer deaths in the future, it is also important to acknowledge that this is only one factor of many which are likely to contribute to the decrease in mortality rates for these cancer types. It is likely that changes in cancer screening and cancer management, and improvements in treatment are all playing a role in the estimated declines in mortality we have reported.[39] Moreover, as the results from this study revealed that the proportion of cancer deaths directly attributable to smoking appears to have declined over time, interventions for other risk factors are also important, as is improving and implementing cancer screening and developing effective treatments, so that cancer mortality not attributable to smoking can also be reduced. As a substantial number of cancer deaths occur among former smokers, ongoing investment in the feasibility of targeted lung cancer screening will also be critical for at-risk former smokers.

As with all modelled projections, this study has some limitations, which should be considered when interpreting the results. The main limitation is that the projections are dependent on the assumptions made. The models did not include possible changes in other factors that can contribute to cancer mortality, including other risk factors, and cancer screening or treatment patterns.[3] In practice, these effects could plateau as they either decrease or impact only a small proportion of cases, respectively, or in the case of new treatment availability, further reduce cancer mortality. Also, the projection models did not capture the impact of the recent COVID-19 pandemic, which led to disruptions in healthcare provision that may contribute to future excess deaths even for those who did not contract COVID-19.[40 41] Estimating these impacts will be the subject of future work. Another limitation of this study is that the SAFs were based on adjusted relative risks from the CPS II, which may not be representative of the Australian population. However, results from a previous study suggest that the relative risk for all-cause mortality for current smokers from the large Australian 45 and Up Study is similar to those for cohorts in the USA.[19] Despite these limitations, the study also has many strengths. Most notable are: the use of long-term high-quality observed data with population coverage[10]; the model design accounted for detailed data on cigarette tar consumption and the degree of association between cancer risk and smoking and the validation of the projections using observed data (online supplemental figure S3). The validated methods presented in this study can be applied to other countries to provide better estimates of cancer mortality related to smoking.

This is the first study to provide longer term national-level projections for the mortality rates for all smoking-related cancers taking into account detailed historical smoking intensity data. These projections for smoking-related cancers can serve as benchmarks against which to measure the impact of future cancer control initiatives, and these projections could also help inform health service planning to meet the future requirements for cancer care and treatment. Recognising that there are other, additional causes of mortality attributable to smoking, our research highlights the ongoing and future impact of smoking on the cancer burden, even in a country with major declines in smoking prevalence. Continued efforts in tobacco control remain an urgent public health priority.

Acknowledgements We would like to acknowledge the Australian Institute of Health and Welfare who provided the data from the National Drug Strategy Household Surveys (NDSHS), and the Australian Data Archive for providing access

to the NDSHS data. However, they hold no responsibility for the analyses presented within this publication or the interpretation of them. We would like to thank Clare Kahn for editorial assistance.

Contributors KC: conceived the study. QL: designed the study, conducted the statistical analysis, interpretation and visualisation of results and drafted the manuscript. KC, JS, MW, XQY, MC, DO'C: contributed to the methods, JS and SY: contributed to the statistical analysis. EB and PG contributed to the interpretation of results and provided advice on policy aspects. All authors contributed to the interpretation of results and critically reviewed and revised the manuscript. KC and QL are guarantors of this study. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests KC is co-principal investigator of an investigator-initiated trial of cervical screening, Compass, run by the Australian Centre for Prevention of Cervical Cancer (ACPCC), which is a government-funded not-for-profit charity; the ACPCC has received equipment and a funding contribution from Roche Molecular Diagnostics, and operational support from the Australian Government. KC is also co-principal investigator on a major investigator-initiated implementation programme Elimination of Cervical Cancer in the Western Pacific (ECCWP) which will receive support from the Minderoo Foundation, the Frazer Family Foundation, and equipment donations from Cepheid. Neither KC nor her institution on her behalf receives direct funding from industry for any project. MC is an investigator on an investigator-initiated trial of cytology and primary human papillomavirus screening in Australia (Compass; ACTRN12613001207707 and NCT02328872), which is conducted and funded by the Australian Centre for the Prevention of Cervical Cancer, a government-funded health promotion charity. The Australian Centre for the Prevention of Cervical Cancer has received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and operational support from the Australian Government. However, neither MC nor his institution on his behalf (the Daffodil Centre, a joint venture between Cancer Council NSW and The University of Sydney) receive direct funding from industry for Compass Australia or any other project. All other authors declare no competing interests.

Patient consent for publication Not applicable.

Ethics approval This population-based study used tabulated data on cancer mortality and smoking intensity released by the Australian Institute of Health and Welfare. Ethics approval was not required to use these aggregated data.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The tabulated data on cancer mortality are available from the Australian Institute of Health and Welfare at https://www.aihw.gov.au/. Access restrictions apply to the National Drug Strategy Household Surveys data on smoking behaviour. Approved release of these data can be obtained through an application to the Australian Institute of Health and Welfare.

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American Cancer Society Position Statement on Electronic Cigarettes

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The American Cancer Society (ACS) first released a position statement on e-cigarettes in February 2018. At that time, the ACS emphasized that no young person should start using any tobacco product, including e-cigarettes. However, the use of e-cigarettes in young people has since skyrocketed to epidemic proportion with nearly 30% of high school students reporting using an e-cigarette in the past 30 days and 12% reporting using an e-cigarette daily. This updated position statement replaces all previous ACS statements on e-cigarettes and guides the organization's tobacco control and cessation efforts regarding these products. The ACS position statement will continue to be updated based upon emerging public health trends and evolving science.

No youth or young adult should begin using any tobacco product, including e-cigarettes.

The ACS encourages young people currently using any of these products to ask for help in quitting and to quit as soon as possible.

E-cigarettes should not be used to quit smoking.

The ACS does not recommend the use of e-cigarettes as a cessation method. No e-cigarette has been approved by the Food and Drug Administration (FDA) as a safe and effective cessation product.

Current e-cigarette users should not also smoke cigarettes or switch to smoking cigarettes, and people who formerly smoked now using e-cigarettes should not revert to smoking.

All tobacco products, including e-cigarettes, pose a risk to the health of the user. Beginning smoking, switching to smoking, or reverting to smoking exposes the user to potentially devastating health effects.

E-cigarettes

Using e-cigarettes, or "vaping," are terms used synonymously to refer to the use of a wide variety of electronic, battery-operated devices that aerosolize, but do not burn, liquids to release nicotine and other substances. Nicotine-containing e-cigarettes are regulated as "tobacco products" by the FDA because the nicotine is derived from the tobacco plant. E-cigarettes pose a threat to the health of users and the harms are becoming increasingly apparent. In the past few years, the use of these products has increased at an alarming rate among young people in significant part because the newest, re-engineered generation of e-cigarettes more effectively delivers large amounts of nicotine to the brain. Many e-cigarettes sold in the U.S. contain far more nicotine than e-cigarettes sold elsewhere, which increases the

risk of addiction and harm to the developing brains of youth and young adults. Marketing tactics targeting young people have contributed to the rapid increase in use. The long-term risks of exclusive use of e-cigarettes are not fully known but evidence is accumulating that e-cigarette use has negative effects on the cardiovascular system and lungs. Without immediate measures to stop epidemic use of these products, the long-term adverse health effects will increase.

Guidance for Youth Who Currently Use E-cigarettes

The harms of e-cigarette use in young people include not only the deleterious effects of nicotine, but also exposure of the lungs and airways to potentially toxic solvents and flavoring chemicals. The rapidly rising rates of use in young people and the high rates of daily use strongly suggest that many are addicted to nicotine and will have difficulty in stopping use of all tobacco products.

While some young people may be able to quit e-cigarette use on their own, others, particularly daily users, are likely to find this to be very difficult. The ACS encourages adolescent users who find it difficult to quit to ask for help from health care professionals. Parents should learn all they can about e-cigarette use and be prepared to help their children get the assistance they need. For more information go to cancer.org/e-cigarettes.

The future pattern of tobacco product use by currently-addicted youth e-cigarette users is unknown, but the only pathway to eliminating the harms of e-cigarettes is to quit using them as soon as possible and to not start using any other tobacco products, such as cigarettes. Without urgent and effective public health action, e-cigarettes will lead to a new generation of nicotine-addicted individuals.

Guidance for Adults Who Currently Use E-cigarettes

Some individuals who smoke choose to try e-cigarettes to help them stop smoking. Since smoking kills fully half of all long-time users, successfully stopping smoking leads to well-documented health benefits. Nonetheless, adults who smoke who switch to using e-cigarettes expose themselves to potentially serious ongoing health risks. Thus, people who smoked formerly who are currently using e-cigarettes, whether alone or in combination with combustible tobacco products, should be encouraged and assisted to stop using all tobacco products, including e-cigarettes, as soon as possible both to eliminate their exposure to ongoing health risks and avoid perpetuating addiction. If they are unable to quit e-cigarettes on their own, they should seek help from a health care professional or quitline. Individuals who are not yet able to stop using e-cigarettes should be strongly discouraged from simultaneous, or “dual,” use of any combustible tobacco products, including cigarettes. Continuing to smoke exposes the individual to enormous harms, irrespective of whether the individual is using e-cigarettes part of the time. All individuals should also be strongly counseled to not revert to smoking.

While some e-cigarette users quit on their own, many have difficulty quitting and should seek help from their healthcare providers or other support services such as their state quitline (1-800-QUIT-NOW) or the American Cancer Society (1-800-ACS-2345).

Guidance for Adults Who Currently Smoke

All adults who smoke conventional cigarettes or other combustible (burned) tobacco products should be advised to quit smoking at the earliest opportunity, recognizing that quitting is hard and often takes repeated, dedicated efforts. Individuals who smoke are strongly encouraged to consult with their doctor, pharmacist or other medical professional to seek cessation support and, where deemed appropriate, to use FDA-approved medications including nicotine replacement therapies (NRT) and/or recommended oral medications, preferably combined with individual or group behavioral counseling, which significantly increases the likelihood of success. Individuals can also seek cessation support by calling 1-800-QUIT-NOW or 1-800-ACS-2345.

Regulation of E-cigarettes

The ACS and the American Cancer Society Cancer Action Network (ACS CAN) support several critical policy approaches to reduce youth e-cigarette use without inadvertently incentivizing the use of the leading cause of preventable death – combustible tobacco products – as an alternative. The FDA must effectively regulate all e-cigarettes as soon as possible, including: enforcing premarket reviews; restricting advertising and marketing to protect youth; preventing the dissemination of false and misleading messages and imagery; and requiring strict product standards. The FDA has the authority to regulate all substances in tobacco products, including, but not limited to, flavoring chemicals and nicotine. The FDA must also continue to demand testing of all substances used in e-cigarettes, as well as the relative safety of the devices themselves (for example, preventing exploding batteries). The ACS and ACS CAN encourage prohibiting the use of all flavors, including mint and menthol, in all tobacco products, including e-cigarettes. Furthermore, the FDA should proceed aggressively with a proposal to reduce nicotine in all combustible tobacco products to non-addictive levels and also strictly limit the amount of nicotine permitted in e-cigarettes.

American Association for Respiratory Care

Electronic Cigarette

The American Association for Respiratory Care (AARC) opposes the use of e-cigarettes, "vapes," or any device that is use to aerosolize or vaporize non-therapeutic liquids to deliver intoxicants, stimulants or other chemicals and compounds through inhalation. Even though the concept of using the e-cigarettes for smoking cessation is attractive, it has not been fully studied and further research is needed. As such, the AARC does not recommend the use of e-cigarettes as a cessation method. For those that would like to quit smoking, there are several U. S. Food and Drug Administration (FDA) approved medications that are safe and effective for the purpose of inhalation. A combination of medication and behavioral counseling has been shown to work best. The AARC supports smoking cessation counseling by respiratory therapists who as allied health professionals have expertise in pulmonary medicine. The Surgeon General's 2020 Report on Smoking Cessation concludes, "Smoking cessation improves health status and enhances quality of life" and is beneficial at any age.' The AARC strongly supports this position.

The use of e-cigarette products had increased at an alarming rate among young people. The latest generation of e-cigarette devices deliver large amount of nicotine to the brain significantly increasing the risk of nicotine addiction and harm to developing brains of young adults. E-cigarettes also contain chemicals harmful to lung Health. These include heavy metals, carcinogens, vegetable glycerin and propylene glycol all of which increase the risk of irreversible lung damage and lung disease. Additional safety concerns are emerging related to the inhalation of the liquid nicotine solution (LNS) by young children as poison control centers report a continual increase in calls as e-cigarettes become more popular.

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Effective 04/2014
Revised 12/2014
Revised 11/2015
Revised 02/2020

E-Cigarettes Linked to Heart Attacks, Coronary Artery Disease ...

American College of Cardiology
https://www.acc.org › press-releases › 2019/03/07 › ec...

7 Mar 2019 — New research shows that adults who report **puffing e-cigarettes, or vaping, *are significantly more likely to have a heart attack*, coronary artery** .

Vaping damages arteries and blood vessels like smoking

Tobacco 21
https://tobacco21.org › vaping-damages-arteries-and-b...

29 Apr 2020 — ***Vaping* damages the arteries and blood vessel function much like smoking** traditional cigarettes, a new study has found. Researchers studied more

A New Warning About E-Cigarettes and Heart Attack Risk

Healthline
https://www.healthline.com › health-news › heart-e-ci...

1 Apr 2019 — **The result can be *atherosclerosis, or hardening of the arteries*, a common cause of heart attacks**. The newly reported research, for which Hai

Effects of e-cigarettes and vaping devices on cardiac and ...

Wiley
https://physoc.onlinelibrary.wiley.com › doi › full

by MC Tsai · 2020 · Cited by 69 — Chronic exposure to e-cigarette aerosols using animal models **caused *increased arterial stiffness***, vascular endothelial changes, ...

Vaping damages arteries and blood vessels in the same way ...

Daily Mail
https://www.dailymail.co.uk › article-8268583 › Vapi...

29 Apr 2020 — **Vaping *causes significant damage to blood vessels* in the same way as smoking traditional cigarettes, a study has found.**

www.abc.net.au /news/2023-03-05/heart-attack-death-of-young-man-prompts-calls-for-health-checks/102049060

Toowoomba mum Christine Handford hopes son's death will prompt young people to get heart checks

David Chen 5/3/2023

ABC Southern Qld / By David Chen
Posted Sun 5 Mar 2023 at 5:43amSunday 5 Mar 2023 at 5:43amSun 5 Mar 2023 at 5:43am, updated Sun 5 Mar 2023 at 7:33amSunday 5 Mar 2023 at 7:33amSun 5 Mar 2023 at 7:33am

Christine Handford says her son's death has encouraged others to get their hearts checked.*(ABC Southern Queensland: David Chen)*

When Christine Handford last saw her 31-year-old son Kade, he was fit and bursting with pride about how he was looking and feeling.

Key points:

More than 17,000 Australians died from coronary heart disease in 2021, including Kade Handford
His mother Christine hopes her son's death will encourage others to get their hearts checked
The Heart Foundation is urging the federal government to make the Medicare subsidy for such checks permanent

"The last time I had lunch with him, he had the stomach [he said he wanted], 'Look at this Mum, I'm doing very well'," she said. But a week later, the relatively healthy Toowoomba man returned home from the gym and died unexpectedly from a heart attack. Despite the efforts of three ambulance crews, the six-foot-four larrikin who loved to give big hugs, died in hospital in the southern Queensland city on July 25, 2021.

The coroner later found Kade Handford died after a build-up of plaque in his arteries.

He was one of the 17,331 Australians to die from coronary heart disease in 2021.

Of the 160,000 Australians who were hospitalised for coronary heart disease that year, 16,000 — or 10 per cent — were aged between 15 and 44.

For many people, the disease has no warning signs and the diagnosis is unexpected.

But Mrs Handford said that in hindsight, Kade did show some symptoms, however, due to his age, no one thought anything of them.

"He was a little bit tired at times, short of breath after he had done a session at the gym," she said.

Kade Handford was a bubbly young man who loved to give big hugs. *(Supplied: Christine Handford)*

"I met up with him one day … and he said he'd had a bit of a headache with the peripheral vision disturbance.

"But being a young person, he just brushed it off."

Battle against complacency

The Heart Foundation says it has been a constant battle to get young people to take their heart health seriously and seek check-ups if anything feels a bit strange.

Research into unexplained cardiac arrests in young people

New research shows cardiac arrest is a leading cause of death for Australians aged under 50.

"We know all the seeds are there in people in their younger times," the foundation's chief medical advisor, Professor Gary Jennings, said.

"But there is a tendency to think you're invulnerable and immortal until something happens to someone around you."
Relatively young, high-profile people including cricketer Shane Warne, Senator Kimberley Kitching and Lisa-Marie Presley have died in the past year of heart-related conditions.
Professor Jennings said coverage of high-profile deaths had led to "record numbers" of heart health checks, but that momentum had been short-lived.
Data from Services Australia showed more than 17,650 checks were done nationally in November 2022, but that's now dropped back to 12,092 in January 2023.
The checks have been subsidised by Medicare since April 2019. Between then and January this year, 9 per cent of the 424,000 checks performed nationally were for people aged between 15 and 44.
The Medicare subsidy is due to end this year and the Heart Foundation has urged the federal government to make it permanent.
A heart health check is performed during a 20-minute GP consultation to assess the patient's risk of a heart attack or stroke.
It is recommended for Aboriginal and Torres Strait Islanders aged over 30 or for those in the general population aged over 40. The cost is determined by the GP.
YouTube Heart Health check
Professor Jennings said it was important for people to have check-ups when they became eligible, and for them to follow advice for a healthy lifestyle.
For Christine Handford, there's been some comfort from her son's death, with many of those who knew him booking themselves in for heart check-ups.
"I've had quite a few people contact me and say thank you for making us aware of what to look out for," she said.
"Otherwise, they might have just brushed it off again. So, if in doubt, get yourself checked out."
Kade Handford was a fit 31-year-old when he died from a heart attack in 2021.*(ABC Southern Queensland: David Chen)*

Is Vaping Bad for Your Heart? - UnityPoint Health

UnityPoint Health
https://www.unitypoint.org › livewell › article

21 Feb 2020 — *Cholesterol Deposits*. **Vaping causing cholesterol deposits in arteries to become more unstable over time and more likely to rupture.**

Vaping linked with heart problems

escardio.org
https://www.escardio.org › Press-Office › Press-releases

Kavousi M, Pisinger C, Barthelemy JC, et al**. Electronic cigarettes and health with special focus on cardiovascular effects: position paper of the European Assoc**

Vaping: A Heart Health Emergency - St. Elizabeth Healthcare

St. Elizabeth
https://www.stelizabeth.com › care › vaping-a-heart-h...

21 Jul 2022 — *Vaping* also increases the risk of coronary *artery* disease and blood ... *causes* an irregular heartbeat, and ***leads to*** **a buildup of** ***plaque*** **in**

Vaping Just Once Could Immediately Change Your Blood ...

ScienceAlert
https://www.sciencealert.com › a-single-vape-could-m...

22 Aug 2019 — Endothelial injury is thought to be a key initiating event in the **build-up of** ***plaque*** **in our** ***arteries*****, and even though the vascular ...**

Nicotine drives cell invasion that contributes to plaque ...

Science Daily
https://www.sciencedaily.com › releases › 2013/12

15 Dec 2013 — Nicotine, the major addictive substance in cigarette smoke, contributes to smokers' higher risk of developing atherosclerosis, the primary *cause* ...

Vaping Could Cause Cardiovascular Harm, Researcher Says

WBUR
https://www.wbur.org › hereandnow › 2019/06/18 › v...

18 Jun 2019 — According to Conklin at the University of Louisville, e-cigarettes are far from harmless. Conklin is looking for a link between *vaping* and

How do nicotine-free e-cigarettes affect blood vessels?

Medical News Today
https://www.medicalnewstoday.com › articles

21 Aug 2019 — ***Vaping*** **impairs endothelial function** ... The scans revealed reduced blood flow in the femoral *artery* — the main *artery* that delivers blood to the

People who vape had worrisome changes in cardiovascular ...

American Heart Association
https://newsroom.heart.org › news › people-who-vape...

31 Oct 2022 — After *vaping* or *smoking*, people who used these nicotine-containing products **also experienced greater constriction of the brachial *artery* and** ...

Is vaping or smoking worse for your heart? - The Healthy Journal

The Healthy Journal
https://www.thehealthyjournal.com › faq › is-vaping-o...

Research has shown that **e-cigarettes raise blood pressure and heart rate, change the *artery* walls so that they become stiffer and less elastic, and inhibit** the

Your Patients Are Rotting Their Teeth With Vaping - Medscape

Medscape
https://www.medscape.com › viewarticle

23 Nov 2022 — "All the ingredients of *vaping* are surely a recipe for overgrowth of cavities *causing* bacteria," said Jennifer Genuardi, MD, an internist and

Vaping and E-cigarettes Linked to Higher Risk of Stroke, Heart ...

Maher Chiropractic
https://www.chiropractic4abetteru.com › blog › 12439...

19 Jun 2019 — *Vaping* allows these chemicals into the lungs and can *cause* inflammation. ... and lead to a **buildup of *artery plaque* (atherosclerosis)**

Vaping without nicotine still harms blood vessels, Penn study ...

Philadelphia Inquirer
https://www.inquirer.com › health › vape-study-nicoti...

22 Aug 2019 — A growing body of research suggests **that electronic cigarettes can damage blood vessels in the short term, *causing* them to become inflamed** .

Vaping linked with heart problems

European Society of Cardiology
https://www.escardio.org › Press-Office › Press-releases

30 Jul 2020 — **Research has shown that e-cigarettes raise blood pressure and heart rate, change the *artery* walls so that they become stiffer and less elastic, ...**

What You Should Know About Vaping and Oral Care

Dental Health Society
https://dentalhealthsociety.com › oral-health › what-yo...

8 Apr 2019 — The act of inhaling the vapor of an *e-cigarette* brings bacteria into the mouth. Just like a diet of sticky, sweet foods, these additional ...

Causes of Coronary Artery Disease - Aurora Health Care

Aurora Health Care
https://www.aurorahealthcare.org › ... › Causes

Nicotine constricts your blood vessels, making your heart work harder to pump blood. Studies have also shown that using e-cigarettes, or *vaping*, increases your ...

vaping and heart palpitations - JustCo

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https://justcoglobal.com › vaping-and-heart-palpitations

5 days ago — **The truth is people who *vape* are 56 percent more likely to have a heart attack than non-smokers and 30 percent more likely to suffer a stroke, ...**

www.cancer.org /healthy/stay-away-from-tobacco/e-cigarettes-vaping/e-cigarette-position-statement.html

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Current e-cigarette users should not also smoke cigarettes or switch to smoking cigarettes, and people who formerly smoked now using e-cigarettes should not revert to smoking.

All tobacco products, including e-cigarettes, pose a risk to the health of the user. Beginning smoking, switching to smoking, or reverting to smoking exposes the user to potentially devastating health effects.

E-cigarettes

Using e-cigarettes, or "vaping," are terms used synonymously to refer to the use of a wide variety of electronic, battery-operated devices that aerosolize, but do not burn,

liquids to release nicotine and other substances. Nicotine-containing e-cigarettes are regulated as "tobacco products" by the FDA because the nicotine is derived from the tobacco plant. E-cigarettes pose a threat to the health of users and the harms are becoming increasingly apparent. In the past few years, the use of these products has increased at an alarming rate among young people in significant part because the newest, re-engineered generation of e-cigarettes more effectively delivers large amounts of nicotine to the brain. Many e-cigarettes sold in the U.S. contain far more nicotine than e-cigarettes sold elsewhere, which increases the risk of addiction and harm to the developing brains of youth and young adults. Marketing tactics targeting young people have contributed to the rapid increase in use. The long-term risks of exclusive use of e-cigarettes are not fully known but evidence is accumulating that e-cigarette use has negative effects on the cardiovascular system and lungs. Without immediate measures to stop epidemic use of these products, the long-term adverse health effects will increase.

Guidance for Youth Who Currently Use E-cigarettes

The harms of e-cigarette use in young people include not only the deleterious effects of nicotine, but also exposure of the lungs and airways to potentially toxic solvents and flavoring chemicals. The rapidly rising rates of use in young people and the high rates of daily use strongly suggest that many are addicted to nicotine and will have difficulty in stopping use of all tobacco products.

While some young people may be able to quit e-cigarette use on their own, others, particularly daily users, are likely to find this to be very difficult. The ACS encourages adolescent users who find it difficult to quit to ask for help from health care professionals. Parents should learn all they can about e-cigarette use and be prepared to help their children get the assistance they need. For more information go to cancer.org/e-cigarettes.

The future pattern of tobacco product use by currently-addicted youth e-cigarette users is unknown, but the only pathway to eliminating the harms of e-cigarettes is to quit using them as soon as possible and to not start using any other tobacco products, such as cigarettes. Without urgent and effective public health action, e-cigarettes will lead to a new generation of nicotine-addicted individuals.

Guidance for Adults Who Currently Use E-cigarettes

Some individuals who smoke choose to try e-cigarettes to help them stop smoking. Since smoking kills fully half of all long-time users, successfully stopping smoking leads to well-documented health benefits. Nonetheless, adults who smoke who switch to using e-cigarettes expose themselves to potentially serious ongoing health risks. Thus, people who smoked formerly who are currently using e-cigarettes, whether alone or in combination with combustible tobacco products, should be encouraged and assisted to stop using all tobacco products, including e-cigarettes, as soon as possible both to eliminate their exposure to ongoing health risks and avoid perpetuating addiction. If they are unable to quit e-cigarettes on their own, they should seek help from a health care professional or quitline. Individuals who are not yet able to stop using e-cigarettes should be strongly discouraged from simultaneous, or "dual," use of any combustible tobacco products, including

cigarettes. Continuing to smoke exposes the individual to enormous harms, irrespective of whether the individual is using e-cigarettes part of the time. All individuals should also be strongly counseled to not revert to smoking.

While some e-cigarette users quit on their own, many have difficulty quitting and should seek help from their healthcare providers or other support services such as their state quitline (1-800-QUIT-NOW) or the American Cancer Society (1-800-ACS-2345).

Guidance for Adults Who Currently Smoke

All adults who smoke conventional cigarettes or other combustible (burned) tobacco products should be advised to quit smoking at the earliest opportunity, recognizing that quitting is hard and often takes repeated, dedicated efforts. Individuals who smoke are strongly encouraged to consult with their doctor, pharmacist or other medical professional to seek cessation support and, where deemed appropriate, to use FDA-approved medications including nicotine replacement therapies (NRT) and/or recommended oral medications, preferably combined with individual or group behavioral counseling, which significantly increases the likelihood of success. Individuals can also seek cessation support by calling 1-800-QUIT-NOW or 1-800-ACS-2345.

Regulation of E-cigarettes

The ACS and the American Cancer Society Cancer Action Network (ACS CAN) support several critical policy approaches to reduce youth e-cigarette use without inadvertently incentivizing the use of the leading cause of preventable death – combustible tobacco products – as an alternative. The FDA must effectively regulate all e-cigarettes as soon as possible, including: enforcing premarket reviews; restricting advertising and marketing to protect youth; preventing the dissemination of false and misleading messages and imagery; and requiring strict product standards. The FDA has the authority to regulate all substances in tobacco products, including, but not limited to, flavoring chemicals and nicotine. The FDA must also continue to demand testing of all substances used in e-cigarettes, as well as the relative safety of the devices themselves (for example, preventing exploding batteries). The ACS and ACS CAN encourage prohibiting the use of all flavors, including mint and menthol, in all tobacco products, including e-cigarettes. Furthermore, the FDA should proceed aggressively with a proposal to reduce nicotine in all combustible tobacco products to non-addictive levels and also strictly limit the amount of nicotine permitted in e-cigarettes.

www.lung.org /media/press-releases/do-not-use-eigarettes

American Lung Association: Do Not Use E-Cigarettes

CHICAGO, IL | September 10, 2019

American Lung Association National President and CEO Harold Wimmer issued the following statement in response to an increase in reported vaping-related illnesses and deaths:

"**E-cigarettes are not safe and can cause irreversible lung damage and lung disease. No one should use e-cigarettes or any other tobacco product. This message is even more urgent today following the increasing reports of vaping-related illnesses and deaths nationwide.**

"E-cigarettes contain chemicals harmful to lung health such as heavy metals, carcinogens, vegetable glycerin and propylene glycol. The developing lungs of youth may be more at risk, making what the Surgeon General refers to as a youth e-cigarette epidemic even more alarming.

"The Centers for Disease Control and Prevention (CDC) and state and local health departments are conducting an ongoing investigation of the current cluster of vaping-related illnesses. There have been six confirmed vaping-related deaths, and as of Friday, September 6, there have been more than 450 possible cases of adults and youth experiencing vaping-related illness across 33 states.

"The Lung Association recommends anyone who has recently used e-cigarette products to seek immediate medical care if they experience any adverse health effects, particularly coughing, shortness of breath or chest pain. The Lung Association also calls on physicians to make sure their patients are aware of the health risks associated with e-cigarettes, and swiftly report any suspected cases of vaping-related illness to their state or local health department. If people are seeking to quit tobacco, the Lung Association urges them to talk with a medical provider, and use one of the seven FDA-approved quit-smoking treatments in combination with

counseling. FDA has not found any e-cigarette to be safe and effective in helping smokers quit.

"To protect public health and end the youth e-cigarette epidemic, we strongly urge the FDA to immediately begin using its authority to fully regulate e-cigarettes and remove all unauthorized products from the market. We also call on the FDA to immediately end the sale of all flavored tobacco products, including mint and menthol, and end marketing practices that target and enhance the appeal of e-cigarette products to youth.

"With the aim to save lives and reduce tobacco-related disease, the American Lung Association will continue to educate the public and advocate for more public health protections and proven effective policies to help prevent and reduce tobacco use, including e-cigarettes."

Learn more about e-cigarettes and lung health at Lung.org/ecigs. For media interested in speaking with a medical or policy expert about lung health, tobacco use or the youth e-cigarette epidemic, contact Allison MacMunn the American Lung Association at Media@Lung.org or 312-801-7628.

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About the American Lung Association

The American Lung Association is the leading organization working to save lives by improving lung health and preventing lung disease through education, advocacy and research. The work of the American Lung Association is focused on four strategic imperatives: to defeat lung cancer; to champion clean air for all; to improve the quality of life for those with lung disease and their families; and to create a tobacco-free future. For more information about the American Lung Association, which has a 4-star rating from Charity Navigator and is a Platinum-Level GuideStar Member, or to support the work it does, call 1-800-LUNGUSA (1-800-586-4872) or visit: Lung.org.

For more information, contact:

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1-800-LUNG-USA

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doi: 10.1111/resp.13904. Epub 2020 Jul 26.

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Affiliations

- PMID: **32713105** PMCID: PMC7540297 DOI: 10.1111/resp.13904

Christine F McDonald et al. Respirology. 2020 Oct.

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Abstract

The TSANZ develops position statements where insufficient data exist to write formal clinical guidelines. In 2018, the TSANZ addressed the question of potential benefits and health impacts of electronic cigarettes (EC). The working party included groups focused on health impacts, smoking cessation, youth issues and priority populations. The 2018 report on the Public Health Consequences of E-Cigarettes from the United States NASEM was accepted as reflective of evidence to mid-2017. A search for papers subsequently published in peer-reviewed journals was conducted in August 2018. A small number of robust and important papers published until March 2019 were also identified and included. Groups identified studies that extended, modified or contradicted the NASEM report. A total of 3793 papers were identified and reviewed, with summaries and draft position statements developed and presented to TSANZ membership in April 2019. After feedback from members and external reviewers, a collection of position statements was finalized in December 2019. **EC have adverse lung effects and harmful effects of long-term use are unknown. EC are unsuitable consumer products for recreational use, part-substitution for smoking or long-term exclusive use by former smokers.** Smokers who require support to quit smoking should be directed towards approved medication in conjunction with behavioural support as having the strongest evidence for efficacy and safety. **No specific EC product can be recommended as effective and safe for smoking cessation. Smoking cessation claims in relation to EC should be assessed by established regulators.**

Keywords: e-cigarettes; public health; smoking cessation; tobacco control; vaping.

New research from Cancer Council Victoria shows Australians back tougher regulation on vaping

⋮ 14/2/2023

Media release

A Cancer Council Victoria survey out today shows most Australians back Australian Medical Association calls for tougher regulations on vaping.

AMA President Professor Steve Robson said the survey's results, which showed almost 9 out of ten Australians want stronger regulation on vaping and vaping products, should provide further impetus for the federal government to tighten regulations.

"This research from the council's Centre for Behavioural Research in Cancer, shows Australians are just as concerned about this issue as the AMA and want tougher regulation," Professor Robson said.

"We have said very clearly to the federal government that Australia is at risk of losing the public health battle on vaping if strong action isn't taken. Vaping is not harmless, it is not safe, it is not part of tobacco control."

The AMA's submission to the recent Therapeutic Goods Administration consultation on potential reforms to the regulation of nicotine vaping products (NVPs) called for changes to regulations to limit access to nicotine vaping products by banning the personal importation of them and reducing the allowed concentration of nicotine.

“The Personal Importation Scheme bypasses many of the product standards contained in regulations, including labelling, packaging, and record-keeping requirements and it’s incredibly challenging to enforce,” Professor Robson said.

While the TGA consultation focuses primarily on NVPs, the AMA supports introducing controls on the importation of all vaping products through customs.

“This would begin to address the public health challenge of tackling both non-nicotine vapes and nicotine products. Nicotine and non-nicotine vaping products are regulated differently which complicates and hinders progress on this issue,” Professor Robson said.

“Vaping products are a gateway to smoking for young people and there are significant risks from vaping that warrant much stronger regulation. For example, we know many products marketed as not containing nicotine have been found to contain nicotine and products have also been found to contain prohibited chemicals that can cause serious harm, like vitamin E acetate and diacetyl, which can cause serious damage to the lungs.”

Professor Robson said the AMA agreed that stronger regulation was needed to curb the proliferation of recreational non-nicotine vaping products, including implementing similar regulation to tobacco products, such as health warnings, better labelling, plain packaging, and tobacco licences.

“We also need a targeted federal response to monitor and act on illegal advertising and promotion of e-cigarettes — particularly online and on social media — and improved enforcement of existing state and territory regulation to help block illegal vape sales both online and through shopfronts.”

Read the AMA’s recent submission to the TGA on vaping regulation

Related Download

AMA Media Release - Vaping Cancer Council Victoria - AMA position.pdf (169.89 KB)

Australian Medical Association Limited
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39 Brisbane Avenue, Barton ACT 2600: PO Box 6090, Kingston ACT 2604
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Tuesday, 14 February 2023

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Respirology

POSITION STATEMENT

Electronic cigarettes: A position statement from the Thoracic Society of Australia and New Zealand*

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ABSTRACT

The TSANZ develops position statements where insufficient data exist to write formal clinical guidelines. In 2018, the TSANZ addressed the question of potential benefits and health impacts of electronic cigarettes (EC). The working party included groups focused on health impacts, smoking cessation, youth issues and priority populations. The 2018 report on the *Public Health Consequences of E-Cigarettes* from the United States NASEM was accepted as reflective of evidence to mid-2017.

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*This document was endorsed by the Thoracic Society of Australia and New Zealand (TSANZ) Board in February 2020 after external review.

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Received 19 February 2020; invited to revise 8 March 2020; revised 8 May 2020; accepted 11 June 2020

Handling Editors: Philip Bardin and Paul Reynolds

Respirology published by John Wiley & Sons Australia, Ltd on behalf of Asian Pacific Society of Respirology. doi: 10.1111/resp.13904

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Key words: e-cigarettes, public health, smoking cessation, tobacco control, vaping.

CONTENTS

INTRODUCTION

Electronic cigarettes (e-cigarettes) are battery-operated devices which contain a heating element that vaporizes liquid solution. The user inhales or 'vapes' the aerosol produced through heating the liquid. E-cigarettes are also referred to as electronic nicotine delivery systems (ENDS) or electronic non-nicotine delivery systems (ENNDS) when they do not use nicotine-based solutions.

The liquid solution used in e-cigarettes contains propylene glycol and/or glycerine liquid to create the aerosol.[1] The solution often contains flavourants and ENDS solutions contain nicotine.

Early attempts to develop e-cigarettes date to the 1960s, but the first device of the modern era was patented in 2003. E-cigarettes have been widely marketed since about 2006. Use of an e-cigarette is commonly termed 'vaping'.

Tobacco smoking in Australia and New Zealand

The advent of e-cigarettes has occurred after sustained success in reducing tobacco smoking rates in Australia and New Zealand.

Australia has led the world in implementing tobacco control measures including substantial increases in excise on tobacco products; education programmes; bans on smoking in indoor and, increasingly, outdoor public places; plain packaging of tobacco products; bans on retail displays of tobacco products; labelling with updated and larger graphic health warnings; prohibiting tobacco advertising, promotion and sponsorship; and providing support for smokers to quit including subsidized nicotine replacement therapy.[2–5] The rates of regular smoking in Australia (that is either daily or at least weekly) have reduced from 27% in 1995 to 14% in 2016.[6]

Smoking rates in New Zealand Aotearoa are also reducing, with 12.5% of adults currently smoking daily compared to 25% in 1996–1997.[7] In 2011, the New Zealand Government set a goal of Smokefree Aotearoa 2025, aiming to reduce smoking prevalence and tobacco availability to minimal levels and make New Zealand essentially a smoke-free nation by 2025.[8] Strategies have included protecting children from exposure to tobacco marketing and promotion; reducing the supply of, and demand for, tobacco; and providing the best possible support for quitting.

Smoking by young people has fallen markedly. Smoking rates among young Australians aged 16–17 years declined from 30% in 1999 to 10% in 2014, while among those aged 12–15 years, the smoking rate declined from 15% to 3% during the same period.[9] The prevalence of smoking among Australian teenagers in 2014 was at its lowest since surveys began more than 30 years earlier. Similar improvements have been achieved in New Zealand, where only 3% of young people aged 15–17 years smoked in 2017–2018, down from 16% in 2006–2007 and the daily smoking rate for 14- and 15-year olds fell to 2.1%, the lowest ever recorded.[7]

Harmful effects of smoking

There is no dispute about the harmful effects and significant costs of tobacco smoking. Smoking causes the premature deaths of two-thirds of its long-term users.[10] Respiratory diseases, notably lung cancer and chronic obstructive pulmonary disease (COPD), dominate as causes of smoking-associated disability and premature mortality in both Australia and New Zealand.

In 2015–2016, the costs of smoking in Australia were estimated at $136.9 billion and smoking was responsible for 20 032 premature deaths and approximately 1.7 million hospitalizations.[11] In New Zealand, approximately one person dies from smoking every 2 hours, while in Australia approximately one person dies from smoking every half an hour.[12,13]

These harmful effects continue to occur despite the significant success in reducing rates of tobacco smoking in Australia and New Zealand, and it is imperative this progress continues. In recent years, the emergence of e-cigarettes has prompted discussion about whether these

devices have a role in supporting smokers to quit or in reducing smoking prevalence rates.

Purpose of this position paper

The Thoracic Society of Australia and New Zealand (TSANZ) position papers reflect the position of the TSANZ where there are insufficient data to support a formal clinical guideline (particularly in areas of public health policy). In contrast to position papers, the TSANZ's guidelines must provide evidence-based recommendations for clinical practice, require a systematic review of the literature and use GRADE levels of evidence.

The TSANZ determined that a position paper was required on e-cigarettes, given the rapidly emerging research in this area, the recognition that the health effects of e-cigarettes are likely to only become fully understood over time and the scant evidence for their use in smoking cessation. This position paper was completed in accordance with the TSANZ requirements for the development of position papers as detailed in the TSANZ publication policy.

The TSANZ is dedicated to ensuring that Australian and New Zealand governments maintain their commitment to reducing smoking prevalence and to the implementation of comprehensive tobacco control measures that include population-wide strategies coupled with individual behavioural support, particularly for groups of people in whom smoking rates have not declined as quickly as they have in others. The TSANZ is committed to preventing and relieving the disability caused by lung disease. Consequently, we are steadfast in our aim to help people stop smoking completely. E-cigarettes are therefore of considerable interest to the TSANZ as we seek to further reduce the morbidity and mortality associated with lung disease. The purpose of this position paper is to outline the TSANZ's position with respect to e-cigarettes. The intended audience is both clinical and non-clinical readers.

This position paper addresses e-cigarettes that use both nicotine-containing and non-nicotine-containing liquids but does not consider 'heat-not-burn' products, a separate product category.

The TSANZ acknowledges the Public Health England Report on e-cigarettes.[14] The TSANZ has considered and accepted the comprehensive report on the *Public Health Consequences of E-Cigarettes* from the United States National Academies of Sciences, Engineering and Medicine (NASEM), January 2018,[15] as well as the June 2018 Literature Review Update from Australia's Commonwealth Scientific and Industrial Research Organisation (CSIRO)[16] as better reflecting the published literature to August 2017 and March 2018, respectively. As such, these reports form the basis for the development of the TSANZ's position.

In developing this position paper, we reviewed the literature to determine if there were new studies that subsequently extended or challenged the findings of the NASEM report. In particular, we reviewed literature predominantly, but not exclusively, post-dating August 2017, that assessed e-cigarettes with respect to:

1. Health impacts,
2. Effects on smoking cessation,
3. Effects on children and young people including the impact of both nicotine- and non-nicotine-containing products on developing lungs and
4. Effects on at-risk groups which included:
   - Aboriginal, Torres Strait Islanders, Maori, Pasifika peoples,
   - Prisoners (or those recently released),
   - People with mental illness,
   - Alcohol and other drug treatment clients and
   - Pregnant women.

Working party membership is listed in Supplementary Appendix S1 and Methodology is outlined in Supplementary Appendix S2.

THE REGULATORY FRAMEWORK

In Australia, the regulation of e-cigarettes is a responsibility shared between Commonwealth and State and Territory Governments across multiple sets of legislation relating to tobacco products, therapeutic goods, poisons and consumer goods. The regulatory frameworks are different in each state and territory. Whereas in New Zealand nicotine-containing e-cigarettes are available as a consumer product, this is not the case in Australia, where e-cigarettes can be purchased as a consumer product, but nicotine cannot. In New Zealand, the *Medicines Act 1981* and the *Smoke-Free Environments Act 1990* regulate the sale, advertising and use of vaping products, including nicotine liquids.

It is illegal in both New Zealand and Australia to sell an e-cigarette while making a claim about therapeutic benefit for smoking cessation unless the product has been approved for that purpose by the Therapeutic Goods Administration (Australia) or Medsafe (New Zealand). In both Australia and New Zealand, e-cigarettes are currently sold as consumer products and not as therapeutic goods.

Smoking cessation products have been subject to stringent regulation through government-managed processes. Regulated therapeutic goods are manufactured under strict codes such as Good Manufacturing Practice to ensure product consistency and quality. E-cigarettes are not regulated as a therapeutic product.

Regulation is the role of government. The Institute for Global Tobacco Control website (https://globaltobaccocontrol.org/e-cigarette_policyscan) provides a detailed overview of how governments internationally have approached the regulation of e-cigarettes.[17] There is no current evidence on the most effective regulatory framework for e-cigarettes.

HEALTH IMPACTS OF E-CIGARETTES

Drawing conclusions about absolute exposure levels and associated risk based on comparisons between e-cigarettes and combustible tobacco use is not possible. There are thousands of e-liquid solution variants and a range of devices with different settings. Exposure to certain toxins in e-cigarettes has been demonstrated to be less than that experienced with conventional cigarette use, whilst for others exposure is greater.[15]

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Although the NASEM report concluded that there was no available evidence regarding whether e-cigarettes cause respiratory diseases in humans, we identified two subsequently published studies which compared the spectrum of bronchial proteins in non-smokers, smokers and e-cigarette users. They demonstrated alterations in the bronchial proteome and identified changes unique to e-cigarettes, including markers of an aberrant neutrophilic response.[18,19] In vivo studies have identified specific e-cigarette flavourants that have potential adverse effects on human health,[20,21] and a study in humans showed addition of a flavourant led to increased plasma nicotine levels.[22]

A recent prospective cohort study, based on a large sample of current or former smokers, found that e-cigarettes used alone or in combination with tobacco cigarettes, compared to smoking tobacco cigarettes alone did not substantially improve self-reported health over 4 years of follow-up or decrease the rate of diseases potentially related to tobacco.[23] Nonetheless, the authors acknowledged that the follow-up period may have been too short to detect long-term effects.

The NASEM report concluded that the implications for long-term effects on morbidity and mortality are not yet clear and noted substantial evidence that e-cigarette aerosol induces cellular dysfunction and can promote the formation of reactive oxygen species/oxidative stress. It also noted, however, that the generation of reactive oxygen species and oxidative stress is generally lower from e-cigarettes than from combustible tobacco smoke.[15] The studies identified above further support the NASEM assessment that lung disease is a biologically plausible potential outcome of long-term exposure to e-cigarette vapour.

Continued smoking is seen in the majority of e-cigarette users.[24] There is sparse evidence in humans of the health outcomes in these dual users of e-cigarettes and tobacco. The NASEM report noted a lack of clarity regarding the balance of positive and negative effects of e-cigarettes on respiratory health, concluding that there is limited evidence for improvement in lung function and respiratory symptoms among adult smokers with asthma who switch to e-cigarettes completely or in part (dual use) and for reduction of COPD exacerbations among adult smokers with COPD who switch to e-cigarettes completely or in part.

Isolated case studies and case series have described adverse effects of e-cigarettes on a range of non-respiratory outcomes including accidental poisoning from e-liquids,[25] acute nicotine toxicity from excessive vaping[26] and increased periodontal inflammation.[27]

During the process of finalization of this document, a substantial number of cases of severe, acute lung injury in e-cigarette users have been reported in the United States. A summary of this outbreak is provided in Appendix S3 (Supplementary Information).

Non-respiratory adverse effects of e-cigarettes from malfunction of the devices have been identified, including lacerations and burns that have resulted from explosions.[28–30]

There is little evidence about the effects of e-cigarette use on pregnancy and foetal health.

Research on the effects of second-hand exposure to e-cigarette aerosols has been challenged by difficulty in creating an effective model of exposure—due to a range of factors including heterogeneity of apparatus and juices, adjustable power settings and varying puff parameters.

The long-term health impact of e-cigarettes remains largely unknown. Given the known short- to mid-term adverse health effects and the risk that chronic lung disease will develop over time, e-cigarettes should not be used by children or non-smokers. Their use by smokers is addressed in the following section on smoking cessation.

EFFECTS ON SMOKING CESSATION

The NASEM[15] and CSIRO[16] reports, together with reports from Australia's National Health and Medical Research Council[31] and a European Respiratory Society Task Force,[32] all conclude that there is limited evidence that e-cigarettes are effective in promoting smoking cessation and a lack of evidence as to whether e-cigarettes are more or less effective than existing approved cessation aids or no treatment.

A literature search identified five additional randomized controlled trials relevant to smoking cessation published since the finalization of the 2018 NASEM report. The trials were heterogeneous in study population and design. In two studies of smokers motivated to quit, one showed an increase in stopping rates with e-cigarettes, with or without nicotine, compared to low-intensity counselling,[33] but the other found no incremental effect when e-cigarettes were added to combined nicotine replacement therapy and counselling.[34] Three studies investigated smokers not motivated to quit. They found that the addition of free e-cigarettes to usual care (information and motivational text messages) did not increase sustained smoking abstinence;[35] provision of free e-cigarettes for use entirely at the discretion of participants did not significantly influence quit attempts or biologically verified abstinence;[36] and randomization to ad libitum nicotine-containing rather than non-nicotine-containing e-cigarettes did not reduce regular cigarette use.[37]

A recent randomized trial investigated the efficacy of e-cigarettes compared with nicotine replacement therapy, in addition to face-to-face cessation counselling, in smokers attending a smoking cessation service.[38] At 1 year, the rate of continuous abstinence from smoking traditional cigarettes among e-cigarette users was 18.0% compared to 9.9% in the nicotine replacement group (relative risk: 1.83; 95% CI: 1.30–2.58; $P < 0.001$). However, after 1 year, 80% of e-cigarette users continued to use e-cigarettes, whereas 9% of nicotine replacement therapy users were still using nicotine replacement.

A time series analysis in the United Kingdom found no significant association between changes in the use of e-cigarettes between 2006 and 2016 and rates of smoking and daily cigarette consumption.[39] It concluded that if e-cigarette use had any effect on cigarette smoking, the effect was likely to be very small at a population level.

Most smokers quit smoking unassisted,[40] but effective healthcare advice and the appropriate use of proven and well-regulated products are essential in providing support for many smokers seeking assistance

in quitting. Guidelines are available for health professionals to assist them in providing expert care.[41,42] If health practitioners are unable to support smokers, they should refer them to appropriate expert care.

Smokers seeking to quit require access to qualified, personal behavioural support regardless of whether they use existing therapies. Smokers who enquire about using e-cigarettes as a cessation aid should be provided with appropriate information about approved medication in conjunction with behavioural support (as these have the strongest evidence of efficacy to date). E-cigarettes are not the first-line treatment for smoking cessation.[41] However, for smokers who express a desire to use e-cigarettes for cessation, health professionals should ensure they have access to, and are utilizing, behavioural support with the aim of achieving complete smoking cessation and subsequent cessation of e-cigarette use as promptly as possible.

IMPLICATIONS FOR CHILDREN AND YOUNG PEOPLE

The NASEM report found substantial evidence that e-cigarette use results in young people taking up smoking of conventional cigarettes (the gateway effect).[15] The reports from the CSIRO,[16] NHMRC[31] and European Respiratory Society Task Force[32] agreed. The Forum of International Respiratory Societies recommends that, to protect youth, e-cigarettes should be considered as tobacco products and regulated as such.[43] The addictive power of nicotine, particularly in the developing adolescent brain, and its adverse effects should not be underestimated. The Forum stated that flavourings further encourage use by young people.

The United States Surgeon General concluded that e-cigarette use among youth and young adults is a public health concern.[44] In 2014, use of e-cigarettes by young adults aged 18–24 years in the United States exceeded that of adults aged 25 years or over. The Surgeon General concluded that e-cigarette use is strongly associated with the use of other tobacco products among youth and young adults, including combustible tobacco products.

One hundred and ninety-four papers concerning the implications of e-cigarettes for children and young people published since the NASEM report were consistent with the NASEM findings. Many provided additional supportive data. Seven reports challenged the cautionary approach recommended by the NASEM analysis.[45–51]

IMPLICATIONS FOR AT-RISK GROUPS

Smoking rates are higher than average in some population groups including Aboriginal and Torres Strait Islander and Māori and Pasifika peoples. Smoking rates are also elevated in people with mental illness or substance-use disorder and people in correctional facilities. Women who are pregnant, or are planning to become pregnant, have special health needs relating to smoking.

We considered any studies published after the NASEM report reporting on the groups identified above in which e-cigarettes were considered as a cessation aid, attitudes towards e-cigarettes were examined or the level of use was assessed. We conclude that, due to the low quality of evidence, it is uncertain whether e-cigarettes are effective for smoking cessation in populations with high smoking rates.[52] Individual studies, reported both before and since the NASEM review, varying in sample size from 12 to 84 participants showed some sustained reduction in the number of cigarettes smoked at 1 year (similar to the efficacy to a nicotine replacement patch),[53,54] reduced tobacco use at 9 weeks,[55] acceptability as a form of nicotine replacement therapy in alcohol-dependent patients during a hospital admission,[56] acceptability and some efficacy in military veterans receiving psychiatric services[57] and reduced smoking rates at 6 weeks in people with severe mental illness.[58]

A 2015 review on behalf of the United States Preventive Services Task Force examined e-cigarette use in all adults.[59] It identified no specific studies on the impact on smoking cessation in pregnant women and stated that the effects of e-cigarette ingredients on the foetus are unknown. Five studies published since this review examined attitudes to e-cigarette use in groups that included pregnant women, people with mental illness and Māori and Pasifika people in New Zealand.[60–64] They identified positive views about e-cigarettes. Participants considered them safer than tobacco products.

The prevalence of e-cigarette use in at-risk populations has been assessed in a number of studies. It was estimated that 11–13% of pregnant women in the United States had prior or current use and 0.6% currently used them daily.[65] In American patients hospitalized for mental illness, the prevalence of e-cigarette use increased from zero in 2009 to 25% in 2013.[66] A survey of 6051 Americans found people with mental illness were 1.5 times more likely to have ever used e-cigarettes and almost twice as likely to be current users compared to people without mental illness.[67] Among Americans with drug- and alcohol-use disorders, two studies showed 30–34% had used e-cigarettes in the last 30 days,[68,69] while another found that 17.7% used them at least weekly.[70]

A study of 390 Indigenous Australians, of whom 184 were current smokers and 75 former smokers, found that only 7 (2%) were currently using e-cigarettes.[71] In a 2013–2014 survey, 21% of Indigenous smokers had tried an e-cigarette, virtually identical to the rate of 20% in all Australian smokers.[5]

The literature and evidence base for cessation, acceptability and prevalence for each population were sparse and the quality of the studies was not sufficiently robust to enable conclusions to be drawn. Given the burden of smoking in these populations, further high-quality research utilizing e-cigarettes and existing cessation aids is urgently required.

POSITION OF THE TSANZ

The TSANZ embarked upon the development of this position paper having accepted the NASEM report as the most comprehensive review on e-cigarettes to date. After reviewing recent literature on e-cigarettes, it is the position of the TSANZ that there is, at present, insufficient evidence to refute the findings of the

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NASEM report. We believe that this position statement is also fully consistent with relevant sections of the 2020 report of the US Surgeon General on Smoking Cessation.[24]

The TSANZ, with its particular concern with respiratory health, has taken the position that:

1. All smokers should be able to easily access effective, existing cessation treatments complemented by behavioural support services.
2. Access to effective, adequately funded smoking cessation support services is particularly important for those smokers in population groups where the prevalence rates have remained high.
3. Smokers who enquire about using e-cigarettes as a cessation aid should be provided with appropriate information about approved medication in conjunction with behavioural support (as these have the strongest evidence for efficacy and safety).
4. For smokers who express a desire to use e-cigarettes for cessation, health professionals should ensure the smokers have access to, and are utilizing, behavioural support with the aim of achieving complete smoking cessation and subsequent cessation of e-cigarette use as promptly as possible. It should be clearly communicated that no product can be recommended, and nor can an assurance be provided as to either effectiveness or safety.
5. As e-cigarettes have been demonstrated to cause adverse lung effects and their safety for long-term use is unknown, they should not be used by non-smokers or for extended periods by ex-smokers. E-cigarettes, whether containing nicotine or not, are not suitable consumer products.
6. Australia and New Zealand must take every action to prevent burgeoning use of e-cigarettes in young people as has occurred in other countries. The sale or supply of e-cigarettes, e-liquids and devices to people under the age of 18 years should not be permitted and active surveillance is required by bodies responsible for enforcing this.
7. Flavours in e-liquids are attractive to young people and never smokers. Bans on flavourings should be actively considered by governments.
8. As Australia and New Zealand both have well-established processes to manage products making a therapeutic claim, we recommend that any product about which a therapeutic claim regarding smoking cessation is made be managed through these processes.
9. Noting existing regulations in Australia and New Zealand, there is a clear need for the development of a more comprehensive regulatory framework for both e-cigarette devices and e-liquids.
10. Further high-quality research is urgently required, including regarding the potential risks and benefits of e-cigarette use in groups with higher rates of smoking and those with special health needs.

CONCLUDING REMARKS

Australia and New Zealand must remain focused on *proven* effective population tobacco control strategies to reduce prevalence rates. We must also ensure smokers have access to behavioural support and, where required, therapeutic products which have been through stringent regulatory approval processes.

TSANZ reconfirms its commitment to Article 5.3 of the World Health Organization (WHO) Framework Convention on Tobacco Control: '*In setting and implementing their public health policies with respect to tobacco control, parties shall act to protect these policies from commercial and other vested interests of the tobacco industry in accordance with national law*'.

Abbreviations: CSIRO, Commonwealth Scientific and Industrial Research Organisation; EC, e-cigarette; ENDS, electronic nicotine delivery system; NASEM, National Academies of Sciences, Engineering and Medicine; TSANZ, Thoracic Society of Australia and New Zealand

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Appendix S1. Working Party Membership and Conflict of Interest Declarations.
Appendix S2. Methodology.
Appendix S3. Outbreak of acute lung injury associated with e-cigarette use.

Electronic cigarette use in youths: a position statement of the Forum of International Respiratory Societies

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@ERSpublications
It is the position of @lungsfirst that nicotine in electronic cigarettes poses a great threat to youth and we must protect them from it http://ow.ly/DfWJ30jIes7

Cite this article as: Ferkol TW, Farber HJ, La Grutta S, *et al*. Electronic cigarette use in youths: a position statement of the Forum of International Respiratory Societies. *Eur Respir J* 2018; 51: 1800278 [https://doi.org/10.1183/13993003.00278-2018].

ABSTRACT Children and adolescents are highly susceptible to nicotine addiction, which affects their brain development, even in those who smoke infrequently. Young people who become addicted to nicotine are at greater risk of becoming lifelong tobacco consumers. The use of nicotine-delivering electronic cigarettes has risen dramatically among youths worldwide. In addition to physical dependence, adolescents are susceptible to social and environmental influences to use electronic cigarettes. The product design, flavours, marketing, and perception of safety and acceptability have increased the appeal of electronic cigarettes to young people, thus leading to new generations addicted to nicotine. Moreover, there is growing evidence that electronic cigarettes in children and adolescents serve as a gateway to cigarette smoking. There can be no argument for harm reduction in children. To protect this vulnerable population from electronic cigarettes and other nicotine delivery devices, we recommend that electronic cigarettes be regulated as tobacco products and included in smoke-free policies. Sale of electronic cigarettes should be barred to youths worldwide. Flavouring should be prohibited in electronic cigarettes, and advertising accessible by youths and young adults be banned. Finally, we recommend greater research on the health effects of electronic cigarettes and surveillance of use across different countries.

Received: Feb 19 2018 | Accepted after revision: April 23 2018

Introduction

Smoking is not safe at any age, but prevention in children and adolescents has long been a public health priority. Tobacco dependence starts in childhood; close to 90% of current cigarette smokers start before their 18th birthday. The tobacco industry understands that youths, often referred as "replacement smokers" or "learners" in industry documents, are their critical market [1, 2]. Advertising campaigns have notoriously targeted youths [3–5]. Despite these pressures, teen smoking prevention strategies have generally been successful. For instance, combustible cigarette smoking among middle and high school students in the USA has fallen over the past few decades [6]. Although smoking remains high in some regions of Europe, the Health Behaviour in School-aged Children study showed that weekly tobacco smoking declined among adolescents in almost all countries between 2009 and 2014 [7].

However, a new threat to the health of children and adolescents has emerged, *i.e.* electronic cigarettes or electronic nicotine delivery systems (ENDS), although these devices need not be in the form of a cigarette nor deliver nicotine [8]. They have many other names, including vapes, vape pens, e-hookahs, electronic shishas, mechanical mods, Juul and others, but for the purposes of this position statement, we will use the term electronic cigarettes. Another related method of delivering nicotine, *i.e.* heat-not-burn devices [9], is not discussed here.

Electronic cigarettes deliver aerosols of nicotine and other chemicals to the lung. Although there are no universal or mandatory regulations or standards on content, these devices contain a vehicle (usually propylene glycol and glycerine), flavouring agents and nicotine. Other toxicants can be present as contaminants or generated by heating the solution, and other substances, such as marijuana and cannabis derivatives, can be added to the solution [10, 11]. Additionally, the aerosol exhaled by the user can involuntarily expose bystanders. Most electronic cigarettes release nicotine and other potentially toxic and irritating substances into the air [12].

Following repeated exposure to nicotine, the human central nervous system undergoes structural and functional adaptations, such that the brain requires nicotine to function normally, resulting in complex, biosocial maladaptive behaviours, known as dependence [13, 14]. Given their developmental stage, adolescents and young adults are uniquely susceptible to social and environmental influences to use tobacco [8, 15–17] and nicotine addiction [18, 19]. Several lines of evidence indicate that nicotine exposure during adolescence may have lasting adverse consequences for brain development [3, 20–22], even in those who smoke infrequently. Signs of nicotine dependence can appear within days to weeks of starting occasional use, often before the onset of daily smoking [23]. Data have shown that monthly smoking greatly increases the likelihood of developing dependence in youths [24, 25]. These findings in humans are supported by many animal studies that have provided mechanisms by which nicotine can lead to a pathway of addiction [26].

In 2014, the Forum of International Respiratory Societies, a collaborative of nine international professional organisations that was created to promote respiratory health worldwide, published a position statement concerning electronic cigarettes that outlined existing scientific data and advised caution until more information about their safety and effect on society are known [27]. During the 4 years since its publication, much has been learned about the claimed health benefits and risks of electronic cigarette use, particularly in adolescents and young adults. The current position statement addresses these issues.

Electronic cigarettes and nicotine addiction

With the public's appreciation of the serious health consequences of smoking [28], manufacturers modified tobacco products and marketed them with claims of fewer "toxins" and "carcinogens". These products, such as filtered, "low tar" and "light" cigarettes, have not resulted in less harm [3, 13, 29–31]. Because they are perceived to have lower health risks, electronic cigarettes are the latest addition to the list of industry products implying a beneficial safety profile. Electronic cigarette promoters, users and some professionals judge these electronic nicotine delivery devices to be safer than cigarettes [32–34], despite a lack of strong empirical evidence to support this claim. These judgements miss the point that comparing anything to a product that kills 7 million people each year should have a favourable conclusion and disregard the current trend of decreasing smoking rates without electronic cigarette use.

As noted previously, various nicotine delivery devices are available, with an array of design features and constituent components that significantly influence their pharmacological and toxicological profiles [35]. Evidence is emerging suggesting compensatory behaviours occur in response to this variation, in a manner similar to that identified in cigarettes several decades ago [36]. Electronic cigarettes are as capable of saturating brain nicotinic receptors as conventional cigarettes [37]. This effect may not concur with the nicotine content listed on refill bottles, which may reflect inaccuracy of labelling and manufacturing. Although some studies have shown that nicotine content corresponded to product labelling, analyses of

the ingredients of different flavoured, nicotine and no-nicotine cartridges showed that quality control processes used to manufacture these products can be inconsistent [38]. Some products labelled "nicotine-free" contained nicotine [38]. Electronic cigarettes with higher nicotine concentrations increased subsequent frequency and intensity of conventional smoking and vaping [39]. Also, although self-reported data suggest that 80% of adolescents choose products that do not contain nicotine [40], 99% of electronic cigarettes sold in US convenience stores, supermarkets, drug stores and through mass merchandisers contain nicotine [41].

Pulmonary toxicity of electronic cigarettes

Although the National Academies of Sciences, Engineering and Medicine found substantial evidence that exposure of potentially harmful ingredients from electronic cigarettes is significantly lower than combustible cigarettes [12], it does not mean that electronic cigarette aerosols are "harmless vapour" as industry has claimed in the past [8]. The vapour contains ultrafine particulates, volatile organic compounds and heavy metals, such as nickel, tin and lead [38, 42–44]. The ultrafine particle concentration, size distribution of the particles and deposition pattern in the lungs is similar for electronic cigarette vapour and conventional cigarettes [45, 46]. Electronic cigarettes often come with added flavourants. A flavouring that has been determined to be safe to eat may be toxic when inhaled. These substances are not inert and have been shown to injure airway epithelial cells *in vitro* [47]. Exposure to aerosol extracts causes significant DNA damage in human oral and lung cells, highlighting the need to further investigate the long-term cancer risk of exposure to these products [48]. Inhalation of electronic cigarette aerosols leads to pulmonary inflammation, impaired innate immunity, reduced lung function and changes consistent with chronic obstructive lung disease (emphysema) in pre-clinical animal models [49–52]. Studies in humans, including adolescents, in the USA, South Korea and China have linked their use to chronic or recurrent respiratory symptoms [53–56]. More recently, proteomic analyses of bronchoalveolar lavage collected from nonsmokers, smokers and vapers clearly showed that electronic cigarette vapours exert marked and extensive biological effects on human airways, albeit different than tobacco smoke. These findings suggest that inhalation of vapour is not innocuous and raises concern that electronic cigarettes "should not be prescribed as a safe or harmless tobacco alternative" [57]. Thus, regardless of the presence or absence of nicotine, exposure to electronic cigarette aerosol in adolescence and early adulthood is not risk-free and can result in pulmonary toxicity.

Electronic cigarette use among children and adolescents

Over the past decade, electronic cigarettes have risen rapidly in popularity among young people in many countries [58]. Based on data collected for the US National Youth Tobacco Survey, over 1.6 million high school students and 500 000 middle school students used electronic cigarettes in 2015, 10 times the number of reported users 4 years earlier [59]. An extensive survey of eighth- and ninth-grade students in the state of Oregon found that they were the most common introductory tobacco product used [60]. The product design, flavours, marketing, and perception of safety and acceptability increase the appeal of these products to young people [61]. Electronic cigarette advertisements on internet sites, retail stores, movies and other media are associated with growing use among students. Greater exposure has been associated with higher odds of use [62]. Much of the marketing is through the internet and social networking sites, with posted personal videos displaying the use of the product.

Data on awareness and electronic cigarette use among 35 000 surveyed youths from 25 countries reported overall that their awareness ranged from 15% in Kazakhstan to 80% in Italy and that the past 30-day use ranged from 0.8% in Guyana to 15% among 15-year-old Danish boys and girls [63]. The International Tobacco Control Four-Country Survey, which included data from the USA, Canada, the UK and Australia, found the prevalence of trying electronic cigarettes was higher in young, nondaily smokers because of the perception that they were safer compared with traditional combustible cigarettes [62].

Another common reason for using electronic cigarettes among both youths and young adults is flavouring or taste. Even though flavourings are limited or banned in conventional combustible cigarettes by some countries, they are widely permitted in electronic cigarettes in all nations [64]. These restrictions reflect the well-known use of flavourings to promote tobacco product initiation among adolescents. The lack of regulation creates a fertile environment for the expansion of flavoured electronic cigarette marketing to the young [65]. In 2014, more than 7500 distinct, flavoured electronic cigarette products and solutions were available on the internet with over 250 new products introduced per month [66]. Data from the Population Assessment of Tobacco and Health Study and the National Tobacco Youth Survey revealed that 63–70% of youth users of tobacco products choose flavoured products [67, 68]. Furthermore, data from the National Tobacco Youth Survey showed that flavoured electronic cigarette use was associated with increased risk of smoking combustible cigarettes, supporting a plausible gateway effect [69].

Child and adolescent use of tobacco products reflects experimentation and initiation behaviours that ultimately lead to nicotine addiction. In a large cohort, 81% of youth users of electronic cigarettes reported that their starter product was flavoured compared with 61% and 46% of young and all adults, respectively [67]. Electronic cigarette manufacturers employ diverse and creative strategies to target marketing to adolescents and teens despite widespread bans on the sale of these products to persons less than 18 years of age. Advertising near middle and high schools, in neighbourhoods with high youth traffic, and on television commercials that appeal to youths are common approaches [70–72]. Packaging and display choices, such as candy and fruit iconography on the packaging, displays close to candy, and marketing materials at or below 3 feet (1 m) all enhance interest by youths [73]. For older adolescents and young adults, claimed safety benefits with flavoured electronic cigarettes have encouraged experimentation.

In the USA, electronic cigarette use among students has increased dramatically, and past-30-day use of electronic cigarettes among eighth-,10th- and 12th-grade students exceeded use of conventional cigarettes in 2015 [74, 75]. Among US middle and high school students, both ever and past-30-day electronic cigarette use has more than tripled since 2011. This phenomenon is not restricted to US youth. Although data is lacking for many countries, several national reports have shown marked increases in electronic cigarette use in children and adolescents. Based on survey data, 10–12% of high school students from the UK and South Korea have used electronic cigarettes [76, 77]. According to the National Health Institute survey conducted in Italy, 14% of consumers were adolescents and young adults. Moreover, 24% of Italian adolescent and young adult smokers preferred electronic cigarettes to combustible cigarettes [78, 79]. A large sample of Polish students showed that 24% had tried an electronic cigarette and 7% used them within 30 days of the survey [80]. Similar data have been reported in older Irish teens, with nearly 70% of combustible smokers also using electronic cigarettes [81]. Among students in Finland, aged 12–18 years, 17% had tried electronic cigarettes [82].

Adolescents who use electronic cigarettes tend to be more likely those at higher risk of initiating cigarette smoking [83, 84]. As nicotine addiction develops, the barriers to the use of other tobacco products decrease. Multiple tobacco product use is common among youths.

Nonetheless, there is “substantial” evidence that vaping increases the risk of combustible cigarette use in children and adolescents [85]. While some publications from Great Britain have downplayed the use of electronic cigarettes and their link to combustible cigarette use in adolescents [86, 87], numerous longitudinal studies have confirmed their role as a gateway to more conventional tobacco products [88–91]. A recent large survey of demographically diverse adolescents from 20 schools across England showed that ever-use of electronic cigarettes was strongly associated with smoking initiation and escalation [92]. Meta-analysis of seven studies that included over 8000 adolescents and young adults who were not cigarette smokers at baseline found that among those who had ever used electronic cigarettes, the probability of combustible cigarette smoking initiation was nearly four-fold greater than nonusers [88]. A longitudinal study of US high school students in Connecticut found that electronic cigarette use was associated with subsequent initiation of combustible cigarette use, whereas combustible cigarette use was not associated with subsequent electronic cigarette use. Furthermore, they found that frequency of both electronic cigarette and combustible cigarette use increased over time, consistent with the development of nicotine addiction [93]. The COMPASS study showed that recent electronic cigarette use among Canadian secondary school students was strongly associated with cigarette smoking status and susceptibility to future use [90]. An internet-based survey of young adults in California, aged 18–24 years, found that increased levels of electronic cigarettes use were associated with increased combustible cigarette use: those who used electronic cigarettes regularly smoked combustible cigarettes more heavily than occasional electronic cigarette users [94]. The association between electronic cigarette use and initiation of combustible cigarette smoking was much stronger among adolescents classified as not susceptible to becoming smokers [8]. These data indicate that electronic cigarette use in adolescents does not decrease the likelihood of combustible cigarette use. Rather, “vaping” is associated with increased combustible cigarette smoking among youths.

Youth marketing of electronic cigarettes

Electronic cigarettes are frequently marketed using tactics and themes that have previously been shown to influence use of conventional tobacco products among youths. Exposure of US middle and high school students to electronic cigarette advertising from any source increased between 2014 and 2016, with greatest exposure in retail stores, followed by the internet, television, and newspapers and magazines [95]. However, in contrast to conventional tobacco products, few studies have examined the effectiveness of electronic cigarette advertising and promotions on children and adolescents. A study of 600 British children, aged 11–16 years, showed that electronic cigarette advertising increased the appeal of electronic cigarettes and interest in trying them [96]. In the National Tobacco Youth Survey, exposure to advertising

was associated with current cigarette use among US middle and high school students [62, 97]. Of the 80% of adolescents who were exposed to electronic cigarette advertising in the Youth Tobacco Policy Survey, the great majority said flavourings were a prominent selling feature and that electronic cigarettes were associated with less perceived harm [98]. Indeed, flavourings and harm reduction are common selling points for electronic cigarettes for both internet electronic vendors and retail stores staff [99]. The 2014 US Surgeon General Report concluded that advertising and promotional activities by the tobacco companies cause the onset and continuation of smoking among adolescents and young adults [3], and evidence to date suggests they have the same impact on electronic cigarette use by youths. For this reason, advertising and promotion of electronic cigarettes in media that can be accessed by youths should be banned, and these activities for electronic cigarette manufacturers must be closely monitored.

Regulation of electronic cigarettes

Electronic cigarettes are variably regulated around the world [100]. In 25 countries, their sale is banned. In other nations, they are regulated as tobacco-related products, medicines, poisons, electrical appliances or consumer goods. Even in Europe, electronic cigarette regulation varies widely. Some countries apply many regulatory domains whereas others apply few. For instance, Portugal has regulations on child safety, advertising, promotion, sponsorship, health warning labelling, ingredients, flavours, minimum age, nicotine volumes and concentrations, reporting, safety, sale, tax, and vape-free areas. In contrast, Switzerland has no regulation but prohibits sale of nicotine-containing devices. Norway recently lifted its ban on electronic cigarettes, but Belgium, Austria and Turkey prohibit the sale of all products.

In 2016, only 23 countries had implemented minimum age-of-purchase policies [100], although a law on a minimum age-of-purchase has little or no effect if it is not enforced. Minors are easily able to purchase electronic cigarettes from the internet because of absent or weak age verification measures used by vendors. A recent study showed that minors successfully received deliveries of electronic cigarettes from 77% of purchase attempts and delivery companies never attempted to verify their age at delivery [101].

Data from six European countries indicated that electronic cigarette sales fall with price increases [102]. Another large study from European countries, which included adolescents and young adults, found that the prevalence of electronic cigarette use was proportionate to current conventional cigarette smoking. Large pictorial health warnings on tobacco products were negatively associated with current electronic cigarette use [103].

Strong regulation can protect youths from electronic cigarettes. In 2008, Korea regulated electronic cigarettes as tobacco products with prohibitions on indoor use, sales to minors, advertising bans, health warnings and taxes. While various municipalities have restricted the sale of electronic cigarettes to adolescents and young adults, there had been little federal regulation in the USA. From 2011 to 2015 the prevalence of the use of electronic cigarettes remained stable at about 4% in Korea, whereas it rose dramatically from 1% to 11% in the USA during the same period [104].

In 2016 there was a decline in electronic cigarette use in US middle school and high school students [74], temporally associated with the Food and Drug Administration enacting the “deeming rule” that broadened the definition of “tobacco products” to include electronic cigarettes, and made them subject to regulations set by the Family Smoking Prevention and Tobacco Control Act [65]. Concurrently, use of combustible cigarettes did not significantly change, which contradicts the hypothesis that use of electronic cigarettes protects adolescents from initiation of regular smoking. Increasing awareness of possible negative health effects of electronic cigarette use and control strategies at the national and state levels may have contributed to the reduction in electronic cigarette use in the USA [65]. However, a longer trend is needed to make firm conclusions, and continued vigilance is needed to further reduce electronic and combustible cigarette use among youths.

Conclusion and recommendations

ENDS are devices that deliver aerosols of nicotine and other volatile chemicals to the lung. Their use has rapidly escalated among youths and they are now the most commonly used tobacco product among adolescents. Initiation of electronic cigarette use is strongly associated with the subsequent initiation of combustible tobacco product use among adolescents. Electronic aerosols contain potentially harmful ingredients that often lead to lung injury and chronic respiratory symptoms in users. Hundreds of electronic cigarette brands with thousands of unique flavours are now on the market and some flavourings have been associated with lung toxicity. Indeed, flavourings increase the appeal to youths. Even though it is widely accepted that electronic cigarettes are harmful to youths and lead to nicotine addiction, their regulation varies widely between countries. Existing laws designed to prevent youth access of electronic cigarettes are frequently not enforced.

Based on this information, the Forum of International Respiratory Societies recommends:

1) To protect youths, ENDS should be considered tobacco products and regulated as such, including taxation of electronic cigarettes and supplies. The addictive power of nicotine and its adverse effects in youths should not be underestimated.
2) Considering the susceptibility of the developing brain to nicotine addiction, the sale of electronic cigarettes to adolescents and young adults must be prohibited by all nations, and those bans must be enforced.
3) All forms of promotion must be regulated and advertising of electronic cigarettes in media that are accessible to youths should cease.
4) Because flavourings increase rates of youth initiation, they should be banned in electronic nicotine delivery products.
5) As electronic cigarette vapour exposes nonusers to nicotine and other harmful chemicals, use should be prohibited in indoor locations, public parks, and places where children and youths are present.
6) While their health risks are increasingly recognised, more research is needed to understand the physiological and deleterious effects of electronic cigarettes.
7) Routine surveillance and surveys concerning combustible and electronic cigarette use should be carried out in many settings to better understand the scope and health threat of tobacco products to youths in different countries and regions.

Acknowledgements: The member societies of the Forum of International Respiratory Societies are the American College of Chest Physicians, the American Thoracic Society, the Asian Pacific Society of Respirology, Asociación Latinoamericana del Tórax, the European Respiratory Society, the International Union Against Tuberculosis and Lung Disease, the Pan African Thoracic Society, the Global Initiative for Asthma, and the Global Initiative for Chronic Obstructive Lung Disease.

Conflict of interest: H.J. Farber reports nonfinancial support from the American Thoracic Society for service as Chair, Tobacco Action Committee, and salary support from Texas Children's Health Plan for service as Associate Medical Director, outside the submitted work. A. Vanker reports receiving grants from the Bill and Melinda Gates Foundation (OPP1017641), the Discovery Foundation, the National Research Fund, South Africa, and the Medical Research Council, South Africa, and a Clinical Infectious Diseases Research Initiative Clinical Fellowship, outside the submitted work. T.W. Ferkol reports receiving personal fees from the American Thoracic Society for society leadership and the American Board of Pediatrics for service as a sub-board member, research grants from the National Institutes of Health and National Health and Medical Research Council, and has been an investigator on clinical and device trials for Parion Sciences and Circassia Pharmaceuticals, all outside the submitted work.

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Facts and fiction on e-cigs

What are they?

Electronic cigarettes, also known as e-cigarettes, e-cigs or, most accurately, Electronic nicotine delivery systems (ENDS), are devices that deliver an aerosol (incorrectly called 'vapour'), inhaled by the users and created by heating a solution, usually composed of propylene glycol or glycerol (glycerin) and flavourings, generally with nicotine. While they both contain nicotine, e-cigarettes and traditional cigarettes are entirely different products. Thus, while the vapour from e-cigarettes does not contain some of the harmful substances in traditional cigarettes, it does contain different harmful substances not found in traditional cigarettes, so the health effects of using both can be expected to be greater than either alone. ENDS have been heavily marketed in some countries in recent years. In 2017, about 15% of the European population had tried e-cigs at least once in their life.[1]

The WHO view on e-cigs

In 2016, the World Health Organization (WHO)[2] noted that, while e-cigarettes *might* be less harmful than conventional cigarettes, e-cigarettes still pose important risks to health, and that ENDS regulation should:

- Deter e-cigarette promotion to non-smokers and young people;
- Minimise potential health risks to e-cigarette users and nonusers;
- Prohibit unproven health claims about e-cigarettes;
- Prevent/Bar/Ban involvement of the tobacco industry in the marketing and promoting of e-cigarettes.

The legislative situation in Europe

As of May 2016 all European Union (EU) countries must comply with the EU Tobacco Products Directive that includes regulations for ENDS. The Directive[3] states that their packaging should provide information on toxicity and addictiveness, health warnings, and a list of all the substances contained in the product, including the exact level of nicotine (that should be in a concentration level of no more than 20 mg/mL). The Directive also requires that advertising and promotion rules for tobacco products also apply to electronic cigarettes.

Answering key-questions about e-cigs

Are e-cigs safe?

- E-cigs have only recently been used widely so there are limited long term data. Consequently, as noted by the WHO, it is impossible to say if and by how much they are safer or more dangerous than traditional cigarettes. The widely cited figure of 95% safer[4] emerged from a discussion among individuals, most of whom had previously advocated for these products,[5] who conceded the lack of evidence on which to base their conclusion.[6]
- E-cigs do not produce the tar produced by traditional cigarettes that is the main cause of lung cancer. However, they do produce formaldehyde, a known carcinogen at levels above recommended levels.[7] In addition, nicotine acts in ways that may encourage spread of established tumours[8] and reduce the effects of cancer chemotherapy.[9] Overall, however, the risk of cancer is unknown, though likely to be lower.
- E-cig use has been tied to lung disease, with a growing body of research, including laboratory studies, case reports and population epidemiology, reporting adverse effects of e-cig vapour, potentially linked to flavourings not found in traditional cigarettes that have been tested.[10,11,12]
- E-cig use adversely affects the cardiovascular system, with a number of studies linking them to impaired functioning of blood vessels. A recent cross-sectional study found that daily e-cigarette use is associated with increased risk of heart attacks, with an additional effect in those also smoking, and while the authors were careful not to claim a causal relationship, they noted that the findings are consistent with the growing body of research on the effects of e-cigarettes on the vascular system.[13]
- The level of nicotine and other components released varies greatly among products, even at equal levels of nicotine in the refill liquid, due to the considerable differences among the different types and brands of e-cigs. The voltage of the system also affects nicotine delivery. Consequently, it is not possible to extrapolate findings from one product to another.

Conclusion:

The health risks associated with e-cigarettes remain uncertain but they cannot be considered safe. What is certain is that statements that they are some percentage safer than conventional cigarettes are so far unjustified.

Are e-cigs effective in helping to quit smoking?

- E-cigarettes are promoted in some countries as a tool to quit conventional smoking. However a recent meta-analysis of 27 studies reports that smokers (the whole population, including heavy smokers and all other smokers) who use e-cigarettes are about 1/3 less likely to quit smoking, compared to smokers who do not use e- cigarettes.[14]
- These findings are consistent with a study using survey data from all 28 EU Member States, which also found that e-cigarette use was associated with reduced quitting.[15]
- A Cochrane Review of the small number of randomized trials concluded that the evidence for their effectiveness was of low quality[16] and a subsequent large randomised controlled trial found that they were of no additional benefit when added to provision of information and motivational text messages.[17]
- One large US study following exclusive e-cig and dual users over a year found that, while some of each group did quit or moved from dual use to sole e-cig use, more than twice as many continued to smoke, with a net increase in risk.[18]

- The largest review to date, conducted by the US National Academies of Science, Engineering and Medicine,[19] concluded that "For youth and young adults, there is substantial evidence that e-cigarette use increases the risk of ever using combustible tobacco cigarettes. For e-cigarette users who have also ever used combustible tobacco cigarettes, there is moderate evidence that e-cigarette use increases the frequency and intensity of subsequent combustible tobacco cigarette smoking."

Conclusion:

Overall, e-cigarettes may help some smokers quit but, for most, e-cigarettes depress quitting.

Do e-cigarettes act as a gateway to tobacco consumption?

- Evaluating the association between e-cig use and subsequent smoking is complicated by the fact that smoking rates among young people are falling in many countries, regardless of whether e-cigs are available or not.
- A recent meta-analysis reports never-smoking adolescents and young adults who have at least tried e-cigarettes have a greater risk of starting conventional smoking (quadruple the odds compared to those that did not try e-cigarettes).[20] This cannot be explained by arguments that these young people would otherwise have started smoking.[21]
- The overall evidence has recently been summarised in a major report for the Australian government as follows: "The evidence for a strong positive relationship between use of e-cigarettes and later cigarette smoking amongst youth continues to accumulate. The evidence is consistent in observational studies and across different countries. A plausible biological pathway from use of e-cigarettes to conventional cigarette smoking operates through developing addiction to nicotine. The use of e-cigarettes with higher concentrations of nicotine is observed to have a stronger association to later conventional cigarette use."[22]
- Among adults, dual use is the predominant pattern.

Conclusion:

The net effect of making e-cigarettes widely available, at population level, seems likely to be an increase in sole and dual use of e-cigarettes and sole smoking unless there is very stringent regulation.

What is the role of the tobacco industry?

- The tobacco industry is promoting e-cigs as well as their related heated tobacco products (which they inaccurately label 'heat-not-burn') intensely, especially in smaller countries where tobacco control communities are weaker. One vehicle for this is the Philip Morris-funded Foundation for a Smoke Free World.[23] Consistent with the views of WHO and many Schools of Public Health, EUPHA's view is that public health organisations should not accept funding from this foundation under any circumstances.

Conclusion:

E-cigarettes and "smoke not burn" products are portrayed publicly by the tobacco industry as a means to reduce smoking yet, at the same time, these companies are actively promoting their combustible products.

EUPHA's view on e-cigs:

Given the available evidence, EUPHA strongly supports the precautionary approach taken in the EU Tobacco Products Directive and in statements by WHO. It is not possible, at this point, to make any claims about the relative safety of e-cigs compared to traditional cigarettes. The overall effect may well be to worsen the tobacco epidemic first by deflecting smokers from using proven smoking cessation strategies and shifting them to e-cigs, which, for most smokers, reduce successful smoking cessation, and second by deflecting discussion from measures opposed by the tobacco industry. E-cigarettes are expanding the nicotine market by attracting youth who were at low risk of initiating nicotine use with conventional cigarettes, but many of whom are now moving on to those conventional cigarettes. Even if they do not progress, promoting nicotine use to youth is bad public health policy.

EUPHA also welcomes the recent Bloomberg Stop! Initiative, which will provide important additional information on the strategies used by the tobacco industry, while commending to journalists, researchers and others the important resource Tobacco Tactics.[24]

As The Lancet noted in a recent Editorial,[25] referring to a heavily criticized UK House of Commons Science and Technology Committee report on e-cigarettes, it is "naive and premature.. to confuse an absence of evidence with an absence of harm."

Meantime, the tobacco industry continues to promote its "core product", traditional cigarettes globally, and with a special focus on low and middle income countries: EUPHA urges all concerned to reduce smoking to maintain their focus on evidence-based measures that will reduce smoking.

> *"The market competes on addiction—the most addictive products win out. With research, they [firms], like the cigarette companies, may find out which of their ingredients is most effective in increasing sales/addiction. […]they are loath to give up these profit opportunities, no matter the costs to society."*
> Joseph E. Stiglitz, Recipient of the Nobel Memorial Prize in Economic Sciences, 2008

For more information, please contact the EUPHA office at office@eupha.org.

EUPHA

The European Public Health Association, or EUPHA in short, is an umbrella organisation for public health associations in Europe. Our network of national associations of public health represents around 20'000 public health professionals. Our mission is to facilitate and activate a strong voice of the public health network by enhancing visibility of the evidence and by strengthening the capacity of public health professionals. EUPHA contributes to the preservation and improvement of public health in the European region through capacity and knowledge building. We are committed to creating a more inclusive Europe, narrowing all health inequalities among Europeans, by facilitating, activating, and disseminating strong evidence-based voices from the public health community and by strengthening the capacity of public health professionals to achieve evidence-based change.

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This report received funding under an operating grant from the European Union's Health Programme (2014-2020).

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Review article

J Atherosclerosis Prev Treat. 2022 Sep-Dec;13(3):119–125
doi.: 10.53590/japt.02.1041

A Collection of Position Statements and Opinions on e-cigarette use and cardiovascular disease: On behalf of the Working Group on Epidemiology of the Hellenic Atherosclerosis Society

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ABSTRACT

There are accumulative evidences that the prevalence of cigarette smoking has gradually declined in most high-income countries since the 1990s, in part due to public health campaigns emphasizing on the relationship between tobacco use and detrimental health effects. In late 2000s electronic (e)-cigarettes were introduced in the world, as less harmful nicotine products that may also help people in quitting smoking. Since then, the use of e-cigarettes has increased rapidly from the time when their introduction in the global market. In this work we present a collection of position statements and opinions of scientific bodies and Organizations, regarding the safety of e-cigarettes, as well as their association with human health, and particularly, cardiovascular diseases.

KEY WORDS: *Position statements, e-cigarettes, vaping, cardiovascular disease*

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INTRODUCTION

It is well constituted that conventional cigarette smoking increases risk for cardiovascular disease, in current smokers and passive smokers[1], even among those smoking

Submission: 09.09.2022, Acceptance: 24.09.2022

cigarettes of low tar[2], compared to non-smokers. Evidence took decades to accumulate since associated health risks to cigarette smoking are both dose and duration dependent[3]. Since this evidence came to light, tobacco related products emerged, one of which is the electronic cigarette/nicotine delivery systems, as safer tobacco products, driven from the tobacco companies themselves, although recent studies suggest increased health risks, at a level that may surpass the traditional cigarette smoking itself[3].

In 2003, electronic (e)-cigarettes were patented by Hon Lik, in China. In the year that followed, they became available for purchase, firstly in China, and then, in the entire world[6]. In the United States of America, they have been available since 2007 and one year prior to that, in the European Union (E.U.)[8]. There are several synonyms of electronic (e)-cigarettes, i.e., Electronic Nicotine Delivery Systems (ENDS), "e-cigs", "vape-pens", "mods", "e-cigars", according to the Centers of Disease Control and Prevention (CDC)[4]. The American Heart Association (AHA) defines electronic cigarettes (e-cigarettes) and vaping, respectively, as "*battery-powered devices that can deliver nicotine and flavorings to the user in the form of an aerosol*", and "*the act of inhaling and exhaling the aerosol, often referred as vapor, which is produced by an e-cigarette or similar device*"[5].

From the time e-cigarettes became available in the market, and up to date, there are controversial findings regarding their effects on health. The principle, promoting idea was that e-cigarettes constituted a healthier option compared to traditional cigarettes, and assist in quitting cigarette smoking[6]. According to the European Heart Network (EHN), "*e-cigarettes are promoted as risk-reducing products compared to combustible tobacco cigarettes*"[7], while the European Association of Preventive Cardiology (EAPC) states that they "*are promoted as safe alternatives for traditional tobacco smoking and are often suggested as a method to reduce or quit smoking*"[8]. In addition, it is stated by the World Health Organization (WHO), that with the pretense of helping public health, ENDS companies, advertise, and promote ENDS and make flavors to attract youths to increase the number of their customers[9]. This is an area of concern since ENDS-related harm perception did not increase among adolescents 12- to 17-year-old that did not have positive tobacco attitude and lived in smoke free home rules[10]. Furthermore, smoke free environments have been established in many countries for tobacco related products for public health prevention, but few for ENDS, which may also expose individuals to nicotine and particulate matters[11]; substances that can trigger inflammation, oxidative stress, and other thrombotic effects[3]. A population survey of ENDS users reported that 58% of dual users (ENDS and cigarettes) used ENDS in public smoke free environments[12], intensifying the need to review position statements and opinions by experts in the field.

POSITION STATEMENTS AND OPINIONS BY SCIENTIFIC ORGANIZATIONS AND REGULATORY BODIES

World Health Organization (WHO)

The past two decades data from the WHO indicated that global tobacco use has been significantly reduced, especially among women[6]; however, e-cigarettes is an emerging trend, especially among younger individuals. These are not harm free since it is stated that toxic materials and nicotine are present in ENDS at varying quantities[6]. Specifically, long-term effects to nicotine exposure have been associated with abnormal brain development, seen in fetuses, children, teenagers, and youths[6]. Chemical addiction can, therefore, occur through e-smoking as well, which in turn can result in the use of traditional tobacco products, instead of the preliminary reason they were marketed, which was tobacco smoke cessation. It has been estimated that the possibility of smoking increases two-fold for underage individuals who e-smoke, although they had never smoked[6]. Public health officials' positions report that e-cigarettes can constitute "*a "gateway" to conventional smoking among young people*"[6].

The health of e-smokers is not the only one harmed by ENDS. As stated previously, ENDS emit nicotine and particulate matters, therefore expose individuals, that are near a person who is e-smoking, to second hand aerosols[6], in an otherwise "smoke-free" environment. In addition, children may be exposed, or even drink e-liquid, and suffer from poisoning. Moreover, ENDS may be altered by their owners or may be faulted from the manufacturer leading to accidents, such as explosions or fires[6].

Based on a recent scoping review, the toxicity of traditional cigarettes is probably higher compared to ENDS, since it was not revealed ENDS to be causative of CVD outcomes as well as that switching to e-cigarettes was associated with improved hypertension control[13]. However, the long-term effects of ENDS remain unknown, due to the inadequacy of evidence, and controversial findings remain due to the variety of ENDS products (device voltage, liquid composition, the amount of vapor inhaled, etc.). It is also important to note that most e-cigarette users are former smokers or dual users, increasing the difficulty to differentiate the effects. Various factors most likely will determine how risky tobacco products or ENDS are and can vary between person and by ENDS product. Specifically, for cardiovascular disease, it is supported that an increased risk can occur from e-smoking, due to various constituents, such as nicotine, carbonyls, and particulate matters, although a recent scoping review found

no such effect[14]. How health will be affected in the long term hasn't yet been determined for all people who breathe aerosols. Also, it hasn't been determined by evidence, so far, that ENDS can serve in smoking cessation, as aids, since most of the e-cigarette users are dual users[15]. Negative consequences have also been added to the previous fact, since it has been shown that never smokers are more likely to start ENDS products by younger individuals, viewed as safe products[13].

Tobacco control measures can be weakened by ENDS, and there is a possibility that the certain devices might "escape" laws, because they change in a quick pace. Regulation of ENDS is suggested for countries where they are allowed[6], and although 48 countries (58.3%) have legislation on e-cigarette use at the national level, only a third regulated e-cigarette indoors, failing to protect bystanders in indoor settings[16].

World Heart Federation (WHF)

The WHF perceives un-regulated e-cigarette use a serious threat and recommends a set of precautionary measures to protect vulnerable population, prevent second-hand exposure and address misleading claims[9]. The following presents some statements from a Policy Brief by the WHF (2021), regarding cardiovascular health and e-cigarettes. It is noted by the WHF that an association exists between increased risk of cardiovascular mortality and morbidity, and vaping. Atherosclerosis, elevation of blood pressure, increased risk of myocardial infarction and oxidative stress are parts of several health problems that have been associated with vaping. Evidence supports that e-cigarettes may lead to similar cardiovascular problems as cigarettes, because they both share the same health-harming substances; yet, the risk is lower in e-cigarette smokers, at least in former smokers. According to the evidence, the short-term cardiovascular health benefits of e-cigarettes seem to be positive. In cases where vaping is used alongside with cigarette, then there is a possibility that the CVD risk rises. The WHF also noted that it is very difficult to determine the exact health effects of vaping, due to the various ways of use, devices, populations, flavors, and e-liquids. Moreover, regarding Public Health and e-cigarettes, it is stated that other diseases must be considered in the evaluation of the consequences.

Another crucial issue, according to the WHF, is the fact that popularity of e-cigarettes/vaping has risen tremendously in the past years, among younger ages. The design, the different flavors and because the new fashion trend are the main reason for increased use in youths. Misleading advertising on the safety of e-smoking and extended marketing remain serious incentives for smoking initiation on that vulnerable age group. It is therefore suggested -among others- that an additional taxation on e-cigarettes, a ban on marketing, sale and distribution can effectively reduce e-cigarettes among those ages. In addition, vaping and smoking should share the same ban regarding the places where is it not allowed, and restrictions regarding commercialization of e-cigarettes shouldn't be lifted by countries who are applying them.

Irrespective of age, all individuals should be safeguarded and preventative strategies against e-smoking/vaping should be implemented. Tobacco control legislation must be reinforced by future laws regarding e-cigarettes, and more scientific evidence is needed regarding the long-term effects of e-smoking/vaping on cardiovascular health. Lastly, further studies must take place on the topic of long-term effects of e-cigarettes on cardiovascular health[9].

European Commission: Scientific Committee on Health, Environmental and Emerging Risks (SCHEER)

The SCHEER was mandated (2019) by the European Commission for an opinion on the potential risks of e-cigarettes use on health. The Committee concluded that, in relation to vaping, risks of long-term systemic effects on cardiovascular system are supported moderately by evidence. Moreover, it is weakly supported that aerosol metals can cause adverse effects, particularly carcinogenicity. Evidence in characterized as weak to moderate, regarding "*risks of carcinogenicity of the respiratory tract due to long-term cumulative exposure to nitrosamines and due to exposure to formaldehyde and acetaldehyde*". In addition, it is not supported by specific data that certain flavors in the European Union are risky for health after repeated exposure. Risks of other adverse health effects, like reprotoxic effects and pulmonary disease, are weakly supported and there is a need for additional data that presents consistency. Also, it is moderately supported that cumulative exposure to aldehydes, polyols and nicotine causes risks of local irritative damage to the respiratory tract. Additionally, risks of poisoning and injuries due to burns and explosion are strongly supported by evidence. The incidence of the last two health problems is described as low.

Equivalently, for people who are exposed to vaping second-hand, evidence is described as weak to moderate regarding "*carcinogenic risk due to cumulative exposure to nitrosamines*". Additionally, it is moderately supported by evidence "*risks of local irritative damage to the respiratory tract mainly due to exposure to glycols*". Specifically, about cardiovascular health, evidence is characterized as weak to moderate, regarding risks of systemic cardiovascular effects due to nicotine exposure.

Possible health effects on people who vape occur

mostly due to the vapor's substances. The particular substances, including nicotine, differ in their quantities. Specifically, for nicotine, it is strongly supported that the pattern of which e-cigarettes are vaped by their owner and the specifications of the e-cigarettes, determine the quantity of the chemical that is being consumed. Moreover, the quantity can be put side by side with traditional cigarettes, regarding long term e-smoking adults.

It is strongly supported that one of the reasons of vaping is appealing to people due to e-liquid flavors. Moreover, evidence is characterized as strong, regarding the involvement of nicotine in people becoming addicted. It is moderately supported that vaping is a "*gateway to smoking*" for young individuals and weakly supported that e-cigarettes are effective for smoking cessation. Evidence is characterized as weak to moderate, regarding e-cigarettes assisting people to decrease smoking. People haven't been exposed to vaping for many years and health effects, especially those of the long term, need to be studied further[17].

US Centers Disease Control (CDC)

The US CDC states that more harm is caused by traditional smoking compared to vaping, and however, vaping is quoted as not entirely safe for young ages[4]. E-cigarettes seem to be risky during pregnancy and for young adults and adults who do not use tobacco products. Children have been poisoned by swallowing, inhaling or ingesting e-cigarette liquid through the skin or eyes. Specifically, almost half of the calls to poison control centers for e-cigarettes, concern preschooler children. As referenced by the CDC, the Food and Drug Administration (FDA) does not recommend e-cigarettes for smoking cessation, and the U.S. Preventative Services Task Force reports evidence as inadequate to support the use of e-cigarettes as a stop smoking aid, regarding adults and pregnant women. However, it seems they may provide a kind of smoking cessation support only if they are not used dually with cigarette smoking. Yet, evidence reveals that most e-smokers are also cigarette smokers. It is obvious that more research is needed regarding the long-term health effects of e-smoking as well as the benefit in smoking cessation[4].

European Heart Network (EHN), European Association of Preventive Cardiology (EAPC)

EHN

The recent report of the EHN addressed two main issues about the effects of e-cigarettes/vaping on cardiovascular health and their effectiveness on smoking cessation. Even though, the short-term effects on cardiovascular health are not quite clear and the evidence seems to be inconclusive, however it is supported that the risk still exists. Compared to conventional smoking, e-smoking is less harmful due to the absence of several toxic and carcinogenic agents, but it does not mean that it is safe and without health complications. For the long-term effects, more robust evidence is needed. However, there is good evidence supporting that heart rate may increase shortly after nicotine intake from vaping and may affect platelet functionality, blood pressure, and oxidative stress[7]. Moreover, up to date there is no sufficient evidence that e-cigarettes constitute an effective mean regarding smoking cessation. Additionally, a large majority of those who use e-cigarettes, as a smoking cessation process, they end up as dual smokers with increased health risks. The increased rate of e-smoking/vaping among young ages, starting from adolescence is quite alarming. A factor that has led to this increase is the appealing flavors provided for e-cigarettes and since the perception of safe to consume in contrast to traditional smoking. There is a possibility that public health will be affected in a negative way by e-cigarettes. The industry-related conflict of interest influence on results of studies to support the safety of e-cigarettes, regarding their health effects, constitutes another problem. Regulations on e-cigarette taxation, on restricting e-smoking in public places and on banning marketing and flavors could eliminate the use of e-cigarettes mainly among young ages[7].

EAPC

The EAPC of the European Society of Cardiology (ESC) published in 2021 a position statement on e-cigarettes and cardiovascular risk[8]. The EAPC concluded that, regarding the prevalence of vaping, it differs from country to country, within a country, and between people who currently vape or have vaped. However, the prevalence, among youth and teenage age groups, is rising. Additionally, it is supported that the possibility of smoking traditional cigarettes rises because of the prevalence of vaping in the certain age groups. Regarding CVD, the effects of vaping haven't been studied extensively. The belief that traditional cigarettes are more damaging than e-cigarettes is because the exposure to potentially toxic chemicals -with the exception of nicotine- is higher in cigarettes, under regular vaping circumstances. Regarding the cardiovascular system, the effects in the long term of vaping are mostly not comprehended. According to research, endothelial dysfunction and arterial stiffness constitute some health problems that can be caused by e-smoking. In addition, due to the rise of e-smoking in vulnerable populations, the "benefit" of lesser damage will not be completely balanced out. EAPC agrees that vaping is harming to the cardiovascular system,

according to evidence and additional research on its effects in the long term must take place, with young people being prone, due to their wrongful healthiness perception. Because of this, it is suggested that a ban should be placed on those flavors. Additionally, indoor smoking or vaping, the attainment of e-cigarettes by bypassing laws and the possible reasons why youths might be drawn to them constitute other existing issues. It can be concluded that young peoples' health can be put in danger, and for vaping to be as limited as possible, public health action must be taken. Regarding the previous, prevention via education and awareness can help. It is stated that regulations haven't been keeping up with the market of e-cigarettes and therefore laws must be adjusted accordingly and enforced. In addition, it is suggested that laws must be formed, regarding e-cigarettes, by countries that don't have them. It is also noted that evidence is described as inadequate, regarding e-cigarettes in smoking cessation and assisting in long-term maintenance of not smoking. It is also supported that abstinence percentages might grow if behavioral therapy and vaping are used together in smoking cessation. However, if e-smoking is utilized exclusively in a clinical environment, there is a possibility that cessation will be weakened for most adults that are trying to quit without attending such environments. Further studies must be conducted for longitudinal data to be attained regarding smoking cessation and the impact of e-cigarettes on it[8].

Existing recommendations in relation to position statements

A recent Scoping Review, upon collecting 81 statements from international health organizations with regards to the use of ENDS, observed that they could be summarized in a total of 5 different types[18]. Overall, two encouraged their use by smokers and three were opposed to it. The most prevalent opposing statement was the restrictive non-use attitude.

a) Support Selective Use

Encouragement of current smokers to use ENDS as a smoking cessation assistance. The user should be informed of alternative licensed drugs and counseling alternatives. Regulating ENDS as pharmaceuticals would increase product safety and permit marketing limits. The availability and usage of ENDS cannot interfere with current tobacco control initiatives, such as smoke-free regulations.

b) Selective Use Encouragement

Encouragement of smokers to transition to only using e-cigarette or to use e-cigarette as a quitting aid. Product innovation, user attractiveness, lower taxation, and health messages emphasizing e-cigarette's lower harm should be prioritized in vaping regulation.

c) Precautionary non-use

Although ENDS are probably less dangerous than cigarettes, it is still unclear whether they expose users to long-term hazards or serve as successful cessation assistance. Until more information is available, use is not advised. To be on the safe side, smokers should be urged to stop using medications that have already received approval. Until new safety precautions are put in place and/or new data is available, these recommendations shouldn't be changed. It is advised to carry on researching.

d) Restrictive non-use

ENDS should be avoided since they undermine tobacco control efforts. According to the evidence that is currently available, consumption is not advised, and restrictions should concentrate on limiting business operations and product accessibility. ENDS need to be governed like tobacco.

e) Prohibit use

To prevent health concerns, ENDS-containing items should be illegally unavailable.

Unresolved issues and evidence gaps

Even though e-smoking/vaping is not considered entirely safe and several efforts have been made to underline the risks posed by the exposure to first-hand and second-hand e-smoking, still several issues need to be clarified. In Table 1 unresolved issues and evidence gaps which need to be addressed by evidence-based research are presented.

Unresolved issues and evidence gaps

Even though e-smoking/vaping is not considered entirely safe and several efforts have been made to underline the risks posed by the exposure to first-hand and second-hand e-smoking, still several issues need to be clarified. In Table 1 unresolved issues and evidence gaps which need to be addressed by evidence-based research are presented.

Conclusive remarks

Although ENDS started as an initiative to help quit traditional smoking, there is week to moderate evidence to support this strategy, as noted by the European Commission as well. On the contrary, there is research depicting

TABLE 1. Unresolved issues and evidence gaps.

Unresolved issues:	Evidence gaps:
• According to the FDA report, it is illegal to sell any type of cigarettes, including e-cigarettes in people under the age of 21 years. However, these products are still available to young adolescents due to limited policies (19). • E-smoking products are advertised as safer compared to other tobacco products and ideal for smoking cessation, but the main message tailored is "safe" not "safer". • The chemical and nicotine content in e-cigarettes' is rarely disclosed by tobacco companies. No policies are in place. • Regardless to the WHO recommendations on banning indoor e-cigarette smoking, it remains unregulated in many countries (20). • Taxation on e-cigarettes and vapor products varies according to the liquid volume and nicotine concentration, and by country as well. • Arguments still exist on the hazards of nicotine content of e-cigarettes.	• Long-term effects of e-smoking on CVD remain unclear, due to the lack of longitudinal and clinical studies • Many e-cigarette smokers are either former smokers or dual smokers, eliminating the causality relationship between e-smoking and CVD • Limited evidence exists on the effectiveness of e-smoking as a smoking cessation tool

that ENDS cannot be regarded as a complete safe alternative to tobacco and further research needs to take place for the determination of its effects on health in the long term. In addition, many ENDS with vaping being higher in the list, has negative effects on the cardiovascular system and further research needs to be conducted for the determination of its effects in the long term on the said system. Moreover, youths may start smoking because of the appealing taste and wrongful perception of vaping and thus, more regulations to ban e-cigarette use for minors are needed. Also, exposure to harmful particulate is rising again since indoor regulation of ENDS are lacking by two-out-of-three of the countries, worldwide[21]. Lastly, public health initiatives that discourage non-smokers from using e-cigarettes and/or conventional cigarettes, by intensifying health awareness programs are urgently required.

Conflict of interest

There are no conflicts of interest

ΠΕΡΙΛΗΨΗ

Τοποθετήσεις οργανισμών για τη χρήση ηλεκτρονικού τσιγάρου και την καρδιαγγειακή νόσο: εκ μέρους της Ομάδας Εργασίας Επιδημιολογίας της Ελληνικής Εταιρείας Αθηροσκλήρωσης

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Υπάρχουν επιστημονικά δεδομένα ότι, από τη δεκαετία του 1990, ο επιπολασμός του καπνίσματος έχει μειωθεί βαθμιαία στις περισσότερες χώρες υψηλού εισοδήματος, εν μέρει λόγω καμπανιών δημόσιας υγείας που έδιναν έμφαση στη σχέση μεταξύ της χρήσης καπνού και επιβλαβών επιδράσεων στην υγεία. Στα τέλη της δεκαετίας του 2000 τα ηλεκτρονικά τσιγάρα εισήχθησαν ως λιγότερο επιβλαβή προϊόντα νικοτίνης που μπορεί παράλληλα να βοηθήσουν και στη διακοπή καπνίσματος. Από τότε η χρήση των ηλεκτρονικών τσιγάρων έχει

αυξηθεί ραγδαία, σε παγκόσμιο επίπεδο. Σε αυτή τη μελέτη παρουσιάζονται τοποθετήσεις επιστημονικών φορέων και οργανισμών, σχετικά με την ασφάλεια των ηλεκτρονικών τσιγάρων, καθώς και τη συσχέτισή τους με την υγεία, και ιδιαίτερα, με την καρδιαγγειακή νόσο.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: *Τοποθετήσεις οργανισμών, ηλεκτρονικό τσιγάρο, άτμισμα, καρδιαγγειακή νόσος*

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AACR and ASCO Release Joint Policy Statement on Electronic Nicotine Delivery Systems

October 26, 2022

PHILADELPHIA and ALEXANDRIA, Va. – The American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) today released a joint policy statement outlining the latest research on the use of e-cigarettes and other electronic nicotine delivery systems (ENDS) and recommendations for regulating these products to protect public health. The statement was published in the AACR's journal *Clinical Cancer Research* and ASCO's *Journal of Clinical Oncology*.

"The popularity of ENDS among young people and adults who do not smoke continues to be a significant public health problem that threatens to derail decades of progress against tobacco use," said AACR President Lisa M. Coussens, PhD, FAACR. "Along with our colleagues at ASCO, we are alarmed by the rapid increase in the number of high schoolers using these products, as well as the growing body of evidence that suggests ENDS expose users to carcinogens while also increasing the likelihood that individuals will begin using other tobacco products. The policy statement published today emphasizes the urgent need for bold regulatory action and more research so that we can mitigate the dangers of these devices and maintain the momentum against the many cancers caused by tobacco use."

The statement builds on an earlier joint AACR/ASCO statement on ENDS, published in 2015, which called on the U.S. Food and Drug Administration (FDA) to regulate such products in order to address the growing rate of ENDS use among youth and young adults. The need for regulation is urgent as ENDS use among youth and young adults, as well as people who have never smoked, rose dramatically from 2015 to 2019.

While the COVID-19 pandemic, along with increased public awareness about the risks of these products and laws raising the minimum age to buy tobacco products to 21 years, likely contributed to a drop in ENDS use during 2020 and 2021, these declines were temporary. Unfortunately, new results from the National Youth Tobacco Survey show that ENDS use among high school students is once again growing. An estimated 2 million high school students use ENDS in 2022, a 24 percent increase compared to 2021. This situation highlights the need for continued regulatory and scientific attention to the public health risks posed by ENDS.

The AACR and ASCO collaborated to summarize the existing research on ENDS and propose policies to mitigate the potential harms caused by these products. According to the statement:

- While ENDS emit fewer carcinogens than combustible tobacco, preliminary evidence nonetheless links ENDS use to DNA damage and inflammation, key steps in cancer development.
- Appealing flavors are key drivers of youth ENDS use, with a 2020 survey reporting that more than 82 percent of youth who use ENDS use flavored products other than tobacco-flavored.

- Despite recent FDA restrictions on flavors other than tobacco and menthol in pod- or cartridge-based ENDS, flavored open tank and single-use products are still on the market and have dramatically increased in popularity among middle and high school students.
- A young person who uses ENDS is more likely to later begin smoking combustible tobacco, with studies finding that people who use ENDS are between 2.9 and 4 times more likely to ever smoke a combustible cigarette than people who have never used ENDS.

"While more research is needed to fully understand the long-term health effects of ENDS use, the harms of nicotine addiction—especially for young people—are well-known," said ASCO President Eric P. Winer, MD, FASCO. "Additionally, since it is increasingly clear that ENDS expose users to carcinogens and increase the odds that a young person will go on to smoke combustible tobacco, state and federal policy makers, along with other stakeholders, must advance policies that curb ENDS use in non-smokers and advance research on the long-term health impacts of these products."

The AACR and ASCO call on policy makers, regulatory authorities, and the research community to take action to combat ENDS use, especially among young people, and support evidence-based smoking cessation therapies. Specific recommendations in the policy statement include:

- Ban all non-tobacco-flavored products that contain nicotine;
- Tax all products that contain natural or synthetic nicotine in a manner that reduces tobacco use and promotes public health;
- Regulate predatory tobacco advertising practices, especially those designed to appeal to youth;
- Limit the sale of tobacco products, including ENDS, to stores or areas within stores that require age verification upon entrance, and increase enforcement of the minimum age to legally purchase tobacco products; and
- Support research to understand the long-term health impacts of ENDS use.

"I am proud to have chaired this effort to build consensus between the world's two leading cancer organizations on such an important topic," said Roy S. Herbst, MD, PhD, chair of the ENDS Statement Writing Committee and the AACR Science Policy and Government Affairs Committee, and deputy director of Yale Cancer Center. "The science is clear that ENDS pose health risks, especially for youth and people who do not smoke. This statement will provide much needed guidance and recent scientific research on the impact of ENDS and what policy makers can do to curtail nicotine addiction."

Electronic Nicotine Delivery Systems: An Updated Policy Statement from the American Association for Cancer Research and the American Society of Clinical Oncology

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ABSTRACT

Combustible tobacco use has reached historic lows, demonstrating the importance of proven strategies to reduce smoking since publication of the 1964 Surgeon General's report. In contrast, the use of electronic nicotine delivery systems (ENDS), specifically e-cigarettes, has grown to alarming rates and threatens to hinder progress against tobacco use. A major concern is ENDS use by youth and adults who never previously used tobacco. While ENDS emit fewer carcinogens than combustible tobacco, preliminary evidence links ENDS use to DNA damage and inflammation, key steps in cancer development. Furthermore, high levels of nicotine can also increase addiction, raise blood pressure, interfere with brain development, and suppress the immune system. The magnitude of long-term health risks will remain unknown until longitudinal studies are completed. ENDS have been billed as a promising tool for combustible tobacco cessation, but further evidence is needed to assess their potential efficacy for adults who smoke. Of concern, epidemiological studies estimate that approximately 15% to 42% of adults who use ENDS have never used another tobacco product, and another 36% to 54% "dual use" both ENDS and combustible tobacco. This policy statement details advances in science related to ENDS and calls for urgent action to end predatory practices of the tobacco industry and protect public health. Importantly, we call for an immediate ban on all non-tobacco-flavored ENDS products that contain natural or synthetic nicotine to reduce ENDS use by youth and adults who never previously used tobacco. Concurrently, evidence-based treatments to promote smoking cessation and prevent smoking relapse to reduce cancer incidence and improve public health remain top priorities for our organizations. We also recognize there is an urgent need for research to understand the relationship between ENDS and tobacco-related disparities.

Introduction

In 2015, the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) published a joint policy statement describing a rapidly growing epidemic of electronic nicotine delivery systems (ENDS), including e-cigarettes, and policies to address this trend (1). The 2015 statement sought to balance curtailing youth use while remaining optimistic that ENDS could be a less harmful alternative to combustible tobacco cigarettes for adult smokers. As detailed in the following sections, youth ENDS use has further increased since the 2015 statement while evidence remains insufficient to show ENDS are more effective than current smoking cessation strategies. Additionally, several major health authorities have determined that the current evidence base is lacking in supporting ENDS as tobacco cessation aids, including the U.S. Surgeon General (2); the National Academies of Science, Engineering, and Medicine (NASEM; ref. 3); the U.S. Preventive Services Task Force (USPSTF; ref. 4); and the National Comprehensive Cancer Network, a coalition of 31 leading cancer centers (5). At the time of this writing, no ENDS manufacturer has applied to the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) for an Investigational New Drug (IND) application, a prerequisite to run a

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This Updated Policy Statement was developed by a joint Writing Group composed of members from the Tobacco Products and Cancer Subcommittee of the American Association for Cancer Research (AACR) Science Policy and Government Affairs (SPGA) Committee and the American Society of Clinical Oncology (ASCO) Tobacco Cessation and Control Subcommittee of the Health Equity and Outcomes Committee (HEOC). The Updated Statement was reviewed by both parent committees (i.e., the AACR SPGA Committee and the ASCO HEOC), and was approved by the AACR Board of Directors on April 8, 2022 and the ASCO Executive Committee on April 21, 2022. This Updated Policy Statement was published jointly by invitation and consent in both *Clinical Cancer Research* and *Journal of Clinical Oncology*.

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Clin Cancer Res 2022;28:4861–70

doi: 10.1158/1078-0432.CCR-22-2429

tobacco cessation clinical trial. The AACR and ASCO are publishing the present statement to detail advances in scientific understanding of the ENDS epidemic, strengthen recommendations to protect public health, promote evidence-based tobacco cessation across all groups, and highlight areas where more research is needed.

Carcinogens from combustible tobacco products are very harmful to health, contributing to nearly half a million deaths each year in the United States and more than 8 million deaths per year globally (6, 7). The process of burning creates a large amount of carcinogens, such as benzo[a]pyrene, that are inhaled in smoke from traditional cigarettes (8). The first ENDS were introduced to the U.S. market in 2006 as a way to deliver nicotine to users without burning tobacco (9). Instead of burning tobacco, ENDS use electricity to power a heating element that aerosolizes an e-liquid, containing a solvent (e.g., propylene glycol or glycerin); nicotine; flavors; and other additives. Some ENDS products can result in rapid delivery of a similar amount of nicotine as modern American cigarettes, which contribute to high addiction potentials (10, 11).

Tobacco would likely not be the top public health issue without the highly addictive properties of nicotine when delivered rapidly. Every time someone consumes nicotine, the brain releases the neurotransmitter dopamine, which provides a sense of pleasure or satisfaction (12). Primarily due to the pharmacology of nicotine, over time, tobacco users become dependent on nicotine to feel pleasure and stave off withdrawal symptoms (13). This rewiring of brain circuitry is especially of concern for the developing brains of youth (14). Nicotine can also harm health by raising blood pressure (15) and suppressing immune function (16). Strong evidence from clinical trials examining very low nicotine cigarettes demonstrates that reducing nicotine to less addictive levels could effectively decrease smoking rates by reducing initiation and increasing cessation of cigarette use (17–21). In 2018, the FDA issued a proposed rule to lower the level of nicotine in cigarettes to nonaddictive or minimally addictive levels (22), but at the time of writing this rule has not advanced. While the present statement focuses on policies related to ENDS, additional regulations to reduce the addictiveness and appeal of combustible tobacco are also highly important.

The following sections outline updates since our previous statement related to the evidence of biological effects from ENDS that can contribute to cancer risk, use trends, effective tobacco cessation efforts, and ENDS regulations. The data support strong, urgent action to reduce ENDS use among youth and adults who never previously used tobacco. Because of the wide use of non-tobacco-flavored ENDS among these groups, we recommend an immediate ban on all non-tobacco-flavored ENDS products that contain natural or synthetic nicotine. However, if non-tobacco-flavored ENDS are reviewed and approved by FDA CDER to increase cessation efficacy, the AACR and ASCO would welcome these as cessation therapies at that time. At the same time, new tobacco regulations should be structured to avoid any increases in combustible tobacco use, including smoking initiation and relapse. The following sections describe the evidence by which we based our recommendations.

ENDS Linked to Key Steps in Cancer Development

ENDS expose users to carcinogens

The cancer-causing potential of ENDS is inferred from the currently available studies investigating the presence of carcinogens, human biomarkers of carcinogenesis, and animal and cell culture experiments. Carcinogens in ENDS can include four classes of chemicals, namely tobacco-specific nitrosamines; metals; volatile organic compounds; and polycyclic aromatic hydrocarbons. **Table 1** highlights several recent reports comparing carcinogens and metabolites in urine or saliva samples from ENDS users and those who never used tobacco. The data show that at least 12 carcinogens are significantly elevated in ENDS users compared with nontobacco users, but that their levels were generally lower than the levels of carcinogens seen in smokers and dual users (**Table 1**; refs. 23–26). Unfortunately, the data are limited by a small number of studies that compared ENDS users with nonusers, and each study reported a different set of carcinogens. Separate studies further characterized carcinogens in ENDS aerosols and found that the power and temperature of devices greatly influences the amount of toxic metals and volatile organic compounds emitted (27–30). Therefore, additional studies are needed for a more thorough and comprehensive understanding of the carcinogen load experienced by ENDS users. Nevertheless, the results of ENDS use investigated to date clearly indicate that vaping exposes the user to carcinogens and therefore likely increases long-term cancer risk, but for most carcinogens at levels far lower than from smoking combustible tobacco cigarettes.

ENDS linked to DNA damage

Several reports have found that ENDS vapor or extracts cause DNA damage in cell culture either by directly changing the chemical structure of DNA or indirectly by increasing highly reactive oxygen-containing molecules (32–36). One of those reports found that potent antioxidant molecules prevented DNA damage in cell culture, confirming the contribution of reactive oxygen species (32). A limitation of some studies is that they use higher concentrations of ENDS vapor than experienced by ENDS users, but DNA damage was also found in studies that used lower concentrations. Chemical modification of DNA by ENDS extracts leads to broken DNA strands (35, 37), which must be repaired by cells, or they will die. Repairing broken DNA strands can cause mutations that predispose cells to become cancerous, depending on how the damage is repaired (38).

Furthermore, nicotine itself and ENDS extracts can inhibit DNA repair processes in cell cultures. The DNA Checkpoint is a critical cellular system that senses damage and prevents cells from making new DNA in order to prevent further damage and initiate DNA repair. Nishioka and colleagues found that nicotine overrides the DNA Checkpoint and allows cells to make DNA even when there is DNA damage (39). Base Excision Repair (BER) is a key repair mechanism for DNA that has been chemically altered; two studies found that ENDS extracts reduce the abundance of BER proteins, thus limiting the ability of cells to repair damage caused by ENDS (33, 34). It is possible inhibition of DNA repair from ENDS use could exacerbate DNA damage and related DNA mutations caused by smoking in people who dual use.

ENDS linked to inflammation and cellular replication

In addition to DNA damage, ENDS vapor could also lead to cancer by promoting inflammation and cellular replication that expands mutations caused by prior carcinogen exposure. A core hallmark of cancer is uncontrolled cellular replication (40). Several constituents in ENDS vapor can cause inflammation, as demonstrated by increased pro-inflammatory cytokines such as IL6 and CXCL8 (41–46). Wang and colleagues found that nicotine signaling in mouse lungs was a significant contributor to inflammation, and that deleting the nicotine

Table 1. Carcinogens significantly increased in ENDS users compared with nonusers.

Class of carcinogen	Name of carcinogen	Metabolite analyzed	Increase compared with nonusers			Sample size	Ref
			ENDS Users	Dual users	Smokers		
Tobacco-specific nitrosamines	4-(N-Nitrosomethylamino)-a-(3-pyridyl)-1-butanone	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol	431%	28,412%	21,996%	5097	23
	4-(N-Nitrosomethylamino)-a-(3-pyridyl)-1-butanone	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol	75%	N/A	3,100%	57	26
	N'-Nitrosonornicotine	N/A	80%	513%	514%	4985	23
	N'-Nitrosonornicotine (saliva)	N/A	5,740%	N/A	37,700%	59	26
Metals	Cadmium	N/A	30%	88%	86%	5091	23
	Lead	N/A	23%	42%	36%	5105	23
Polycyclic aromatic hydrocarbons	2-Naphthylamine	N/A	29%	N/A	N/A	23	24
Volatile organic compounds	Acrylonitrile	N-Acetyl-S-(2-cyanoethyl)-L-cysteine	201%	11,018%	9,322%	4,877	23
	Acrylonitrile	N-Acetyl-S-(1-cyano-2-hydroxyethyl)-L-cysteine	30%	1,242%	1,066%	4,877	23
	N,N-Dimethylformamide	N-Acetyl-S-(N-methylcarbamoyl)-L-cysteine	46%	424%	359%	4,844	23
	Acrylamide	N-Acetyl-S-(2-carbamoylethyl)-L-cysteine	95%	583%	N/A	103	25
	Propylene oxide	2-Hydroxy-Propyl Methacrylate	89%	94%	N/A	103	25
	Crotonaldehyde	N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine	48%	85%	N/A	103	25
	Acrolein	3-hydroxypropyl mercapturic acid	32%	128%	N/A	103	25
	ortho-Toluidine	N/A	133%	N/A	N/A	22	24

Note: The table lists carcinogens identified by Goniewicz and colleagues (23), Fuller and colleagues (24), Rubinstein and colleagues (25), and Bustamante an colleagues (26), to be elevated in the urine (or saliva where noted) of adults who use ENDS products compared with adults who do not use any tobacco products. All listed carcinogens are rated "Possibly Carcinogenic" (Group 2B) to "Carcinogenic to Humans" (Group 1) by the International Agency for Research on Cancer (31). "ENDS Users" refers to exclusive ENDS use. "Smokers" refers to exclusive combustible cigarette use. "Dual Users" refers to people who use both ENDS and combustible cigarettes.

receptor in lung cells reduced inflammation, confirming nicotine directly causes inflammation (44). However, even use of ENDS that only contained propylene glycol and vegetable glycerin had moderate pro-inflammatory effects in human lungs (43). An additional study found that ENDS users had significantly elevated levels of IL6 and CXCL8 in the blood compared with never smokers (45). IL6 is well documented to induce cell signaling pathways that promote cellular replication and transform precancerous cells into cancerous cells (47–49). Singh and colleagues also found that ENDS users had elevated levels of growth signaling molecules commonly implicated in cancer progression compared with never tobacco users, including epidermal growth factor, vascular endothelial growth factor, and hepatocyte growth factor (45). These findings suggest that ENDS vapor can promote replication of precancerous cells and therefore promote cancer-predisposing DNA mutations.

Summary

A growing body of evidence points toward a biologically plausible role for ENDS use in contributing to human carcinogenesis, based on the presence of carcinogens in ENDS aerosols; metabolites of carcinogens in human urine samples; inflammation markers in human lung swabs and blood samples; and cell culture and mouse experiments exhibiting DNA damage and inflammation. It is important to note that the evidence from biomarker studies tends to show lower carcinogen exposures in ENDS users compared with dual users and exclusive smokers of combustible tobacco, likely due to the absence of combustion-related carcinogens. Additionally, the lack of well-designed epidemiologic studies is a critical hurdle to definitively characterizing cancer risk. ENDS remain relatively new products, so it may take decades for enough exposure to occur that would enable studies with sufficient follow-up to fully characterize the associations between ENDS use and cancer. Even less is known about the harms of second-hand exposure to ENDS vapor. In contrast, the scientific evidence very clearly demonstrates smoking combustible tobacco increases the risk of being diagnosed with lung cancer by approximately 25-fold compared with never smoking (6), and is an established cause of at least 17 other human cancers (6, 50).

Patterns of ENDS Use Support a Ban on ENDS Flavors

While youth and adult use of combustible tobacco has decreased to historic lows (2), the epidemic of youth ENDS use threatens to diminish progress against nicotine addiction. The AACR and ASCO published our first ENDS statement in 2015 due to concerns regarding the almost 400% rise between 2012 and 2014 in ENDS use among U.S. high school students, according to the 2014 National Youth Tobacco Use Survey (NYTS; **Fig. 1**; ref. 51). The number of high school students who had used ENDS in the past 30 days increased by an additional 46% in 2020 compared with 2014 levels, to a total of 3.6 million youth (52). A separate national survey,

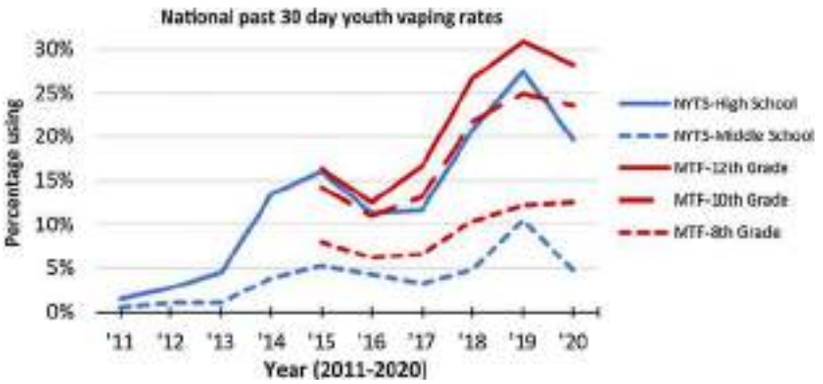

Figure 1.
Percentage of various school age groups who vaped in the past 30 days. Blue lines indicate data from the NYTS (51, 52, 54–60), and red lines indicate data from the MTF survey (53). MTF, Monitoring the Future; NYTS, National Youth Tobacco Use Survey.

Monitoring the Future (MTF), also found a dramatic 73% increase between 2015 and 2020 among 12th grade students who had vaped in the past 30 days (**Fig. 1**; ref. 53). This continued increase in the youth ENDS epidemic underscores the need for urgent action to save a generation of youth from life-long nicotine addiction.

Numerous studies have clearly demonstrated that appealing flavors are key drivers of youth initiation of ENDS use, with the pharmacology of nicotine as the key driver of addiction to ENDS (61–68). The 2020 NYTS found that 82.9% of youth ENDS users used flavored products. Among high school ENDS users, 73% reported vaping fruit-flavored ENDS, 55.8% vaped mint, and 37% vaped menthol (percentages add to greater than 100 % due to use of multiple flavors by one person) (52). In comparison, the 2020 MTF found that only 2.9% of youth ENDS users vaped tobacco-flavored products (69). Youth who are offered fruit flavored ENDS by peers are 6.49-fold more likely to try ENDS compared with tobacco-flavored ENDS (61). In contrast, adults are 21-fold more likely to exclusively use tobacco-flavored ENDS compared with youth (63). Flavored ENDS follow a long history of the tobacco industry using flavors to attract youth towards nicotine by disguising the otherwise unpleasant taste of tobacco and purposefully altering perceptions of risk (61).

In February 2020, the FDA implemented restrictions on pod- or cartridge-based ENDS product flavors, except for menthol and tobacco flavors (70). The policy lacked definitions of "mint" or "menthol," thus allowing manufacturers to simply relabel products to avoid the flavor restriction (71). Open tank and single-use ENDS were also exempted from any flavor restrictions, which left thousands of appealing flavors on the market. Consequently, youth switched to exempted products. The 2020 NYTS found that disposable products were used by 2.4% of high school ENDS users in 2019 (52), but this increased 11-fold to 26.5% in 2020. The prevalence of flavored disposable ENDS also increased among middle schoolers, with a 5-fold increase in disposable product use between 2019 and 2020 (3.0% vs. 15.2%). Flavoring chemicals and other additives of ENDS have not been studied to determine the health risks associated with inhalation. The ability to mix flavors at the point of sale also increases the difficulty of regulators to gain a complete understanding of the health impact of these chemicals in real-world use.

The use of ENDS among adults has also increased in recent years, particularly among young adults. According to the Behavioral Risk Factor Surveillance System (BRFSS, $N = 1{,}156{,}411$), the prevalence of ENDS use increased among U.S. adults from 4.5% in 2016 to 5.4% in 2018 (72), and was 15.0% among adults under the age of 24 years. These data correspond to almost 14 million adults using ENDS in 2018. A second study analyzed data from the Population Assessment of Tobacco and Health (PATH) study ($N = 30{,}191$), which is also representative of the population of U.S. adults, and found that 6.5% of U.S. residents used ENDS in 2018 (73). Concerningly, the BRFSS study found that 42% of adult ENDS users had never previously used another tobacco product (72), and the PATH study found 15% of adult ENDS users had never used another type of tobacco product (73). While the high variability between analyses necessitates further study, the data suggest ENDS are being used by millions of adults who never previously used tobacco. In addition, approximately 36% of ENDS users in the BRFSS study and 52% in the PATH study "dual use" ENDS and combustible tobacco. A separate nation-wide survey ($N = 5{,}989$) found that 27.7% of adults who smoked also dual used ENDS in 2018 (74). Notably, dual use rates were higher in adults who wanted to quit smoking within 6 months (33.1%), compared with 18.7% of those who did not plan to quit smoking. Similar to the general population, adult patients with cancer and survivors who use ENDS are more likely to be under the age of 50 years (75, 76), but patients with cancer who use ENDS are far more likely to be current or former smokers than never smokers. As presented in **Table 1**, dual users continue to be exposed to similarly high levels of carcinogens as exclusive users of combustible tobacco and the current evidence of the efficacy of dual using ENDS to help quit smoking remains unclear. The evidence is clear that any combustible smoking, even one cigarette per day, has significant negative health impacts (77).

As stated in the introduction, major U.S. public health authorities have found insufficient evidence to conclude ENDS effectively help smokers quit combustible tobacco (2–5). In contrast, there is evidence that demonstrates ENDS significantly increase the likelihood youth and young adults start smoking combustible tobacco. A 2021 meta-analysis analyzed nine studies (combined baseline $N = 32{,}286$), which compared the likelihood of smoking initiation between youth ENDS users and never users (78); youth who used ENDS were 4-fold more likely to ever smoke a combustible cigarette than never users, even after accounting for potentially confounding factors. Similarly, a 2020 meta-analysis analyzed 17 studies (combined baseline $N = 57{,}514$), which compared the likelihood of smoking initiation between young adult ENDS users and never users; young adults who used ENDS were approximately three-fold more likely to ever smoke a combustible cigarette compared with never users (79). On the other hand, the nation-wide increased rates of e-cigarette use among youth is accompanied by a substantial decrease in past month smoking rates (53, 80), and the extent to which ENDS use leads to established or regular smoking to date appears to be low (81). Nonetheless, the well-documented ability of ENDS to roughly triple smoking initiation by youth and young

adults is of concern and overshadows the more limited evidence suggesting the efficacy of ENDS for smoking cessation (82). As stated above, flavors are a key driver of youth initiation of ENDS, with the pharmacology of nicotine leading to addiction and continued, repetitive use. Therefore, to limit youth nicotine dependence, we recommend an immediate ban on all non-tobacco-flavored ENDS products that contain natural or synthetic nicotine, unless an ENDS product is approved by FDA CDER as a smoking cessation therapy.

Advertising Contributes to Youth ENDS Initiation

Advertising has a powerful effect on youth tobacco initiation, including for ENDS. Many studies have found that advertisements from social media influencers, television, radio, print, and in retail stores significantly increases the probability that youth will start using ENDS (83–90). Additionally, a national survey ($N = 4{,}604$) found that high exposure to tobacco use during television shows more than doubled the likelihood of initiating ENDS use among youth and young adults (91). These findings demonstrate a strong link between ENDS advertising or imagery exposure and subsequent initiation. Therefore, in addition to a ban on flavors, we support efforts to prevent all forms of advertisement for nicotine products from reaching youth.

Figure 2.
Evidence-based cessation therapies. FDA, U.S. Food and Drug Administration.

Leveraging Evidence-Based Smoking and ENDS Cessation Therapies and Awareness Campaigns

There are currently no evidence-based pharmacologic therapies to help ENDS users quit vaping (92). However, it is reasonable to conclude that lessons learned from smoking cessation could aid in treating nicotine dependence from ENDS. The 2021 USPSTF tobacco cessation recommendation concluded that the most effective treatment for tobacco use includes both FDA-approved pharmacotherapies and behavioral counseling (**Fig. 2**; ref.4). Additional research is critically needed to identify effective cessation therapies specifically for ENDS users. A major hurdle to assessing tobacco use in clinical research studies is the lack of standardized definitions for terms describing tobacco use history, such as "current smoking," "current ENDS use," "former smoking," etc. Evidence-based definitions provided by the FDA or National Cancer Institute will be helpful to further advance tobacco research.

Little is known about the interaction of smoking and ENDS use and subsequent impact on different anticancer treatments or on cancer prognoses. In the context of cancer treatment, smoking by patients with cancer and survivors increases the risk of overall or cancer related mortality by roughly 50% to 60%, increases risk for a second primary cancer, and has strong associations with increased cancer treatment toxicity (6). Consequently, it is important to consider the biologic and clinical effects of smoking when considering the effects of ENDS use by patients with cancer. Quitting smoking after a cancer diagnosis is associated with a median 45% improvement in survival (2). Therefore, evidence-based smoking cessation is considered a critical component of cancer care by AACR, ASCO, and other major oncology organizations (93). However, large surveys demonstrate that few oncology providers regularly assist patients with quitting (94, 95). Compared with the general adult population, the data are even less clear on whether ENDS will have a positive or negative effect on cancer treatment. This is further complicated by frequent transitions between smoking and ENDS. However, smoking cessation confers significant benefits by reducing cancer risk, improving cancer treatment outcomes, and improving several other health outcomes beyond cancer (2). Given the clear and strong evidence for the adverse effects of smoking on cancer treatment outcomes, quitting smoking should remain the top priority for patients with cancer and providers, with emphasis on the importance of quitting smoking to improve cancer treatment outcomes. When considering these important data and findings, it is critical that patients with cancer who are using ENDS currently not return to cigarette smoking.

A significant hurdle to evidence-based cessation therapies is inconsistent insurance coverage. This is most pronounced among uninsured smokers, who are 33% less likely than the general population to use evidence-based therapies (96). After Massachusetts implemented comprehensive Medicaid smoking cessation coverage in 2006, the smoking rate of beneficiaries dropped by 26% in two years (97); every dollar spent on cessation coverage saved $3.12 in U.S. dollars (USD) in spending on tobacco-related illnesses (98). Unfortunately, most state Medicaid plans do not cover all FDA-approved medications, and coverage of behavioral therapy is inconsistent (99). Additional barriers such as extreme shortages of healthcare workers, demanding physician schedules, medical preauthorizations, co-payments, and limits on quit attempts per year also reduce success rates (100–102). Nonphysician certified tobacco cessation specialists are also often not reimbursed by insurance plans. Payment reform for cessation specialists, FDA-approved therapies, and addressing other barriers to cessation could be powerful cost-saving interventions to increase quit rates by making it as easy as possible to receive evidence-based help. An improved coverage and reimbursement environment for tobacco cessation services and medications will benefit population health; this would even apply should an ENDS product ever become an FDA-approved cessation device.

A number of awareness campaigns and free cessation resources (**Fig. 2**) have emerged over the past decade to prevent initiation and help tobacco users quit, some of which could be used or repurposed in the context of ENDS cessation. The "This is Quitting" campaign by the Truth Initiative increased seven-month quit rates among young adult ENDS users to 24.1% compared with 18.6% among participants who did not participate in the campaign (103). The FDA's "The Real Cost" advertising campaign helped prevent an estimated 380,000–587,000 youth from smoking between 2013 and 2016 (104). The CDC's "Tips from Former Smokers" campaign saved an estimated $11 billion (USD) in tobacco-related healthcare spending over 6 years at a cost of $490 million (USD) (105) and helped more than 1 million smokers permanently quit (106). Among smokers who visited the free cessation services website, SmokeFree.gov (107), as part of a randomized clinical trial, 26% successfully quit one year later (108). Finally, Quitline counseling services increased quit rates by 60% (109). Increasing resources for these excellent evidence-based tobacco treatment services could help significantly to expand their reach and quality of service.

Evidence needed to determine if ENDS can help smokers quit smoking

To our knowledge, to date, there is a lack of sufficient evidence for the use of ENDS as tobacco cessation therapies (2–5). This is because very few randomized clinical trials have directly compared the efficacy of ENDS to standard cessation therapies; the failure of ENDS manufacturers to submit an IND application is the primary reason for a lack of ENDS clinical trials in the United States. However, a 2021 systematic review found that preliminary evidence suggests ENDS could be more effective for smoking cessation than nicotine-replacement therapy alone (82), although the authors caution that the small number of studies and variations in study design limit the strength of their conclusions. The moderate strength conclusion of the review was primarily based on two clinical trials that investigated the efficacy of ENDS to help with smoking cessation. The first trial (N = 886), from the United Kingdom, found ENDS helped smokers quit at statistically significantly higher rates than nicotine patches (110); the trial found 18% of participants who used ENDS plus behavioral therapy had quit smoking by one year, compared with 9.9% of participants who used nicotine patches plus behavioral therapy. The second trial (N = 1,124), from New Zealand, found that 18% of those randomly assigned to patches plus a nicotine e-cigarette quit smoking, compared with 10% randomized to a nicotine-free e-cigarette plus patches and 8% randomized to patches alone (111). It is noteworthy in both trials that a large proportion of participants continued using ENDS at the long-term follow-up visit in these studies. Moreover, all groups in the above studies experienced slightly lower but comparable rates of successful cessation as found for 6-month follow-up when using FDA-approved nicotine patches alone (22%; ref. 112). Therefore, we recommend that ENDS manufacturers apply for IND applications to facilitate randomized clinical trials to definitively assess the cessation efficacy of their products compared with FDA-approved cessation therapies.

Regulation of ENDS Needs Improvement

During the last 15 years, the FDA has attempted to regulate ENDS products with limited success. In 2009, Congress passed the Family Smoking Prevention and Tobacco Control Act (TCA; ref. 113), which granted the FDA the authority to regulate tobacco products. In May 2016, the FDA "deemed" ENDS as tobacco products under the TCA (114). This ruling required ENDS manufacturers to submit a premarket tobacco product application (PMTA) to prove that the product is "appropriate for the protection of public health" (112). In 2017, the FDA elected to delay the PMTA deadlines for ENDS from 2018 to 2022. During this time, many users believed that ENDS were safe and did not contain nicotine (61, 69, 115). As described in the epidemiology section, perceptions of safety contributed to alarming increases in ENDS use among those who never previously used tobacco.

In 2019, U.S. District Judge Paul W. Grimm ruled that the FDA had acted improperly by delaying ENDS regulations (116). Citing a "clear public health emergency," Judge Grimm required PMTA applications for ENDS to be submitted by May 2020, but this was delayed to September 2020 due to the COVID-19 pandemic. By September 2020, more than 6 million PMTAs for ENDS products were submitted for FDA review (117). The FDA has denied marketing orders for more than 98% of those products, which requires those products to be removed from the market (118). However, the FDA is still reviewing PMTAs for ENDS products from manufacturers with the largest market shares and permitting those products to remain on the market in the meantime.

Two additional policies have also had a major impact on the use of ENDS products: age restrictions and taxation. In 2015, Hawaii became the first state to raise the minimum legal age to purchase tobacco products to 21 years (119), based on a NASEM report that estimated nearly 250,000 premature deaths could be prevented over 30 years (120). Following Hawaii's lead, 18 additional states and Washington D.C. also raised the minimum age to 21 years between 2016 and 2019. As part of the federal fiscal year 2020 appropriations package, Congress raised the minimum legal age to purchase tobacco products to 21 years in the entire United States (121). Separately, for every 1% increase in the price of tobacco products, consumption decreases by 0.4% on average (122). While the federal government does not yet tax ENDS, 24 states have passed ENDS taxes (123). Due to the powerful disincentivizing effect of taxes on tobacco use, the AACR and ASCO support imposing a federal excise tax on all products that contain natural or synthetic nicotine in a manner that promotes public health benefit (124, 125). Additional policy recommendations are included in **Table 2**.

Conclusion

ENDS emit fewer carcinogens than combustible tobacco primarily due to the absence of combustion products, and for some ENDS, the absence of some tobacco-specific nitrosamines, but it is clear that they still pose health risks. Additionally, e-cigarettes have addicted a new generation of youth and young adults to nicotine and threaten to hinder progress against tobacco-related illnesses. For these reasons, the AACR and ASCO call for urgent action by Congress, state legislatures, and regulatory agencies to implement the various legislative, regulatory, and research recommendations outlined in this report, including calling for an immediate ban on all non-tobacco-flavored ENDS products that contain natural or synthetic nicotine with the goal of reducing ENDS use by youth and adults who never previously used tobacco. The top tobacco control priorities for the AACR and ASCO continue to be preventing initiation of tobacco use, including ENDS, preventing smoking relapse, and promotion of evidence-based tobacco cessation treatment for all groups.

Table 2. AACR and ASCO recommendations.

Legislative Recommendations
Ban all non-tobacco-flavored products that contain natural or synthetic nicotine; flavors may only be used for research purposes or FDA-approved tobacco cessation therapies.
Tax all products that contain natural or synthetic nicotine in a manner that reduces tobacco use and promotes public health.
Increase funding for evidence-based tobacco control programs and campaigns such as the CDC's Office on Smoking and Health, state tobacco control programs, and Quit Lines.
Prohibit the use of ENDS in places where combustible tobacco use is prohibited by federal, state, or local laws. All tobacco use should be prohibited at medical facilities.
Limit the sale of tobacco products to stores or areas within stores that require age verification upon entrance.
Require health insurance plans, including Medicare/Medicaid, to cover all FDA-approved cessation therapies, expand coverage limits, and reimburse healthcare providers, including cessation specialists, for time helping patients quit smoking and vaping.
Regulatory Recommendations
Regulate predatory tobacco advertising practices including packaging, product designs, and labeling appealing to youth; misleading statements about cessation efficacy; athletic, musical, social, or cultural event sponsorship; giveaways when buying tobacco products; branded clothing; social media, digital, and print advertising; and tobacco use in movies and television.
The FDA should enforce removal of ENDS products from the market that have not received a marketing order, publish PMTAs with confidential information redacted, and update PMTA review progress with a publicly available database.
The FDA should develop product standards for tobacco products to improve public health, including but not limited to minimizing appeal to youth; capping the amount of nicotine delivery to minimize addictiveness; eliminating or substantially reducing human exposure to known carcinogens (e.g., heavy metals) and other toxicants (e.g., additives, contaminants, and manufacturing residues); and regulating the power and operating temperature of ENDS products.
PMTAs should require information regarding: composition of ENDS and e-liquid components; appeal to people who have never used tobacco products; impacts on health; geotracking or biometric capabilities; and steps taken to protect consumer privacy.
Require health warning and safety labels on ENDS packaging and advertising; these labels should contain ENDS/e-liquid composition information from PMTAs.
The FDA and/or NCI should provide evidence-based, non-stigmatizing definitions for categories of tobacco use for human studies, for example no tobacco history; no smoking history; no ENDS history; currently smoking; currently using ENDS; former smoking history. The FDA and/or NCI should provide guidance on best practices for measuring tobacco use data in human studies. The FDA should require all oncology clinical trials to assess tobacco use and report findings.
The FDA should increase enforcement of the minimum age to legally purchase tobacco products
Additional Research Needs
Research is needed to determine effective ENDS cessation therapies for youth, young adults, and adults, as well as cessation therapies for youth combustible tobacco users.
Large prospective epidemiological studies are needed to investigate the long-term health impacts of ENDS use and disparities in tobacco-related illness.
Additional research is needed for a comprehensive understanding of the acute and long-term biologic effects of ENDS use, carcinogen exposures, and the use of ENDS in the context of smoke exposure.
Additional research is needed on how patients diagnosed with cancer use tobacco products, their reasons for use, perceptions of health impacts, impact of cessation on cancer-related outcomes, and interactions with anticancer therapies.
Randomized clinical trials are needed to investigate the cessation efficacy of ENDS compared to FDA-approved cessation therapies. Investigational New Drug applications are necessary to facilitate such trials.
Research is needed to monitor the impacts of federal, state, and local tobacco policies on youth and adult use patterns, as well as the use of evidence-based approaches to develop policy.

Abbreviations: AACR, American Association for Cancer Research; ASCO, American Society of Clinical Oncology; ENDS, electronic nicotine delivery systems; FDA, US Food and Drug Administration; NCI, National Cancer Institute; PMTA, premarket tobacco product application.

Authors' Disclosures

R.S. Herbst reports personal fees from Cybrexa Therapeutics, personal fees from eFFECTOR Therapeutics, Inc., personal fees from Eli Lilly and Company, personal fees from EMD Serono, personal fees from Genentech, personal fees from Gilead, personal fees from Janssen, personal fees from Merck and Company, personal fees from Mirati Therapeutics, personal fees from NextCure, personal fees from Novartis, personal fees from Ocean Biomedical, Inc, personal fees from Oncocyte Corp, personal fees from Oncternal Therapeutics, personal fees from Pfizer, personal fees from Regeneron Pharmaceuticals, personal fees from Revelar Biotherapeutics, Inc, personal fees from Ribbon Therapeutics, Inc, personal fees from Roche, personal fees from Sanofi, personal fees from Xencor, Inc, other support from American Association for cancer Research, other support from International Association for Cancer Research, other support from Society for Immunotherapy of Cancer, other support from Southwest Oncology Group, other support from Merck and Company, and other support from Eli Lilly and Compamy outside the submitted work. M. Giuliani reports other support from AstraZeneca, other support from Bristol Myers Squibb, and other support from International Journal of Radiation Oncology, Biology and Physics outside the submitted work. B.A. Toll reports grants from National Cancer Institute and personal fees from Expert Testimony outside the submitted work. G.W. Warren reports grants and other support from National Cancer Institute, Agency for Healthcare Research and Quality, Canadian Partnership Against Cancer outside the submitted work. No disclosures were reported by the other authors.

Received August 3, 2022; accepted September 1, 2022; published first October 26, 2022.

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American Cancer Society Position Statement on Electronic Cigarettes

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The American Cancer Society (ACS) first released a position statement on e-cigarettes in February 2018. At that time, the ACS emphasized that no young person should start using any tobacco product, including e-cigarettes. However, the use of e-cigarettes in young people has since skyrocketed to epidemic proportion with nearly 30% of high school students reporting using an e-cigarette in the past 30 days and 12% reporting using an e-cigarette daily. This updated position statement replaces all previous ACS statements on e-cigarettes and guides the organization's tobacco control and cessation efforts regarding these products. The ACS position statement will continue to be updated based upon emerging public health trends and evolving science.

No youth or young adult should begin using any tobacco product, including e-cigarettes.

The ACS encourages young people currently using any of these products to ask for help in quitting and to quit as soon as possible.

E-cigarettes should not be used to quit smoking.

The ACS does not recommend the use of e-cigarettes as a cessation method. No e-cigarette has been approved by the Food and Drug Administration (FDA) as a safe and effective cessation product.

Current e-cigarette users should not also smoke cigarettes or switch to smoking cigarettes, and people who formerly smoked now using e-cigarettes should not revert to smoking.

All tobacco products, including e-cigarettes, pose a risk to the health of the user. Beginning smoking, switching to smoking, or reverting to smoking exposes the user to potentially devastating health effects.

E-cigarettes

Using e-cigarettes, or "vaping," are terms used synonymously to refer to the use of a wide variety of electronic, battery-operated devices that aerosolize, but do not burn, liquids to release nicotine and other substances. Nicotine-containing e-cigarettes are regulated as "tobacco products" by the FDA because the nicotine is derived from the tobacco plant. E-cigarettes pose a threat to the health of users and the harms are becoming increasingly apparent. In the past few years, the use of these products has increased at an alarming rate among young people in significant part because the newest, re-engineered generation of e-cigarettes more effectively delivers large amounts of nicotine to the brain. Many e-cigarettes sold in the U.S. contain far more nicotine than e-cigarettes sold elsewhere, which increases the

risk of addiction and harm to the developing brains of youth and young adults. Marketing tactics targeting young people have contributed to the rapid increase in use. The long-term risks of exclusive use of e-cigarettes are not fully known but evidence is accumulating that e-cigarette use has negative effects on the cardiovascular system and lungs. Without immediate measures to stop epidemic use of these products, the long-term adverse health effects will increase.

Guidance for Youth Who Currently Use E-cigarettes

The harms of e-cigarette use in young people include not only the deleterious effects of nicotine, but also exposure of the lungs and airways to potentially toxic solvents and flavoring chemicals. The rapidly rising rates of use in young people and the high rates of daily use strongly suggest that many are addicted to nicotine and will have difficulty in stopping use of all tobacco products.

While some young people may be able to quit e-cigarette use on their own, others, particularly daily users, are likely to find this to be very difficult. The ACS encourages adolescent users who find it difficult to quit to ask for help from health care professionals. Parents should learn all they can about e-cigarette use and be prepared to help their children get the assistance they need. For more information go to cancer.org/e-cigarettes.

The future pattern of tobacco product use by currently-addicted youth e-cigarette users is unknown, but the only pathway to eliminating the harms of e-cigarettes is to quit using them as soon as possible and to not start using any other tobacco products, such as cigarettes. Without urgent and effective public health action, e-cigarettes will lead to a new generation of nicotine-addicted individuals.

Guidance for Adults Who Currently Use E-cigarettes

Some individuals who smoke choose to try e-cigarettes to help them stop smoking. Since smoking kills fully half of all long-time users, successfully stopping smoking leads to well-documented health benefits. Nonetheless, adults who smoke who switch to using e-cigarettes expose themselves to potentially serious ongoing health risks. Thus, people who smoked formerly who are currently using e-cigarettes, whether alone or in combination with combustible tobacco products, should be encouraged and assisted to stop using all tobacco products, including e-cigarettes, as soon as possible both to eliminate their exposure to ongoing health risks and avoid perpetuating addiction. If they are unable to quit e-cigarettes on their own, they should seek help from a health care professional or quitline. Individuals who are not yet able to stop using e-cigarettes should be strongly discouraged from simultaneous, or “dual,” use of any combustible tobacco products, including cigarettes. Continuing to smoke exposes the individual to enormous harms, irrespective of whether the individual is using e-cigarettes part of the time. All individuals should also be strongly counseled to not revert to smoking.

While some e-cigarette users quit on their own, many have difficulty quitting and should seek help from their healthcare providers or other support services such as their state quitline (1-800-QUIT-NOW) or the American Cancer Society (1-800-ACS-2345).

Guidance for Adults Who Currently Smoke

All adults who smoke conventional cigarettes or other combustible (burned) tobacco products should be advised to quit smoking at the earliest opportunity, recognizing that quitting is hard and often takes repeated, dedicated efforts. Individuals who smoke are strongly encouraged to consult with their doctor, pharmacist or other medical professional to seek cessation support and, where deemed appropriate, to use FDA-approved medications including nicotine replacement therapies (NRT) and/or recommended oral medications, preferably combined with individual or group behavioral counseling, which significantly increases the likelihood of success. Individuals can also seek cessation support by calling 1-800-QUIT-NOW or 1-800-ACS-2345.

Regulation of E-cigarettes

The ACS and the American Cancer Society Cancer Action Network (ACS CAN) support several critical policy approaches to reduce youth e-cigarette use without inadvertently incentivizing the use of the leading cause of preventable death – combustible tobacco products – as an alternative. The FDA must effectively regulate all e-cigarettes as soon as possible, including: enforcing premarket reviews; restricting advertising and marketing to protect youth; preventing the dissemination of false and misleading messages and imagery; and requiring strict product standards. The FDA has the authority to regulate all substances in tobacco products, including, but not limited to, flavoring chemicals and nicotine. The FDA must also continue to demand testing of all substances used in e-cigarettes, as well as the relative safety of the devices themselves (for example, preventing exploding batteries). The ACS and ACS CAN encourage prohibiting the use of all flavors, including mint and menthol, in all tobacco products, including e-cigarettes. Furthermore, the FDA should proceed aggressively with a proposal to reduce nicotine in all combustible tobacco products to non-addictive levels and also strictly limit the amount of nicotine permitted in e-cigarettes.

E-cigarettes and nicotine abstinence: a meta-analysis of randomised controlled trials

Objectives To determine the effects of electronic cigarettes (e-cigarettes) as a therapeutic intervention compared to nicotine replacement therapy (NRT) on nicotine abstinence.

Methods Two authors independently searched the PubMed, Embase, PsycInfo and Cochrane Central Register of Controlled Trials databases for articles published up to and including 10 July 2021. We included randomised controlled trials (RCTs) in which nicotine e-cigarettes were compared to NRT among current cigarette users. The primary outcome was abstaining from all nicotine-delivery devices. Secondary outcomes were 1) allocated product use (e-cigarettes or NRT) among successful cigarette quitters and 2) quitting cigarettes at the end of the trial using fixed-effect Mantel–Haenszel models.

Results We included four RCTs representing 1598 adult participants (51.0% females). The mean age of participants in these studies ranged from 41 to 54 years, while average baseline smoking ranged from 14 to 21 cigarettes per day. Compared to NRT, e-cigarette use was associated with lower nicotine abstinence rates at the longest follow-up (risk ratio 0.50 (95% CI 0.32–0.77)). Among successful cigarette quitters, the risk of allocated product use by the end of the observational time was higher for e-cigarette users compared to NRT (risk ratio 8.94 (95% CI 3.98–20.07)). E-cigarette users had higher cigarette smoking cessation rates compared to NRT users (risk ratio 1.58 (95% CI 1.20–2.08)).

Conclusions The use of e-cigarettes as a therapeutic intervention for smoking cessation may lead to permanent nicotine dependence.

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Clinicians should not recommend e-cigarettes for smoking cessation due to the risk of permanent nicotine dependence https://bit.ly/358oToy

Introduction

Electronic cigarettes (e-cigarettes) deliver an aerosol by heating a solution typically consisting of propylene glycol, glycerine, flavourings and nicotine [1]. In the United States, Europe, and many countries around the world, e-cigarettes are mass-marketed consumer products [2]. As consumer products, in observational studies, e-cigarettes were not associated with increased smoking cessation in the adult population [3]. Nevertheless, e-cigarettes have been promoted for smoking cessation even though, up to now, no e-cigarette has been approved as a smoking cessation medication by the Federal Drug Administration or the European Medicines Agency [3].

In 2014, a Cochrane review concluded that there was evidence from two randomised controlled trials (RCTs) that e-cigarettes help smokers to stop smoking [4]. The confidence in the result was rated “low”. In an updated 2016 Cochrane review, the same conclusion was reached [5]. Further, in the recently published 2021 update, based on the results of four RCTs with 1924 participants, the authors concluded that there is moderate-certainty evidence that e-cigarettes with nicotine increase quit rates compared to nicotine replacement therapy (NRT) [6]. However, the authors have noted an overall lack of available RCT studies, while existing studies generally had small sample sizes. Finally, another recently published meta-analysis found no difference in smoking cessation and smoking reduction between e-cigarette and

NRT users [7]. Nevertheless, none of these review studies reported information on overall nicotine abstinence at the end of the observational period of these RCTs.

The Cochrane review suggests that an additional three people for every 100 would quit smoking with nicotine e-cigarettes compared to NRT [6]. Nonetheless, it has been questioned if the benefit of the three extra people who quit with e-cigarettes will outweigh the harms of long-term (maybe lifelong) use of e-cigarettes in the many people who continue using them after smoking cessation and the possible uptake of e-cigarettes among young people [8]. Unfortunately, neither the Cochrane review nor other systematic reviews provide any information on the long-term use of e-cigarettes or NRT of participants included in the RCTs.

The primary goal of this systematic review is to systematically analyse the evidence found in RCTs to evaluate the effectiveness of e-cigarettes compared to standard NRT for nicotine abstinence among current cigarette smokers. The secondary aims of this study are to examine the allocated product use (*i.e.* e-cigarettes and NRT) among successful cigarette quitters and cigarette cessation rates at the end of the observational period of these RCTs.

Methods

The systematic review and meta-analysis were conducted following the guidelines in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [9] statement. The protocol for this study was registered in the International Prospective Register of Systematic Review with the registration number CRD42021268682.

Search methods for identification of studies

Two authors (KN and AG) independently searched PubMed, Embase, PsycINFO and Cochrane Central Register of Controlled Trials databases for articles published up to and including 10 July 2021. Search terms included: “electronic nicotine delivery system”, “ENDS”, “e-cig*”, “electr* cigar*”, “electronic nicotine”, “vape”, “vaping” AND “tobacco use cessation devices”, “NRT”, “nicotine replacement therapy”, “nicotine patch”, “nicotine gum”, “nicotine inhalator”, “nicotine lozenge*”, “nicotine nasal spray”, “nicotine mouth spray”, “nicotine mouth strips”, “nicotine microtab*”, “nicotine tablet*” AND “randomised controlled trial”, “clinical trial”, and “controlled trial”. Search results were not limited by publication year, language or for being an abstract only, but were limited to studies conducted in humans.

Records identified through the search were downloaded and imported into a reference manager database to remove duplicates. Two review authors (KN and AG) independently screened titles and abstracts for inclusion eligibility. Further, full texts of all potentially eligible manuscripts were screened independently by the authors to determine eligibility. Any inconsistencies were resolved by discussion with the third author (RH).

Eligibility criteria

Studies were included if they met the following criteria: 1) all included studies had to be RCTs; 2) the exposure was nicotine e-cigarette use, and NRT as therapeutic intervention (smoking cessation); 3) the primary outcome was quitting cigarette use; and 4) the target population was adults aged 18 years or

older. We excluded studies that compared nicotine e-cigarettes to non-nicotine e-cigarettes and studies that compared different e-liquid nicotine concentrations only.

Study population

All participants were current cigarette smokers at enrolment into the trials and the amount of combustible cigarette use differed. Participants could be motivated or unmotivated to quit smoking. All healthcare and community settings were included.

Intervention of interest

The intervention of interest included the use of all types, models and brands of e-cigarettes for smoking cessation.

Comparators

All included studies compared e-cigarettes with all forms of NRT (*e.g.* nicotine patches, gums, inhalators, lozenges, nasal sprays, mouth sprays, mouth strips, microtabs, and combination of products). Studies that compared nicotine e-cigarettes to non-nicotine e-cigarettes and studies that only compared different e-liquid nicotine concentrations were excluded.

Outcome measures

The primary outcome measure was nicotine abstinence at the longest follow-up point, defined as abstinence from any nicotine-containing products, measured on an intention-to-treat basis (preferring biochemically validated results).

Secondary outcomes were: a) the use of allocated products (defined as the use of the intervention nicotine product (e-cigarettes or NRT) allocated to the participants at the beginning of the trial) at the end of the observational period among successful cigarette quitters, and b) smoking cessation at the longest follow-up point, defined as abstinence from combustible cigarette smoking, measured on an intention-to-treat basis (preferring biochemically validated results).

Study selection and data extraction

All studies that met the criteria for inclusion in this meta-analysis were full peer-reviewed journal publications. Two review authors (KN and AG) independently extracted data from included studies to a data collection form; any inconsistencies were resolved by discussion with the third author (RH). The following information was extracted: author, date and place of publication, study dates, design and setting, participants' demographic characteristics (age and gender distribution), sample size (and number in each arm), a summary of intervention and control conditions, outcomes, and type biochemical validation (if any). All studies reported data on smoking cessation, but none of the eligible studies reported information on nicotine abstinence and the use of allocated products among successful cigarette quitters at the end of the trial in the original paper. For that reason, we contacted the corresponding author for further information *via* e-mail. Two reminder e-mails were sent if the corresponding author did not respond to the first e-mail. If no response was given, the studies were excluded from the nicotine abstinence and use of allocated products analyses.

Risk of bias assessment for included studies

The overall quality of evidence for each outcome was evaluated (independently by two review authors) using the five Grading of Recommendations Assessment, Development and Evaluation framework [10], which provides a systematic approach to presenting evidence summaries by rating the overall quality and risk of bias of all included studies jointly. Additionally, two authors independently assessed the risks of bias for each included study using the revised Cochrane Risk of Bias Tool for RCTs [11]. Any inconsistencies were resolved by discussion with the third author. Reporting bias can be assessed using funnel plots; however, there are insufficient studies to use this approach (at least 10 studies should be included in the meta-analysis) [12].

Data synthesis

We provide a narrative summary of the included studies. Where appropriate, data have been pooled for meta-analyses. Fixed-effect Mantel–Haenszel models were used to calculate the risk ratio with a 95% confidence interval [6]. Three meta-analyses were conducted: 1) a first meta-analysis synthesised the evidence from three RCTs to evaluate the effectiveness of e-cigarettes compared to standard NRT for achieving nicotine abstinence; 2) a second meta-analysis examined the allocated product use (*i.e.* e-cigarettes and NRT) among successful cigarette quitters at the end of the observational period; and 3) finally, a third meta-analysis assessed the effectiveness of e-cigarettes compared to standard NRT for achieving smoking cessation (four RCTs). Statistical heterogeneity between studies was assessed with I^2 statistic [13] and chi-square test (Cochrane Q). An I^2 value of >50% and a p-value of 0.10 for the Cochrane Q test were used as indicators of substantial heterogeneity. Additional sensitivity analyses were conducted to evaluate whether pooled results were sensitive to the removal of studies judged to be at high risk of bias. All statistical analyses were conducted using Stata software (version 16.0; Stata Corp, College Station, Texas, USA).

Results

Our initial bibliographical search yielded 189 records. After excluding 24 duplicate records, 158 manuscripts were included in the title and abstract screening, and seven of those were selected for full-text screening. After screening and checking the full text of seven articles [14–20], we retained four RCT studies that were eligible for data extraction and were included in smoking cessation meta-analysis: Bonevski *et al*. [14], Bullen *et al*. [17], Hajek *et al*. [18] and Lee *et al*. [20] Reasons for exclusion are summarised in a flow diagram (see figure 1). Further, we e-mailed the corresponding author of each included study to obtain unavailable data; three authors [14, 17, 18] delivered data on nicotine abstinence and the use of allocated products for the present meta-analyses.

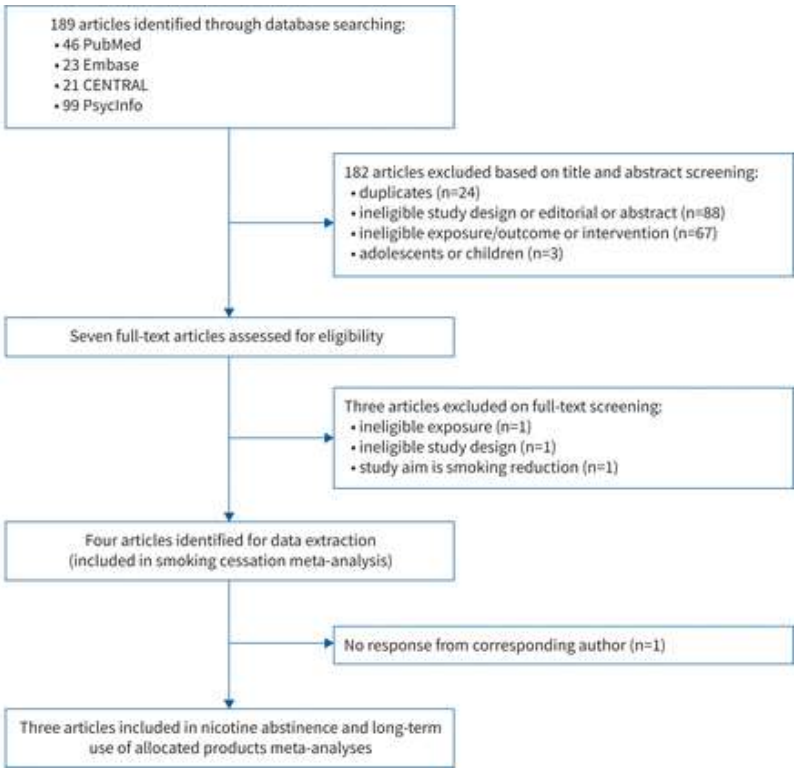

FIGURE 1

Flow diagram of the systematic review process. CENTRAL: Cochrane Central Register of Controlled Trials.

The four included RCTs represented 1598 participants (51.0% female). These trials were conducted in Australia, New Zealand, the UK and the United States. All studies excluded potential participants if they reported pregnancy or breastfeeding, those with severe medical conditions, and those already enrolled in an existing cessation programme. Three of these studies were sampled among patient populations, including participants who visited cessation and withdrawal services, while one study recruited participants from the community *via* newspaper advertisements. The length of these trials varied between 6 and 12 weeks, while the longest follow-up point ranged between 12 weeks, 6 months and 52 weeks (see table 1). All these trials were conducted among adults (over 18 years old); the mean age of participants in these studies ranged from 41 to 54 years, while average baseline smoking ranged from 14 to 21 cigarettes per day. All studies evaluated tobacco smoking abstinence *via* self-reports, while three validated their results through exhaled breath carbon monoxide measurements [14, 17, 18]. More detailed information on included studies is presented in table 1; a summary of findings for each study outcome is presented in table 2.

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TABLE 1

Characteristics of included studies

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TABLE 2

Summary of findings: e-cigarettes *versus* nicotine replacement therapy (NRT) for nicotine abstinence, allocated product use and smoking cessation

Risk of bias in included studies

Overall, the Bullen *et al*. [17], Hajek *et al*. [18] and Lee *et al*. [20] studies were judged be at low risk of bias, while the Bonevski *et al*. [14] study was judged to be at high risk of bias. Detailed information on the risk of bias assessment of each included study is reported in table 3. Figure 2 summarises the risk of bias in included studies.

TABLE 3

Detailed information on the risk of bias in included studies

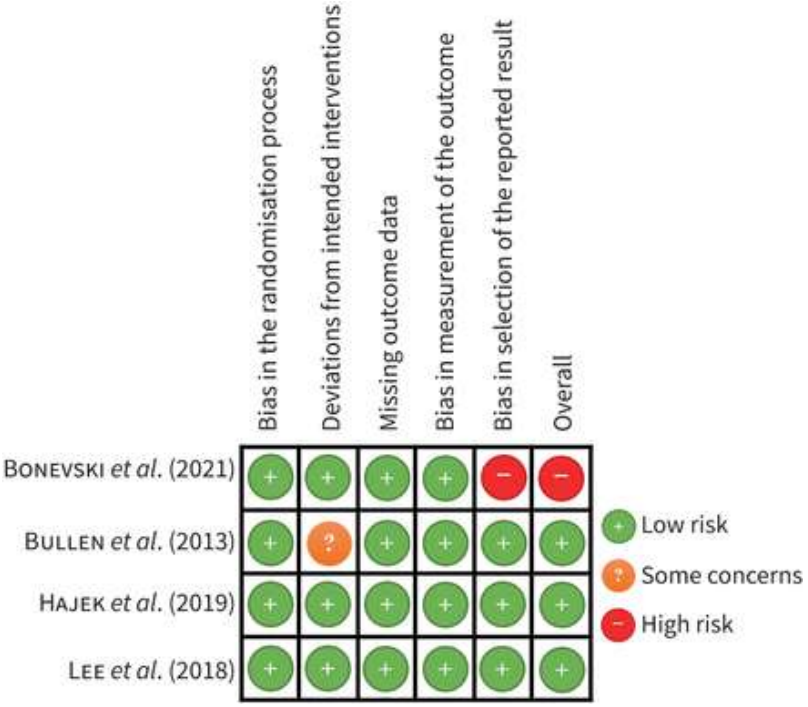

FIGURE 2

Risk of bias for each study. Studies: Bonevski *et al*. (2021) [14], Bullen *et al*. (2013) [17], Hajek *et al*. (2019) [18], Lee *et al.* (2018) [20].

Effects of interventions

Nicotine abstinence

The corresponding authors for the three studies provided data on nicotine abstinence and the allocated product use at the end of the trial. Data from the Bonevski *et al*. [14] (risk ratio 0.05 (95% CI 0.01–0.88)) and Hajek *et al*. [18] (risk ratio 0.46 (95% CI 0.25–0.85)) studies demonstrated that participants randomised to e-cigarettes had significantly lower nicotine abstinence rates compared to those

randomised to NTRs; in the Bullen *et al*. [17] study, this difference between two groups was not significant (risk ratio 0.83 (95% CI 0.41–1.69)). Pooled data from these three studies showed lower nicotine abstinence rates in participants randomised to e-cigarettes than in those randomised to NTRs (risk ratio 0.50 (95% CI 0.32–0.77); I^2=55%, Cochrane Q p=0.11; 1568 participants; see figure 3).

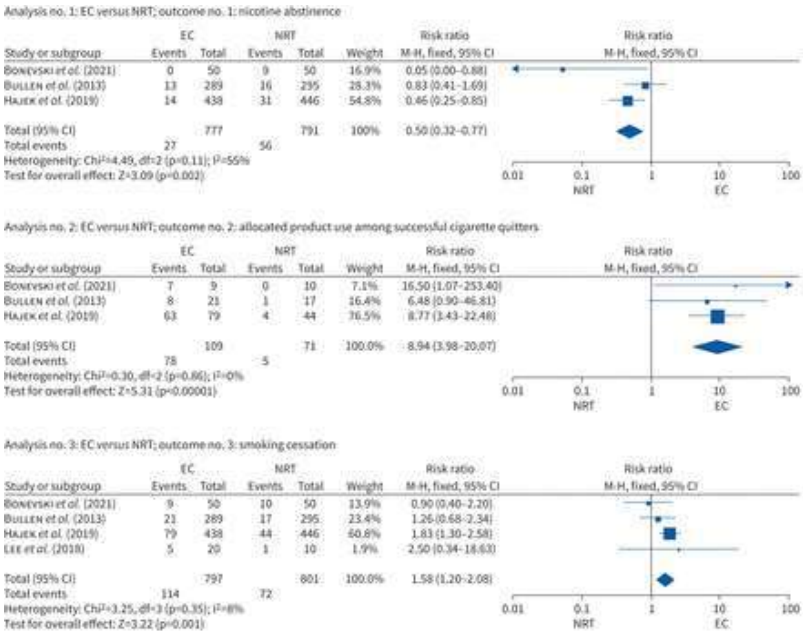

FIGURE 3

Pooled results for nicotine abstinence, allocated product use and smoking cessation. Studies: Bonevski *et al*. (2021) [14], Bullen *et al*. (2013) [17], Hajek *et al*. (2019) [18], Lee *et al.* (2018) [20]. EC: e-cigarette; df: degree of freedom; M–H: Mantel–Haenszel; NRT: nicotine replacement therapy.

Allocated product use among successful tobacco quitters

Data from the Hajek *et al*. [18] and Bonevski *et al*. [14] studies demonstrated that allocated product use among successful tobacco quitters at the end of the trial was statistically significantly higher among participants randomised to e-cigarettes (risk ratio 8.77 (95% CI 3.42–22.48) and risk ratio 16.50 (95% CI 1.07–253.40), respectively) than among those randomised to NTRs. This difference between the two groups was not found to be significant in the Bullen *et al*. [17] study (risk ratio 6.48 (95% CI 0.90–46.81)). Pooled data from these three studies showed higher allocated product use at the end of the trial in successful tobacco quitters randomised to e-cigarettes than in those randomised to NTRs (risk ratio 8.94 (95% CI 3.98–20.07); I^2=0%; 180 participants; see figure 3).

Smoking cessation

All studies included in this review reported on tobacco smoking cessation outcomes. In the Bonevski *et al*. [14] study, there was no significant difference between the e-cigarette and NRT groups in self-reported 6-week continuous tobacco abstinence at 12 weeks (risk ratio 0.90 (95% CI, 0.40–2.02)). Similarly, there was no significant difference between groups in 7-day self-reported point prevalence smoking abstinence at 6 months (risk ratio 2.50 (95% CI 0.34–18.63)) in the Lee *et al*. [20] study, and in carbon monoxide validated self-reported continuous smoking abstinence at 6 months (risk ratio 1.26 [95% CI 0.68–2.34)) in the Bullen *et al*. [17] study. Contrary to the other three studies, in the Hajek *et al*. [18] study, participants

randomised to the e-cigarette group had a higher self-reported carbon monoxide validated smoking cessation rate at 52 weeks (risk ratio 1.83 (95% CI 1.30–2.58)) than those randomised to the NRT group. Further, pooled data from these four studies demonstrated higher smoking cessation rates in participants randomised to e-cigarettes than to NTRs (risk ratio 1.58 (95% CI 1.20–2.08); I^2=8%; 1598 participants; see figure 3).

The data from these studies suggest that for every 100 people using e-cigarettes to stop smoking, 14 or 15 might successfully quit, but 10 or 11 of them will continue using e-cigarettes; whereas only nine out of 100 people might quit using NTRs, but only two of them will continue using nicotine (see figure 4).

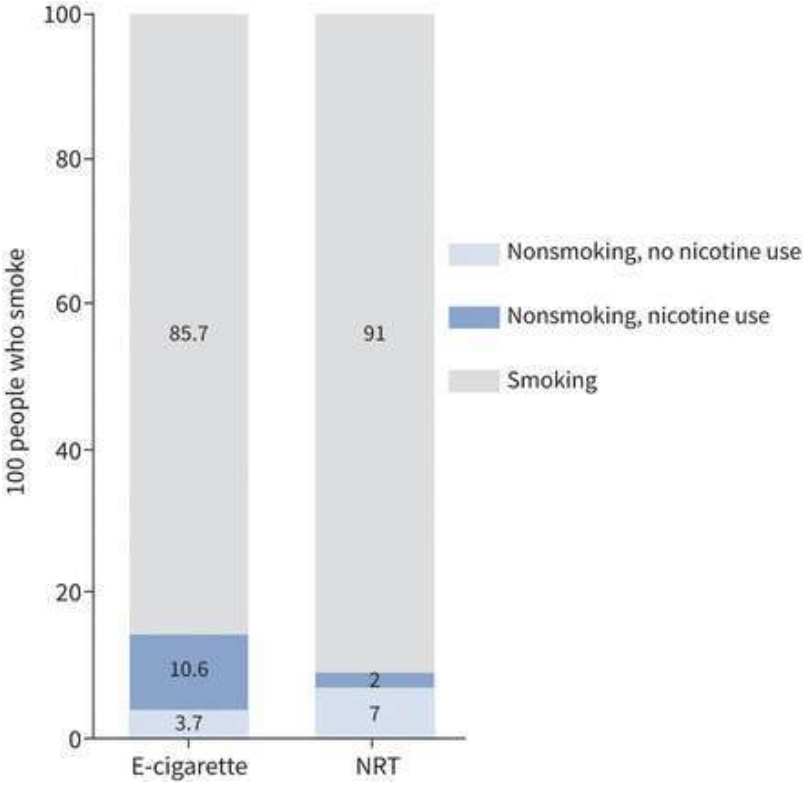

FIGURE 4

Anticipated absolute effects. NRT: nicotine replacement therapy.

Sensitivity analyses

Additional sensitivity analyses for all study outcomes were performed by removing the Bonevski *et al*. study [14], which was judged to be at high risk of bias and had the shortest follow-up period. After removing this study, the effect size for smoking cessation (risk ratio 1.69 (95% CI 1.26–2.27); I^2=0%), nicotine abstinence (risk ratio 0.59 (95% CI 0.37–0.93); I^2=33.5%), and allocated product use outcomes (risk ratio 8.37 (95% CI 3.57–19.59); I^2=0%) remained in the same direction and significant.

Discussion

We summarised the literature comparing the effectiveness of e-cigarettes *versus* NRT for nicotine abstinence. The results of our meta-analyses based on RCTs indicate that using e-cigarettes as a therapeutic intervention decreased nicotine abstinence rates compared to standard NRT.

Results of a recent Cochrane review [6] and other systematic reviews and meta-analyses [3, 7, 21] indicating a therapeutic effect of e-cigarettes have been replicated by the present study. However, our study is the first to show that the use of e-cigarettes as a therapeutic intervention may have a negative effect on nicotine abstinence in RCTs compared to NRTs. In other words, most of the smokers who quit smoking with the help of e-cigarettes continue to use e-cigarettes until the end of the observational period of the RCTs. This can be seen as an indicator of nicotine dependence [22]. While there is a wealth of literature on the harmful effects of smoking, much less is known about nicotine itself isolated from tobacco. Nicotine is a stimulant in low doses and a depressant of nervous activity in very high doses [23].

Although e-cigarettes were introduced to help abstain from smoking and as a less harmful alternative for those not willing to quit cigarettes, there is growing evidence suggesting that thousands of chemicals can be found in the e-cigarette liquid and aerosol [24]. These include metal nanoparticles, propylene glycol, acrolein, diacetyl, and other additives which can cause toxic, carcinogenic and epigenetic modifications and adversely impact health [25–27]. Furthermore, it has been demonstrated that e-cigarette aerosol exposure could lead to increased epithelial cell and macrophage death in the lung and impair important macrophage functions that are essential for the maintenance of lung function [28]. Another review study reported that e-cigarette aerosol exposure might contribute to DNA damage, pulmonary inflammation, oxidative stress, and oral diseases [29]. In addition, there is consistent evidence that e-cigarette use is associated with asthma and COPD, even after controlling for cigarette use and other covariates, which is of concern for respiratory and public health [30].

It has consistently been shown that children and adolescents are highly susceptible to nicotine addiction, which affects their brain development, even in those who smoke infrequently. Furthermore, young people who become addicted to nicotine are at greater risk of becoming lifelong tobacco consumers [31]. Given this background, concerns have been raised that the use of nicotine-containing liquids in e-cigarettes could be a gateway to the use of conventional cigarettes [32].

The current evidence for this concern is strong. The latest meta-analysis reported the pooled results for 23 studies from the United States (n=13), Germany (3), UK (2), Canada (1), Mexico (1), Netherlands (1) and Scotland (1), Finland (1), Taiwan (1) and Romania (1) of young people up to age 20. Among young people who had never smoked a cigarette at baseline, the risk of smoking among e-cigarette users at follow-up was about tripled [33]. In line with the results of an earlier meta-analysis [34], it was shown that in all 23 individual studies, there were elevations in risk of ever-e-cigarette use at baseline and subsequent ever-cigarette use at follow-up.

A Cochrane Collaboration review lists nine main adverse events related to NRT: headache, dizziness/light-headedness, nausea/vomiting, gastrointestinal symptoms, sleep/dream problems, non-ischaemic palpitations and chest pain, skin reactions, oral/nasal reactions, and hiccups, but many of these side effects were also common in the placebo group without nicotine [35]. In a large-scale study of people with chronic obstructive pulmonary disease, users of nicotine gum (who used nicotine gum over a 5-year study period) showed no indication of harm and also had lower hospitalisation rates for cardiovascular conditions compared to those who did not use the gum [36]. NRTs are a proven, safe and effective method for quitting smoking; nonetheless, their persistent use remains low. For instance, two studies estimated that persistent use of over-the-counter nicotine gum for recommended 6 months (or more) was as low as 6% [37]. Thus, whenever possible, clinicians should encourage their patients to use

NRT for an adequate duration, to not drop NRT when they lapse and to combine patch treatment with other NRT forms [37].

Our findings suggest that for every 100 people using e-cigarettes to stop smoking, only four might successfully quit and abstain from nicotine, compared with seven per 100 people in the NTR group. In such a way, a few systematic reviews demonstrated that there is an increased risk of subsequent combustible smoking initiation and smoking relapse among users of e-cigarettes [38, 39]. A substantial number of individuals using e-cigarettes as a cessation device may initiate dual use of e-cigarettes and combustible tobacco [40], which is the most common use pattern, and probably riskier for health than using tobacco or e-cigarettes alone [41].

Limitations

Publication bias is always a potential concern. We should be very cautious in drawing conclusions from the present meta-analyses' results because they are only based on four RCTs with a small number of participants. Whether the results from these clinical trials can be extrapolated to other countries beyond Australia, New Zealand, the United States and the UK, or to the thousands of products available on the global market is unknown. Differences in e-cigarette products, the nicotine concentration of e-liquids, nicotine formulation (salt *versus* free-base), flavouring agents, distribution strategy (free e-liquid refills *versus* limited e-liquid refills; e-liquids with a consistent nicotine concentration *versus* e-liquids with a declining nicotine concentration) and cointerventions may reduce the external validity of our findings when extrapolated to different e-cigarette products or when extrapolated outside of the clinical trial setting. Biases within existing studies and their heterogeneity may have impacted our study results.

Policy implications

Before recommending e-cigarettes to smokers, we must remember the Hippocratic Oath: "first do no harm" [8]. A strong association between industry-related conflict of interests and tobacco- and e-cigarette industry-favourable results, indicating that e-cigarettes are harmless, have been found [42]. Industry-independent research indicates that e-cigarettes are not harmless, even though the long-term health consequences are unknown [43, 44]. The Cochrane review suggests that an additional three people for every 100 would quit smoking with nicotine e-cigarettes compared to NRTs [6]. Our data indicate that only a tiny minority of smokers will stay abstinent from nicotine. We must question ourselves if the benefit of the three extra people who quit smoking with e-cigarettes will outweigh the harms of long-term e-cigarette use. We estimate from our data that 10–11 people quit tobacco use but continue e-cigarette use after the end of the intervention. Data from the largest RCT [18] indicate that 80% of the e-cigarette intervention group participants who successfully quit cigarette smoking are still using e-cigarettes. Further, recent research findings demonstrate that compared to e-cigarette only or cigarette-only use, dual use substantially increases the odds of developing respiratory symptoms [45] and cardiovascular risk factors [46].

The Cochrane review did not detect any serious side effects of e-cigarette use [6], but long-term use has not been documented, nor have the (long-term) health consequences been discussed. We recommend that updated versions of the review should also report long-term use of e-cigarettes as an outcome of the trials in order to be able to further evaluate the benefits and harms of e-cigarettes as a therapeutic intervention.

Conclusions

NRT is a proven, safe and effective method for quitting smoking. As long as e-cigarette manufacturers, now to a large extent tobacco companies, are not willing to develop their “product” as a proven smoking cessation aid, it is an ethical question why public health advocates should promote an unsafe device [47] that may lead to permanent nicotine addiction.

Acknowledgements

We are grateful to Dunja Przulj (Health and Lifestyle Research Unit, Wolfson Institute of Population Health, Queen Mary University of London, London, UK), Billie Bonevski (School of Medicine and Public Health, University of Newcastle, Callaghan, NSW, Australia) and Chris Bullen (National Institute for Health Innovation, University of Auckland, Auckland, New Zealand) for providing data for this study.

Footnotes

- Provenance: Submitted article, peer reviewed.
- Conflicts of interest: R. Hanewinkel reports receiving grants from the German Ministries of Health and Research, German Cancer Aid and German Health Insurances, payments made to the institution, outside the submitted work. J.B. Unger reports receiving NIH grants, outside the submitted work. A. Galimov reports receiving NCI/FDA Grant #U54CA180905, paid to the University of Southern California, PIs: Mary Ann Pentz and Adam Leventhal, outside the submitted work. The remaining authors have nothing to disclose.
- Support statement: A. Galimov and J.B. Unger are partially supported by the National Cancer Institute and the FDA Center for Tobacco Products (CTP) Award (NCI/FDA Grant #U54CA180905). NCI, or the FDA had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Funding information for this article has been deposited with the Crossref Funder Registry.
- Received September 27, 2021.
- Accepted January 17, 2022.

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E-Cigarettes Increase Risk of Lung and Bladder Cancer More Than Traditional Cigarettes

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People with a history of e-cigarette use have a higher risk of developing both lung and bladder cancer than never smokers or even users of regular cigarettes, according to study findings researchers reported during the 2022 American Society of Clinical Oncology Genitourinary Cancers Symposium.

Using data from the National Health Interview Survey database for 2016–2018, the researchers looked at lung and bladder cancer incidence among patients aged 18 years or older and compared them to patients' smoking histories. Although use of both traditional and e-cigarettes increased patients' risk for those cancers, it was higher among e-cigarette users. Additionally, e-cigarette users were significantly younger at bladder cancer diagnosis than either of the other groups.

"Tobacco smoking has been concretely proven to increase the risk of many cancers, including lung and bladder cancer," the researchers said. "To date, there is little data on how e-cigarette smoking impacts the incidence of these cancers. Our findings showed that compared to never smokers, history of e-cigarette smoking was associated with increased risk of lung and bladder cancer development and earlier bladder cancer diagnosis."

In its Use of E-Cigarettes and Vaping position statement, ONS calls for nurses "to educate the public, particularly parents and children, about the adverse effects of e-cigarettes and vaping." Read ONS's full position statement and learn more about e-cigarettes in the E-Cigarettes and Vaping Learning Library.

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ASCO special articles

Electronic Nicotine Delivery Systems: An Updated Policy Statement From the American Association for Cancer Research and the American Society of Clinical Oncology

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abstract

Combustible tobacco use has reached historic lows, demonstrating the importance of proven strategies to reduce smoking since publication of the 1964 Surgeon General's report. In contrast, the use of electronic nicotine delivery systems (ENDS), specifically e-cigarettes, has grown to alarming rates and threatens to hinder progress against tobacco use. A major concern is ENDS use by youth and adults who never previously used tobacco. While ENDS emit fewer carcinogens than combustible tobacco, preliminary evidence links ENDS use to DNA damage and inflammation, key steps in cancer development. Furthermore, high levels of nicotine can also increase addiction, raise blood pressure, interfere with brain development, and suppress the immune system. The magnitude of long-term health risks will remain unknown until longitudinal studies are completed. ENDS have been billed as a promising tool for combustible tobacco cessation, but further evidence is needed to assess their potential efficacy for adults who smoke. Of concern, epidemiological studies estimate that approximately 15%-42% of adults who use ENDS have never used another tobacco product, and another 36%-54% dual use both ENDS and combustible tobacco. This policy statement details advances in science related to ENDS and calls for urgent action to end predatory practices of the tobacco industry and protect public health. Importantly, we call for an immediate ban on all non–tobacco-flavored ENDS products that contain natural or synthetic nicotine to reduce ENDS use by youth and adults who never previously used tobacco. Concurrently, evidence-based treatments to promote smoking cessation and prevent smoking relapse to reduce cancer incidence and improve public health remain top priorities for our organizations. We also recognize there is an urgent need for research to understand the relationship between ENDS and tobacco-related disparities.

J Clin Oncol 40:4144-4155. © 2022 by American Association for Cancer Research and American Society of Clinical Oncology

INTRODUCTION

In 2015, the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) published a joint policy statement describing a rapidly growing epidemic of electronic nicotine delivery systems (ENDS), including e-cigarettes, and policies to address this trend.[1] The 2015 statement sought to balance curtailing youth use while remaining optimistic that ENDS could be a less harmful alternative to combustible tobacco cigarettes for adult smokers. As detailed in the following sections, youth ENDS use has further increased since the 2015 statement while evidence remains insufficient to show ENDS are more effective than current smoking cessation strategies. Additionally, several major health authorities have determined that the current evidence base is lacking in supporting ENDS as tobacco cessation aids, including the US Surgeon General[2]; the National Academies of Science, Engineering, and Medicine (NASEM)[3]; the US Preventive Services Task Force[4]; and the National Comprehensive Cancer Network, a coalition of 31 leading cancer centers.[5] At the time of this writing, no ENDS manufacturer has applied to the US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) for an Investigational New Drug (IND) application, a prerequisite to run a tobacco cessation clinical trial. The AACR and ASCO are publishing the present statement to detail advances in scientific understanding of the ENDS epidemic, strengthen recommendations to protect public health, promote evidence-based tobacco cessation across all groups, and highlight areas where more research is needed.

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on September 1, 2022 and published at ascopubs.org/journal/jco on October 26, 2022: DOI https://doi.org/10.1200/JCO.22.01749

Carcinogens from combustible tobacco products are very harmful to health, contributing to nearly half a million deaths each year in the United States and more than eight million deaths per year globally.[6,7] The process of burning creates a large amount of carcinogens, such as benzo[a]pyrene, that are inhaled in smoke from traditional cigarettes.[8] The first ENDS were introduced to the US market in 2006 as a way to deliver nicotine to users without burning tobacco.[9] Instead of burning tobacco, ENDS use electricity to power a heating element that aerosolizes an e-liquid, containing a solvent (eg, propylene glycol or glycerin), nicotine, flavors, and other additives. Some ENDS products can result in rapid delivery of a similar amount of nicotine as modern American cigarettes, which contribute to high addiction potentials.[10,11]

Tobacco would likely not be the top public health issue without the highly addictive properties of nicotine when delivered rapidly. Every time someone consumes nicotine, the brain releases the neurotransmitter dopamine, which provides a sense of pleasure or satisfaction.[12] Primarily due to the pharmacology of nicotine, over time, tobacco users become dependent on nicotine to feel pleasure and stave off withdrawal symptoms.[13] This rewiring of brain circuitry is especially of concern for the developing brains of youth.[14] Nicotine can also harm health by raising blood pressure[15] and suppressing immune function.[16] Strong evidence from clinical trials examining very low nicotine cigarettes demonstrates that reducing nicotine to less addictive levels could effectively decrease smoking rates by reducing initiation and increasing cessation of cigarette use.[17-21] In 2018, the FDA issued a proposed rule to lower the level of nicotine in cigarettes to nonaddictive or minimally addictive levels,[22] but at the time of writing, this rule has not advanced. While the present statement focuses on policies related to ENDS, additional regulations to reduce the addictiveness and appeal of combustible tobacco are also highly important.

The following sections outline updates since our previous statement related to the evidence of biological effects from ENDS that can contribute to cancer risk, use trends, effective tobacco cessation efforts, and ENDS regulations. The data support strong, urgent action to reduce ENDS use among youth and adults who never previously used tobacco. Because of the wide use of non-tobacco flavored ENDS among these groups, we recommend an immediate ban on all non–tobacco-flavored ENDS products that contain natural or synthetic nicotine. However, if non–tobacco-flavored ENDS are reviewed and approved by FDA CDER to increase cessation efficacy, the AACR and ASCO would welcome these as cessation therapies at that time. At the same time, new tobacco regulations should be structured to avoid any increases in combustible tobacco use, including smoking initiation and relapse. The following sections describe the evidence by which we based our recommendations.

ENDS LINKED TO KEY STEPS IN CANCER DEVELOPMENT

ENDS Expose Users to Carcinogens

The cancer-causing potential of ENDS is inferred from the currently available studies investigating the presence of carcinogens, human biomarkers of carcinogenesis, and animal and cell culture experiments. Carcinogens in ENDS can include four classes of chemicals, namely tobacco-specific nitrosamines, metals, volatile organic compounds, and polycyclic aromatic hydrocarbons. Table 1 highlights several recent reports comparing carcinogens and metabolites in urine or saliva samples from ENDS users and those who never used tobacco. The data show that at least 12 carcinogens are significantly elevated in ENDS users compared with non–tobacco users, but that their levels were generally lower than the levels of carcinogens seen in smokers and dual users (Table 1).[23-26] Unfortunately, the data are limited by a small number of studies that compared ENDS users with nonusers, and each study reported a different set of carcinogens. Separate studies further characterized carcinogens in ENDS aerosols and found that the power and temperature of devices greatly influences the amount of toxic metals and volatile organic compounds emitted.[28-31] Therefore, additional studies are needed for a more thorough and comprehensive understanding of the carcinogen load experienced by ENDS users. Nevertheless, the results of ENDS use investigated to date clearly indicate that vaping exposes the user to carcinogens and therefore likely increases long-term cancer risk, but for most carcinogens at levels far lower than from smoking combustible tobacco cigarettes.

ENDS Linked to DNA Damage

Several reports have found that ENDS vapor or extracts cause DNA damage in cell culture either by directly changing the chemical structure of DNA or indirectly by increasing highly reactive oxygen-containing molecules.[32-36] One of those reports found that potent antioxidant molecules prevented DNA damage in cell culture, confirming the contribution of reactive oxygen species.[32] A limitation of some studies is that they use higher concentrations of ENDS vapor than experienced by ENDS users, but DNA damage was also found in studies that used lower concentrations. Chemical modification of DNA by ENDS extracts leads to broken DNA strands,[35,37] which must be repaired by cells, or they will die. Repairing broken DNA strands can cause mutations that predispose cells to become cancerous, depending on how the damage is repaired.[38]

Furthermore, nicotine itself and ENDS extracts can inhibit DNA repair processes in cell cultures. The DNA checkpoint is a critical cellular system that senses damage and prevents cells from making new DNA in order to prevent further damage and initiate DNA repair.

TABLE 1. Carcinogens Significantly Increased in ENDS Users Compared With Nonusers

Class of Carcinogen	Name of Carcinogen	Metabolite Analyzed	Increase Compared With Nonusers, %			Sample Size	Reference
			ENDS Users	Dual Users	Smokers		
Tobacco-specific nitrosamines	4-(N-nitrosomethylamino)-a-(3-pyridyl)-1-butanone	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol	431	28,412	21,996	5,097	[23]
	4-(N-nitrosomethylamino)-a-(3-pyridyl)-1-butanone	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol	75	NA	3,100	57	[24]
	N′-nitrosonornicotine	NA	80	513	514	4,985	[23]
	N′-nitrosonornicotine (saliva)	NA	5,740	NA	37,700	59	[24]
Metals	Cadmium	NA	30	88	86	5,091	[23]
	Lead	NA	23	42	36	5,105	[23]
Polycyclic aromatic hydrocarbons	2-naphthylamine	NA	29	NA	NA	23	[25]
Volatile organic compounds	Acrylonitrile	N-acetyl-S-(2-cyanoethyl)-L-cysteine	201	11,018	9,322	4,877	[23]
	Acrylonitrile	N-acetyl-S-(1-cyano-2-hydroxyethyl)-L-cysteine	30	1,242	1,066	4,877	[23]
	N,N-dimethylformamide	N-acetyl-S-(N-methylcarbamoyl)-L-cysteine	46	424	359	4,844	[23]
	Acrylamide	N-acetyl-S-(2-carbamoylethyl)-L-cysteine	95	583	NA	103	[26]
	Propylene oxide	2-hydroxy-propyl methacrylate	89	94	NA	103	[26]
	Crotonaldehyde	N-acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine	48	85	NA	103	[26]
	Acrolein	3-hydroxypropyl mercapturic acid	32	128	NA	103	[26]
	Ortho-toluidine	NA	133	NA	NA	22	[25]

NOTE. The table lists carcinogens identified by Goniewicz et al,[23] Fuller et al,[25] Rubinstein et al,[26] and Bustamante et al,[24] to be elevated in the urine (or saliva where noted) of adults who use ENDS products compared with adults who do not use any tobacco products. All listed carcinogens are rated possibly carcinogenic (group 2B) to carcinogenic to humans (group 1) by the International Agency for Research on Cancer.[27] ENDS users refers to exclusive ENDS use. Smokers refers to exclusive combustible cigarette use. Dual users refers to people who use both ENDS and combustible cigarettes.

Abbreviations: ENDS, electronic nicotine delivery systems; NA, not available.

Nishioka et al[39] found that nicotine overrides the DNA checkpoint and allows cells to make DNA even when there is DNA damage. Base excision repair is a key repair mechanism for DNA that has been chemically altered; two studies found that ENDS extracts reduce the abundance of base excision repair proteins, thus limiting the ability of cells to repair damage caused by ENDS.[33,34] It is possible that inhibition of DNA repair from ENDS use could exacerbate DNA damage and related DNA mutations caused by smoking in people who dual use.

ENDS Linked to Inflammation and Cellular Replication

In addition to DNA damage, ENDS vapor could also lead to cancer by promoting inflammation and cellular replication that expands mutations caused by prior carcinogen exposure. A core hallmark of cancer is uncontrolled cellular replication.[40] Several constituents in ENDS vapor can cause inflammation, as demonstrated by increased proinflammatory cytokines such as interleukin-6 (IL-6) and CXCL8.[41-46] Wang et al[44] found that nicotine signaling in mouse lungs was a significant contributor to inflammation and that deleting the nicotine receptor in lung cells reduced inflammation, confirming nicotine directly causes inflammation. However, even use of ENDS that only contained propylene glycol and vegetable glycerin had moderate proinflammatory effects in human lungs.[43] An additional study found that ENDS users had significantly elevated levels of IL-6 and CXCL8 in the blood compared with never-smokers.[45] IL-6 is well documented to induce cell signaling pathways that promote cellular replication and transform precancerous cells into cancerous cells.[47-49] Singh et al[45] also found that ENDS users had elevated levels of growth signaling molecules commonly implicated in cancer progression compared with never–tobacco users, including epidermal growth factor, vascular endothelial growth factor, and hepatocyte growth factor. These findings suggest that ENDS vapor can promote replication of precancerous cells and therefore promote cancer-predisposing DNA mutations.

Summary

A growing body of evidence points toward a biologically plausible role for ENDS use in contributing to human carcinogenesis, based on the presence of carcinogens in ENDS aerosols, metabolites of carcinogens in human urine samples, inflammation markers in human lung swabs and blood samples, and cell culture and mouse experiments exhibiting DNA damage and inflammation. It is important to note that the evidence from biomarker studies tends to show lower carcinogen exposures in ENDS users compared with dual users and exclusive smokers of combustible tobacco, likely due to the absence of combustion-related carcinogens. Additionally, the lack of well-designed epidemiologic studies is a critical hurdle to definitively characterizing cancer risk. ENDS remain relatively new products, so it may take decades for enough exposure to occur that would enable studies with sufficient follow-up to fully characterize the associations between ENDS use and cancer. Even less is known about the harms of secondhand exposure to ENDS vapor. In contrast, the scientific evidence very clearly demonstrates smoking combustible tobacco increases the risk of being diagnosed with lung cancer by approximately 25-fold compared with never smoking[6] and is an established cause of at least 17 other human cancers.[6,50]

PATTERNS OF ENDS USE SUPPORT A BAN ON ENDS FLAVORS

While youth and adult use of combustible tobacco has decreased to historic lows,[2] the epidemic of youth ENDS use threatens to diminish progress against nicotine addiction. The AACR and ASCO published our first ENDS statement in 2015 due to concerns regarding the almost 400% rise between 2012 and 2014 in ENDS use among US high school students, according to the 2014 National Youth Tobacco Use Survey (NYTS; Fig 1).[51] The number of high school students who had used ENDS in the past 30 days increased by an additional 46% in 2020 compared with 2014 levels, to a total of 3.6 million youth.[52] A separate national survey, Monitoring the Future, also found a dramatic 73% increase between 2015 and 2020 among 12th grade students who had vaped in the past 30 days (Fig 1).[60] This continued increase in the youth ENDS epidemic underscores the need for urgent action to save a generation of youth from life-long nicotine addiction.

Numerous studies have clearly demonstrated that appealing flavors are key drivers of youth initiation of ENDS use, with the pharmacology of nicotine as the key driver of addiction to ENDS.[61-68] The 2020 NYTS found that 82.9% of youth ENDS users used flavored products. Among high school ENDS users, 73% reported vaping fruit-flavored ENDS, 55.8% vaped mint, and 37% vaped menthol (percentages add to > 100% due to use of multiple flavors by one person).[52] In comparison, the 2020 Monitoring the Future found that only 2.9% of youth ENDS users vaped

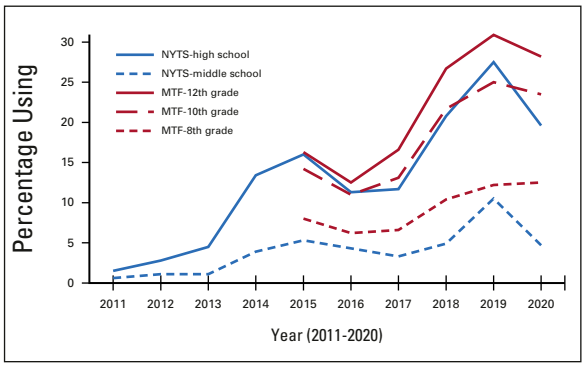

FIG 1. Percentage of various school age groups who vaped in the past 30 days. Blue lines indicate data from the NYTS,[51-59] and red lines indicate data from the MTF survey.[60] MTF, Monitoring the Future; NYTS, National Youth Tobacco Use Survey.

tobacco-flavored products.[69] Youth who are offered fruit-flavored ENDS by peers are 6.49-fold more likely to try ENDS compared with tobacco-flavored ENDS.[61] In contrast, adults are 21-fold more likely to exclusively use tobacco-flavored ENDS compared with youth.[63] Flavored ENDS follow a long history of the tobacco industry using flavors to attract youth toward nicotine by disguising the otherwise unpleasant taste of tobacco and purposefully altering perceptions of risk.[61]

In February 2020, the FDA implemented restrictions on pod- or cartridge-based ENDS product flavors, except for menthol and tobacco flavors.[70] The policy lacked definitions of mint or menthol, thus allowing manufacturers to simply relabel products to avoid the flavor restriction.[71] Open-tank and single-use ENDS were also exempted from any flavor restrictions, which left thousands of appealing flavors on the market. Consequently, youth switched to exempted products. The 2020 NYTS found that disposable products were used by 2.4% of high school ENDS users in 2019,[52] but this increased 11-fold to 26.5% in 2020. The prevalence of flavored disposable ENDS also increased among middle schoolers, with a five-fold increase in disposable product use between 2019 and 2020 (3.0% *v* 15.2%). Flavoring chemicals and other additives of ENDS have not been studied to determine the health risks associated with inhalation. The ability to mix flavors at the point of sale also increases the difficulty of regulators to gain a complete understanding of the health impact of these chemicals in real-world use.

The use of ENDS among adults has also increased in recent years, particularly among young adults. According to the Behavioral Risk Factor Surveillance System (BRFSS; N = 1,156,411), the prevalence of ENDS use increased among US adults from 4.5% in 2016 to 5.4% in 2018[72] and was 15.0% among adults under the age of 24 years. These data correspond to almost 14 million adults using ENDS in 2018. A second study analyzed data from the Population Assessment of Tobacco and Health (PATH) study (N = 30,191), which is also representative of the population of US adults, and found that 6.5% of US residents used ENDS in 2018.[73] Concerningly, the BRFSS study found that 42% of adult ENDS users had never previously used another tobacco product,[72] and the PATH study found 15% of adult ENDS users had never used another type of tobacco product.[73] While the high variability between analyses necessitates further study, the data suggest ENDS are being used by millions of adults who never previously used tobacco. Additionally, approximately 36% of ENDS users in the BRFSS study and 52% in the PATH study dual use ENDS and combustible tobacco. A separate nationwide survey (n = 5,989) found that 27.7% of adults who smoked also dual used ENDS in 2018.[74] Notably, dual use rates were higher in adults who wanted to quit smoking within 6 months (33.1%), compared with 18.7% of those who did not plan to quit smoking. Similar to the general population, adult patients with cancer and survivors who use ENDS are more likely to be under the age of 50 years,[75,76] but patients with cancer who use ENDS are far more likely to be current or former smokers than never-smokers. As presented in Table 1, dual users continue to be exposed to similarly high levels of carcinogens as exclusive users of combustible tobacco, and the current evidence of the efficacy of dual using ENDS to help quit smoking remains unclear. The evidence is clear that any combustible smoking, even one cigarette per day, has significant negative health impacts.[77]

As stated in the introduction, major US public health authorities have found insufficient evidence to conclude ENDS effectively help smokers quit combustible tobacco.[2-5] In contrast, there is evidence that demonstrates ENDS significantly increase the likelihood youth and young adults start smoking combustible tobacco. A 2021 meta-analysis analyzed nine studies (combined baseline, n = 32,286), which compared the likelihood of smoking initiation between youth ENDS users and never users[78]; youth who used ENDS were four-fold more likely to ever smoke a combustible cigarette than never users, even after accounting for potentially confounding factors. Similarly, a 2020 meta-analysis analyzed 17 studies (combined baseline, n = 57,514), which compared the likelihood of smoking initiation between young adult ENDS users and never users; young adults who used ENDS were approximately three-fold more likely to ever smoke a combustible cigarette compared with never users.[79] On the other hand, the nationwide increased rates of e-cigarette use among youth is accompanied by a substantial decrease in past-month smoking rates,[60,80] and the extent to which ENDS use leads to established or regular smoking to date appears to be low.[81] Nonetheless, the well-documented ability of ENDS to roughly triple smoking initiation by youth and young adults is of concern and overshadows the more limited evidence suggesting the efficacy of ENDS for smoking cessation.[82] As stated above, flavors are a key driver of youth initiation of ENDS, with the pharmacology of nicotine leading to addiction and continued, repetitive use. Therefore, to limit youth nicotine dependence, we recommend an immediate ban on all non–tobacco-flavored ENDS products that contain natural or synthetic nicotine, unless an ENDS product is approved by FDA CDER as a smoking cessation therapy.

ADVERTISING CONTRIBUTES TO YOUTH ENDS INITIATION

Advertising has a powerful effect on youth tobacco initiation, including for ENDS. Many studies have found that advertisements from social media influencers, television, radio, print, and in retail stores significantly increases the probability that youth will start using ENDS.[83-90] Additionally, a national survey (N = 4,604) found that high exposure to tobacco use during television shows more than

doubled the likelihood of initiating ENDS use among youth and young adults.[91] These findings demonstrate a strong link between ENDS advertising or imagery exposure and subsequent initiation. Therefore, in addition to a ban on flavors, we support efforts to prevent all forms of advertisement for nicotine products from reaching youth.

LEVERAGING EVIDENCE-BASED SMOKING AND ENDS CESSATION THERAPIES AND AWARENESS CAMPAIGNS

There are currently no evidence-based pharmacologic therapies to help ENDS users quit vaping.[92] However, it is reasonable to conclude that lessons learned from smoking cessation could aid in treating nicotine dependence from ENDS. The 2021 US Preventive Services Task Force tobacco cessation recommendation concluded that the most effective treatment for tobacco use includes both FDA-approved pharmacotherapies and behavioral counseling (Fig 2).[4] Additional research is critically needed to identify effective cessation therapies specifically for ENDS users. A major hurdle to assessing tobacco use in clinical research studies is the lack of standardized definitions for terms describing tobacco use history, such as *current smoking*, *current ENDS use*, *former smoking*, etc. Evidence-based definitions provided by the FDA or National Cancer Institute will be helpful to further advance tobacco research.

Little is known about the interaction of smoking and ENDS use and subsequent impact on different anticancer treatments or on cancer prognoses. In the context of cancer treatment, smoking by patients with cancer and survivors increases the risk of overall or cancer-related mortality by roughly 50%-60%, increases risk for a second primary cancer, and has strong associations with increased cancer treatment toxicity.[6] Consequently, it is important to consider the biologic and clinical effects of smoking when considering the effects of ENDS use by patients with cancer. Quitting smoking after a cancer diagnosis is associated with a median 45% improvement in survival.[2] Therefore, evidence-based smoking cessation is considered a critical component of cancer care by AACR, ASCO, and other major oncology organizations.[93] However, large surveys demonstrate that few oncology providers regularly assist patients with quitting.[94,95] Compared with the general adult population, the data are even less clear on whether ENDS aid cessation efforts by patients with cancer or whether ENDS will have a positive or negative effect on cancer treatment. This is further complicated by frequent transitions between smoking and ENDS. However, smoking cessation confers significant benefits by reducing cancer risk, improving cancer treatment outcomes, and improving several other health outcomes beyond cancer.[2] Given the clear and strong evidence for the adverse effects of smoking on cancer treatment outcomes, quitting smoking should remain the top priority for patients with cancer and providers, with emphasis on the importance of quitting smoking to improve cancer treatment outcomes. When considering these important data and findings, it is critical that patients with cancer who are using ENDS currently not return to cigarette smoking.

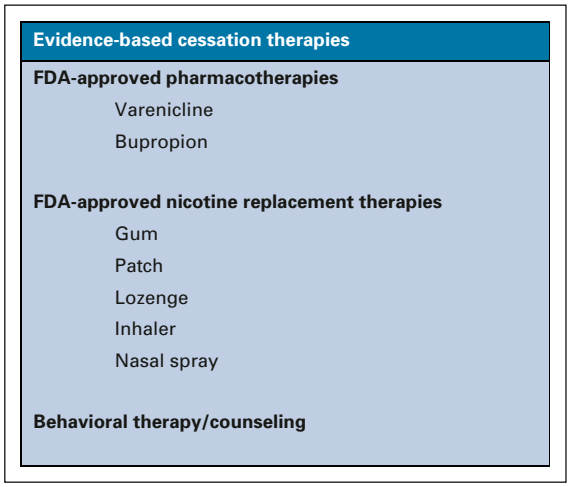

FIG 2. Evidence-based cessation therapies. FDA, US Food and Drug Administration.

A significant hurdle to evidence-based cessation therapies is inconsistent insurance coverage. This is most pronounced among uninsured smokers, who are 33% less likely than the general population to use evidence-based therapies.[96] After Massachusetts implemented comprehensive Medicaid smoking cessation coverage in 2006, the smoking rate of beneficiaries dropped by 26% in 2 years[97]; every dollar spent on cessation coverage saved $3.12 in US dollars (USD) in spending on tobacco-related illnesses.[98] Unfortunately, most state Medicaid plans do not cover all FDA-approved medications, and coverage of behavioral therapy is inconsistent.[99] Additional barriers such as extreme shortages of health care workers, demanding physician schedules, medical preauthorizations, copayments, and limits on quit attempts per year also reduce success rates.[100-102] Nonphysician-certified tobacco cessation specialists are also often not reimbursed by insurance plans. Payment reform for cessation specialists, FDA-approved therapies, and addressing other barriers to cessation could be powerful cost-saving interventions to increase quit rates by making it as easy as possible to receive evidence-based help. An improved coverage and reimbursement environment for tobacco cessation services and medications will benefit population health; this would even apply should an ENDS product ever become an FDA-approved cessation device.

A number of awareness campaigns and free cessation resources (Fig 2) have emerged over the past decade to prevent initiation and help tobacco users quit, some of which could be used or repurposed in the context of ENDS cessation. The This is Quitting campaign by the Truth Initiative increased 7-month quit rates among

young adult ENDS users to 24.1% compared with 18.6% among participants who did not participate in the campaign.[103] The FDA's The Real Cost advertising campaign helped prevent an estimated 380,000-587,000 youth from smoking between 2013 and 2016.[104] The CDC's Tips from Former Smokers campaign saved an estimated $11 billion (USD) in tobacco-related health care spending over 6 years at a cost of $490 million (USD)[105] and helped more than one million smokers permanently quit.[106] Among smokers who visited the free cessation services website, SmokeFree.gov,[107] as part of a randomized clinical trial, 26% successfully quit 1 year later.[108] Finally, Quitline counseling services increased quit rates by 60%.[109] Increasing resources for these excellent evidence-based tobacco treatment services could help significantly to expand their reach and quality of service.

EVIDENCE NEEDED TO DETERMINE IF ENDS CAN HELP SMOKERS QUIT SMOKING

To our knowledge, to date there is a lack of sufficient evidence for the use of ENDS as tobacco cessation therapies.[2-5] This is because very few randomized clinical trials have directly compared the efficacy of ENDS with standard cessation therapies; the failure of ENDS manufacturers to submit an IND application is the primary reason for a lack of ENDS clinical trials in the United States. However, a 2021 systematic review found that preliminary evidence suggests ENDS could be more effective for smoking cessation than nicotine-replacement therapy alone,[82] although the authors caution that the small number of studies and variations in study design limit the strength of their conclusions. The moderate strength conclusion of the review was primarily based on two clinical trials that investigated the efficacy of ENDS to help with smoking cessation. The first trial (N = 886), from the United Kingdom, found ENDS helped smokers quit at statistically significantly higher rates than nicotine patches[110]; the trial found 18% of participants who used ENDS plus behavioral therapy had quit smoking by 1 year, compared with 9.9% of participants who used nicotine patches plus behavioral therapy. The second trial (N = 1,124), from New Zealand, found that 18% of those randomly assigned to patches plus a nicotine e-cigarette quit smoking, compared with 10% randomly assigned to a nicotine-free e-cigarette plus patches and 8% randomly assigned to patches alone.[111] It is noteworthy in both trials that a large proportion of participants continued using ENDS at the long-term follow-up visit in these studies. Moreover, all groups in the above studies experienced slightly lower but comparable rates of successful cessation as found for 6-month follow-up when using FDA-approved nicotine patches alone (22%).[112] Therefore, we recommend that ENDS manufacturers apply for IND applications to facilitate randomized clinical trials to definitively assess the cessation efficacy of their products compared with FDA-approved cessation therapies.

REGULATION OF ENDS NEEDS IMPROVEMENT

During the past 15 years, the FDA has attempted to regulate ENDS products with limited success. In 2009, Congress passed the Family Smoking Prevention and Tobacco Control Act,[113] which granted the FDA the authority to regulate tobacco products. In May 2016, the FDA deemed ENDS as tobacco products under the Tobacco Control Act.[114] This ruling required ENDS manufacturers to submit a premarket tobacco product application (PMTA) to prove that the product is "appropriate for the protection of public health."[114(p28992)] In 2017, the FDA elected to delay the PMTA deadlines for ENDS from 2018 to 2022. During this time, many users believed that ENDS were safe and did not contain nicotine.[61,69,115] As described in the epidemiology section, perceptions of safety contributed to alarming increases in ENDS use among those who never previously used tobacco.

In 2019, US District Judge Paul W. Grimm ruled that the FDA had acted improperly by delaying ENDS regulations.[116] Citing a clear public health emergency, Judge Grimm required PMTA applications for ENDS to be submitted by May 2020, but this was delayed to September 2020 because of the COVID-19 pandemic. By September 2020, more than six million PMTAs for ENDS products were submitted for FDA review.[117] The FDA has denied marketing orders for more than 98% of those products, which requires those products to be removed from the market.[118] However, the FDA is still reviewing PMTAs for ENDS products from manufacturers with the largest market shares and permitting those products to remain on the market in the meantime.

Two additional policies have also had a major impact on the use of ENDS products: age restrictions and taxation. In 2015, Hawaii became the first state to raise the minimum legal age to purchase tobacco products to 21 years,[119] based on a NASEM report that estimated nearly 250,000 premature deaths could be prevented over 30 years.[120] Following Hawaii's lead, 18 additional states and Washington, DC also raised the minimum age to 21 years between 2016 and 2019. As part of the federal fiscal year 2020 appropriations package, Congress raised the minimum legal age to purchase tobacco products to 21 years in the entire United States.[121] Separately, for every 1% increase in the price of tobacco products, consumption decreases by 0.4% on average.[122] While the federal government does not yet tax ENDS, 24 states have passed ENDS taxes.[123] Due to the powerful disincentivizing effect of taxes on tobacco use, the AACR and ASCO support imposing a federal excise tax on all products that contain natural or synthetic nicotine in a manner that promotes public health benefit.[124,125] Additional policy recommendations are included in Table 2.

TABLE 2. AACR and ASCO Recommendations

Legislative Recommendations
Ban all non-tobacco-flavored products that contain natural or synthetic nicotine; flavors may only be used for research purposes or FDA-approved tobacco cessation therapies
Tax all products that contain natural or synthetic nicotine in a manner that reduces tobacco use and promotes public health
Increase funding for evidence-based tobacco control programs and campaigns such as the CDC's Office on Smoking and Health, state tobacco control programs, and Quit Lines
Prohibit the use of ENDS in places where combustible tobacco use is prohibited by federal, state, or local laws. All tobacco use should be prohibited at medical facilities
Limit the sale of tobacco products to stores or areas within stores that require age verification upon entrance
Require health insurance plans, including Medicare/Medicaid, to cover all FDA-approved cessation therapies, expand coverage limits, and reimburse healthcare providers, including cessation specialists, for time helping patients quit smoking and vaping
Regulatory Recommendations
Regulate predatory tobacco advertising practices including packaging, product designs, and labeling appealing to youth; misleading statements about cessation efficacy; athletic, musical, social, or cultural event sponsorship; giveaways when buying tobacco products; branded clothing; social media, digital, and print advertising; and tobacco use in movies and television
The FDA should enforce removal of ENDS products from the market that have not received a marketing order, publish PMTAs with confidential information redacted, and update PMTA review progress with a publicly available database
The FDA should develop product standards for tobacco products to improve public health, including but not limited to minimizing appeal to youth; capping the amount of nicotine delivery to minimize addictiveness; eliminating or substantially reducing human exposure to known carcinogens (eg, heavy metals) and other toxicants (eg, additives, contaminants, and manufacturing residues); and regulating the power and operating temperature of ENDS products
PMTAs should require information regarding: Composition of ENDS and e-liquid components; appeal to people who have never used tobacco products; impacts on health; geotracking or biometric capabilities; and steps taken to protect consumer privacy
Require health warning and safety labels on ENDS packaging and advertising; these labels should contain ENDS/e-liquid composition information from PMTAs
The FDA and/or NCI should provide evidence-based, non-stigmatizing definitions for categories of tobacco use for human studies, for example no tobacco history; no smoking history; no ENDS history; currently smoking; currently using ENDS; former smoking history. The FDA and/or NCI should provide guidance on best practices for measuring tobacco use data in human studies. The FDA should require all oncology clinical trials to assess tobacco use and report findings
The FDA should increase enforcement of the minimum age to legally purchase tobacco products
Additional Research Needs
Research is needed to determine effective ENDS cessation therapies for youth, young adults, and adults, as well as cessation therapies for youth combustible tobacco users
Large prospective epidemiological studies are needed to investigate the long-term health impacts of ENDS use and disparities in tobacco-related illness.
Additional research is needed for a comprehensive understanding of the acute and long-term biologic effects of ENDS use, carcinogen exposures, and the use of ENDS in the context of smoke exposure
Additional research is needed on how patients diagnosed with cancer use tobacco products, their reasons for use, perceptions of health impacts, impact of cessation on cancer-related outcomes, and interactions with anticancer therapies
Randomized clinical trials are needed to investigate the cessation efficacy of ENDS compared to FDA-approved cessation therapies. Investigational New Drug applications are necessary to facilitate such trials
Research is needed to monitor the impacts of federal, state, and local tobacco policies on youth and adult use patterns, as well as the use of evidence-based approaches to develop policy

Abbreviations: AACR, American Association for Cancer Research; ASCO, American Society of Clinical Oncology; ENDS, electronic nicotine delivery systems; FDA, US Food and Drug Administration; NCI, National Cancer Institute; PMTA, premarket tobacco product application.

In conclusion, ENDS emit fewer carcinogens than combustible tobacco primarily due to the absence of combustion products, and for some ENDS the absence of some tobacco-specific nitrosamines, but it is clear that they still pose health risks. Additionally, e-cigarettes have addicted a new generation of youth and young adults to nicotine and threaten to hinder progress against tobacco-related illnesses. For these reasons, the AACR and ASCO call for urgent action by Congress, state legislatures, and regulatory agencies to implement the various legislative, regulatory, and research recommendations outlined in this report, including calling for an immediate ban on all non–tobacco-flavored ENDS products that contain natural or synthetic nicotine with the goal of reducing ENDS use

by youth and adults who never previously used tobacco. The top tobacco control priorities for the AACR and ASCO continue to be preventing initiation of tobacco use (including ENDS), preventing smoking relapse, and promotion of evidence-based tobacco cessation treatment for all groups.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.22.01749.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Electronic Nicotine Delivery Systems: An Updated Policy Statement From the American Association for Cancer Research and the American Society of Clinical Oncology

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

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Research Funding: AstraZeneca, Merck, Lilly, Genentech/Roche

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No other potential conflicts of interest were reported.

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No other potential conflicts of interest were reported.

Smoking or Vaping? The DNA Damage May Be the Same

Cara Murez ⋮⋮ 16/2/2023

THURSDAY, Feb. 16, 2023 (HealthDay News) -- A new study builds upon earlier evidence that vaping isn't any healthier than smoking.

In analyzing epithelial cells taken from the mouths of vapers, smokers and people who had never vaped or smoked, researchers found that vapers and smokers had more than twice the amount of DNA damage as found in non-users.

Those who vaped or smoked more frequently had higher DNA damage.

Epithelial cells line the mouth. DNA damage is an early change associated with an increased risk for cancer and inflammatory diseases.

"For the first time, we showed that the more vapers used e-cigarettes, and the longer they used them, the more DNA damage occurred in their oral cells," said senior study author Ahmad Besaratinia. He is a professor of research population and public health sciences at the Keck School of Medicine in Los Angeles.

"The same pattern held up in smokers," Besaratinia said in a school news release.

In the study, the researchers recruited 72 healthy adults who were interviewed and underwent biochemical testing.

The study participants were divided into three groups: vapers who had never smoked cigarettes; smokers who had never vaped; and people with no history of smoking or vaping.

The researchers also collected data on how often, and for how long, participants had smoked or vaped. They asked vapers what devices and flavors they used.

The investigators then collected a sample of epithelial cells from each participant's mouth and tested for damage to specific genes known to indicate assault to the genome.

These tests showed similar levels of DNA damage between vapers and smokers: 2.6 times and 2.2 times that of non-users, respectively.

The most popular products, including flavored vapes, also appear to be the most harmful.

"The devices and flavors that are most popular and highly consumed by youth vapers, as well as adults, are the ones that are associated with the most DNA damage," Besaratinia said. "Clearly these results have significant implications, both for public health and regulatory agencies."

The new study builds on earlier research that found vaping was linked to alterations in gene expression, epigenetic changes and other biological changes that could foster disease.

About 10% of U.S. teens and more than 3% of adults regularly use e-cigarettes.

Vapers are difficult to study because many have a history of cigarette smoking or are dual users.

"We designed our study to tease out the effects of vaping in e-cigarette users who were neither cigarette smokers nor dual users at any point in their lives," Besaratinia said.

The research team now plans to replicate the findings in a larger group of participants and to study other biological effects resulting from DNA damage that are even more closely related to the onset of chronic disease.

The findings were published Feb. 14 in the journal *Nicotine & Tobacco Research*.

The study was supported by the U.S. National Cancer Institute, the National Institute of Dental and Craniofacial Research, and the University of California Tobacco-Related Disease Research Program.

What This Means for You

Don't kid yourself. Vaping causes as much genetic damage as smoking does, new research shows.

More information

The U.S. Centers for Disease Control and Prevention has more on e-cigarettes.

SOURCE: Keck School of Medicine of USC, news release, Feb. 13, 2023

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Vaping May Affect Lungs' Lubricant, Making Breathing Tougher

Cara Murez ⋮⋮ 20/12/2022

TUESDAY, Dec. 20, 2022 (HealthDay News) -- Researchers have uncovered another health hazard associated with vaping.

Inhaling vape products may damage a critical layer of the lungs called surfactant. Made of lipids and proteins, surfactant makes it possible to breathe with minimal effort by reducing surface tension. Researchers say breathing would require more effort and possibly mechanical help without this layer.

"Vaping continues to be popular, but not much is known about what happens with the aerosol when it enters the lungs," said researcher Ruud Veldhuizen, a scientist at the Lawson Health Research Institute in Ontario, Canada.

"We realized that the first thing the vapor aerosol comes in contact with in the lungs is pulmonary surfactant, which is an area our team specializes in," he said in an institute news release.

The investigators studied the effects of vaping by placing a film of surfactant inside a syringe, and then using a vaping device to push aerosol into the syringe.

The vapor could then directly interact with the surfactant. Researchers mimicked inhaling and exhaling vapor into the syringe 30 times to resemble a standard vaping session.

"In particular, we were looking at the surface tension in the surfactant," said co-researcher Emma Graham, a master's student at Western University's Schulich School of Medicine and Dentistry in Ontario. "After vaping, we saw high surface tension, which suggests the surfactant would not be as effective at supporting proper lung functioning."

The team further studied the effect of vaping using different devices, flavors, additives and nicotine.

"Nicotine didn't have any worse effects on surface tension of surfactant compared to other e-liquids, but some flavorings, like menthol e-liquid, did," Graham said in the release.

Veldhuizen said the findings could indicate why people that vape have a susceptibility to develop lung injury, including those with respiratory viruses such as COVID-19.

"We would like to get this information out there so that people know vaping may be damaging to the lungs," Veldhuizen said. "As a next step, we hope to further investigate the effects of vaping on the lungs and how we can treat resulting injury."

The findings were published recently in the journal PLOS ONE.

What This Means for You

Vaping, specifically additives and flavorings in vape liquids, damages a layer of lubrication in the lungs, new research shows.

More information

The U.S. National Institutes of Health has more on the effects of vaping.

SOURCE: Lawson Health Research Institute, news release, Dec. 14, 2022

Many Smokers Who Want to Quit Just End Up Vaping, Too

Alan Mozes ⋮⋮ 27/7/2022

WEDNESDAY, July 27, 2022 (HealthDay News) -- Many smokers eager to quit embrace electronic cigarettes as a tool for kicking the habit, but a new study warns the move may raise the risk for becoming addicted to *both* cigarettes and vaping.

The finding follows a look at the experience of nearly 112,000 smokers who sought outpatient care at a single hospital between 2018 and 2020.

"Most smokers try to vape to quit smoking," explained study author Dr. Li-Shiun Chen, an associate professor of psychiatry at the Washington University School of Medicine (WUSM) in St. Louis.

Given that 40 million American smokers want to quit, that's a lot of potential vaping, the researchers noted.

The problem? Like cigarettes, e-cigarettes contain nicotine. And that, Chen said, means that "vaping is as addictive as cigarette smoking."

To see how that risk plays out among smokers who embrace vaping as a tool for quitting, she and her colleagues pored over a couple of years of data collected by the Barnes Jewish Hospital/WUSM electronic health record system.

The investigators found that over the study period the number of cigarette smokers who also started to vape tripled, rising from 0.8% in the first year to more than 2% in the second year.

About one in five of those "dual-use" smokers did end up quitting smoking within a year, a slightly higher success rate (pegged at about one in six) than what was observed among those who stuck to traditional cigarettes alone.

But roughly two-thirds of patients who ended up both smoking and vaping remained smokers a year out, the team noted.

The good news: dual-use smokers who also used traditional smoking cessation programs were much more likely to quit.

Such programs — which involve nicotine replacement therapies and/or addiction counseling — helped about one in three dual-use smokers kick their habit, the team noted.

The finding, said Chen, suggests that vaping — at least on its own — is not the answer, "unless they [also] get treatment to reduce craving and withdrawal."

On that front, Chen said that a number of non-vaping cessation treatments approved by the U.S. Food and Drug Administration "are very helpful."

Alongside counseling, she mentioned nicotine patches and lozenges, and the prescription nicotine-blocker medication Chantix (varenicline).

Priti Bandi, a principal scientist in the risk factors surveillance research division of the American Cancer Society, said that while prior research into the cessation benefits of vaping have produced mixed results, she was not surprised by the latest findings.

For one thing, "no e-cigarette has been approved by the FDA as a safe and effective cessation product," Bandi stressed.

And while vaping exposes users to fewer toxic and cancer-causing agents than smoking, "e-cigarettes have serious health risks, including negative short-term effects on airways and blood vessels," Bandi said. "And we do not know the long-term effects of their use. That is why it is important to help e-cigarette users quit using these products completely."

Bindi's bottom line: "Any potential benefit of quitting cigarettes with vaping will only be realized if smokers completely switch, instead of using both products concurrently. That is why, in my opinion, the more novel finding from this study, and the most relevant for public health, is that treatment with established cessation treatments was able to help dual users of both e-cigarettes and cigarettes quit smoking completely."

The study, which was funded by the U.S. National Heart, Lung, and Blood Institute, the National Cancer Institute, and the U.S. National Institute on Drug Abuse, was published in the July 21 issue of *Thorax*.

More information

There's more on effective ways to quit smoking at the American Cancer Society.

SOURCES: Li-Shiun Chen, MD, MPH, ScD, associate professor, psychiatry, Washington University School of Medicine, St. Louis; Priti Bandi, PhD, principal scientist, risk factors surveillance research, American Cancer Society; *Thorax*, July 21, 2022

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BMJ 2018; 360 doi: https://doi.org/10.1136/bmj.k1262 (Published 19 March 2018) Cite this as: BMJ 2018;360:k1262

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We were struck by the permissiveness of the report commissioned by Public Health England on e-cigarettes compared with a contemporaneous US academy report.[1,2,3]

The PHE review states that "e-cigarette use alone or in combination with licensed medication and behavioural support . . . appear to be helpful in the short term."[1] By contrast, the US review says, "There is insufficient evidence . . . about the effectiveness of e-cigarettes as cessation aids."[3]

PHE says that "e-cigarettes are attracting very few young people who have never smoked into regular use,"[1] but the US report concludes, "There is substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth."[3]

Both reports corroborate the purported reduction in harm afforded by e-cigarettes compared with tobacco cigarettes.[1,3] But the US reviewers say that "there is no available evidence whether or not e-cigarette use is associated with clinical cardiovascular outcomes . . . and respiratory diseases,"[3] whereas PHE concludes that these putative risks are "substantially below" those of smoking.[1]

The US review says that "there is no available evidence whether or not e-cigarette use is associated with intermediate cancer endpoints."[3] Yet PHE promotes the finding that "the cancer potencies of e-cigarettes" are "largely under 0.5% of the risk of smoking."[14]

We understand that such conflict, existing as it does among tobacco experts, reflects a wider uncertainty surrounding the long term health risks of e-cigarettes. That PHE, whose purpose is "to protect and improve the nation's health,"[5] should sanction e-cigarette use citing an embryonic and inconclusive evidence base, is astonishing. When over 75% of acute NHS trusts are in financial deficit,[6] a decision backing NHS investment in e-cigarettes is even more perplexing. The PHE report represents an unduly premature endorsement of e-cigarettes to the smoking public.

Footnotes

- Competing interests: None declared.
- Full response at: http://www.bmj.com/content/360/bmj.k575/rr.

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