



# The FETAL TOBACCO SYNDROME

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- Fetal Tobacco Syndrome - A statement of the Austrian Societies for General- and Family Medicine (ÖGAM)  
Gynecology and Obstetrics (ÖGGG)  
Hygiene, Microbiology and Preventive Medicine (ÖGHMP)  
Pediatrics and Adolescence Medicine (ÖGKJ)  
Pneumology (ÖGP)
- Not only active smoking can harm the fetus, also ETS

Horak F, Fazekas T, Zacharasiewicz A et al.  
Wien Klin Wochenschr. 2012;124(5-6):129-45.

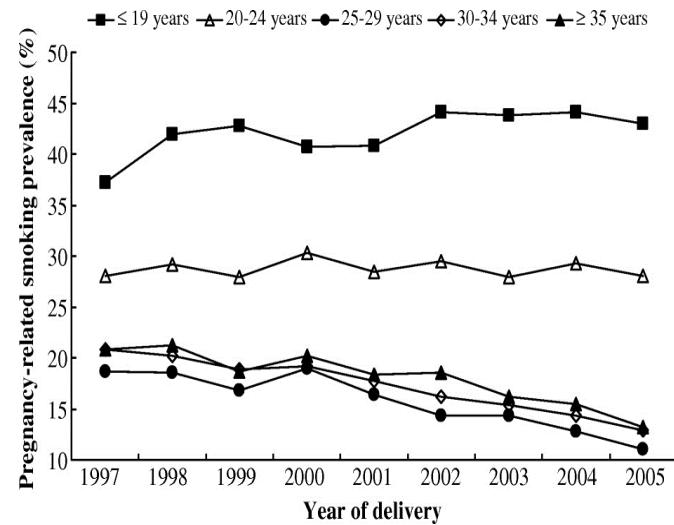
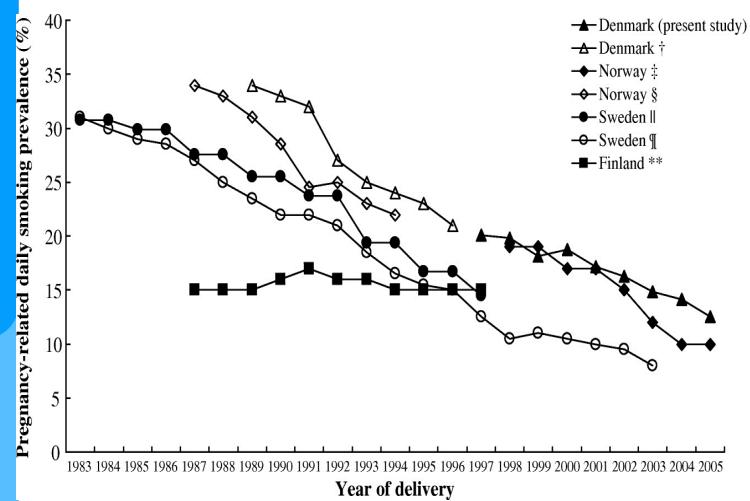
- 1986 “first description“ of the fetal tobacco syndrome<sup>1</sup>
- Smoking of  $\geq 5$  cig/d during pregnancy and symmetric growth retardation without other detectable cause
- ~ 10.000 publications to date on the detrimental effects of tobacco in pregnancy on the fetus

1) Nieburg et al. Fetal tobacco syndrome JAMA 1986 15;256(7):862-863

- Mechanism: Pathophysiology
- Recent scientific findings of health effects
- Possibilities for smoking cessation in pregnancy

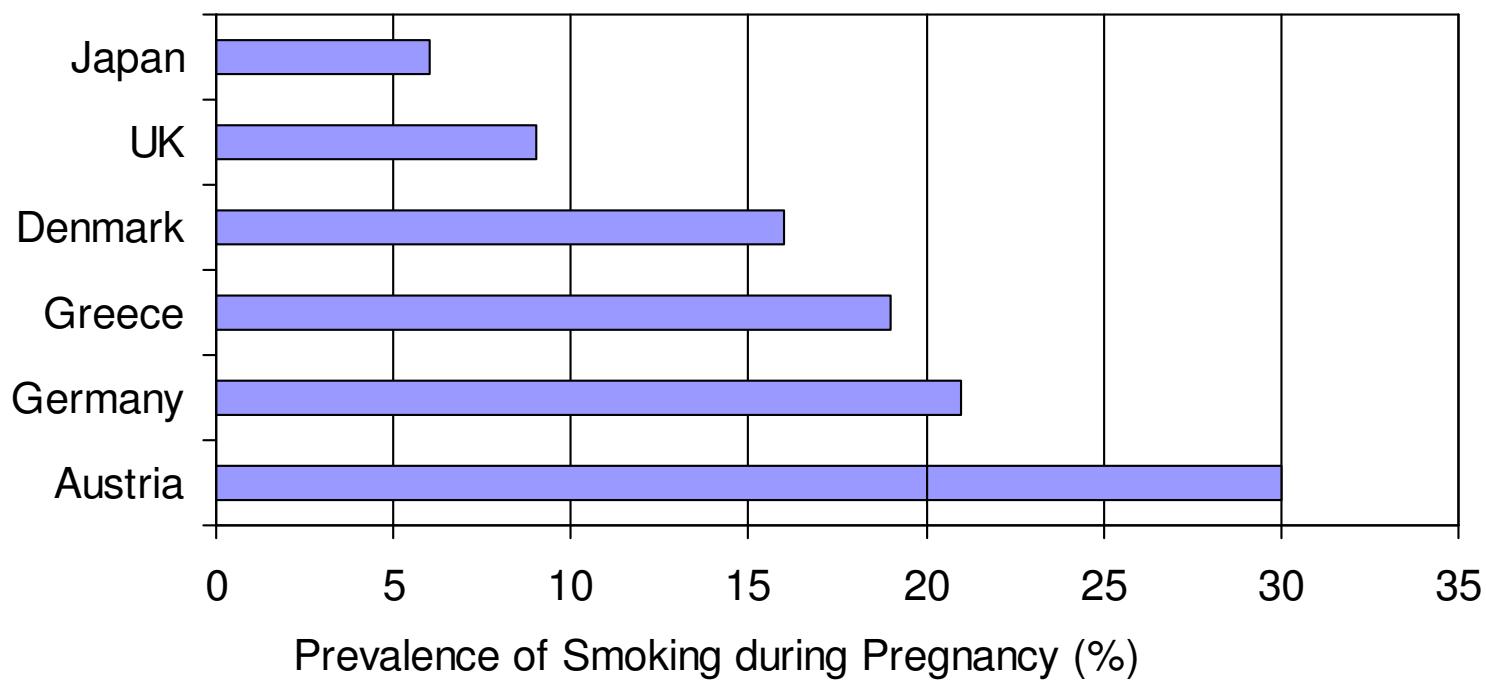
# Epidemiology

- 15-25% of all pregnant woman smoke<sup>1</sup>
- Overall decreasing trend in prevalence<sup>2</sup>
- Woman <20 a: increase in prevalence



- 1) Cnattingius S et al. Nicotine & Tobacco Research 2004
- 2) Jensen KE et al. Acta Obstet Gynecol Scand. 2008

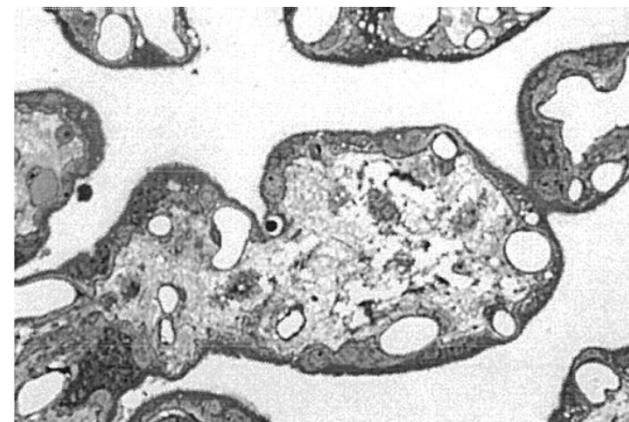
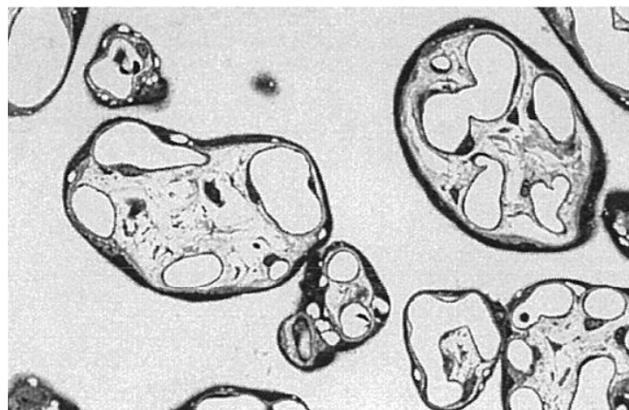
## Definition



Horak F, Fazekas T, Zacharasiewicz A et al. Wien Klin Wochenschr. 2012

# Fetoplacental Unit

- morphological changes in the placenta are seen in the 1<sup>st</sup> Trimenon
- direct damage of Cytotrophoblast proliferation and differentiation<sup>1</sup>
- Thickening of the basement membrane of the Trophoblast
- Collagen increase in villous mesenchyme & decreased vascularisation<sup>2</sup>



1) Jauniaux et al. Obstet Gynaecol 1992

2) Asmussen I. Brit J Obstet Gynaecol 1980

3) Zdravkovic et al. Placenta 2005

# Fetoplacental Unit

## NICOTINE:

- AA uptake decreased
- Bindes to nicotinic Acetylcholin-Receptors (nACh = Signal for AA uptake, blood flow and vascularisation)<sup>1</sup>, chronic stimulation might cause unbalanced activation or functional desensitisation

## CADMIUM:

- Quick uptake through placenta<sup>2</sup>
- Accumulation in placenta
- 11 beta HSD2 expression reduced in Cadmium-exposed cells → potential effect on fetal growth <sup>3</sup>

1) Jauniaux et al. Early Human Dev. 2007

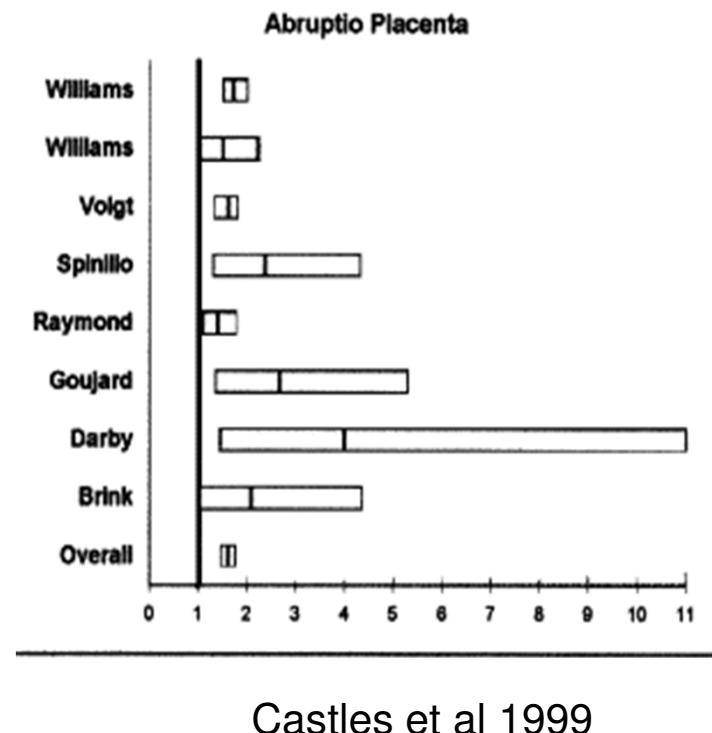
2) Salpietro J.Perinatal Medicine 2002

3) Yang et al. Am J Physiol Endocrinol Metab 2006

# Fetoplacental Unit

## Placenta:

- placental abruption: high evidence in many studies (OR 1.4-4.0)<sup>1</sup>
- dose response relationship<sup>2</sup>
- risk reduction by smoking cessation in early pregnancy<sup>3</sup>



- 1) Goujard et al 1975, Voigt et al 1990, Ananth et al 2001, Castles et al 1999
- 2) Ananth CV et al. Am J Epidemiol 1996 + 2001
- 3) Naeye RL. Obstet Gynecol 1980

# Small for gestational age

- strong and direct association with smoking  
OR 1.5-2.9 <sup>1</sup>
- birth weight reduced  
by approx. 10-12g per cigarettes/d <sup>2</sup>
- effect doubles during the 3<sup>rd</sup> Trimenon <sup>2</sup>
- no increase of risk in woman with smoking cessation in 1<sup>st</sup> Trimenon <sup>3</sup>
- mothers with certain Genotypes especially at risk <sup>4</sup>

1) Cnattingius S. Nicotine & Tobacco Research 2004

2) Bernstein et al. Obstet Gynecol. 2005

3) Jauniaux et al. Early Hum Dev 2007

4) Wang et al. JAMA 2002

# Fetal Mortality

- spontaneous abortion (OR 1.2-1.8)<sup>1</sup>;  
some studies show no effect<sup>2</sup>
- stillbirth (=fetal death  $\geq 20\text{GA}$ ): RR 1.2-1.8  
some find a dose response (1-9; >9 cig/d)<sup>4</sup>

1) Einarson et al. Eur J of Clin Pharmacol 2009

2) Wisborg et al. Act Obstet Gynecol Scand 2003

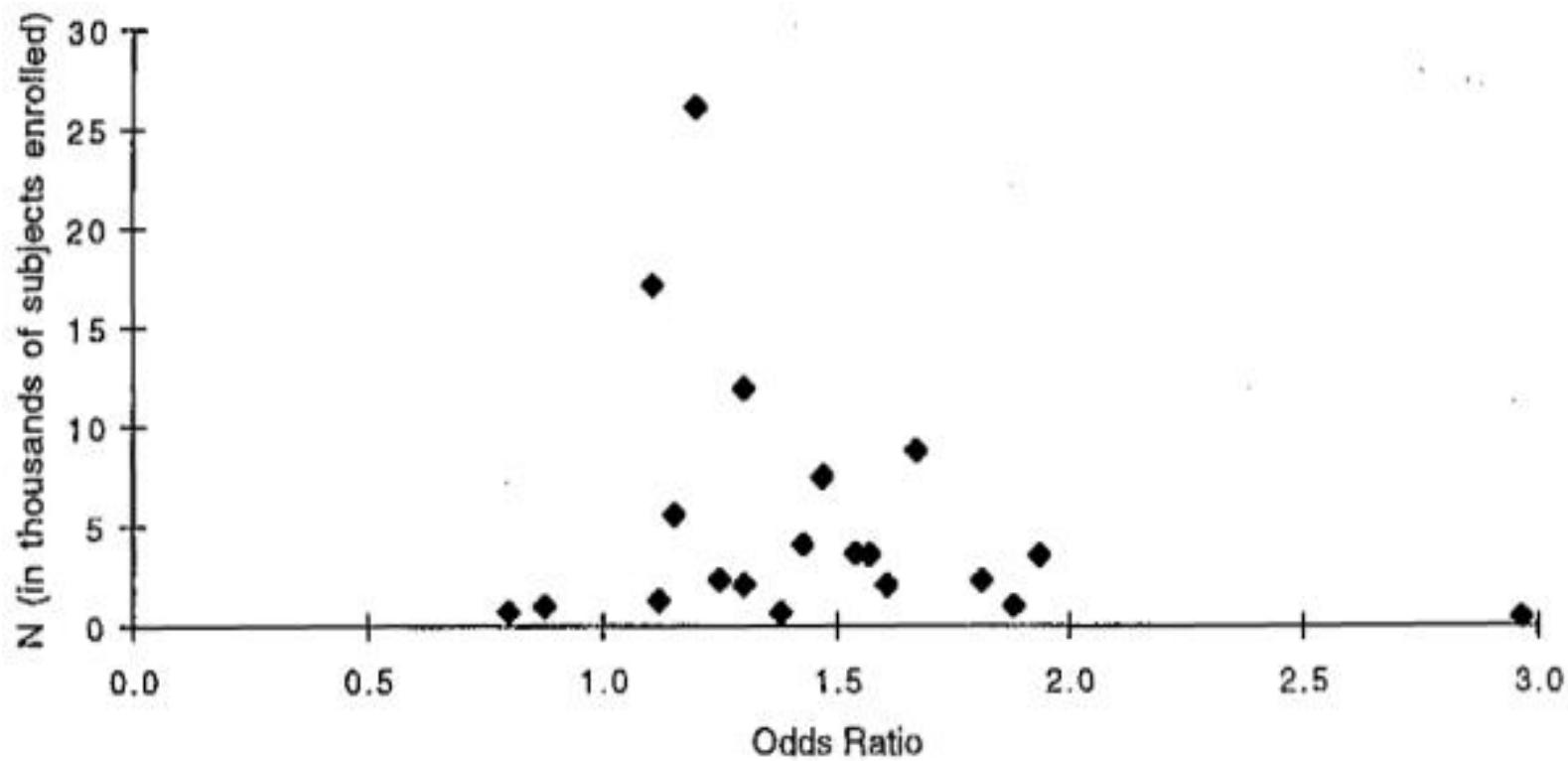
3) Cnattinguis S. Nicotine Tobac Res 2004

4) Högberg et al. BJOG 2007

# Preterm Birth



- increase in risk for preterm birth: 1.2-1.6



1) Shah et al. Am J Obstet Gynecol 2000

# Preterm Birth



- increase in risk for preterm birth: 1.2-1.6  
(vs. non smokers)<sup>1</sup>
- stronger association with „very preterm“ infants  
(<32.GA)<sup>2</sup>
- association with premature rupture of the membranes  
(reason for preterm birth) 2.0-3.0<sup>3</sup>

1) Shah et al. Am J Obstet Gynecol 2000

2) Cnattingius et al. NEJM 1999

3) Hadley et al. Am J Perinatol 1990

# Mortality in the First Year of Life

- SIDS: RR 2.0-3.0<sup>1</sup>, Metanalysis:  
very consistant results,  
dose response relationship <sup>2</sup>; 1/3 preventable  
separation of current ETS effect not possible  
in all studies
- Mortality before 1<sup>st</sup> bithday increase by 4%  
for every 10 cig/d<sup>3</sup>

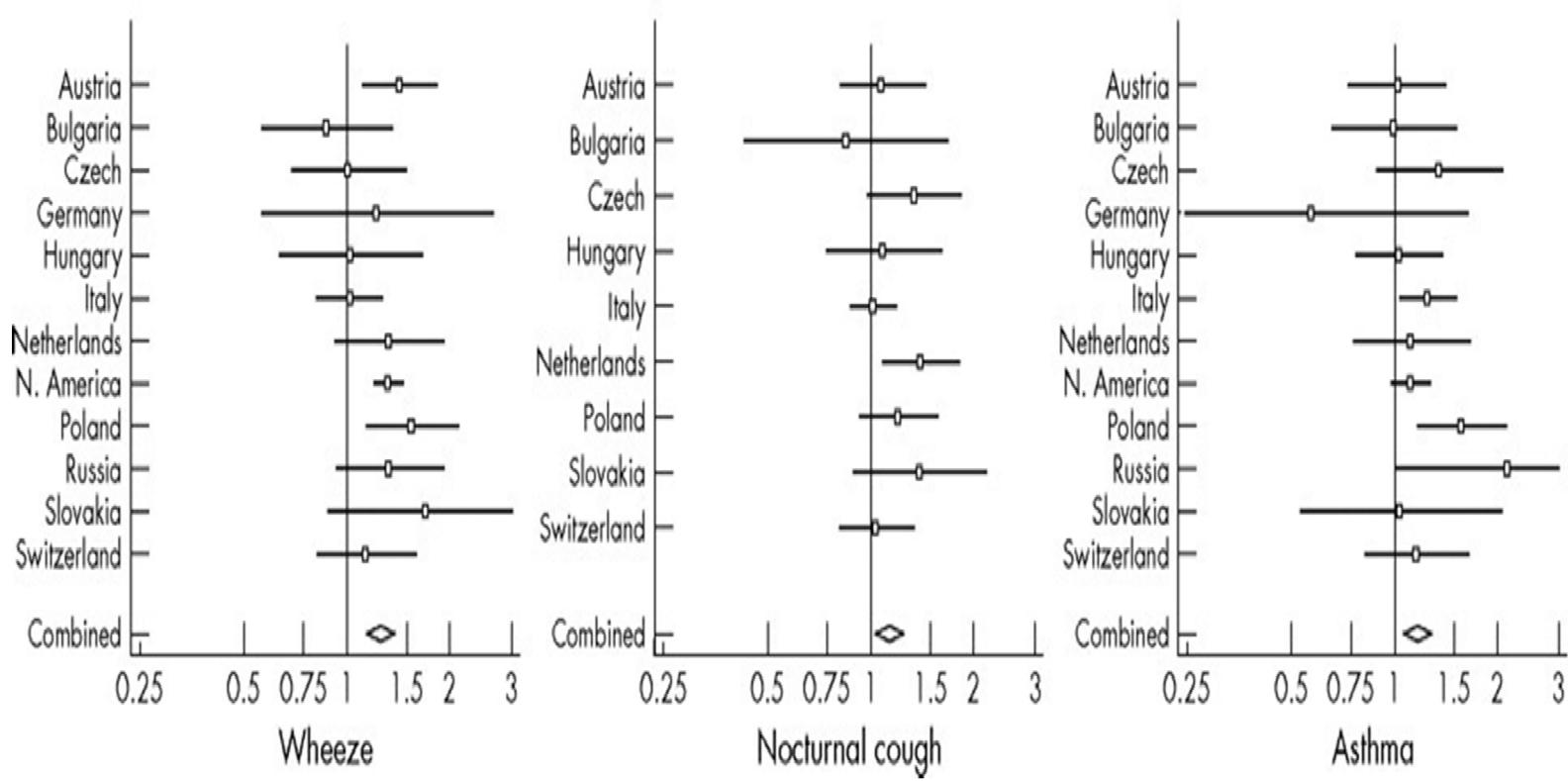
1) Mitchell et al. Rev Environ Health 2006

2) MacDorman et al. Am J Epidemiol 1997

3) Salihu et al. Matern. Child Health J 2003

# Asthma and wheezing

Increased risk for asthma<sup>1</sup> (OR 1.8 95% CI 1.1 to 2.9) and „wheezing“<sup>2</sup>



# Orofacial Clefts

- consistant results in various studies<sup>1</sup>
- Metaanalysis: RR 1.2-1.3<sup>2</sup>
- dose-response 1-20, >20 cig. (OR 1.7)<sup>3</sup>

1) Honein et al. Epidemiology 2007

2) Little et al. Cleft Palate Craniofac J 2004

3) Chung et al. Plast Reconstr Surg 1999

# Congenital Malformations

## Metaanalyses:

50 a

172 studies

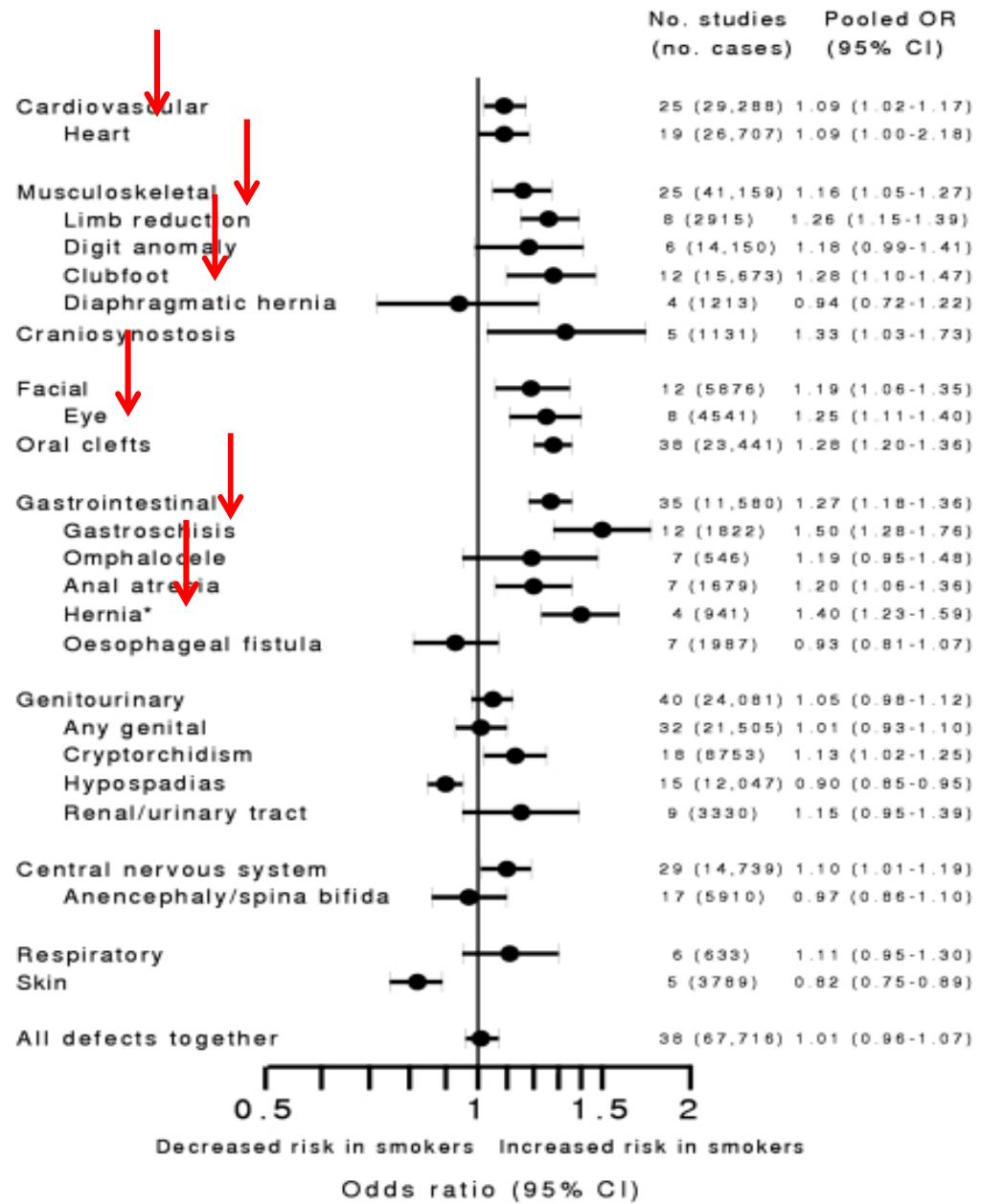
173 687 cases

11 674 332 controls

# Congenital Malformations

## Metaanalyses:

50 a  
 172 studies  
 173 687 cases  
 11 674 332 controls



# Congenital Malformations

- anecdotal evidence for  
CNS-malformations<sup>1</sup>  
intra and periventricular hemorrhage <sup>2</sup>  
neural tube defects<sup>3</sup>

1. Lavezzi et al. 2005
2. Maturri et al 2011
3. Suarez et al. 2008

# Obesity



- Metaanalysis of 17 Publications<sup>1</sup>:  
signifikant association in children  $\geq 3$  a
- OR for BMI>95.Percentile: 1,6 (95%CI 1,4-1,9)

1) Ino T. Pediatr Int 2010

# Psychosocial Pathologies



- Metaanalysis of 13 population based studies
- various different study designs:  
association OR 2,4 (95%CI 1,6-3,5) for ADHD

1) Langley et al. Minerva Pediatr 2005

# Neurodevelopment

Prenatal tobacco and postnatal secondhand smoke exposure is consistently associated <sup>1</sup> with problems in multiple domains of children's neurodevelopment and behavior.

PTE affects speech processing, levels of irritability and hypertonicity, attention levels, ability to self-regulate, need to be handled, and response to novelty preference in infants

**Early childhood:** mostly behavioral outcomes including activity and inattention and externalizing behaviors, including conduct and antisocial behavior

**Adolescents:** PTE predicted increased ADHD, modulation of the cerebral cortex & white matter structure & nicotine addiction<sup>2</sup>

1) Hermann et al. Curr Opin Ped 2008

2) Cornelius et al. Curr Opin Neurol 2009

# Smoking cessation in pregnancy

- 20-40% stop smoking during pregnancy <sup>1</sup>
- Success of interventions (Metaanalysis of 34 studies): 16% intervention, 9% controls<sup>2</sup>
- high relapse-rate after pregnancy (up to 80%)<sup>3</sup>

1) Einarson et al. Eur J Clin Pharmacol 2009

2) Lumley et al. Cochrane Review 2009

3) Lawrence et al. J Health Psychol 2005

# Smoking cessation in pregnancy

- Multi-Media campaign, Telephone Consulting, Financial Incentives, Biofeedback  
→ relatively weak effects<sup>1</sup>
- Probleme: Nicotine metabolism increased in pregnancy<sup>2</sup>
- Motivation!

1) Schnoll et al. J Womens Health 2007

2) Dempsey et al. J Pharmacol Exp Ther 2002

# Nicotine replacement

- patch, gum, Inhaler, nasal spray<sup>1</sup>
- Metaanalyis: 5 Trails, insufficient evidence for success and safety <sup>2</sup>

- 1) Hotham et al. Drug Alcohol Rev. 2002
- 1) Coleman et al. Addiction 2011

# Medication

- Studies with antidepressants<sup>1</sup>, Bupropion<sup>2</sup>, MAO-Inhibitors<sup>3</sup>
- Cochrane-Analyse<sup>4</sup>: selektive Serotonin Reuptake inhibitors (Fluoxetin) ineffektiv, Nortryptilin moderately effective, Bupropion most effective
- Safety of Bupropion: no teratogenicity;

1) Haggstram 2006

2) Fossati 2007

3) Berlin 1995

4) Hughes et al. Cochrane database review 2007

# Medication during pregnancy

- **Bromocriptin:** indirect evidence in study on subfertile women (n=4600)<sup>1</sup>:  
50 % less smokers in the Interventiongroup,  
Safety shown in ~2500 pregnancies prospectively
- **Varenicline:** Nicotine rec. Agonist: No studies in Pregnancy <sup>2</sup>
- **Nicotine - Injection:** Antibody against Nicotine: no Phase III<sup>3</sup>

1) Murphy et al. Addict Biol 2002

2) Stack et al. Pharmacotherapy 2007

3) Murtagh et al. Issues Emerg Health Technol 2007

	Ektopic pregnancy	Class II
Fetus:	<b>Reduced fetal growth</b>	<b>Class I a</b>
	<b>Preterm Birth</b>	<b>Class I a</b>
	Placenta-associated disease	Class II
	<b>Stillbirth</b>	<b>Class I a</b>
	<b>Orofacial clefts</b>	<b>Class I a</b>
	<b>Malformations</b>	<b>Class I a</b>
Newborn/Baby:	<b>SGA</b>	<b>Class I a</b>
	<b>SIDS</b>	<b>Class I</b>
	Reduced lung function	Class II
Child:	<b>Obesity</b>	<b>Class I a</b>
	Reduced lung function	Class I/II
	<b>Asthma</b>	<b>Class I a</b>
	Psychiatric dis. & develop. delay	Class II
	<b>ADHS</b>	<b>Class I a/b</b>
	Cardiovascular disease	Class II

## Take Home Message

- FTS results in increased Morbidity and Mortality in prenatal & postnatal life
- recommend earliest possible cessation

# The Fetal Tobacco Syndrome

Damage of the  
Fetoplacental Unit



Infant Mortality



Lung function  
Asthma



Malformations

SIDS

obesity

Preterm birth

ADHS

Placental complications

Learning difficulties

Fetal growth retardation