



# **Epidemiology of Child Psychiatric Disorders: major milestones and future**

STraMeHS, Venice, 2014

Frank Verhulst

ErasmusMC-Sophia Children's  
Hospital, Rotterdam

*f.verhulst@erasmusmc.nl*



- Epidemiology is the medical science which studies the frequency of disease
- .....and the factors (determinants) that influence the variation in frequency
- .... as guide to **preventing** disease

---

# child psychiatric epidemiology: major milestones

Frank C. Verhulst & Henning Tiemeier (European Child and Adolescent Psychiatry)

- Lapouse and Monk (1958)
- from descriptive, cross-sectional studies in the 1960's using ad hoc procedures to assess problem behaviours reported by one informant
- to the current large-scale prospective cohorts integrating biological measures and multi-informant behavioural assessments

## Milestone Epidemiological Studies

< 1960	1960-1970	1970-1980	1980-1990	1990-2000	> 2000
National Survey of Health and Behavior (1946)	Isle of Wight Study (1964)	The Dunedin Multidisciplinary Health and Development Study (1972)	Montreal Longitudinal and Experimental Study (1984)	ALSPAC (1991)	GenerationR (2002)
National Child Development Survey (1958)	Sudan Study (1964/1965)	The Christchurch Health and Development Study (1977)	Pittsburgh Youth Study (1987)	NICHD (1991)	MoBa/ABC (1999, 2002)
Kauai Longitudinal Study (1955)		ASEBA Studies (1976)	Population-based twin samples	Great Smokey Mountains Study (1993)	

---

# GenerationR

Behavioral Research in a Cohort From Fetal Life  
Onwards

*[f.verhulst@erasmusmc.nl](mailto:f.verhulst@erasmusmc.nl)*



---

## Research Aims

- To examine whether prospectively measured fetal growth and intra-uterine influences are related to child behavioral/emotional and cognitive problems
- To understand mechanisms involved in the influence of early postnatal factors on child behavioral/emotional and cognitive problems

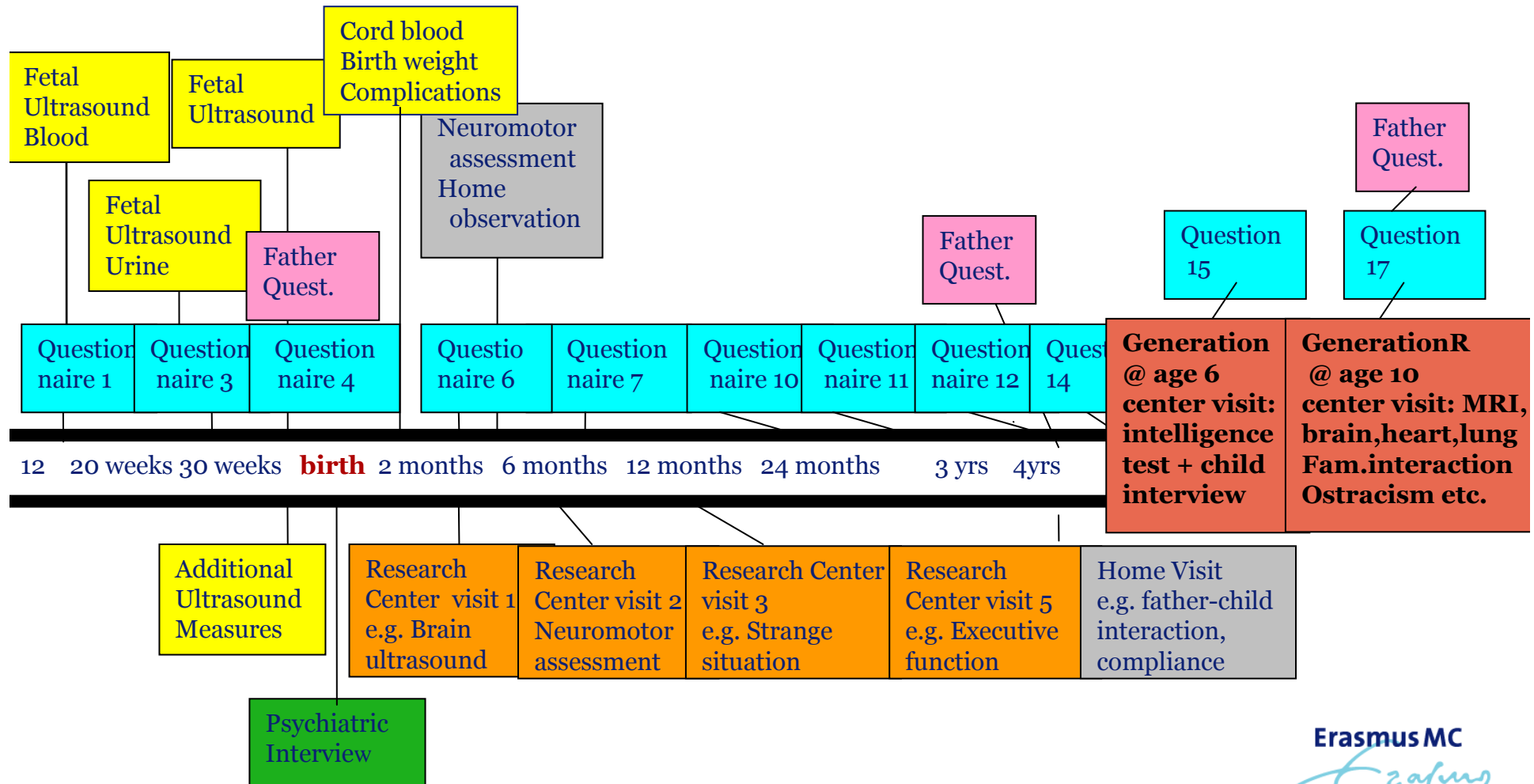
# Design Generation R

- Prospective cohort design
- From early foetal life
- 9.778 mothers and their children
- Detailed measures in the Focus cohort (~1.000 mothers)
- Urban, multi-ethnic population



# Data collection flowchart

## Assessments in Generation R Cohort



## Additional Assessments in Generation R Focus Cohort



---

# Prenatal Influences

- Maternal stress/depression
- Maternal smoking
- Maternal cannabis use
- Maternal folic acid
- Maternal thyroid hormone
- Maternal diet
- Maternal SSRI use

# Maternal psychological distress and foetal growth trajectories

Difference in foetal weight gain (grams/week)

	Beta	95% CI	<i>p</i> -value
Depressive symptoms	<b>-2.86</b>	<b>-4.48; -1.23</b>	<b>&lt;0.001</b>
Anxious symptoms	<b>-3.23</b>	<b>-4.91; -1.55</b>	<b>0.002</b>
Family stress	-1.78	-3.70; 0.13	0.07

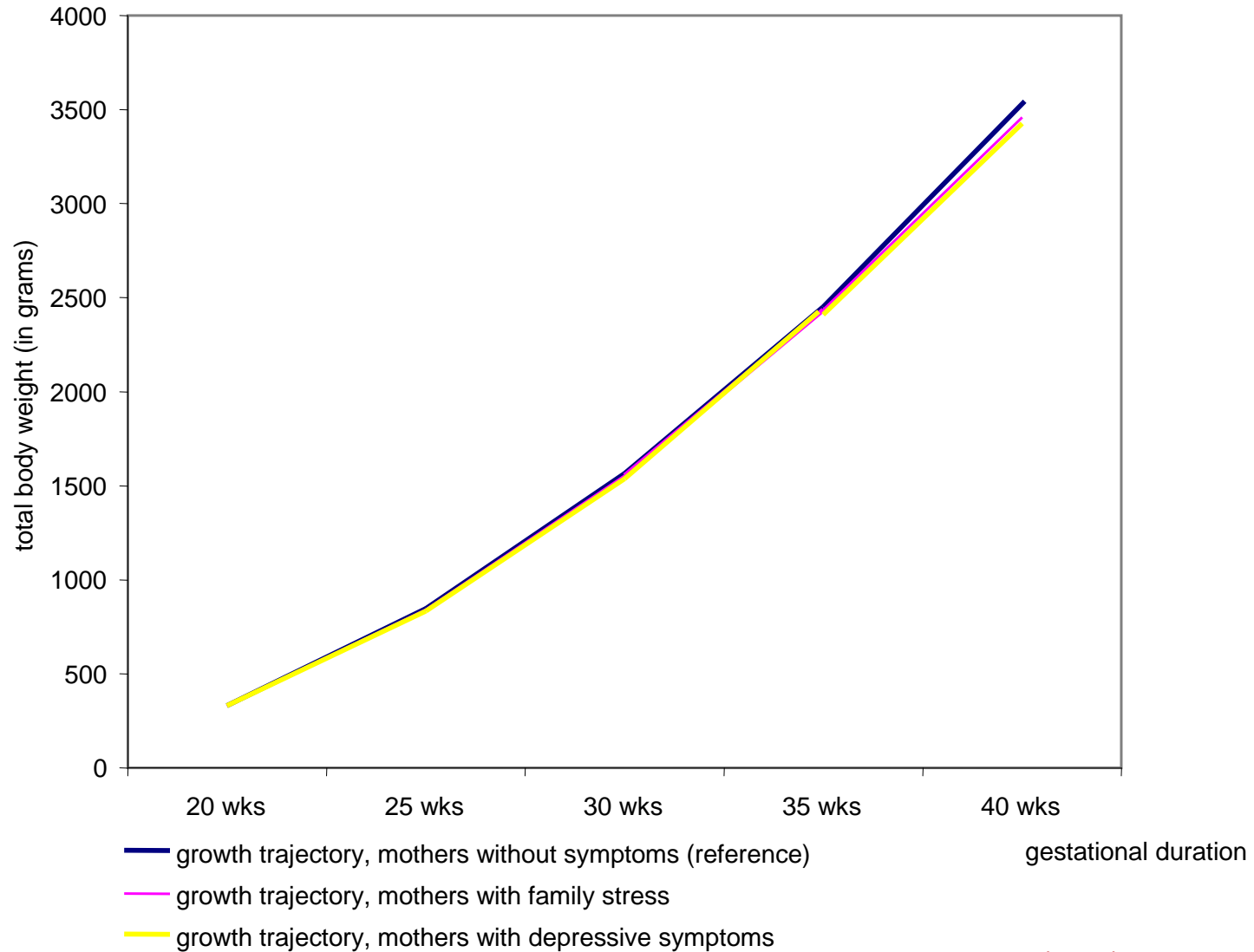


PhD student  
J. Henrichs

Difference in head circumference growth (mm/week)

Depressive symptoms	<b>-0.07</b>	<b>-0.13; -0.01</b>	<b>0.03</b>
Anxious symptoms	<b>-0.10</b>	<b>-0.17; -0.04</b>	<b>0.002</b>
Family stress	-0.06	-0.14; 0.01	0.11

## Maternal distress: Growth trajectory of foetal weight



*Henrichs et al.,(2010) Psychol Med*

---

# Intrauterine growth and infant temperamental difficulties

After controlling for several genetic and socioeconomic status related factors, we found **little indication** of an association between intrauterine growth trajectories and temperamental difficulties in infants.

*J Am Acad Child Adolesc Psychiatry. 2008 Mar;47(3):264-72.*

---

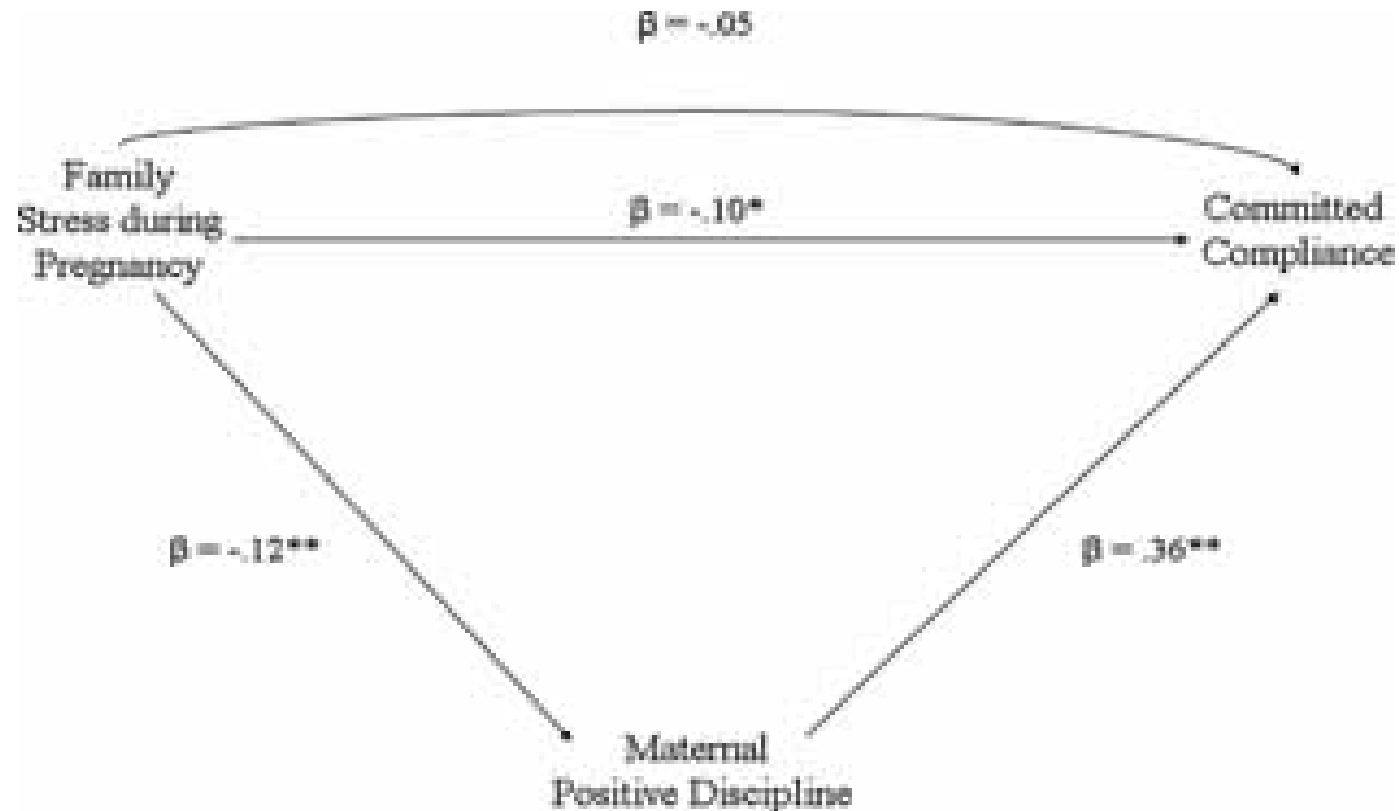
# Maternal distress and postnatal child behavior

---

## Prenatal and postnatal parental psychological symptoms and family functioning and its impact on child behavior at age 3

- Prenatal depression in mothers and fathers are associated with child problem behavior
- However, this was accounted for by **postnatal** parental hostility (mothers and fathers)

# The role of maternal stress during pregnancy, maternal discipline, and the child's compliance at 3 years



---

# Conclusion

- Prenatal psychological stress associated with fetal development
- Fetal development does not influence child problem behavior
- Prenatal depression associated with child behavior through parental hostility
- Prenatal family stress may indirectly affect child development through **spillover** of prenatal stress on parenting behavior



---

## Maternal smoking during pregnancy – is it harming the mother or fetus most?

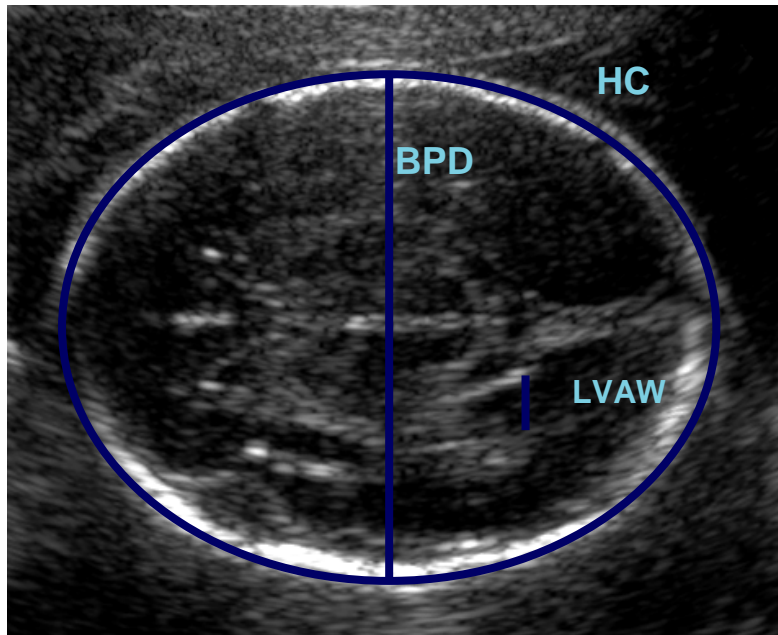


Erasmus MC

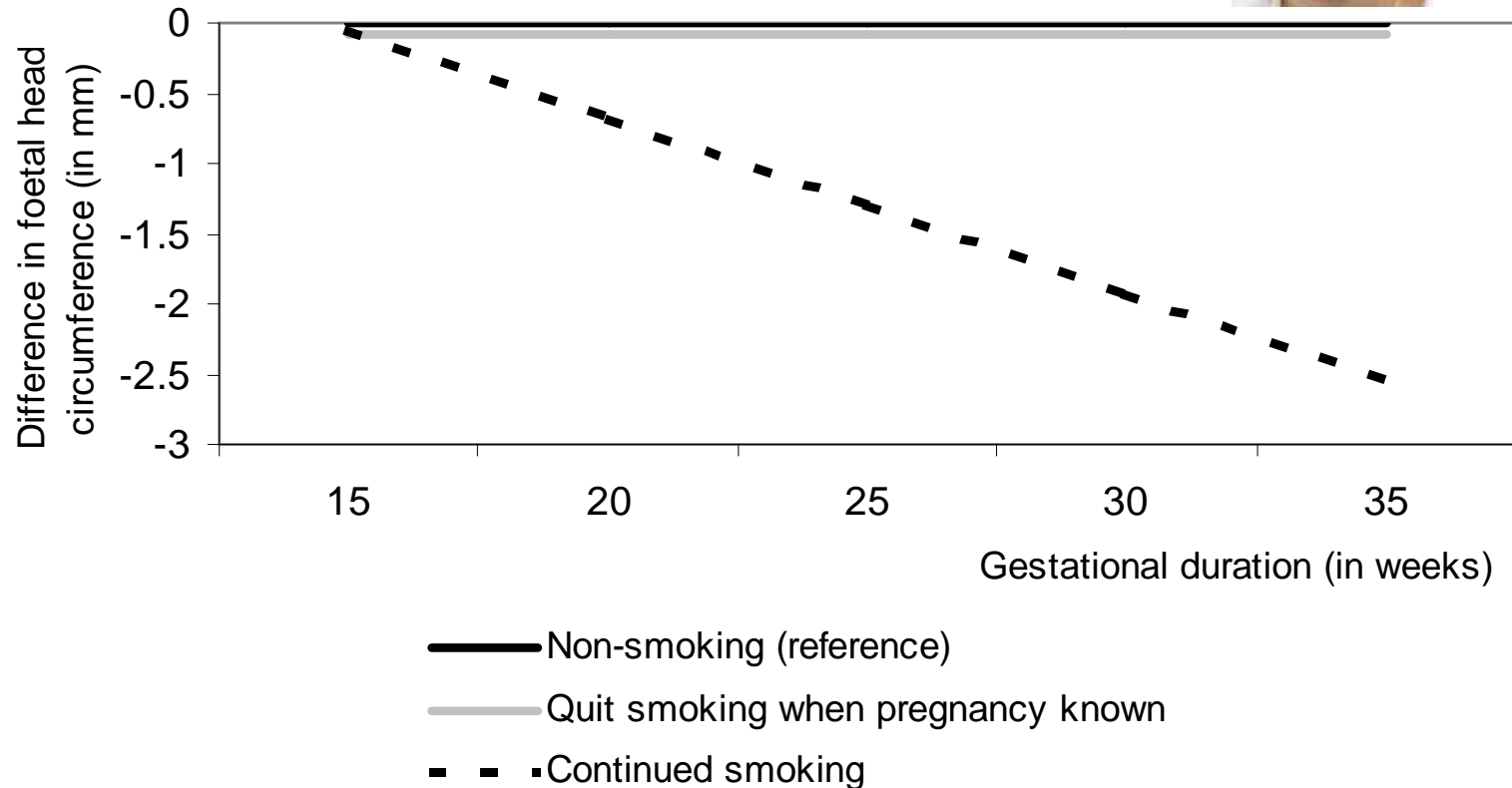


---

# Prenatal Ultrasound Measurements



# Smoking and Prenatal Head Growth



**Children of mothers who continue smoking also have smaller cerebelli and smaller cerebral ventricles**

**Adjusted for: maternal BMI, age, height, ethnicity, parity, SES, gender child; maternal alcohol, prenatal anx, depression did not change regression coeff for smoking**

Erasmus MC  
*Erasmus*  
*Roza et al., Eur Neuroscience 2007*

# Smoking and Problem Behaviors at 18 Months

## Parental smoking habits

### CBCL Total Problems

Model 1	n	OR (95% CI)	P
No active or passive smoking	2205	<i>Reference</i>	
Father smoked outside, mother did not smoke	998	1.15 (0.86 – 1.52)	0.35
Father smoked indoors, mother did not smoke	397	<b>1.97 (1.40 – 2.76)</b>	<b>&lt; 0.001</b>
Mother smoked	608	<b>1.98 (1.48 – 2.64)</b>	<b>&lt; 0.001</b>

### CBCL Total Problems Fully Adjusted

Model 2	n	OR (95% CI)	P
No active or passive smoking	2205	<i>Reference</i>	
Father smoked outside, mother did not smoke	998	1.16 (0.87 – 1.56)	0.32
Father smoked indoors, mother did not smoke	397	1.19 (0.82 – 1.71)	0.36
Mother smoked	608	1.22 (0.89 – 1.69)	0.22



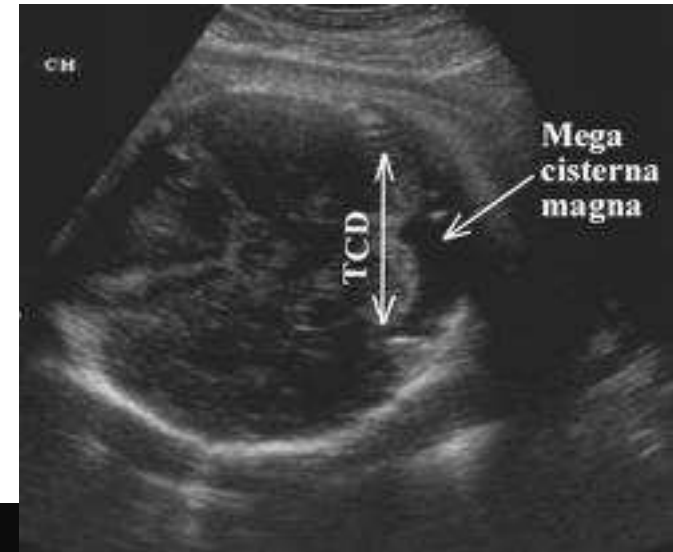
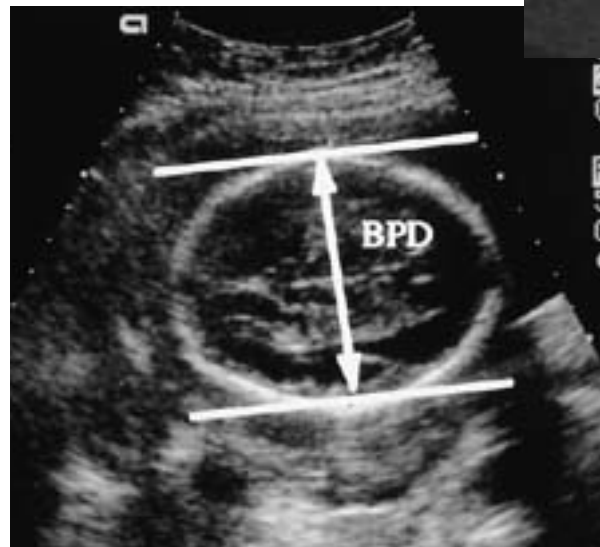
---

## Antidepressant use during pregnancy

- SSRI use at any time in pregnancy (n=99)
- Depressive symptoms without SSRI use (n=570)
- Control group, low depressive symptoms, no SSRI use

# Outcome

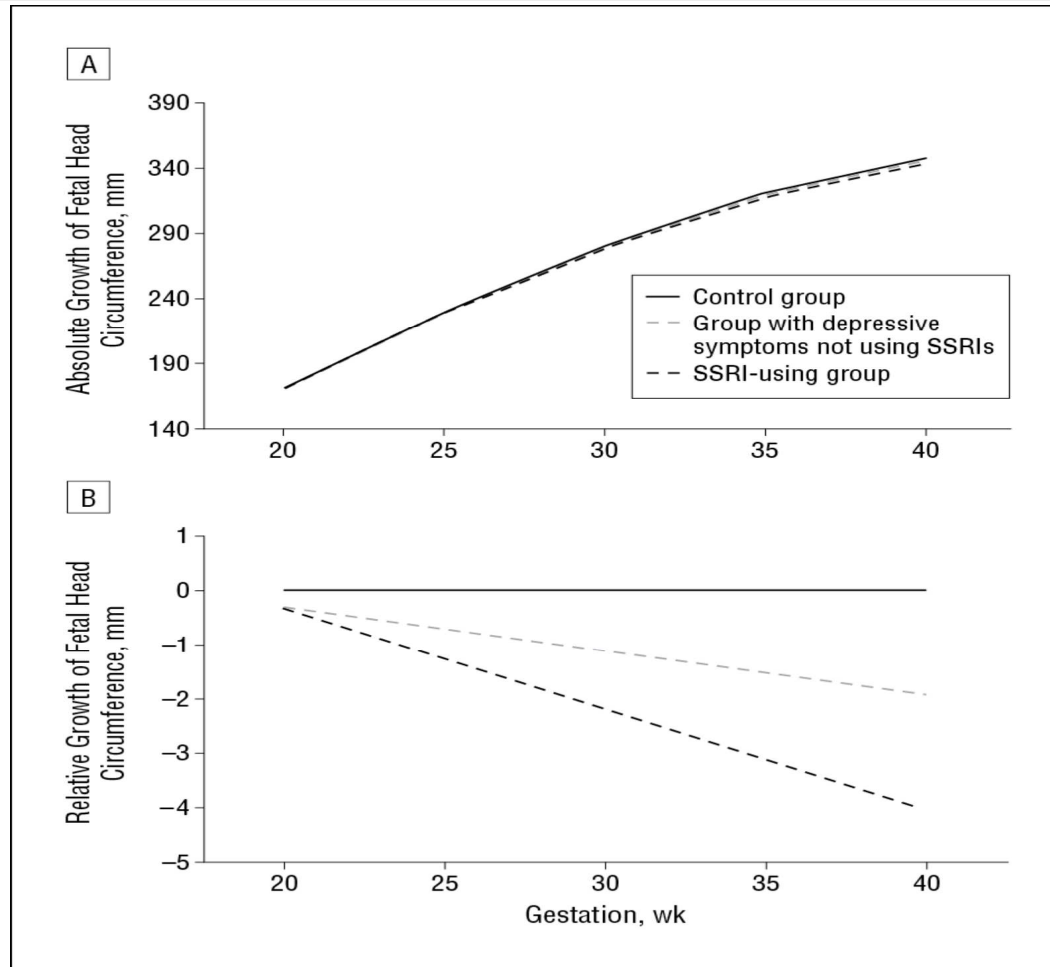
- Biparietal Diameter: the fetal cranium perpendicular to the midline in the occipitofrontal plane
- Transcerebellar diameter



# Results

Association between SSRI exposure and fetal growth/fetal head growth		
	B + 95%CI	P-value
<b>Fetal weight gain in grams per week</b>		
SSRI use	-2.0 (-6.6 to 2.5)	.39
Depressive symptoms	<b>-4.4 (-6.4 to -2.5)</b>	<b>&lt;0.001</b>
Control group	Reference	Reference
<b>Fetal head growth in mm/week</b>		
SSRI use	<b>-0.18 (-0.31 to -0.06)</b>	<b>.003</b>
Depressive symptoms	<b>-0.08(-0.13 to -0.03)</b>	<b>.003</b>
Control group	Reference	Reference

All values were adjusted for maternal age, maternal Body Mass Index, parity, gender of the child, maternal educational level and ethnicity, and maternal smoking and drinking habits.



**Figure Legend:**

Figure. The absolute (A) and relative (B) growth of fetal head circumference in 3 groups: fetuses exposed to selective serotonin reuptake inhibitors (SSRIs) during pregnancy, fetuses exposed to high levels of depressive symptoms during pregnancy, and fetuses in the control group. Estimates were obtained from fitting a fractional polynomial model adjusted for maternal age, maternal body mass index, parity, sex of the child, maternal educational level and ethnicity, and maternal smoking habits and benzodiazepine use.

Date of download: 9/16/2012

Copyright © 2012 American Medical Association. All rights reserved.

Erasmus MC  
2012/09/16



---

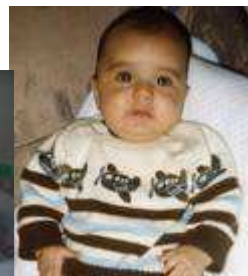
# Postnatal Influences

- Brain structure and problem behavior
- Socioeconomic influences: ethnicity, poverty
- Maternal depression and attachment
- Breast feeding
- Harsh parenting
- TV watching

---

# National Origin and Problem Behavior

Pauline Jansen



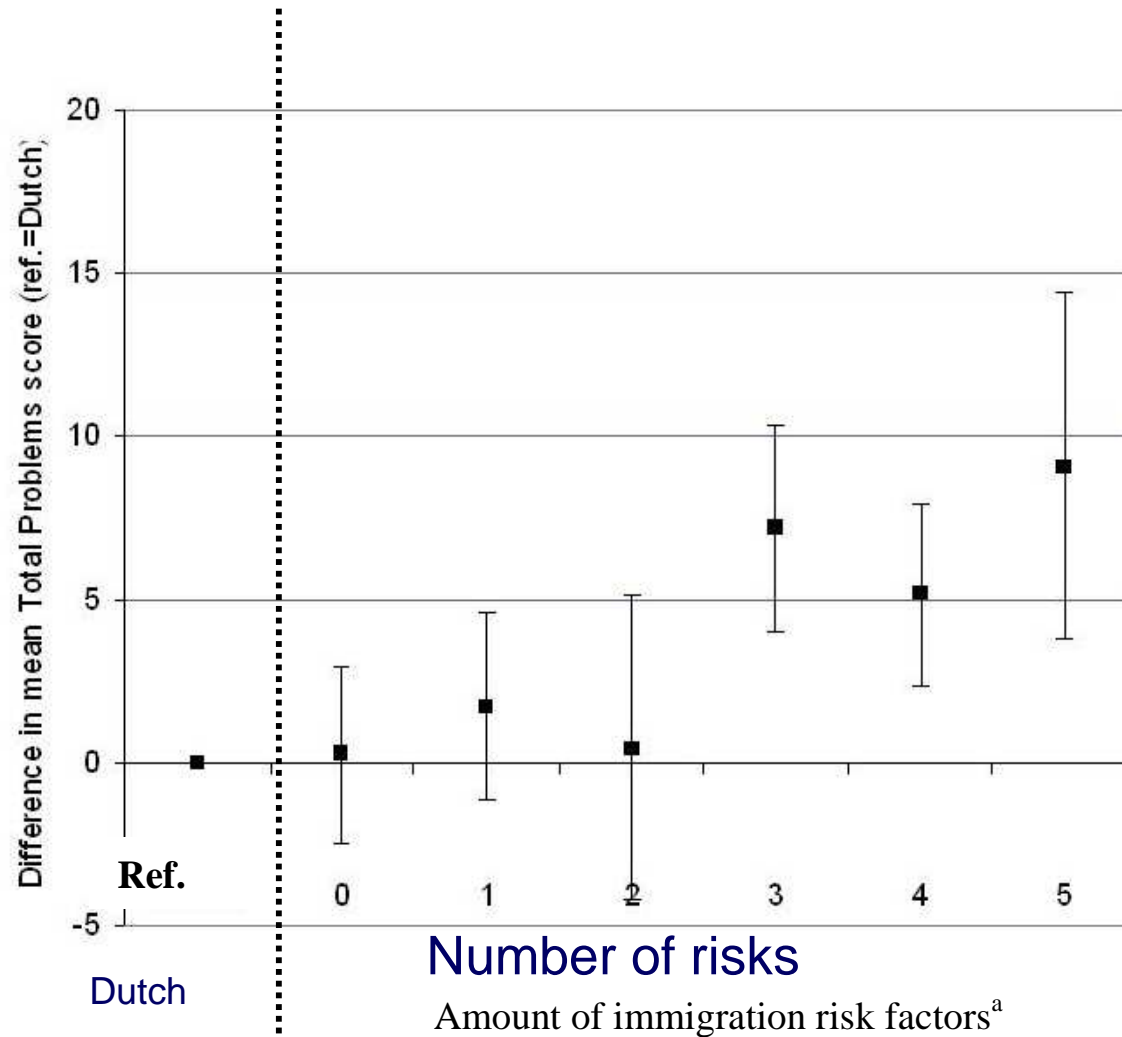
# Maternal National origin and Child Problems at age 18 months

Maternal national origin	N	CBCL Total Problems
<b>Estimated means adjusted for family risk factors</b>		
Western		
Dutch	3190	20.9 (20.0, 21.8)
European	406	24.3 (22.6, 26.0) ***
Non-Western		
Antillean	84	26.2 (22.8, 29.8) **
Cape Verdian	110	29.3 (26.2, 32.6) ***
Indonesian	190	23.7 (21.4, 26.0) *
Moroccan	164	23.4 (20.9, 26.0) *
Surinamese	278	22.7 (20.9, 24.5)
Turkish	301	29.5 (27.3, 31.7) ***
Other Non-Western	220	29.3 (27.0, 31.7) ***
<i>All Non-Western</i>	1347	26.0 (24.9, 27.1) ***

\* p-value <0.05, \*\* <0.01, \*\*\* <0.001.

# Adjusted for parity, maternal age, marital status, maternal education, family income, maternal psychopathology, and smoking habits during pregnancy.

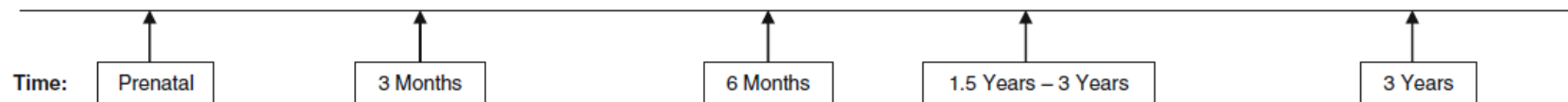
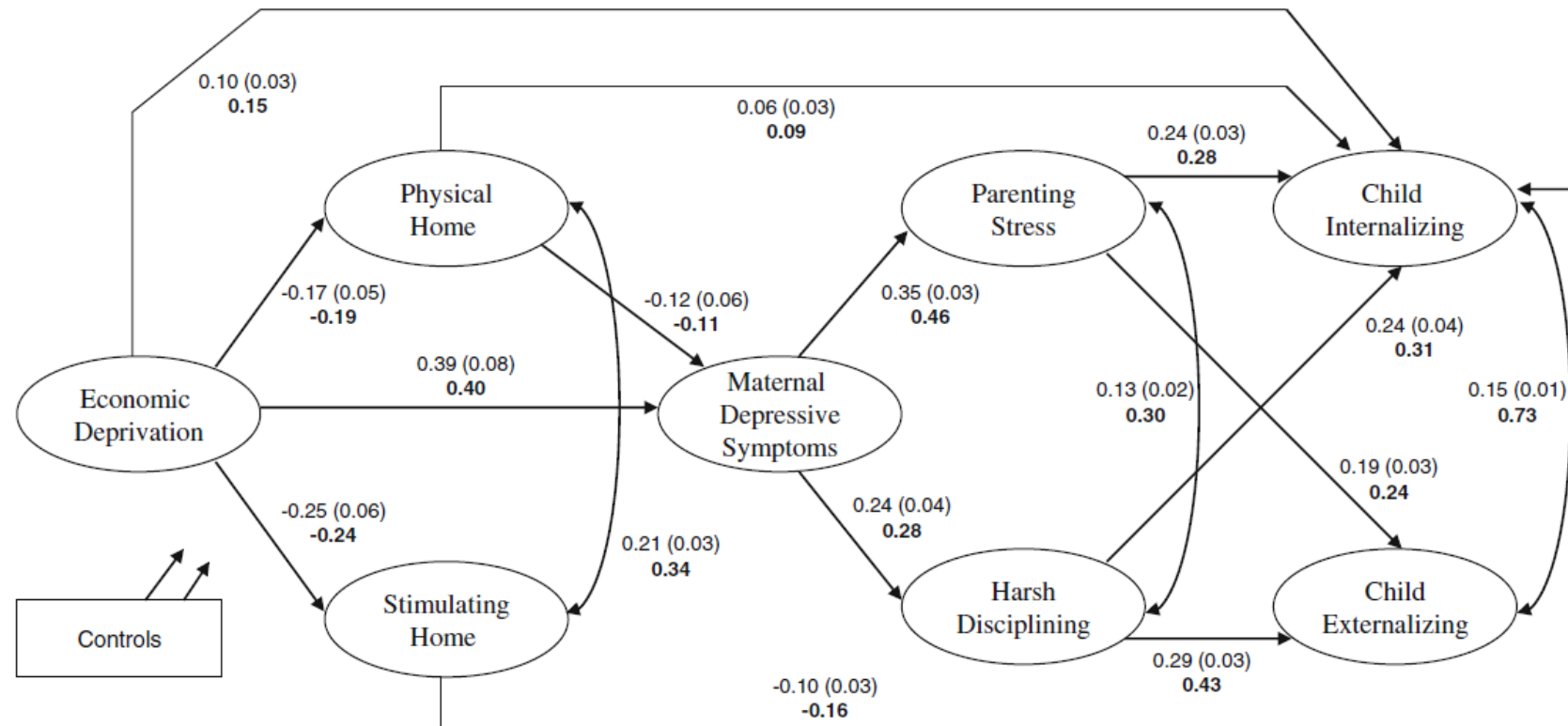
# Multiple Risk Factors



Examples Risk factors:

- Poverty
- Does not speak Dutch
- Migrated >15 years
- Feels discriminated
- Poor education
- Psychopathology mother

# Economic Disadvantage: Mechanisms of Risk



Rijlaarsdam et al., J Abnorm Child Psychol. 2012

- 
- ....mechanisms underlying the effect of economic disadvantage included maternal depressive symptoms, along with parenting stress and harsh disciplining.....

# Parental Behavior, Attachment and Child Development

- Attachment: Strange Situation Procedure (Ainsworth)
- Attachment Classification: Secure (B) - Insecure (A,C)
  - Organized (D) - Disorganized (nonD)

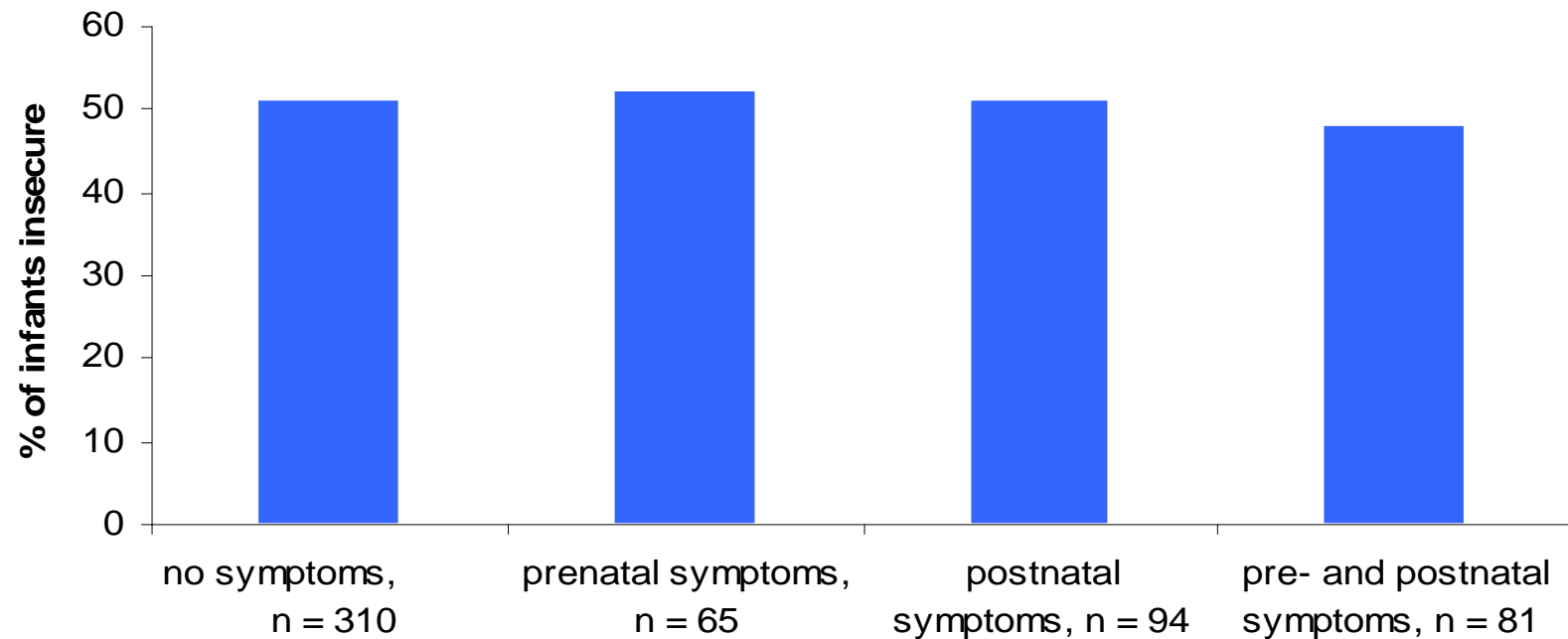


Anne  
Tharner and  
Rianne Kok



# Infant Attachment and Maternal Depression

Maternal depressive symptoms and infant attachment security



maternal depressive symptoms, assessed by BSI





---

## Mother-child interaction at age 3

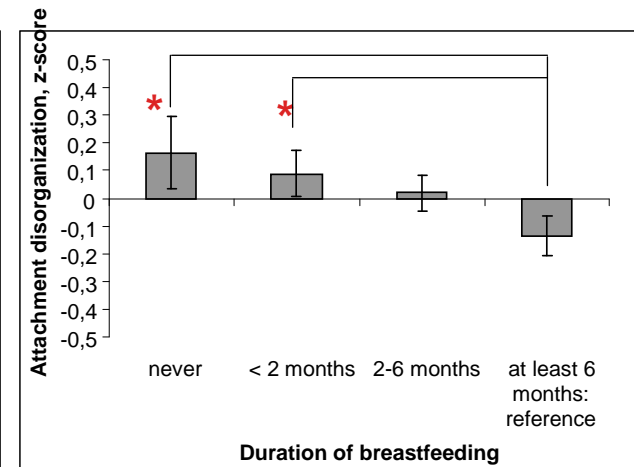
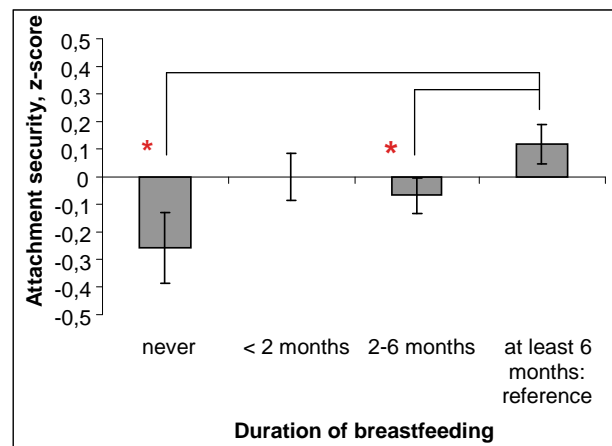
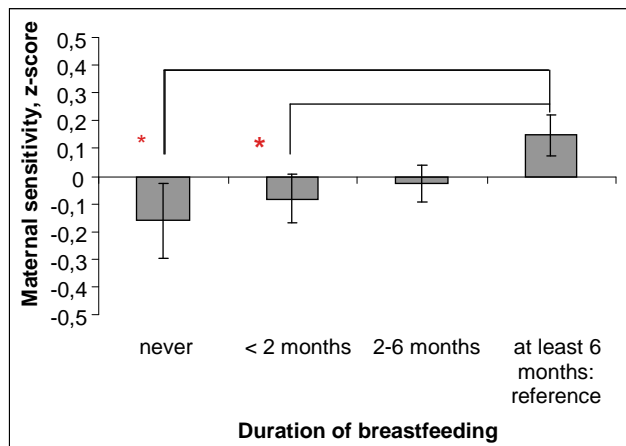
## Father-child interaction at age 4

- Teaching tasks
- Do tasks
- Don't tasks





# Duration of Breastfeeding and Maternal Sensitivity, Attachment Security and Attachment Disorganization



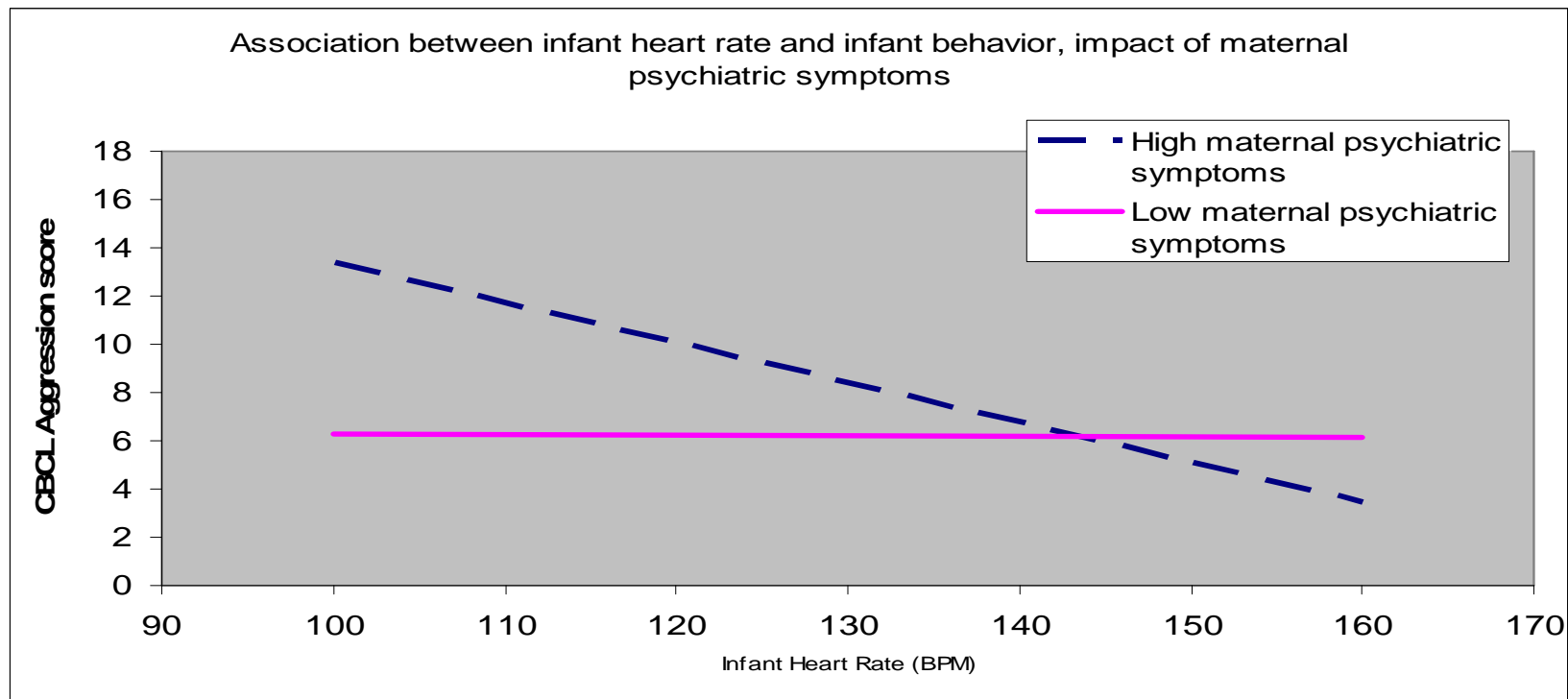
**Note:** Scores for sensitivity, security and disorganization were z-standardized (Mean = 0, SD = 1).

Depicted are estimated marginal means taken from ANCOVA adjusted for parity and educational level.

Error bars represent standard errors of estimated means. Group differences in means are indicated: \*\*  $p < .01$ , \*  $p < .05$ .

# Heart Rate and Aggression

- Interaction between child heart rate at 14 months and maternal psychopathology associated with child aggressive behavior at 18 months



Bram Dierckx



---

# What we have learned and implications

- Large number of factors with each contributing relatively small effects
- Cumulative risk model: multiple risks are additive and interact ( i.e. the child is at progressively greater risk, despite the small impact any single factor is likely to have)
- The most prominent factor is parental behavior (prenatal and postnatal). Implications for intervention:
  - start early
  - do'nt forget the fathers

---

# What we have learned and methodological implications

- **Confounding and causal inference**
- **Reverse causality**
- **Shared method variance bias**
- **Replication**
- **Selection bias**

---

## Successes, failures and future of CP epidemiology

- frequency and course of child psychiatric problems
- associations between social disadvantage and child maltreatment with behavioural and emotional development
- **but:** the high expectations that biological factors (candidate gene, cGXE and GWAS) can be used to better explain, diagnose or predict child psychiatric problems have not been met
- to apply genetics, neuroscience, or other molecular research to better understand how the brain produces maladaptive behavior, we need to conduct more ambitious large-scale child psychiatric cohort studies or to pool studies that use similar methodologies across multiple sites.



---

# Thanks



*f.verhulst@erasmusmc.nl*