kinder- en jeugdpsychiatrie karakter

UMC St Radboud

Gene-Environment Interaction

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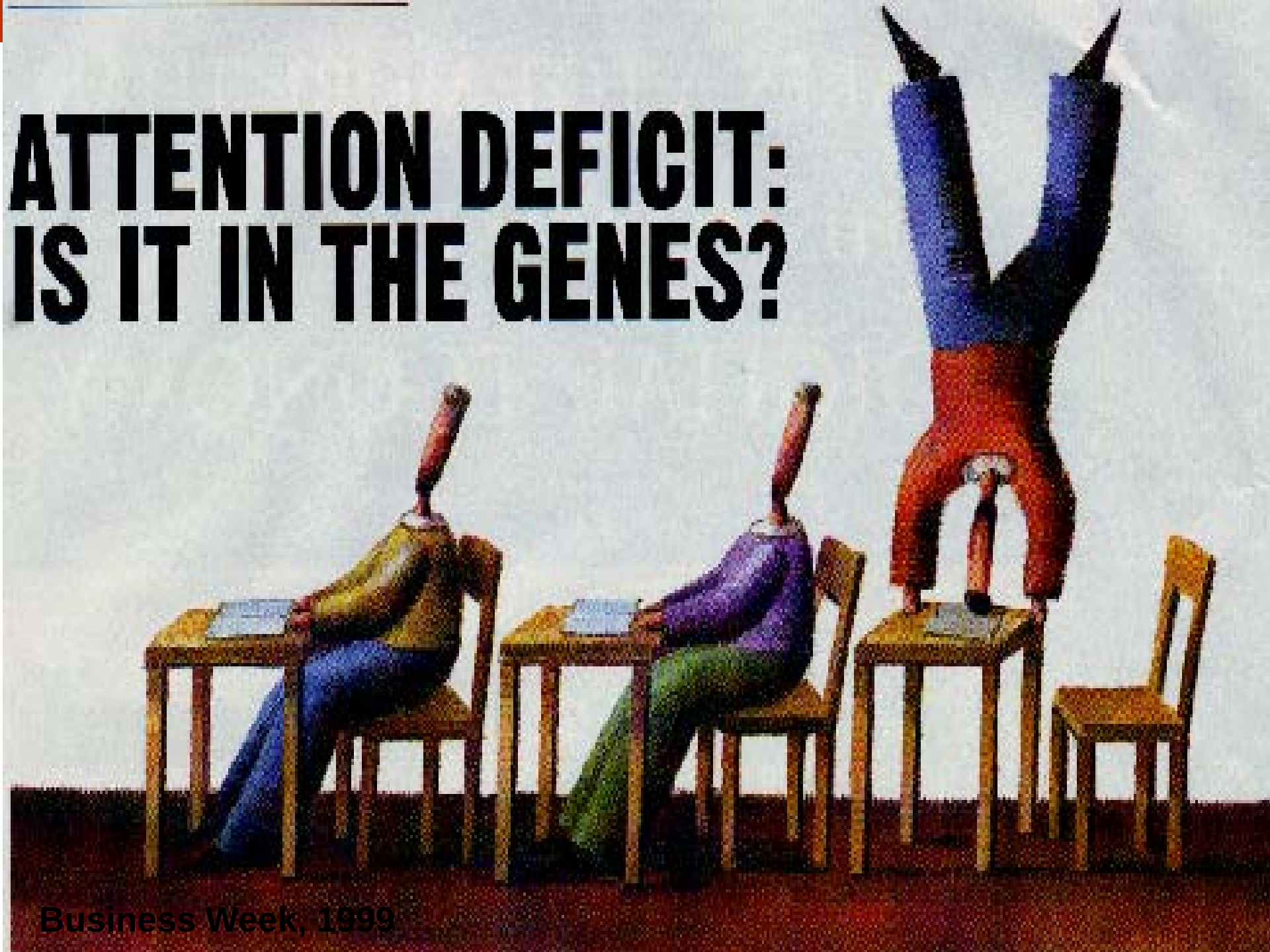
ADHD Symposium, Hamburg, March 7, 2009



Business Week, 1999

Complicating factors in genetic studies in multifactorial disorders

- Multiple genes of small main effects
- The relevant phenotype is unknown
- Clinical heterogeneity
- Genetic heterogeneity
- Gene-environment correlation
- Gene-environment interaction
- Importance of developmental factors
- Multiple endophenotypes

Buitelaar (2005) J Neural Transm Suppl. 69:1-17

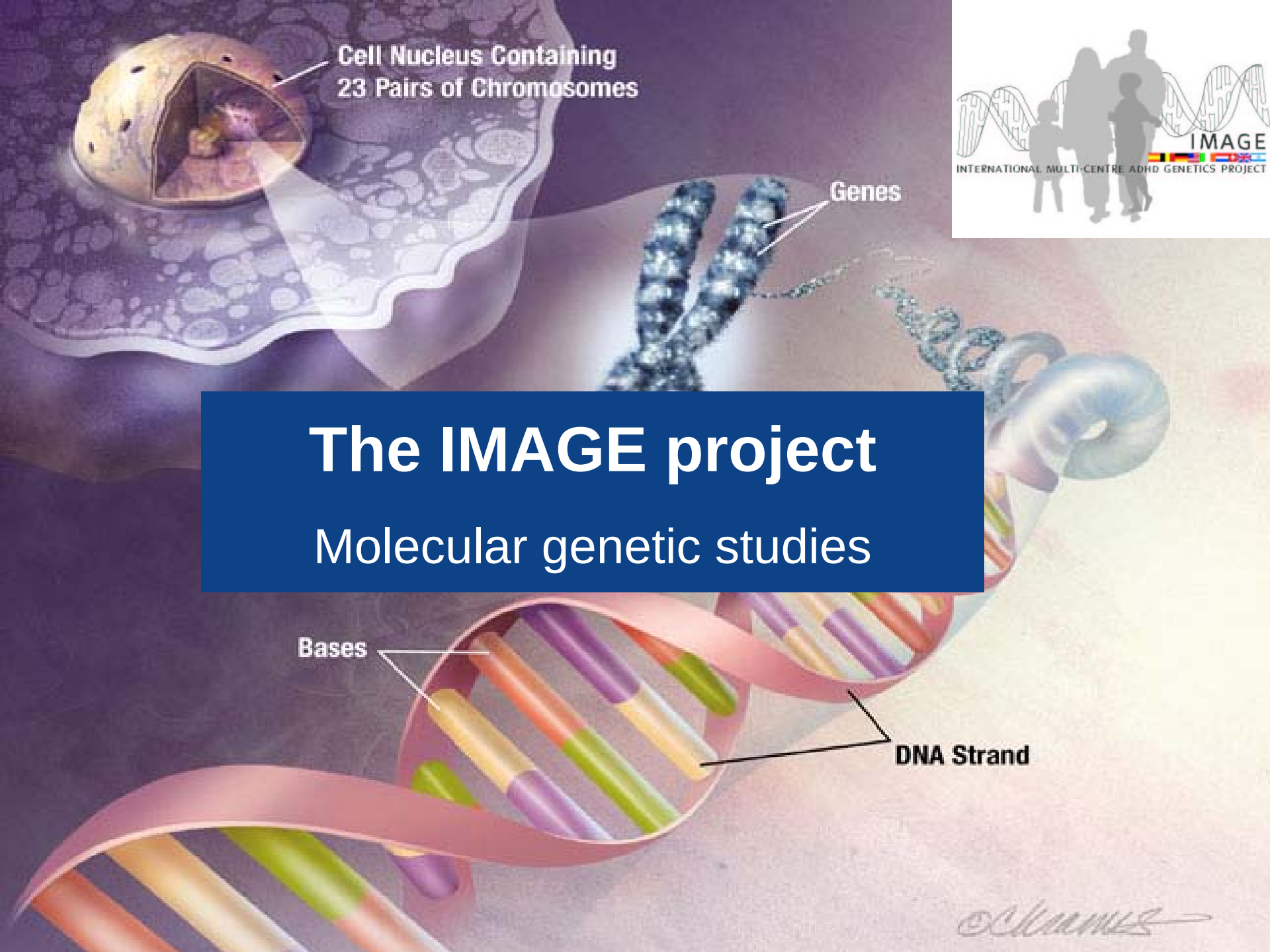
Gene-Environment Interplay

- Epigenetic effects of environments on genes
- Variations in heritability according to the environment
- Gene-environment correlations
- Gene-environment interactions

Rutter, Moffitt & Caspi (2006) JCPP, 47, 226-261

GxE and ADHD – current findings

- DAT1 and prenatal E risks (alcohol, smoking) (Kahn 2003, Brookes 2006, Neuman 2007) and psychosocial adversity (Laucht, 2007)
- DRD4 and maternal insensitive behavior (Bakermans-Kranenburg 2006) and paternal warmth (Propper 2007)
- SERT and adverse environment (Reif 2007) and socioeconomic status (Nobile 2007)
- COMT and low birth weight (Thapar 2005)



The IMAGE project

Molecular genetic studies

International Study of the Mapping of ADHD Genes
IMAGE Data Collection 2003 - 2007

- **Present study:**
  - **Focus on prenatal exposure to smoking and GxE and GEr**
  - **IMAGE subsample with measures of prenatal exposure**
  - **IMAGE subsample with cognitive measures**

Altink et al. (2008a), JCPP; Altink et al (2008b), ECAP, in press

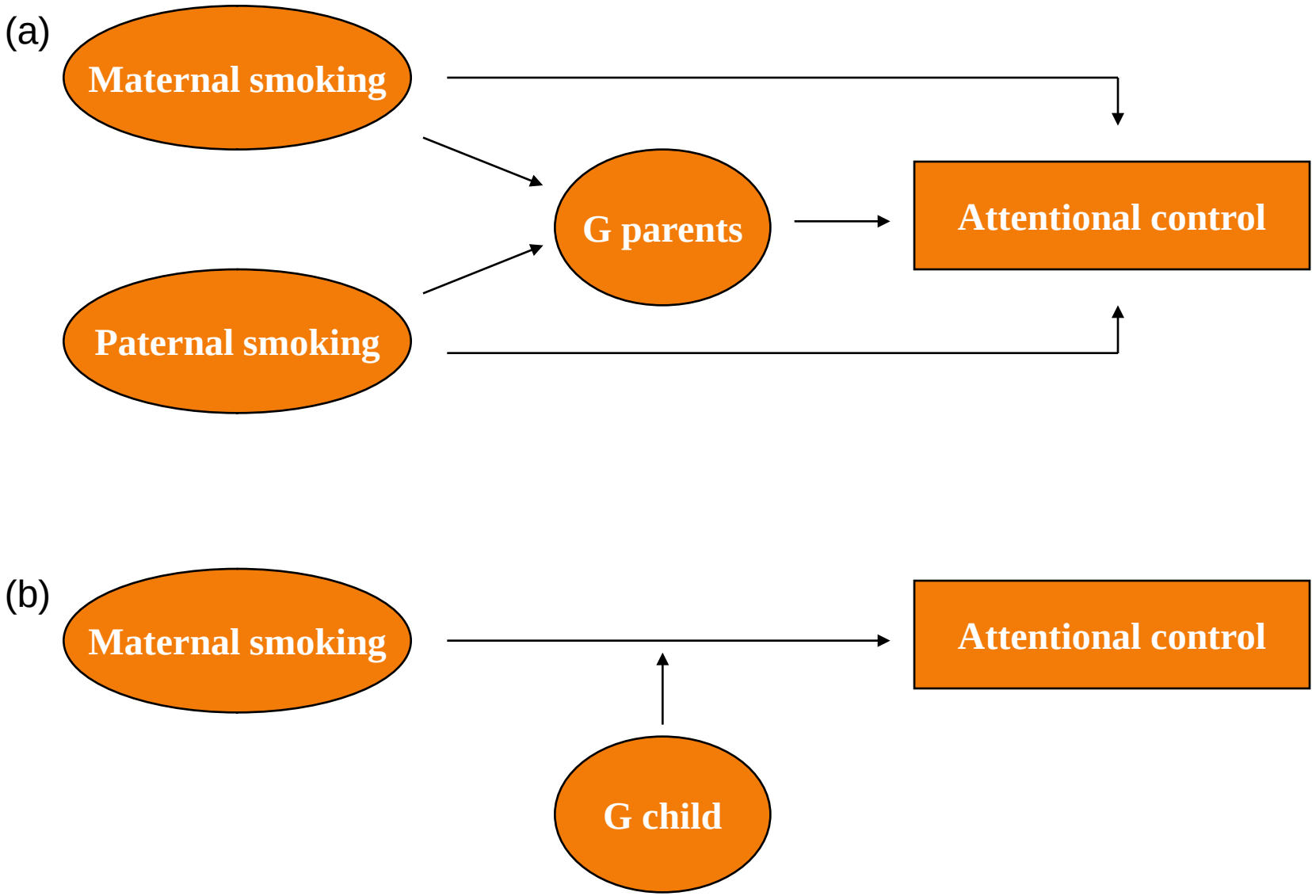
Netherlands, UK, Israel, Ireland, Germany, Spain, Switzerland, Belgium

Prenatal maternal smoking & ADHD

- Maternal smoking is an environmental risk factor for ADHD, increased risk between 2 and 4 (Linnet al., 2003, Langley et al., 2005)
- Increased risk found for
  - Categorical and dimensional definitions of ADHD
  - Case-control and cohort studies
- Control for genetic factors (twin studies) reduces effect of smoking considerably

Prenatal maternal smoking & ADHD - Questions

- Is this an environmental effect? Or is is genetically mediated ? Due to GEr ?
  - What is the effect of paternal smoking?
  - Does the transfer of ADHD risk genes explain the smoking effect ?
- Does prenatal smoking also affect cognitive endophenotypes of ADHD? Is this effect specific for ADHD ? Or is it also presence in controls ?
- Does prenatal smoking interact with ADHD risk genes in the child in affecting the cognitive endophenotype?



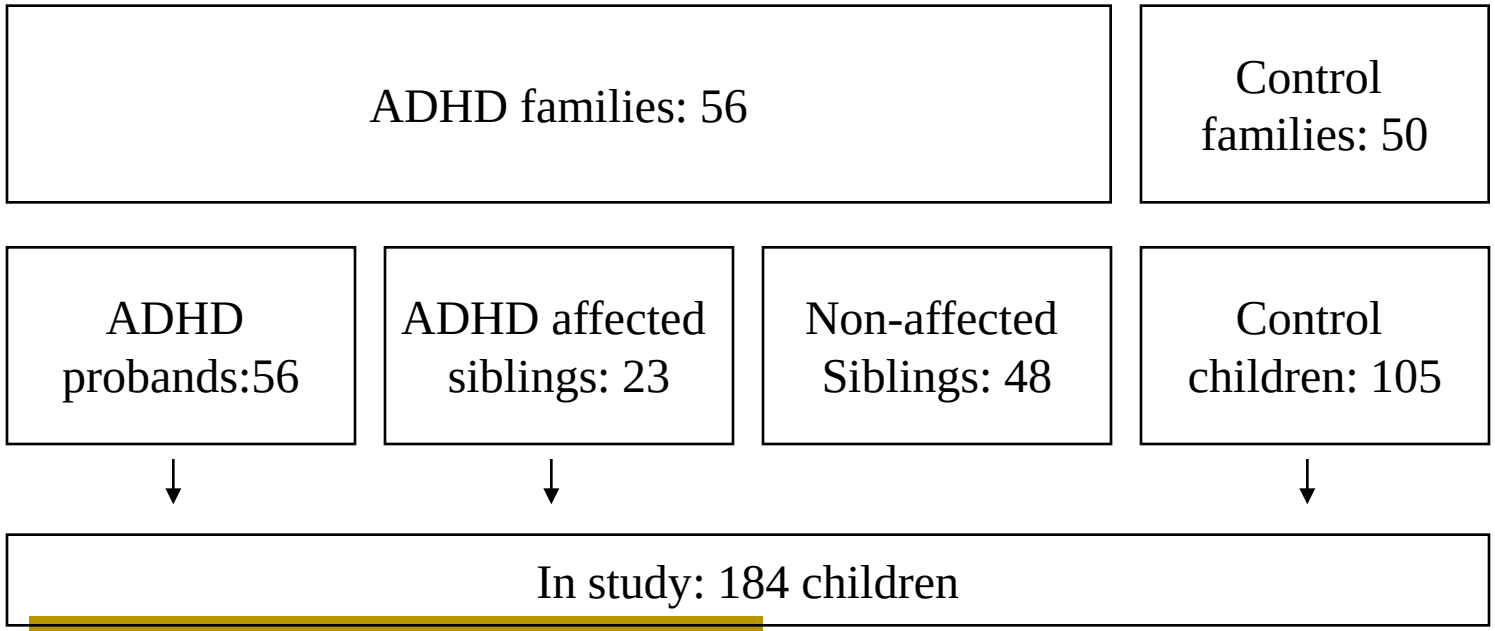
Models of analyses. (a) Genetic mediation hypothesis, where smoking reflects a proxy risk for ADHD genes. (b) Gene by Environment (GxE) interaction.

Parental smoking

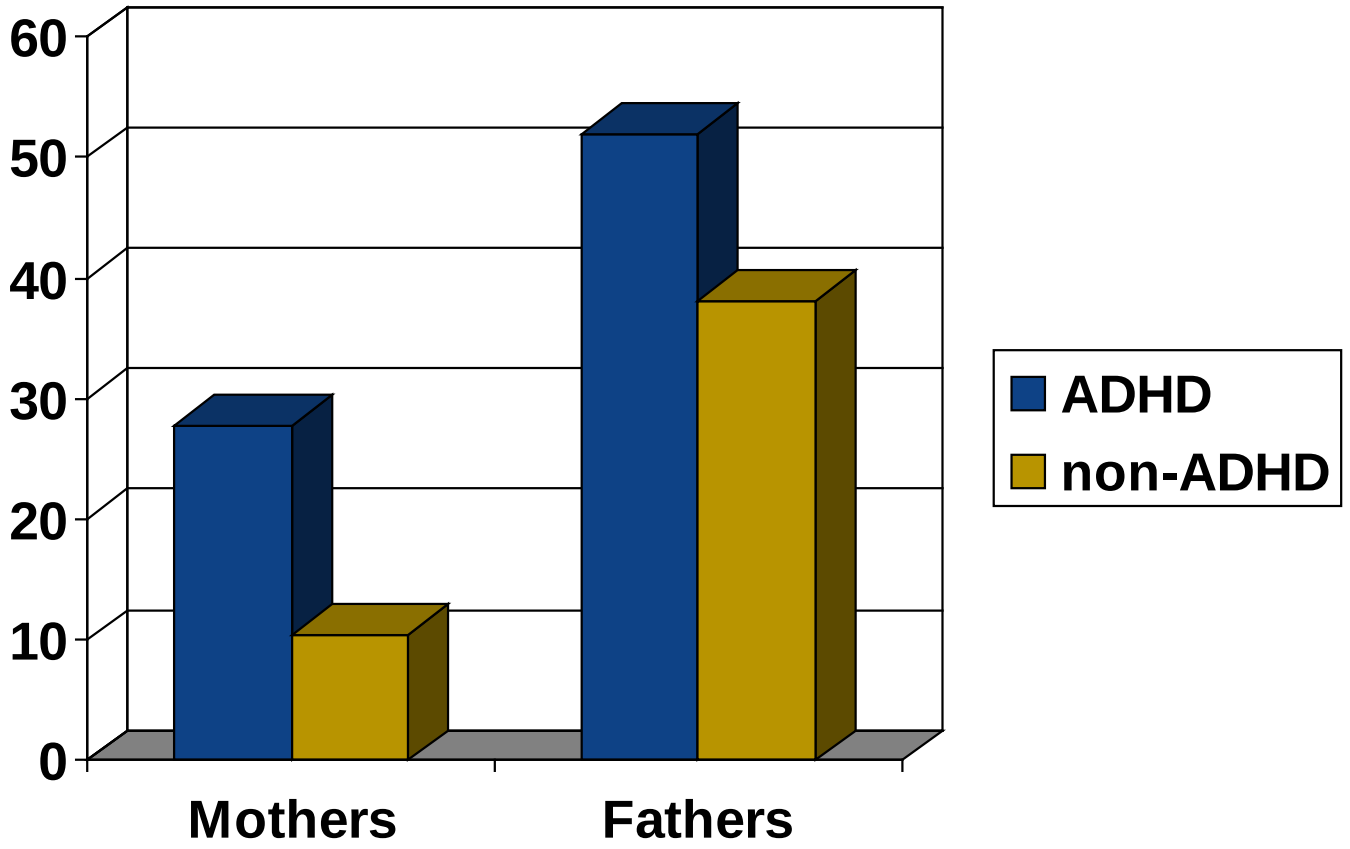
- Collected by questionnaire
- (1) ‘0 cigarettes’
- (2) ‘1-5 cigarettes per day’
- (3) ‘6 or more cigarettes a day’

Approach

- Sustained Attention Task of the Amsterdam Neuropsychological Tasks (ANT). Duration of the task was on average 15 minutes and the target rate was 33%.
- Sample:



Percentage maternal and paternal smoking



Smoking, ADHD / non-ADHD, and attentional performance

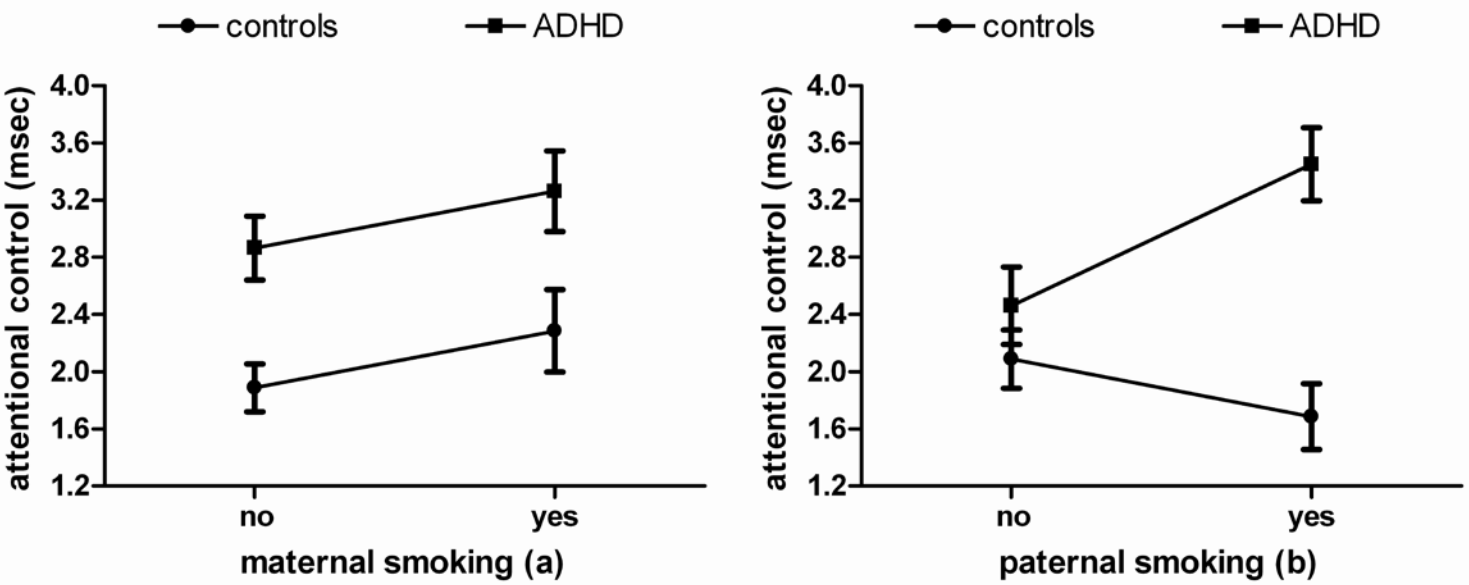


Figure 3. The effect of paternal and maternal smoking stratified by ADHD status. In panel (b) the interaction effect between paternal smoking and ADHD status is shown (p=0.007). For maternal smoking (a) the effect of smoking is the same in both groups. A higher score means a more variable performance.

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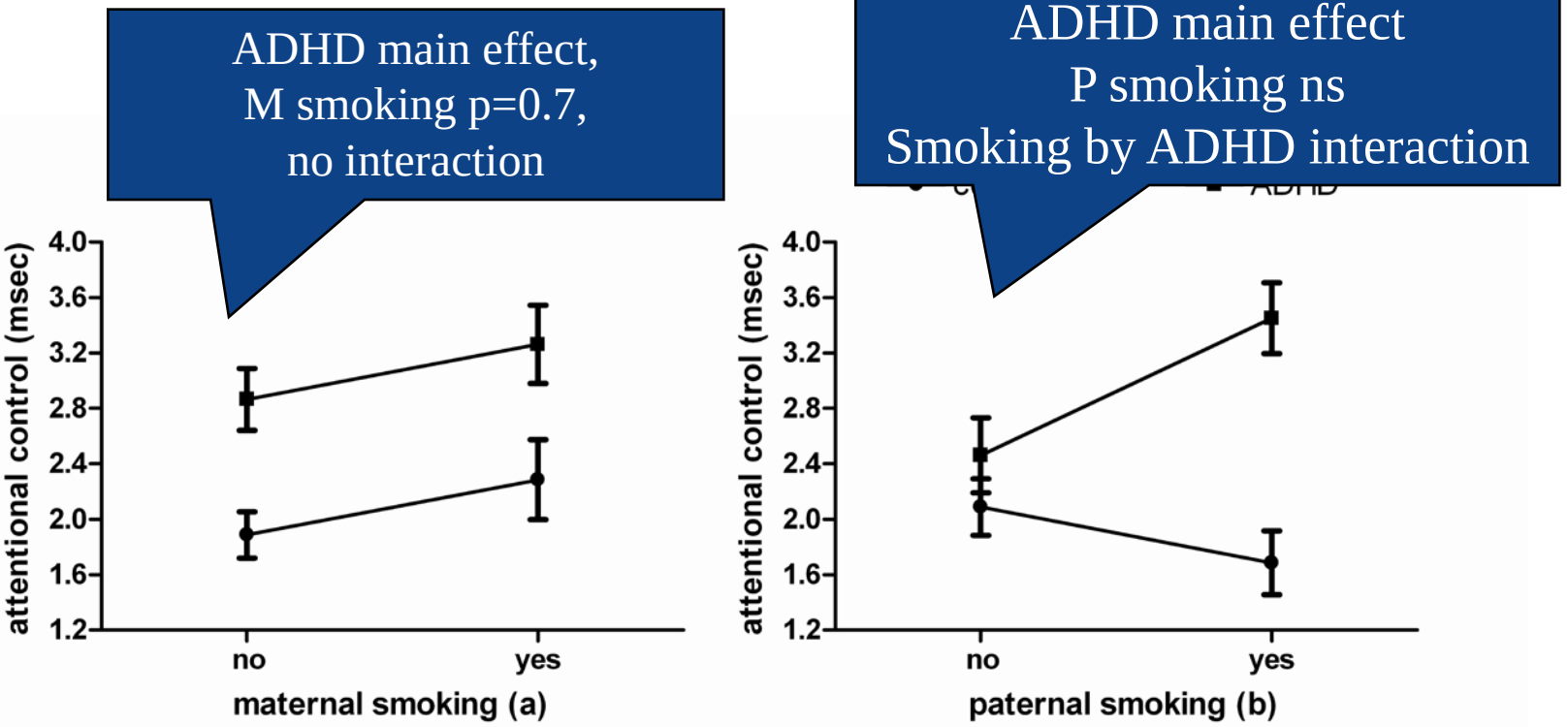

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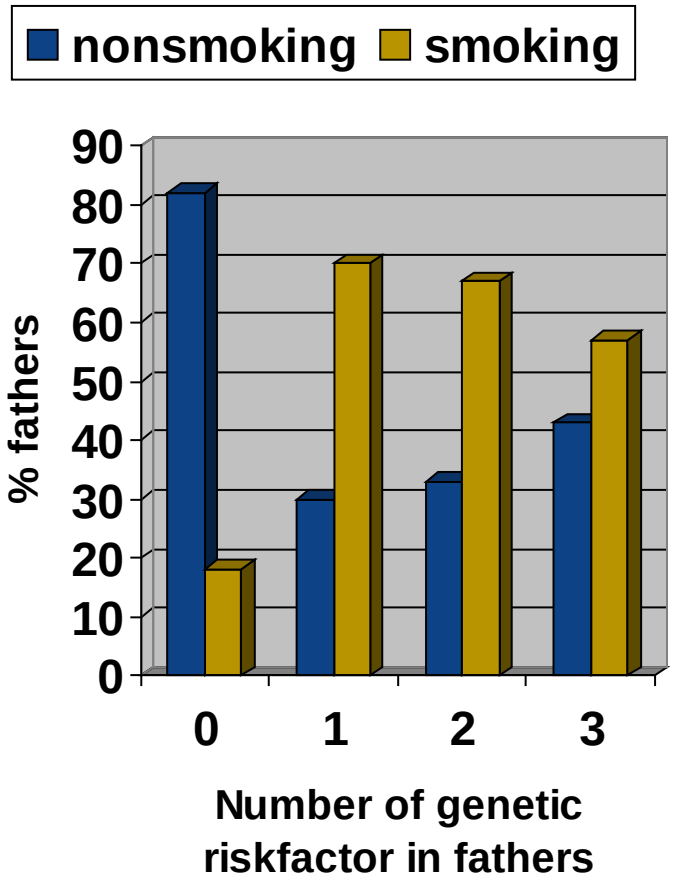
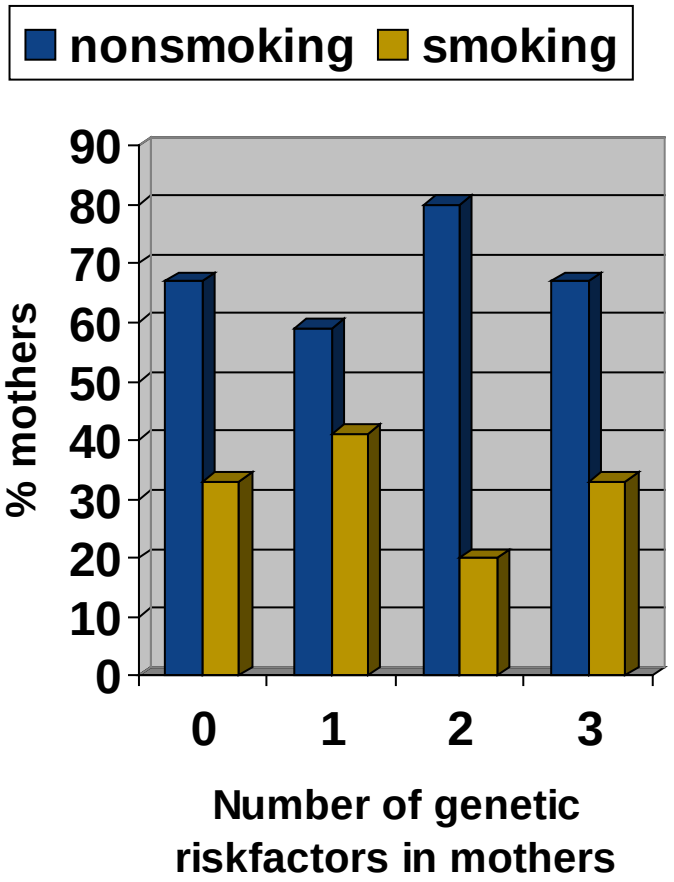
Smoking and parental ADHD risk genes





Percentages of smoking and non-smoking fathers and mothers by the number of genetic risk factors (range 0-3): DRD4 7R allele, DAT1 3'UTR 10/10, DAT1 INT8 6/6)

Results

- Paternal smoking is significantly associated with presence of ADHD risk genes in fathers
- Maternal smoking is not associated with presence of ADHD risk genes in mothers

- No indication for GxE interaction effects of prenatal smoking and ADHD risk genes in the child in affecting attentional control

Altink et al., 2008, ECAP, in press

Interpretation

- The paternal smoking effect on attentional control was dependent on the child's ADHD status
- The effects of paternal smoking is suggested to be genetically mediated

→ Effect of paternal smoking may reflect gene-gene interaction

- The effect of maternal smoking is not suggested to be genetically mediated

Maternal smoking & IQ (Frazier et al., Neuropsychology 2004, 18, 543-555)

- Children exposed to prenatal smoking have IQ scores between 4 to 15 points lower on standardized tests across different ages compared to their non-exposed peers.
- This holds when IQ, educational level or socio-economic class of the parents are controlled for.
- A dose-response relation between the amount of cigarettes smoked by the mother and their children's IQ.

- ADHD children have on average a lower IQ than unaffected children

→ **Does exposure to prenatal smoking contribute to the association between ADHD and lower IQ?**

Or, is the assocaation ADHD-low IQ due to shared genetic factors? Genetic factors in ADHD & IQ

- Heritability estimates:
  - ADHD: 76%
  - IQ: 30%-80%

- In ADHD familial relationship verbal IQ (Rommelse et al., 2008)

- Association between lower IQ and ADHD may be due to shared genetic risk factors (Kuntsi et al., 2004)

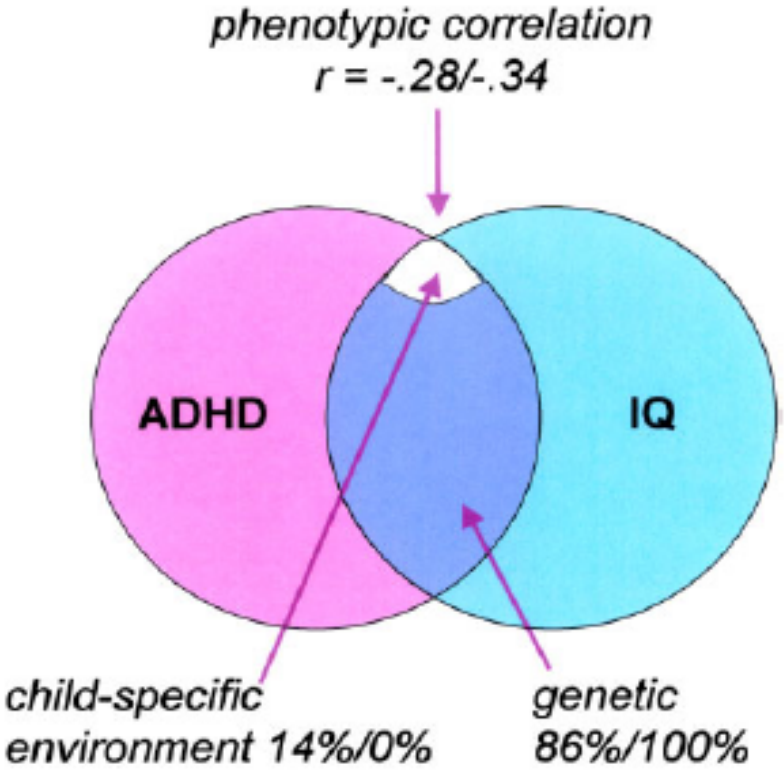
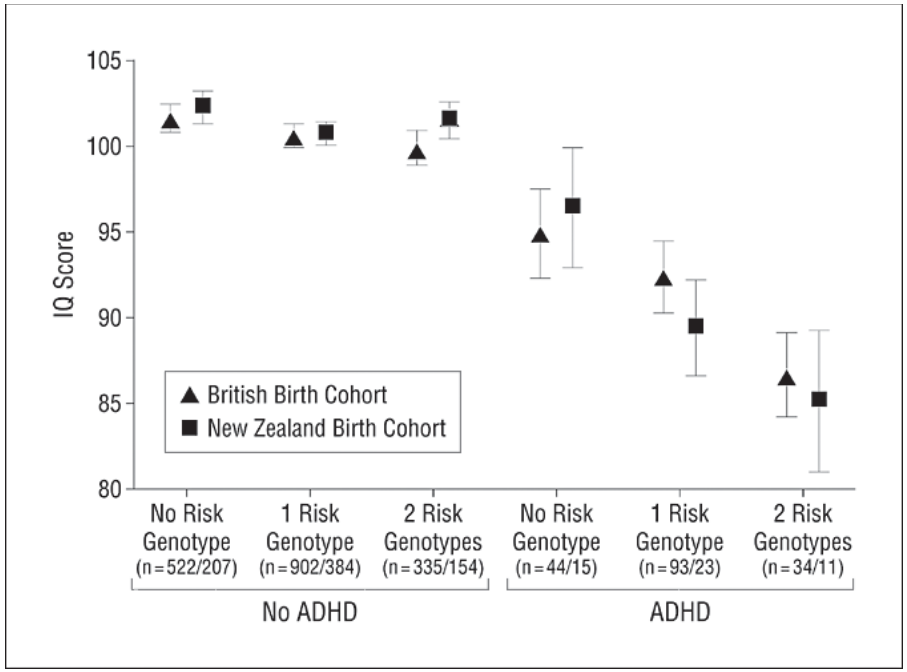


Fig. 1. Genetic and environmental contributions to the negative phenotypic correlation between IQ and both ADHD symptom scores and ADHD diagnosis. [Colour figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Genes related to ADHD may affect IQ



- DRD4, DAT1
- However, several failures to replicate !

Mill et al., 2006, AGP

Aims

To study:

1. The effect of maternal smoking during pregnancy on IQ in ADHD-affected children and their unaffected siblings in a large sample from the IMAGE study controlling for SES, birthweight and alcohol use.
2. Whether polymorphisms in *DRD4* (exon 3 VNTR) and *SLC6A3* (VNTR located in the 3' untranslated region (3' UTR) modulated the relationship between maternal smoking, ADHD and IQ.

Methods

- **United Kingdom**
- **Ireland**
- **Netherlands**
- Germany
- Belgium
- Switzerland
- Spain
- Israel

Methods

- 432 families
  - 397 ADHD affected probands
  - 119 affected siblings
    - 63 combined subtype
    - 33 inattentive subtype
    - 23 hyperactive-impulsive subtype
  - 391 unaffected siblings

N = 516
mean age = 10.9
% boys = 80.6

N = 195
mean age = 10.8
% boys = 42.2

Statistical Analyses

Linear Mixed Models (LMM)

1. Effect smoking and ADHD on IQ
   - All children
   - ADHD and non-affected children
2. Effect smoking, ADHD, genotype on IQ
   - All children
   - ADHD children only

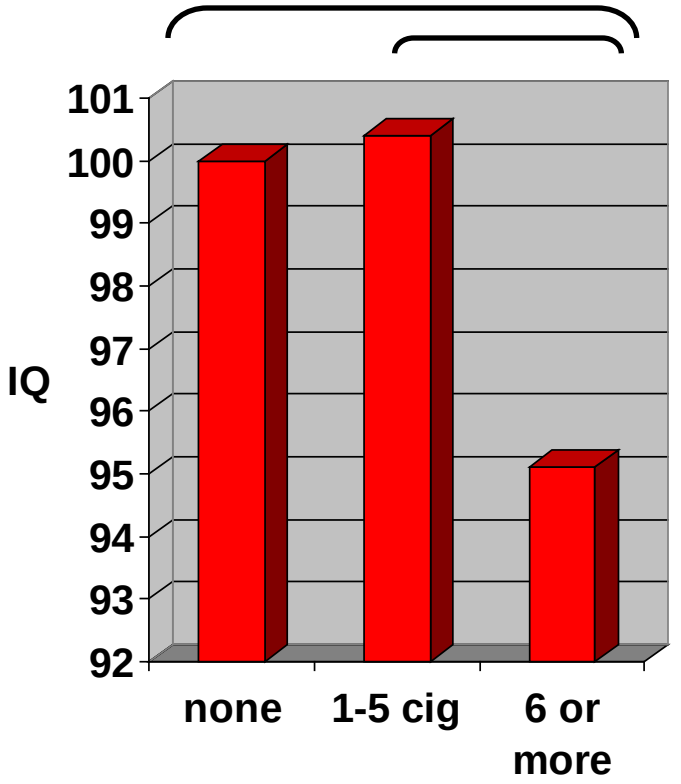
Covariates:

- Birth weight (grams)
- Parental occupational status (3 groups)
- Alcohol use during pregnancy (yes/no)
- Centre (UK, IRL, NL)
- Gender

Effect maternal smoking on IQ, whole group

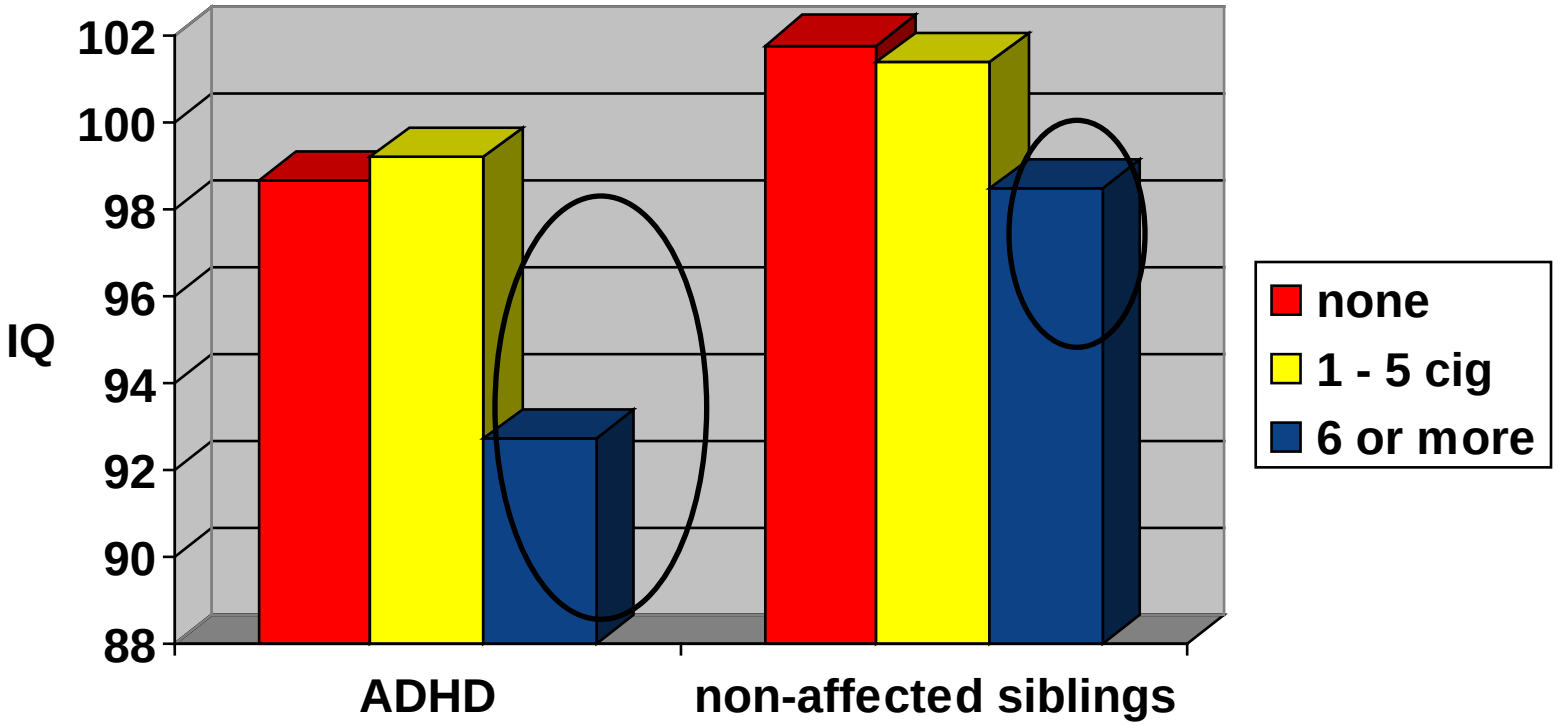
- Significant main effect of smoking on IQ

  corrected for: birth weight, parental occupation status, centre, maternal alcohol use during pregnancy
- No main gene effects on IQ, and no GxE interaction effects on IQ
- Parental educational status strong predictor for IQ



***F*(2, 538.01) = 4.19, *p* = 0.016**

Effect maternal smoking on IQ, separately in ADHD and non-ADHD



F (2, 363.1) = 4.04, *p* = 0.018

F (2, 285.1)=0.79, *p* = 0.451

Conclusion

- Our results clearly suggest the possibility that variation in prenatal exposure to smoking between different studies may explain discrepant findings on the involvement of ADHD risk genes in IQ

Altink et al. (2008) submitted