Drawing causal inferences in epidemiological studies of early life influences

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Structure of this talk

- Challenges of early life studies
- The Avon Longitudinal Study of Parents and Children
- Examples of chance, bias and confounding
- Approaches to chance, bias and confounding

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Challenges of early life studies

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Evidence for importance of early life

- Ecological studies of infant mortality
- Cohorts of size in early life
- Trials of early feeding
- Range of exposures and outcomes
- Animal studies of extreme exposures

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Challenges of early life studies

- Long latency
- Possible critical periods
- Complex confounding structure
- Cohort effects
- Trait based outcome measures

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The Avon Longitudinal Study of Parents and Children

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The Avon Longitudinal Study of Parents and Children (ALSPAC)

- A.k.a. Children of the nineties
- Cohort study
- Pregnant with a due date 1.4.91-31.12.92
- Resident in Avon

Boyd A et al. Cohort Profile. International Journal of Epidemiology 2012

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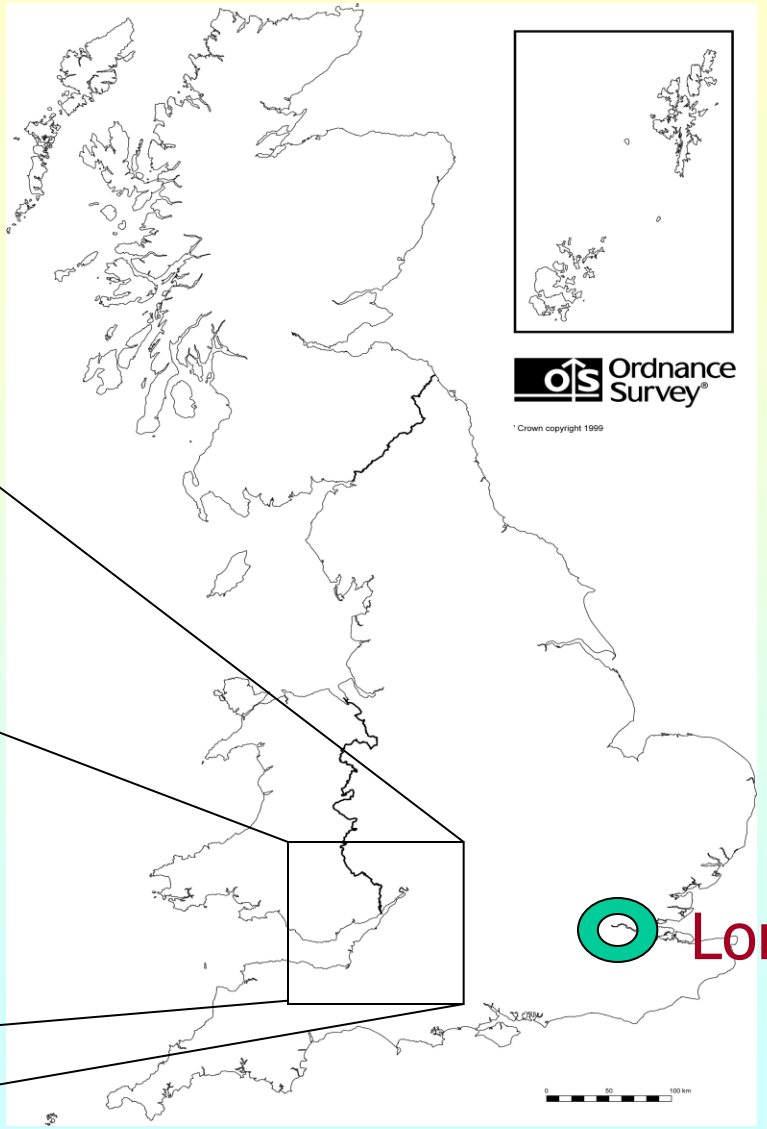

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The Avon Longitudinal Study

ALSPAC

of Parents and Children

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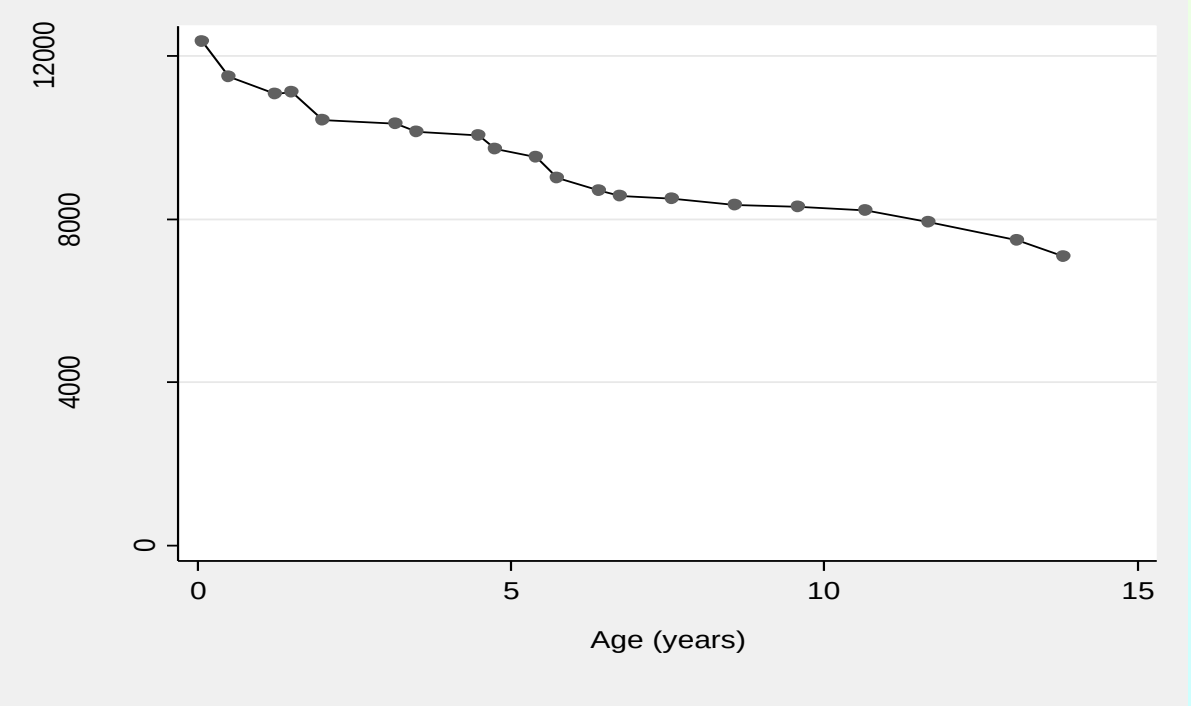
Missing data in early life studies

- **May be years/decades between the early life exposure and the outcome of interest**
- **Loss to follow-up (usually) increases with time**

ALSPAC questionnaire responses: birth to 15yrs



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Your Son
16+ Years On

ALSPAC resource

- **Before birth to age 15+ (n~5,500)***
- **DNA bank on children (n~10,000)**
- **DNA bank on mothers (n~10,000)**
- **Blood for cell lines on children (n~7,000)**
- **Blood for cell lines on mothers (n~5,700)**
- **Blood for cell lines on fathers (n~1,400)**

*** At recent data collection points**

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Examples of chance, bias and confounding

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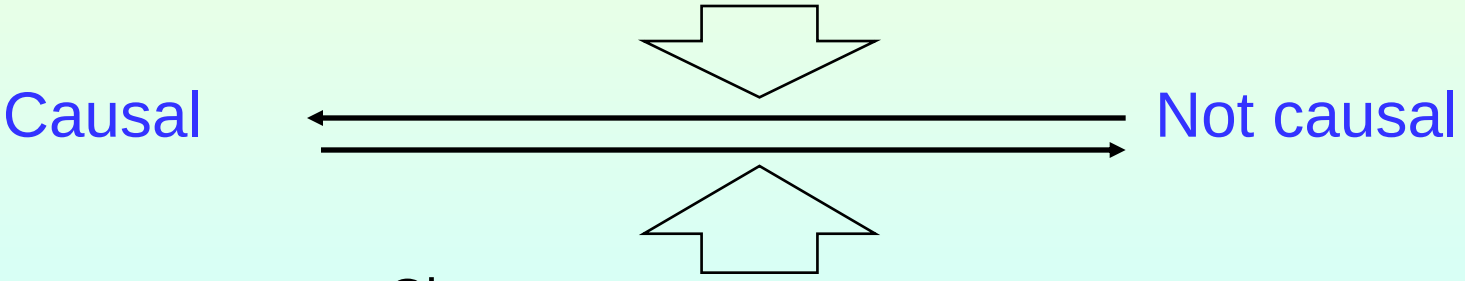
Is the association causal ?

Strength of the association
Biological credibility
Consistency with other studies
Time sequence
Dose response
Specificity



Chance
Bias
Confounding
Reverse causality

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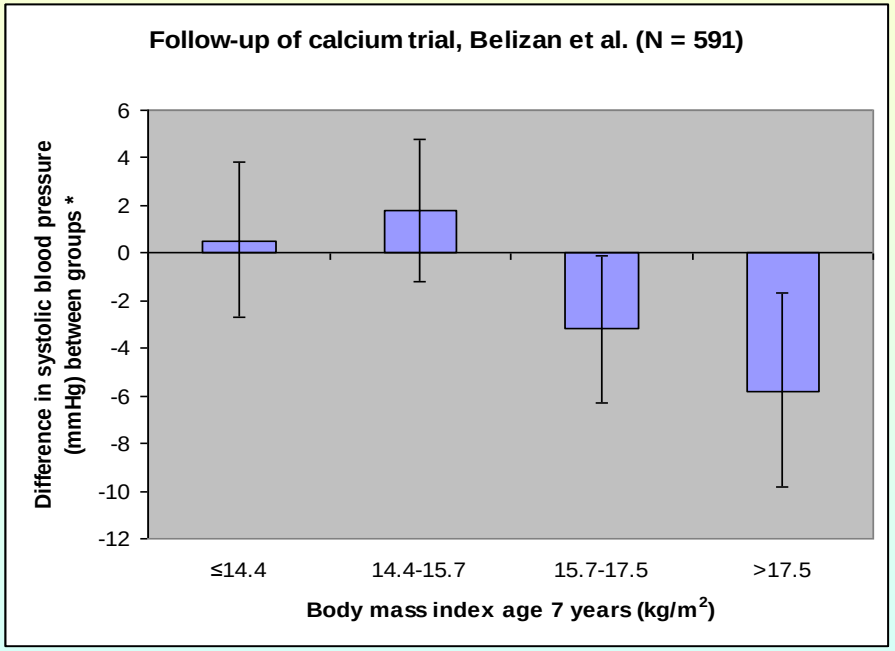
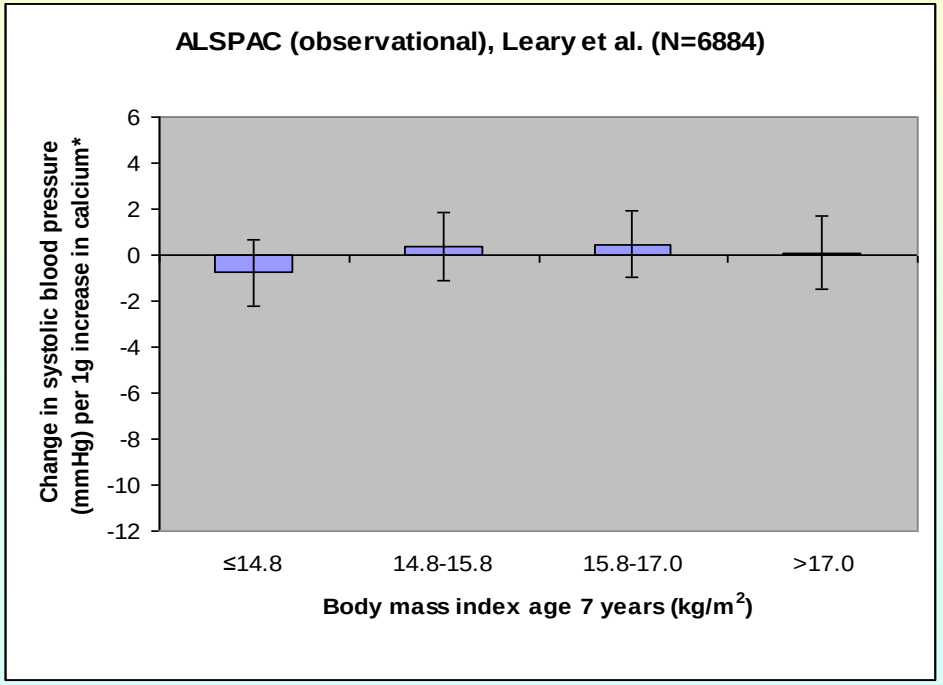
Subgroup analyses

Calcium intake during pregnancy and offspring blood pressure at age 7, according to body mass index



* Intervention (2g calcium/day during pregnancy) vs placebo



* Mean calcium intake during pregnancy approx 1g day

Findings from subgroup analysis may not be replicable

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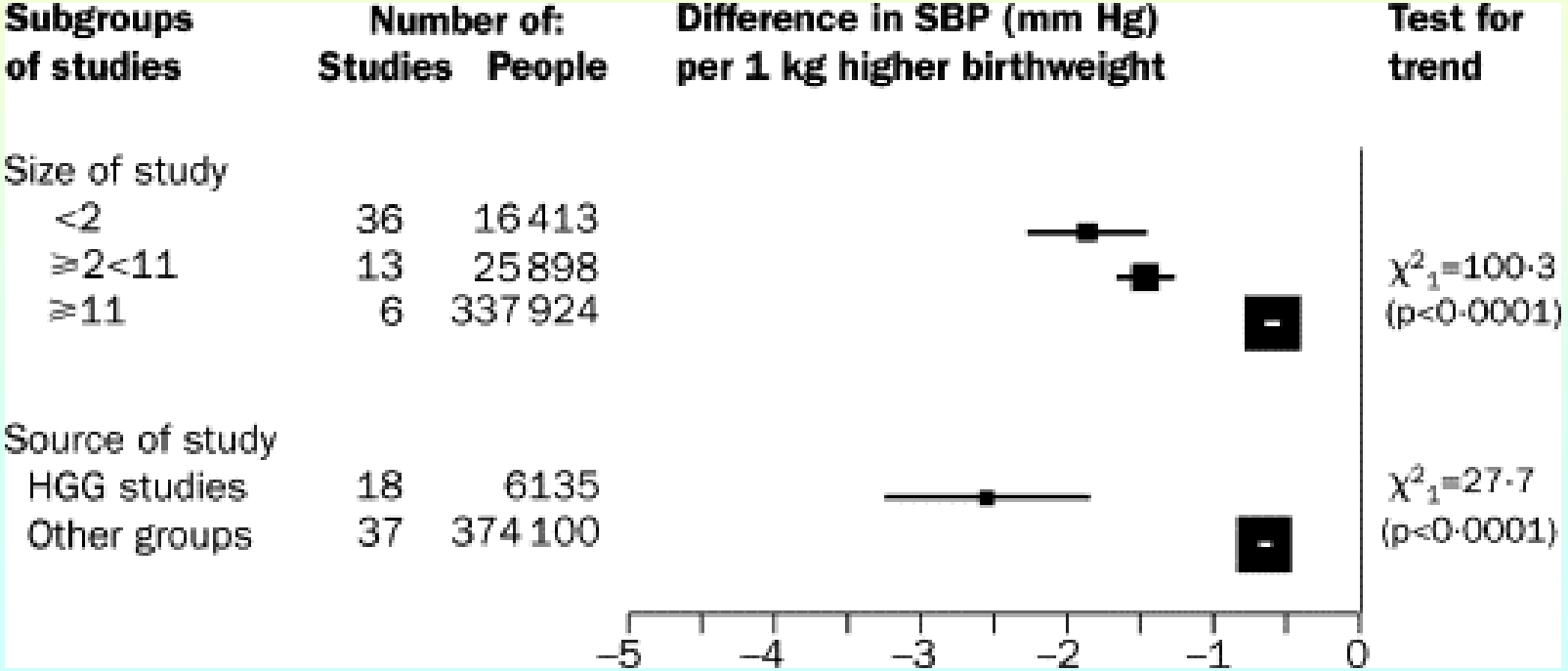
Belizan et al. BMJ 1997;315:281-5
Leary et al. Archives of Disease in Childhood 2005;90:492-3

Birthweight and blood pressure



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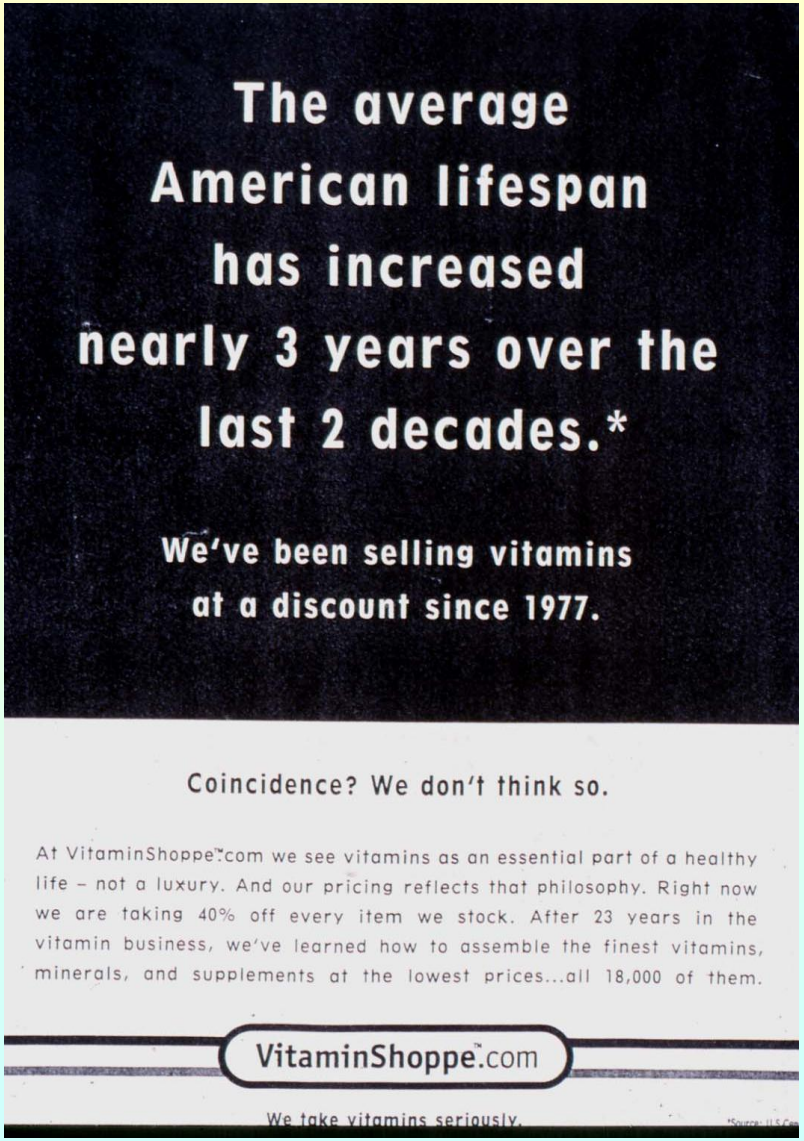
Rachel Huxley et al Lancet 2002



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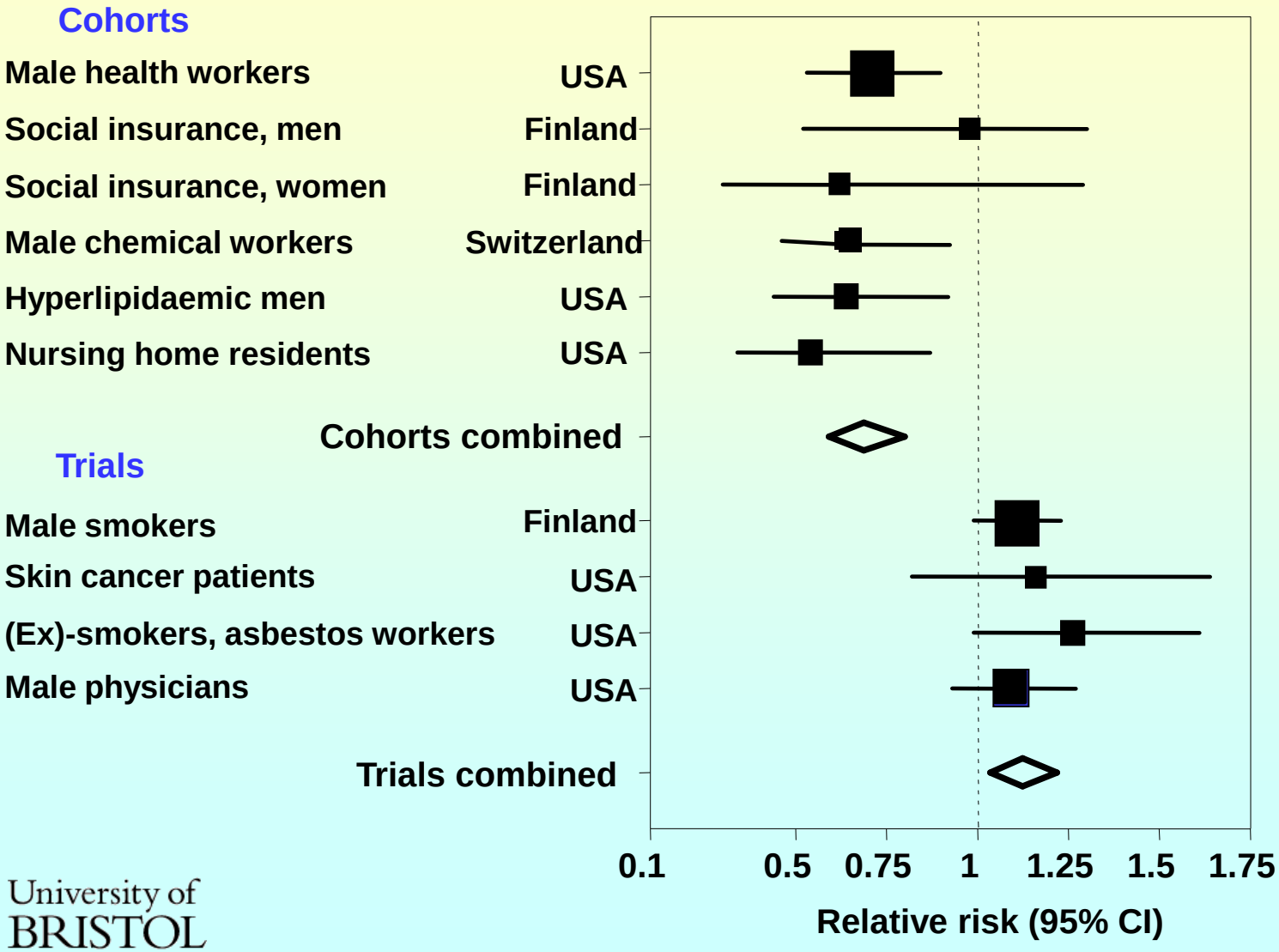
Advertisement in Boston Globe

Beta-carotene and Cardiovascular mortality



Egger et al
BMJ;1998:316:61-66

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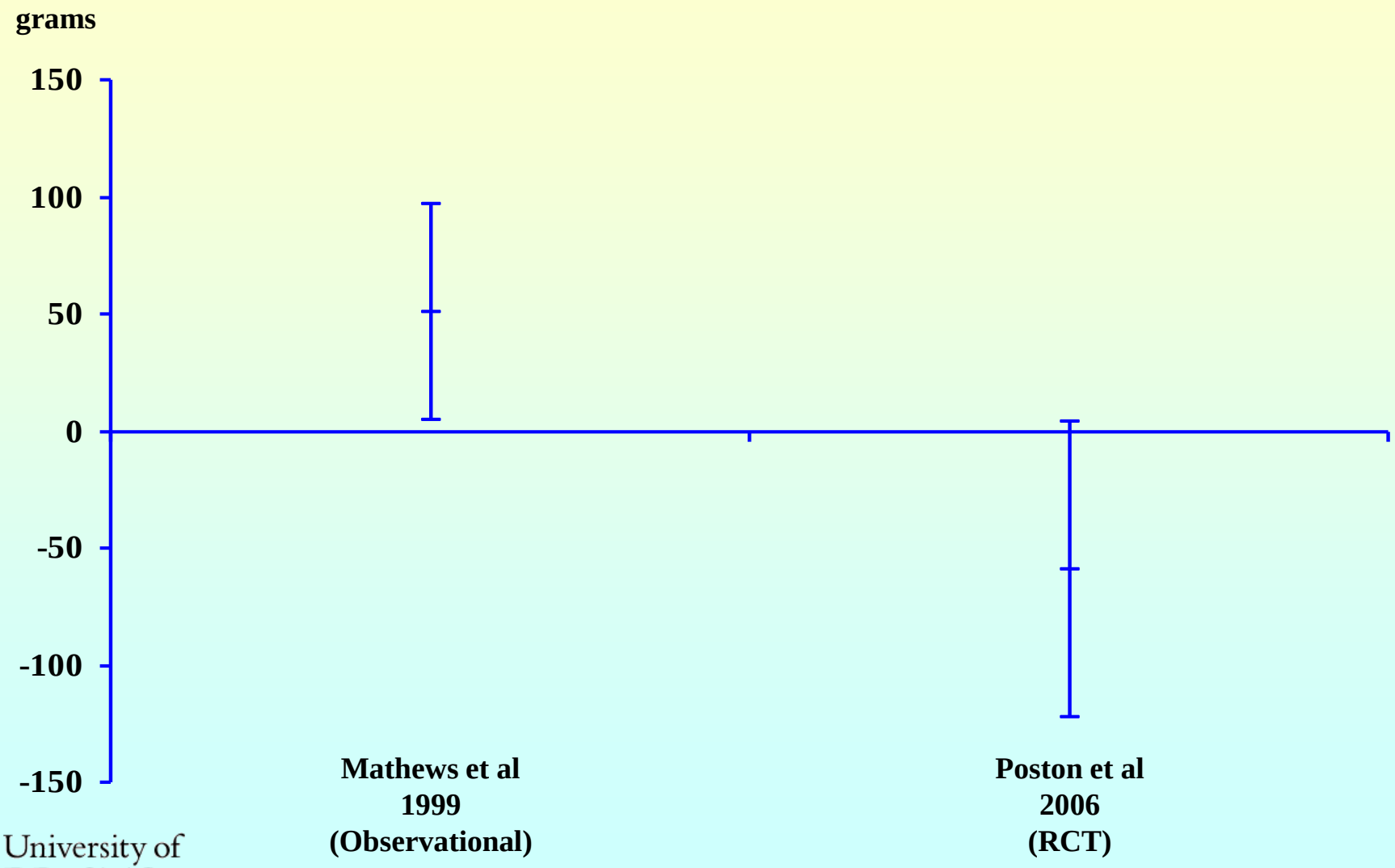
Vitamin C and birth weight: Observational study and RCT



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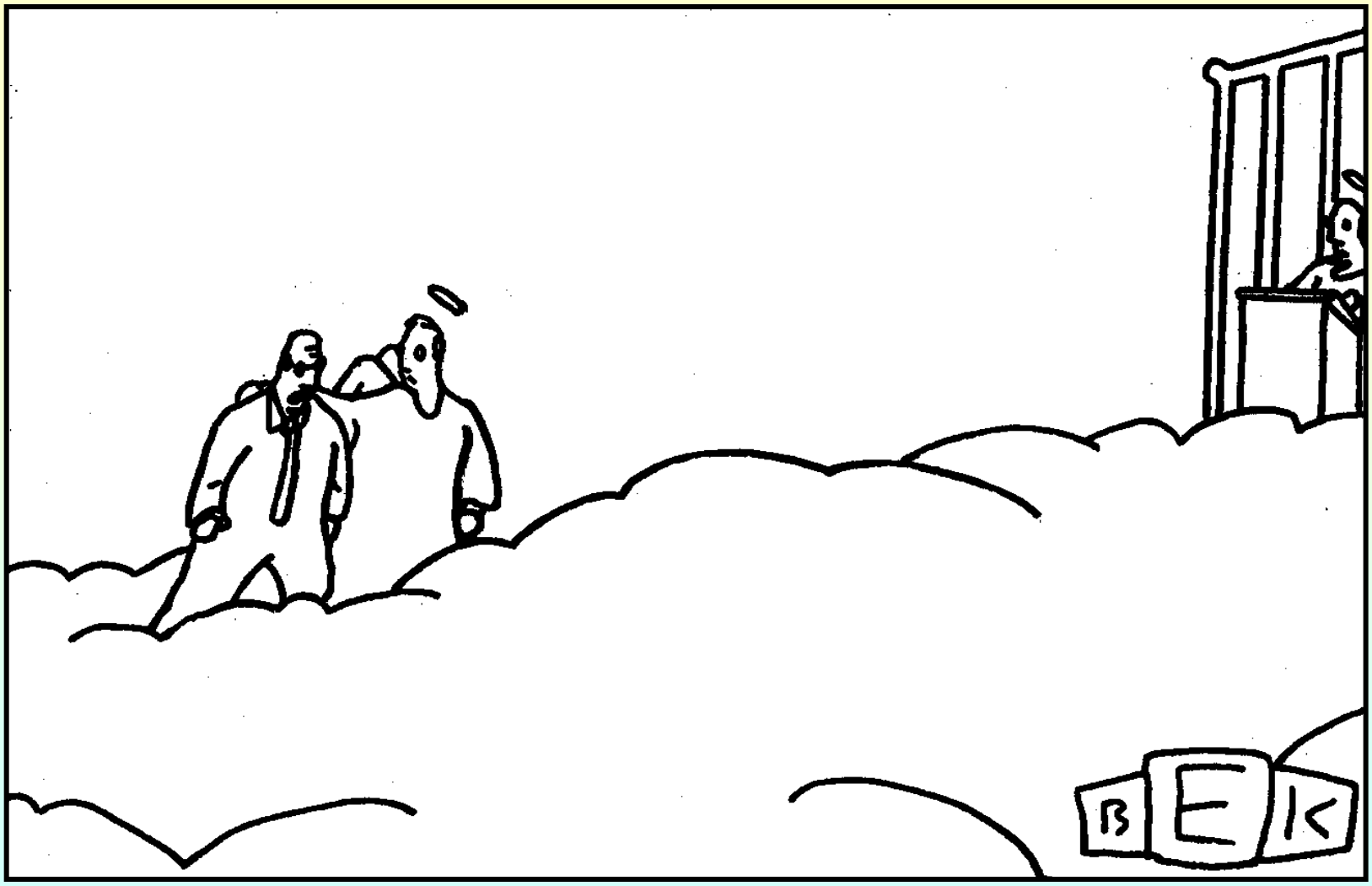

"Well, so much for antioxidants."

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Approaches to chance, bias and confounding

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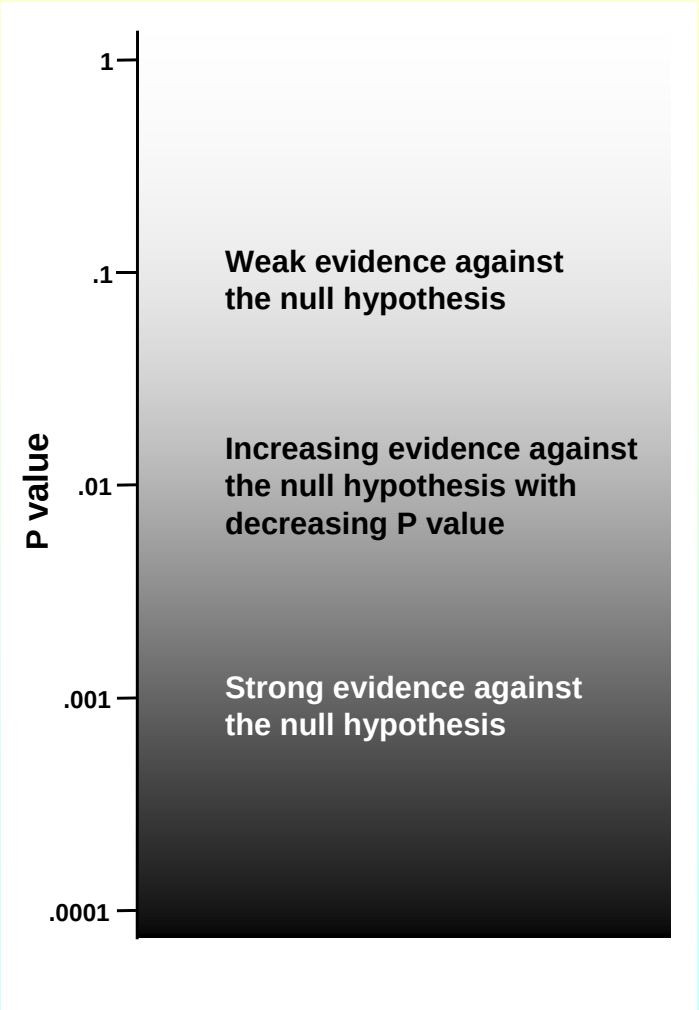
Observational epidemiology?

Avoiding chance

- Design adequately powered studies
- Do the correct analysis
- Avoid statistical significance
- Present p values and confidence intervals
- Look at effect sizes and their clinical importance
- Focus on pre-specified main effects
- Report exploratory analyses as such
- Replicate subgroup findings

Interpretation of p values



The smaller the p-value, the stronger the evidence against the null hypothesis

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Sterne JAC, Davey Smith G. *British Medical Journal* 2001;**322**:226-31
Sifting the evidence: what's wrong with significance tests?

Clinical significance?

Weight at birth and systolic blood pressure at age 3

1860 children (ALSPAC)

After adjustment for current size:

Regression coefficient = -1.9 mmHg/kg

Confidence interval = -2.61, -1.21 mmHg/kg

$P < 0.0001$

Interpretation:

Strong evidence against null hypothesis, blood pressure BUT differences small considering birthweight changes achievable

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How much can we modify birthweight ?

- Effect sizes often presented per 500g or per kg
- Smokers 100-200g lower
- Smoking cessation trials ~50g increase
- Dutch Hunger Winter 300g lower
- Gambia trial 200g in wet season and 80g in dry

Avoiding bias (in cohorts)

- Reduce losses to follow up (NB linkage)
- Report characteristics of those lost to follow up
- Compare complete case analysis versus analysis in subjects with missing data
- If missingness is related to values of *observed* data, consider multiple imputation
- If missingness is related to values of *unobserved* data, unbiased effect estimates are not possible

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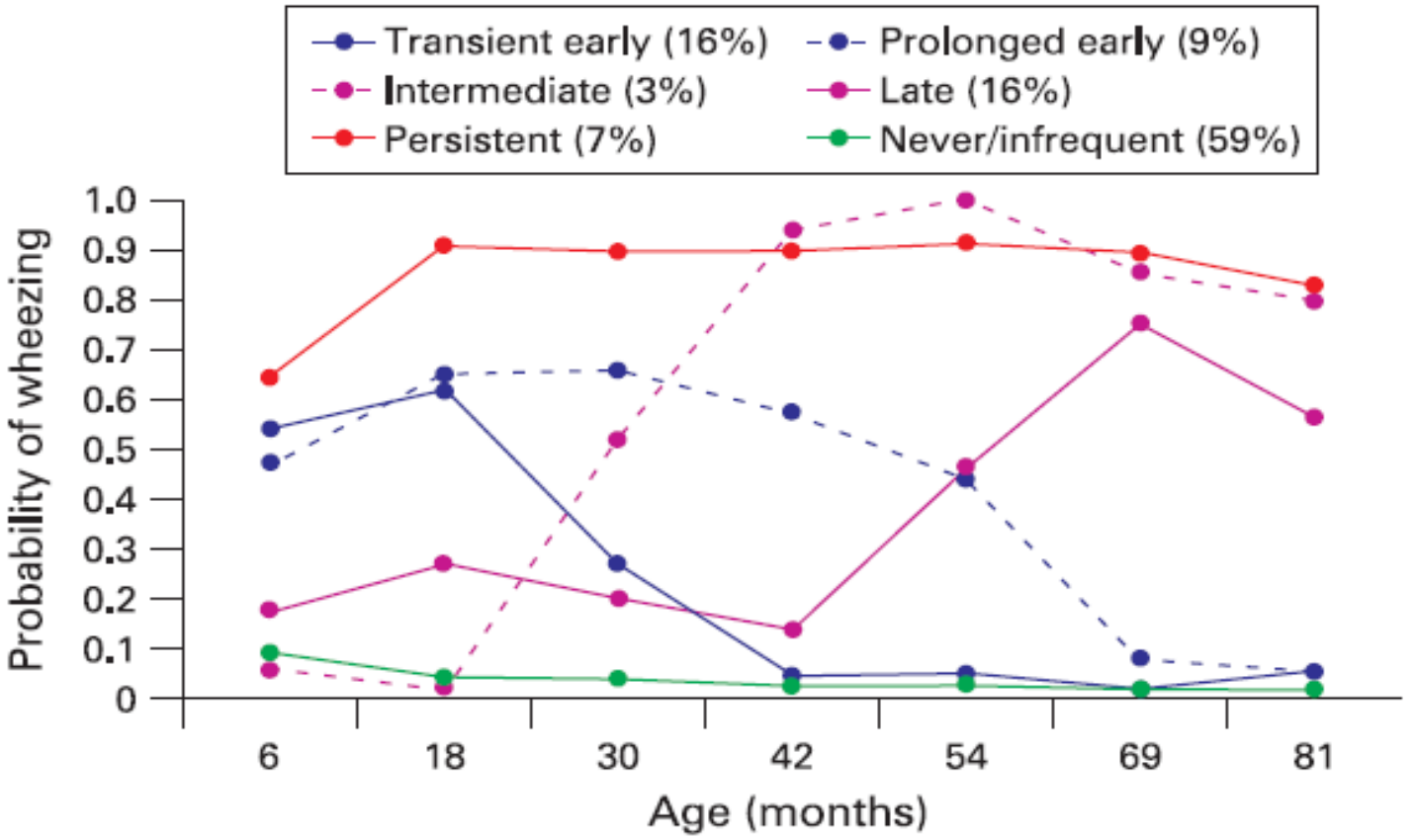

Figure 1 Estimated prevalence of wheezing at each time point from birth to 81 months for each of the six wheezing phenotypes identified by latent class analysis in 6265 children with complete data.

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Henderson et al, *Thorax* 2008;63:974-980

Avoiding confounding

- Follow up of trials
- **Temporal trends**
- **Ecological explanatory power**
- **Heterogeneity of confounding structure**
- Specificity
- Critical time periods
- Sibling and twin studies
- **Maternal versus paternal comparisons**
- **Instrumental variable approaches**

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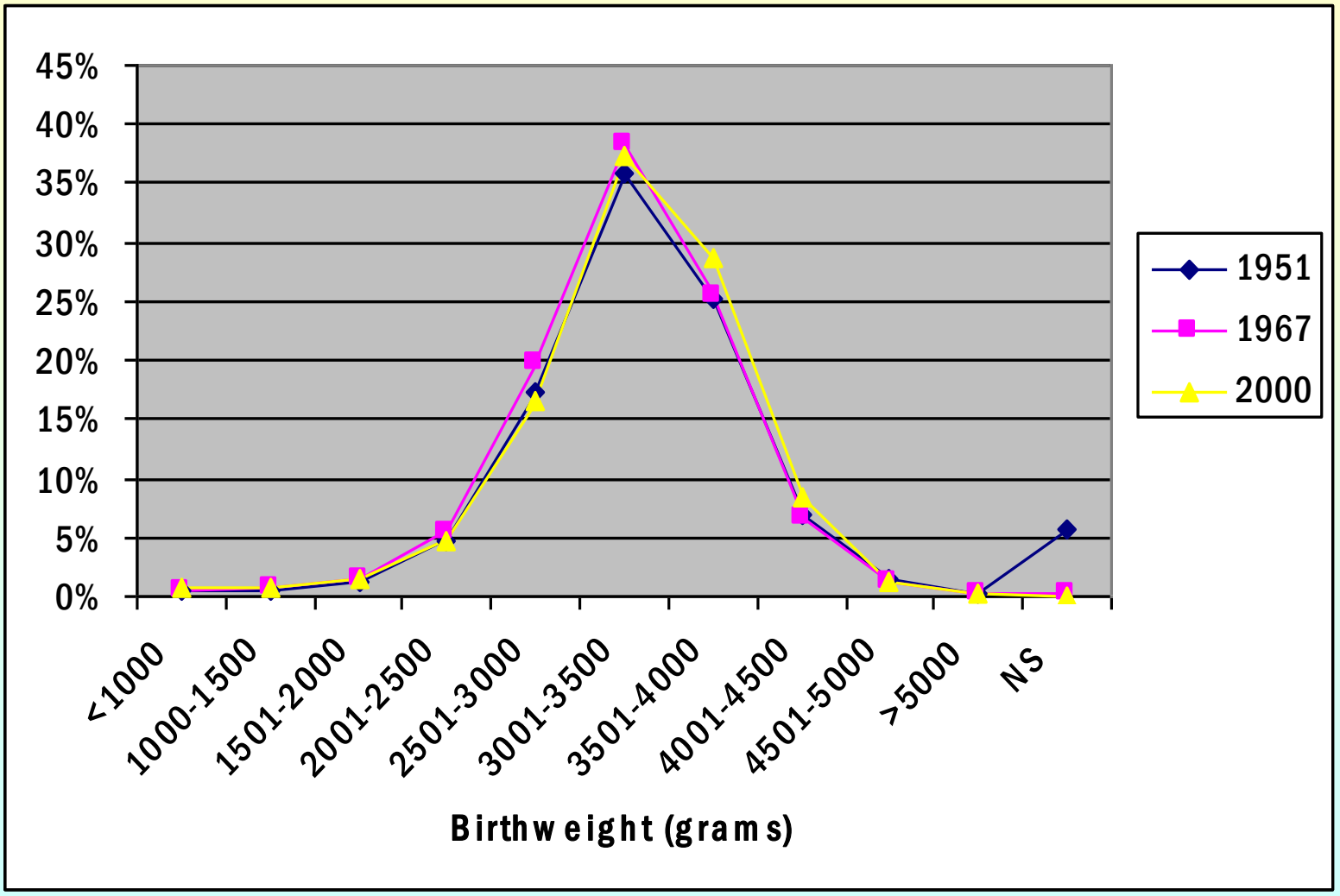
US Birthweight Distribution 1950-2000



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Personal Communication Professor John Lynch

Mean Birthweight and systolic blood pressure (INTERSALT)

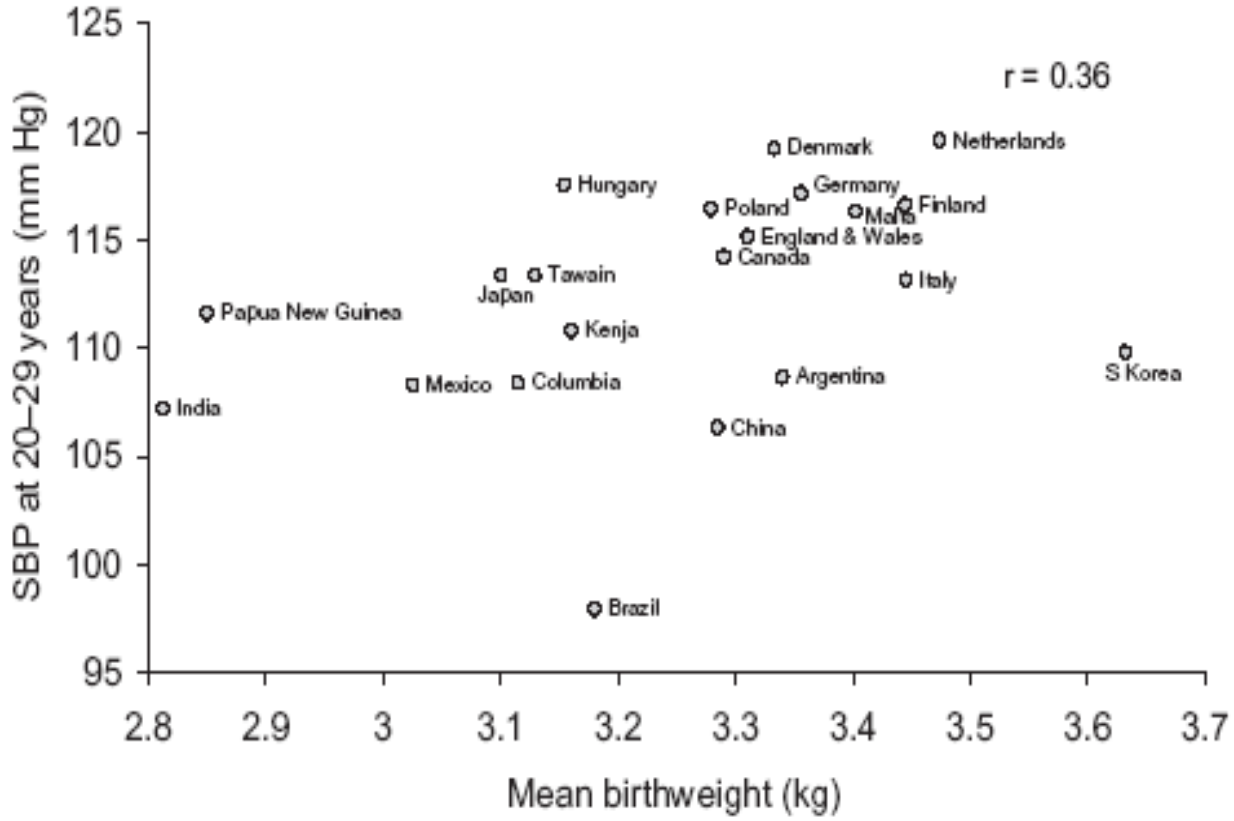

Figure 1 Association between SBP at 20–29 years and mean birthweight, for different countries included in the INTERSALT study

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Owen et al. *IJE* (2005)

Breastfeeding in ALSPAC and Pelotas 1993

- **Breastfeeding in infancy associated with more favourable outcomes in later life**
- **BUT most studies in cohorts, where breastfeeding shows strong social patterning**
- **? Biological or confounded?**

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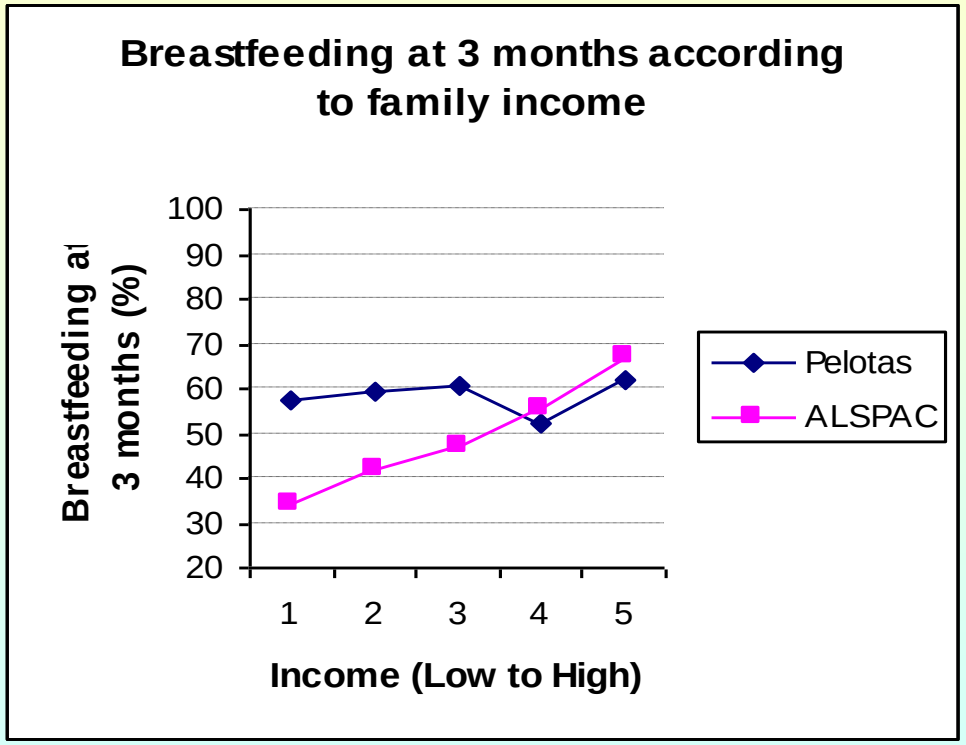
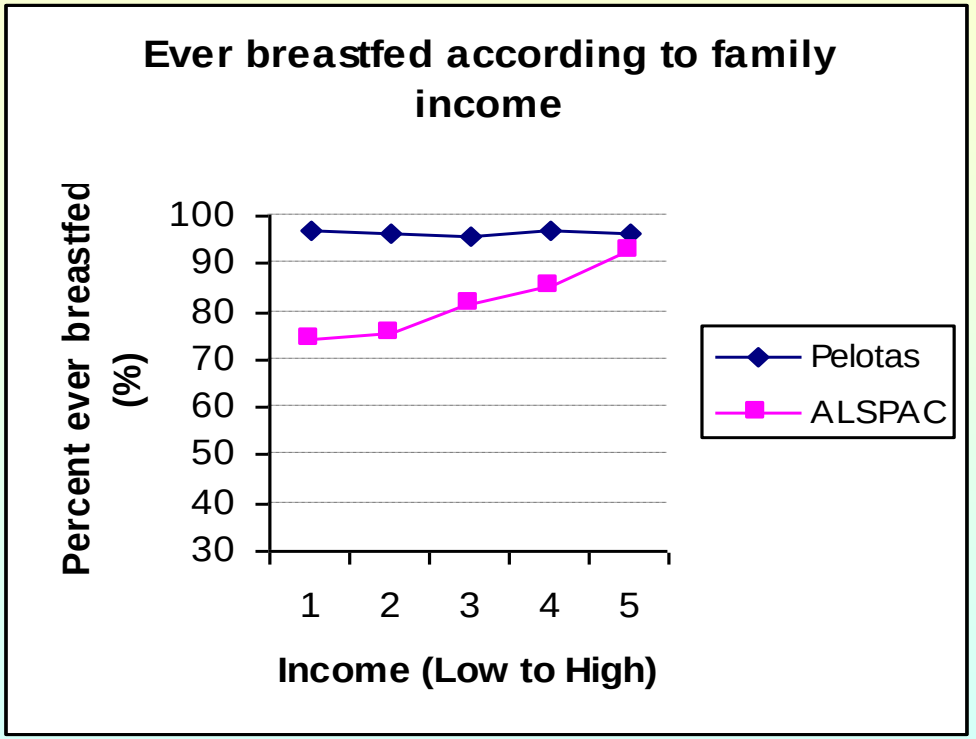
Breastfeeding in ALSPAC and Pelotas 1993





Confounding structure of the data different in the two cohorts

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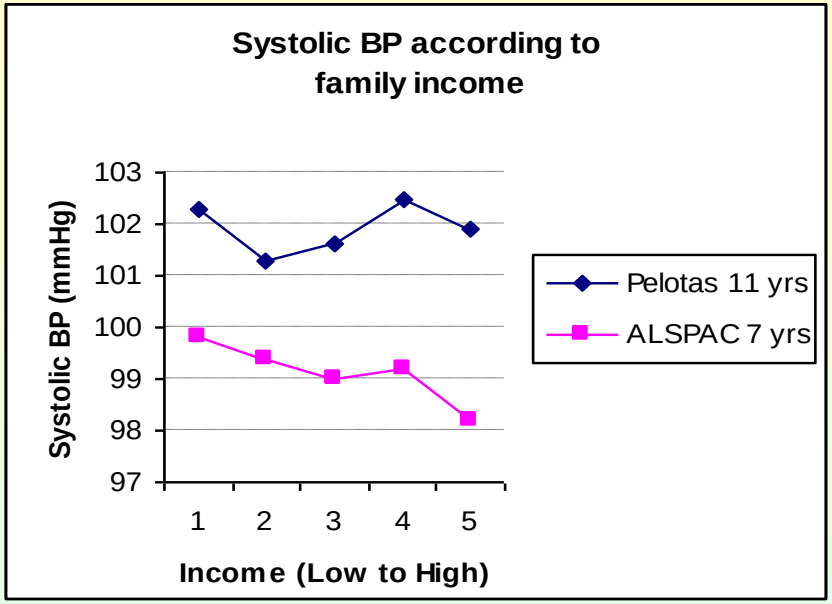
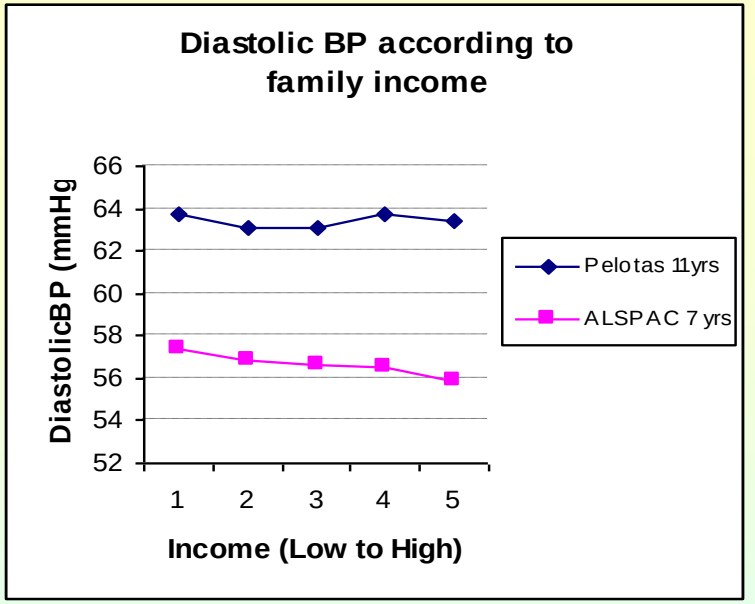
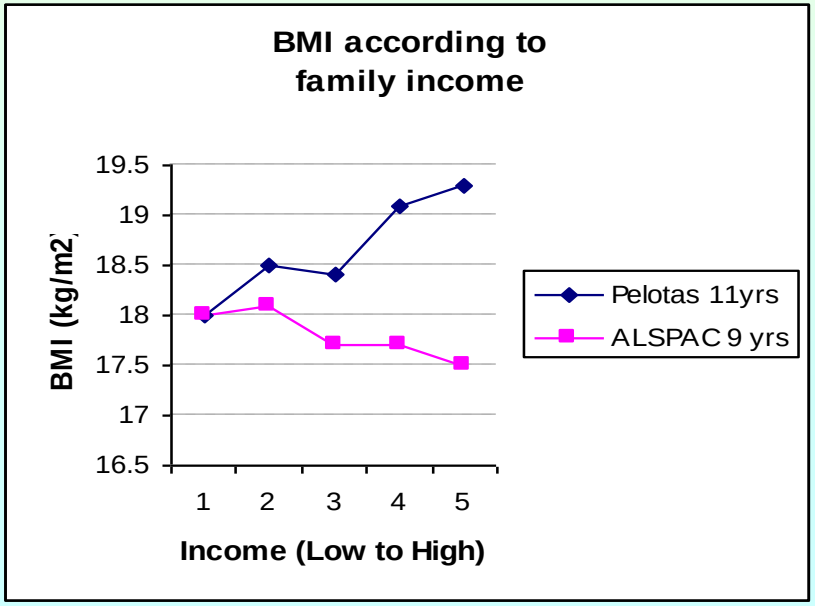
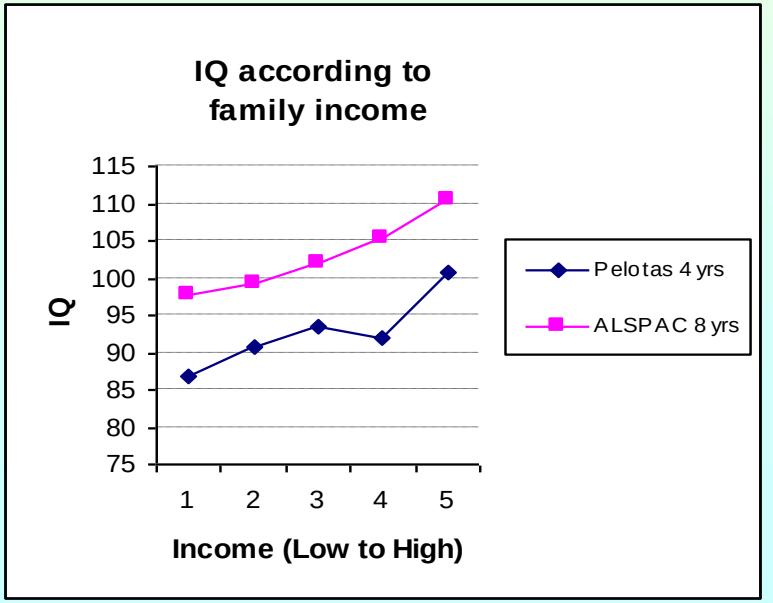
Brion et al 2010

Socioeconomic Patterning of Child Outcomes









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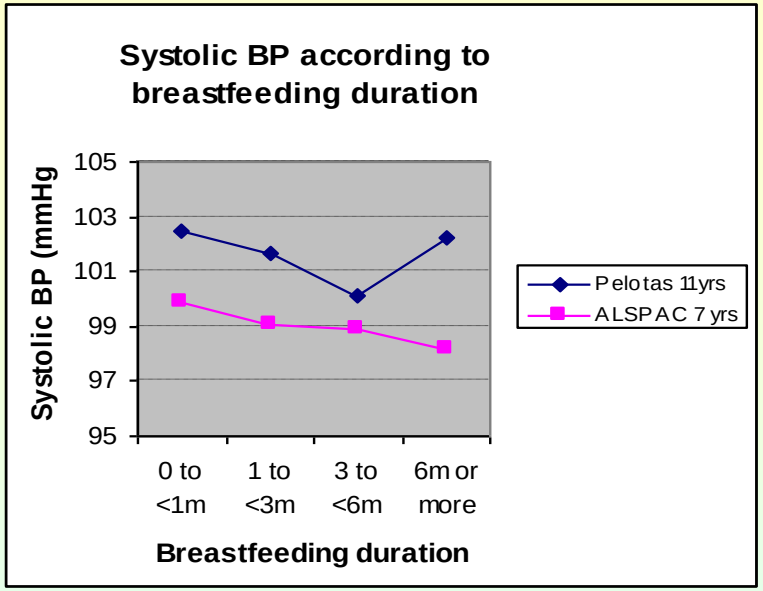
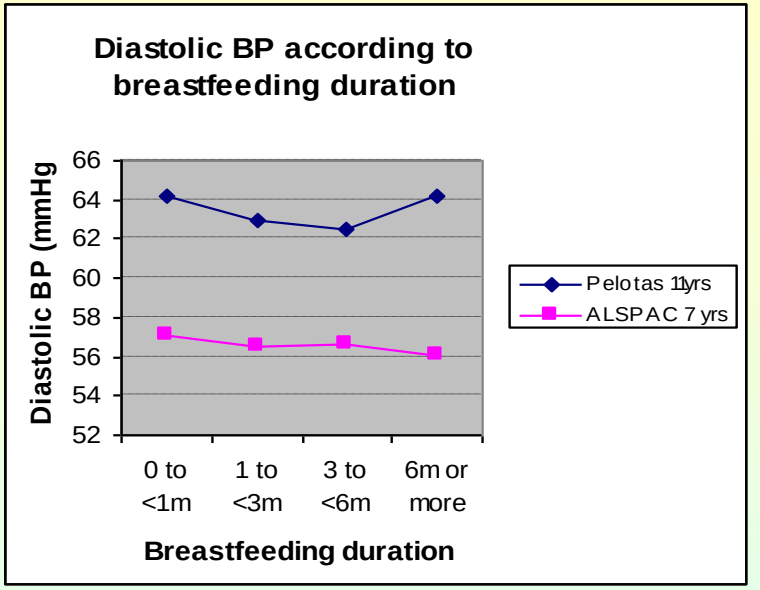
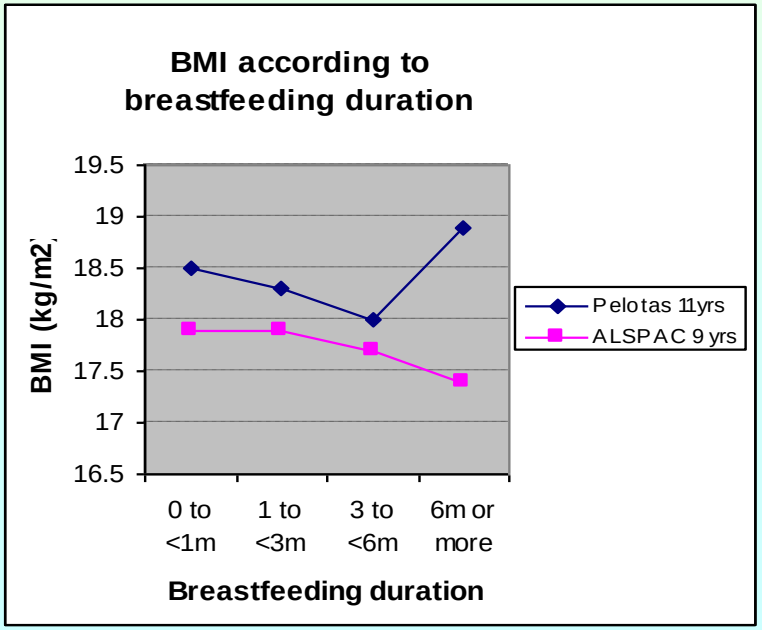
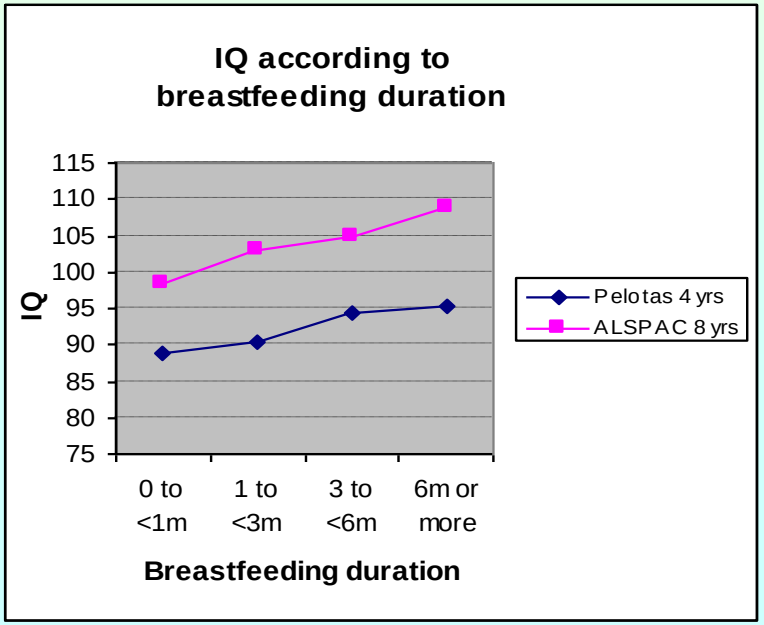
Breastfeeding and Child Outcomes









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Breastfeeding and outcomes

	ALSPAC	Pelotas	Belarus
	SES gradient	No SES gradient	Trial
BP	Inverse	No association	No effect
BMI	Inverse	No association	No effect
IQ	Higher IQ	Higher IQ	Higher IQ

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Brion et al 2010, Kramer et al 2008, 2009

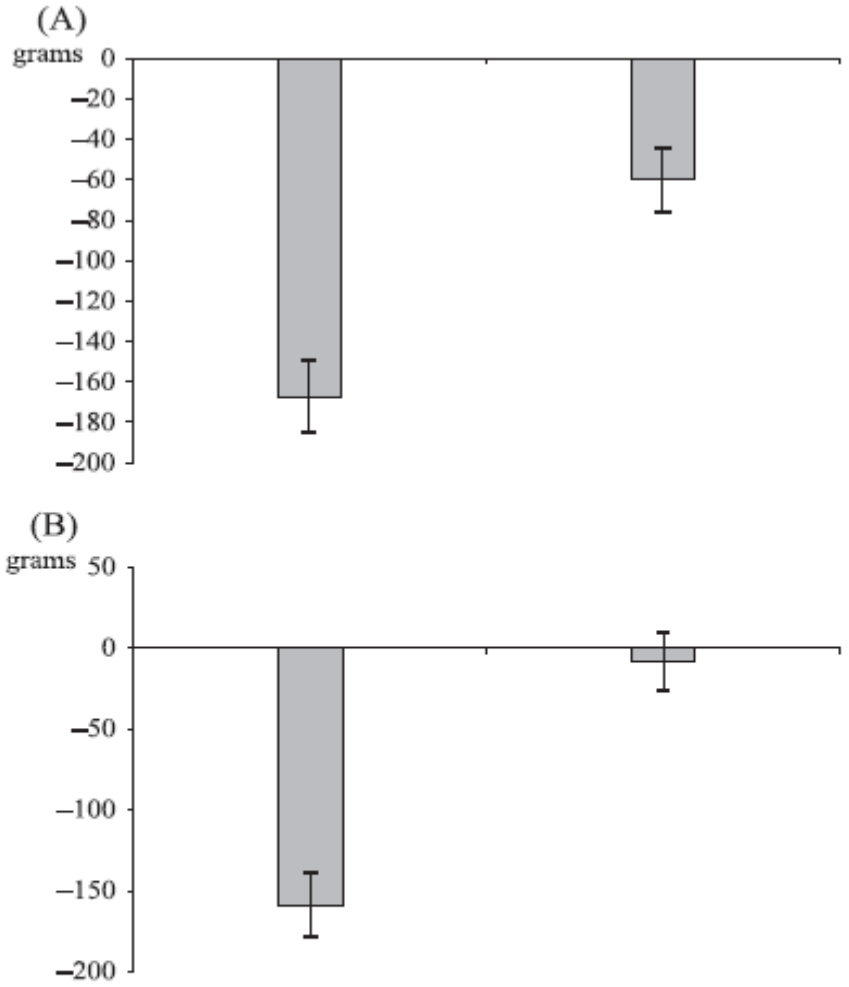

Fig. 4. (A) Effect of maternal and paternal smoking on offspring birth weight (difference in birth weight between offspring of smokers and non-smokers in grams). (B) Effect of maternal and paternal smoking during pregnancy on offspring birth weight (in grams) with mutual adjustment.

Maternal smoking and offspring birth weight

- **Maternal smoking associated with greater decrease in birth weight than paternal smoking**

- **Paternal smoking has little effect after adjusting for maternal smoking**

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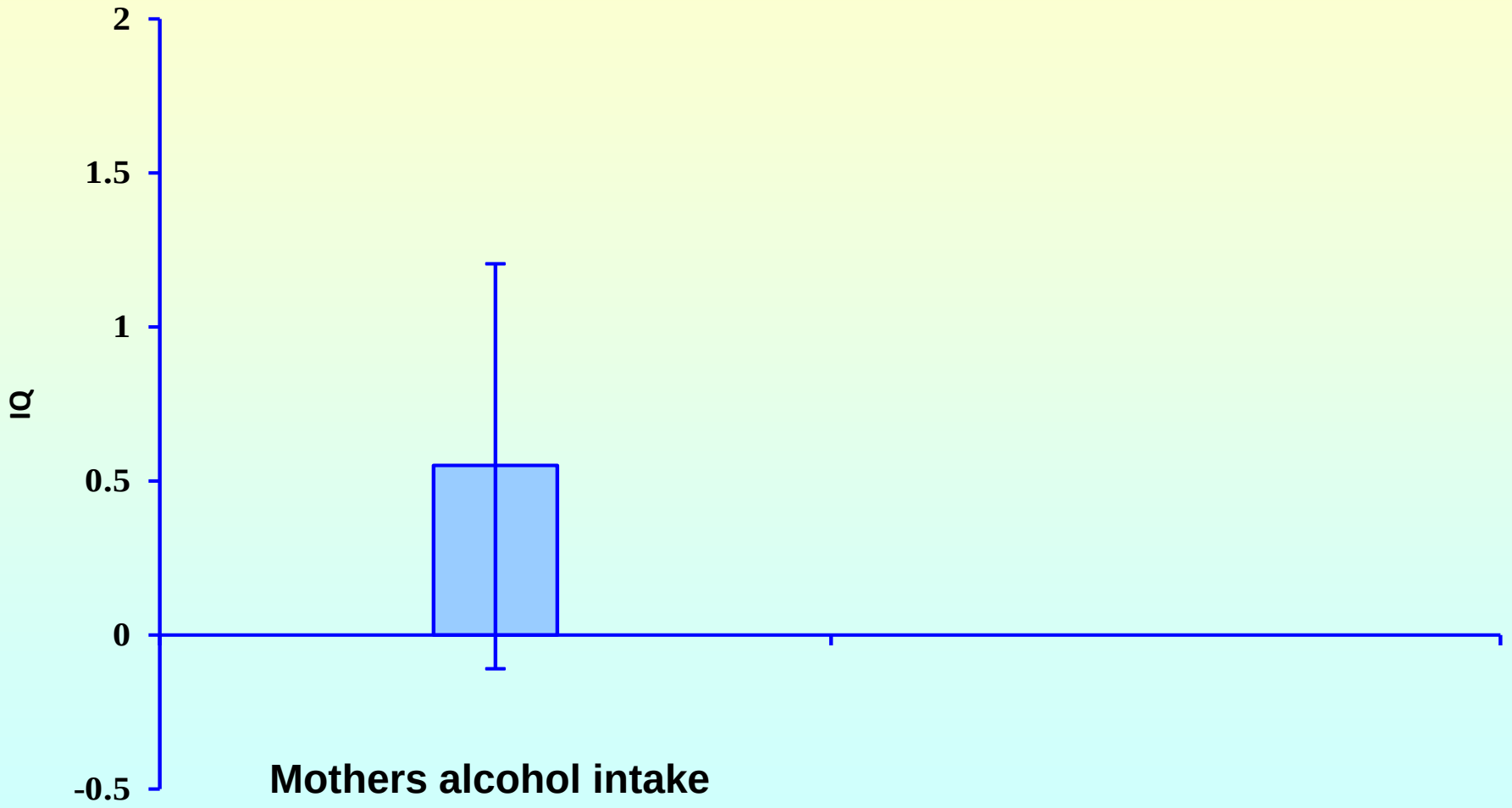
Davey Smith, *BCPT 2*008;**102**:245-256

Maternal alcohol intake (during the first 3 months of pregnancy) and offspring IQ



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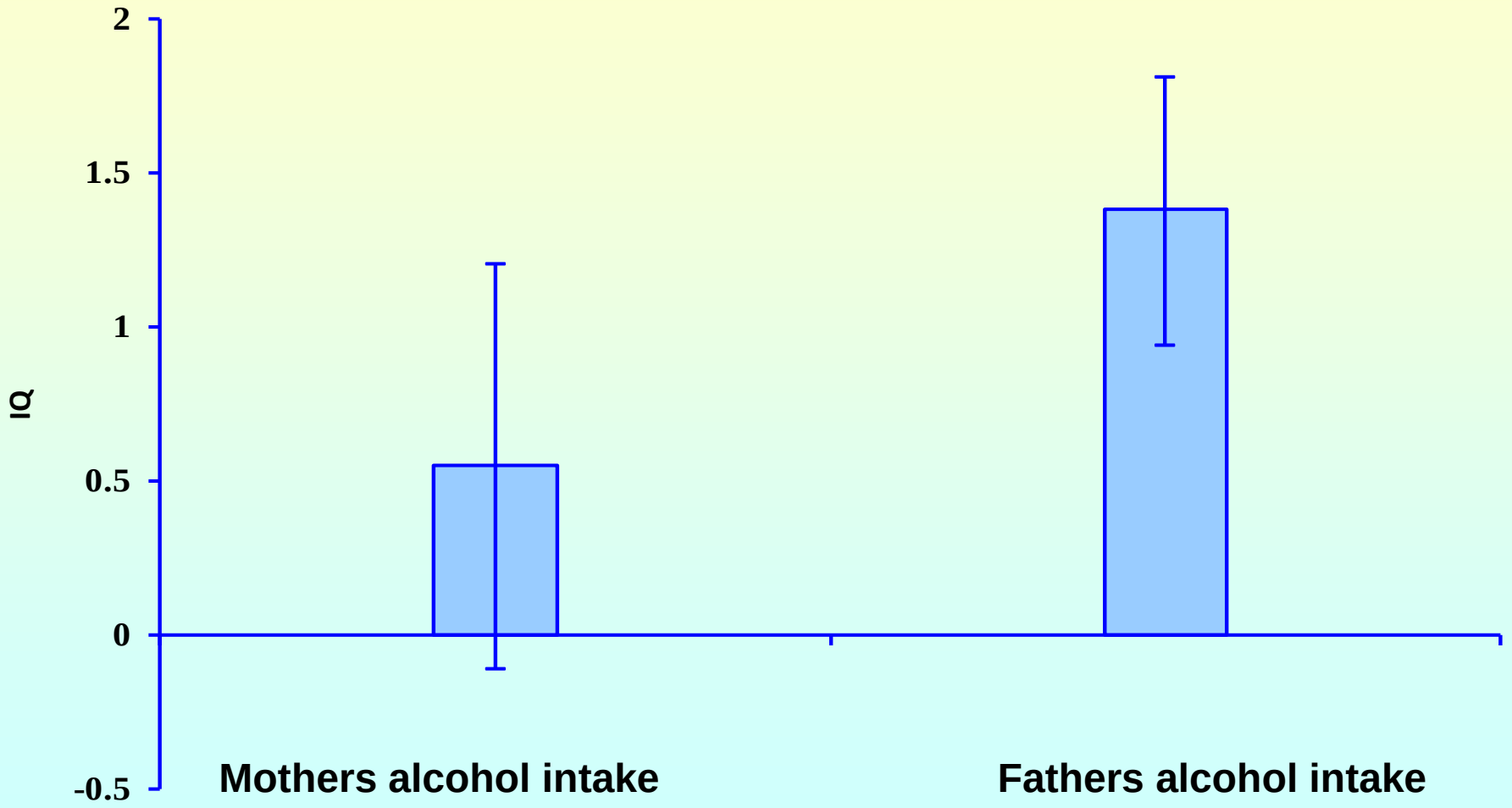
.....greater effect with fathers' alcohol intake



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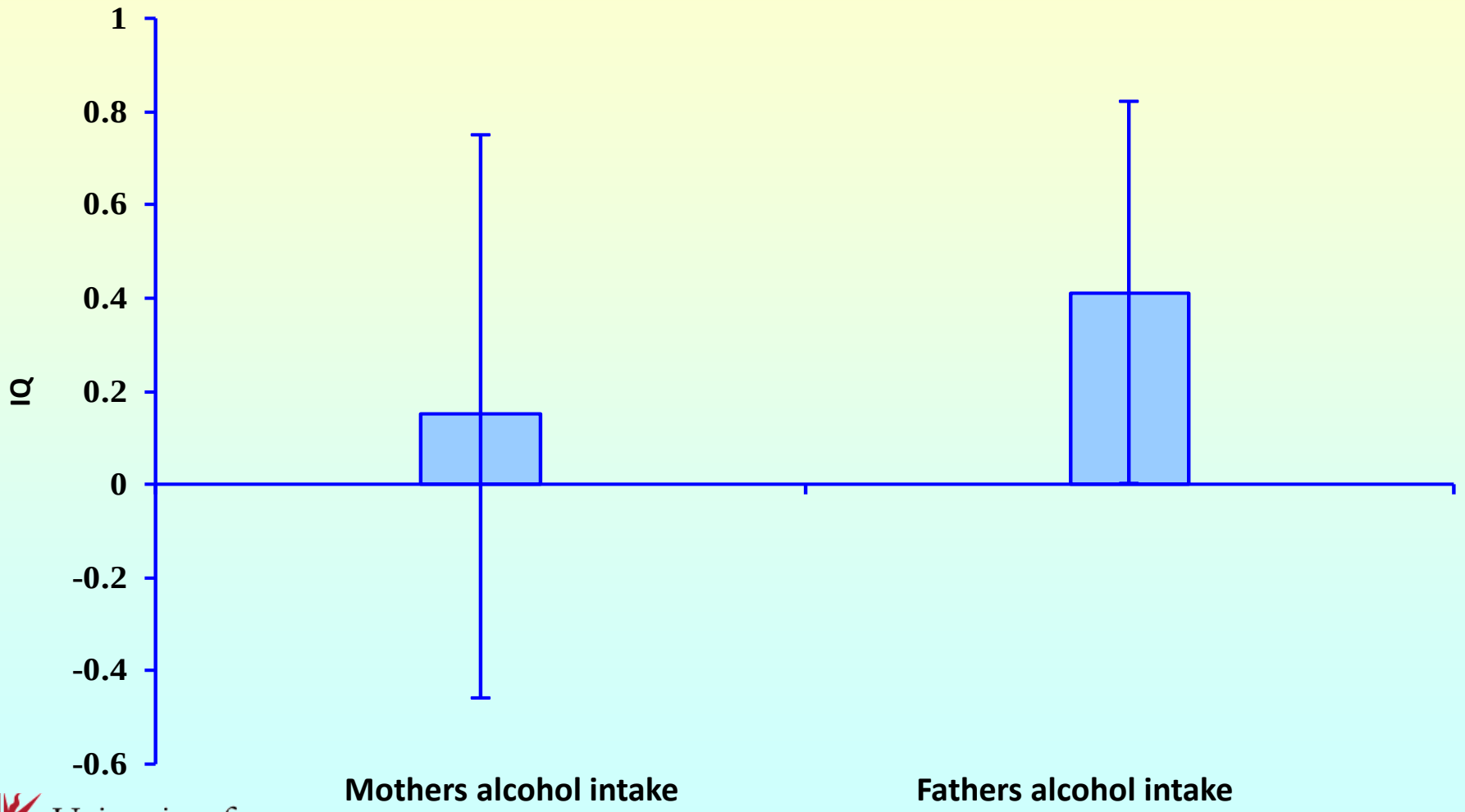
Mothers' and fathers' alcohol intake (during the first 3 months of pregnancy) in same model



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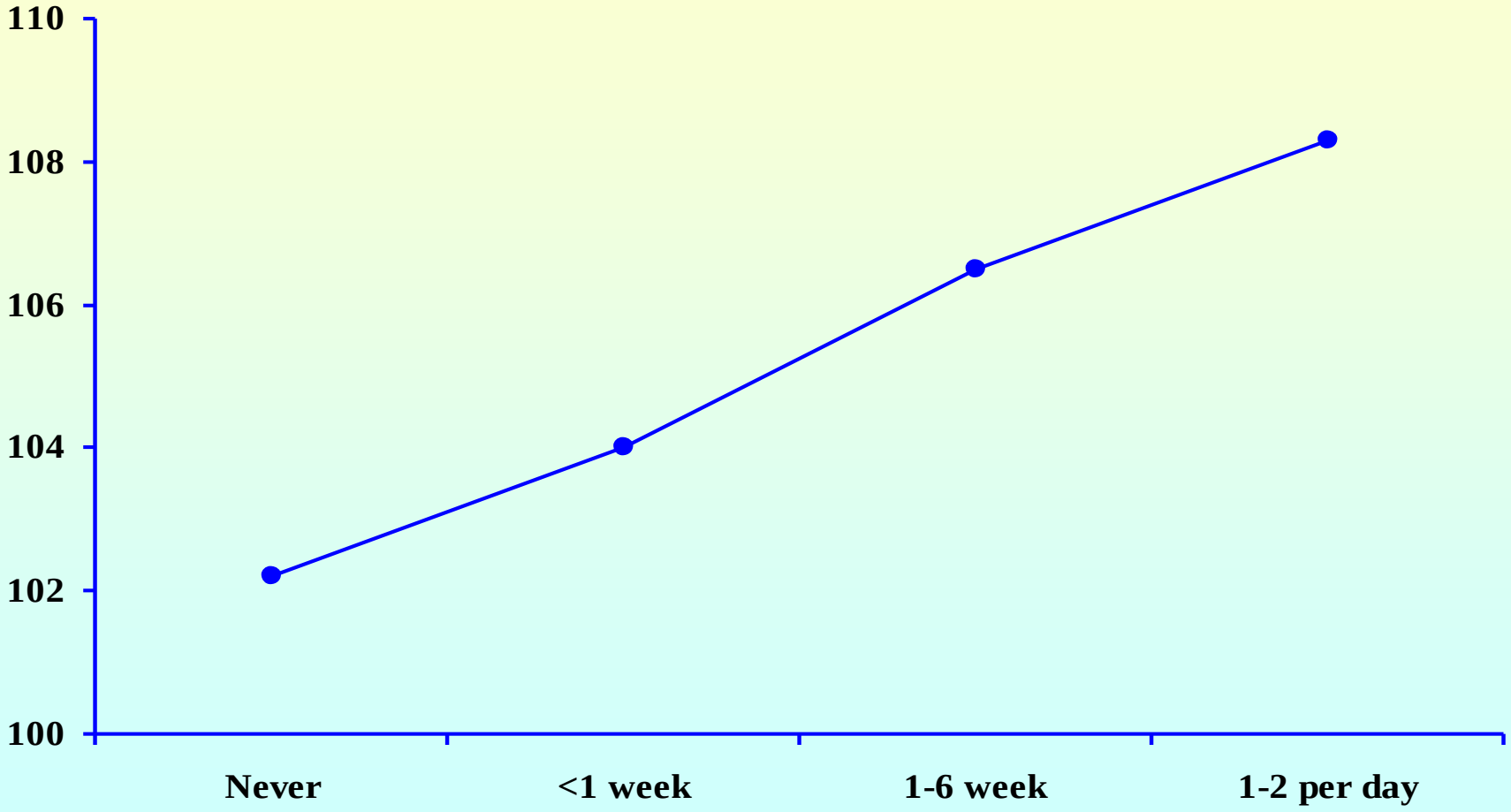
Offspring IQ and fathers' drinking during mothers pregnancy



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Instrumental variables

Need to find a variable which:

- **is associated with the exposure of interest**
- **is not related to confounders**
- **has no direct effect on the outcome of interest (i.e. affects the outcome only indirectly through the exposure)**

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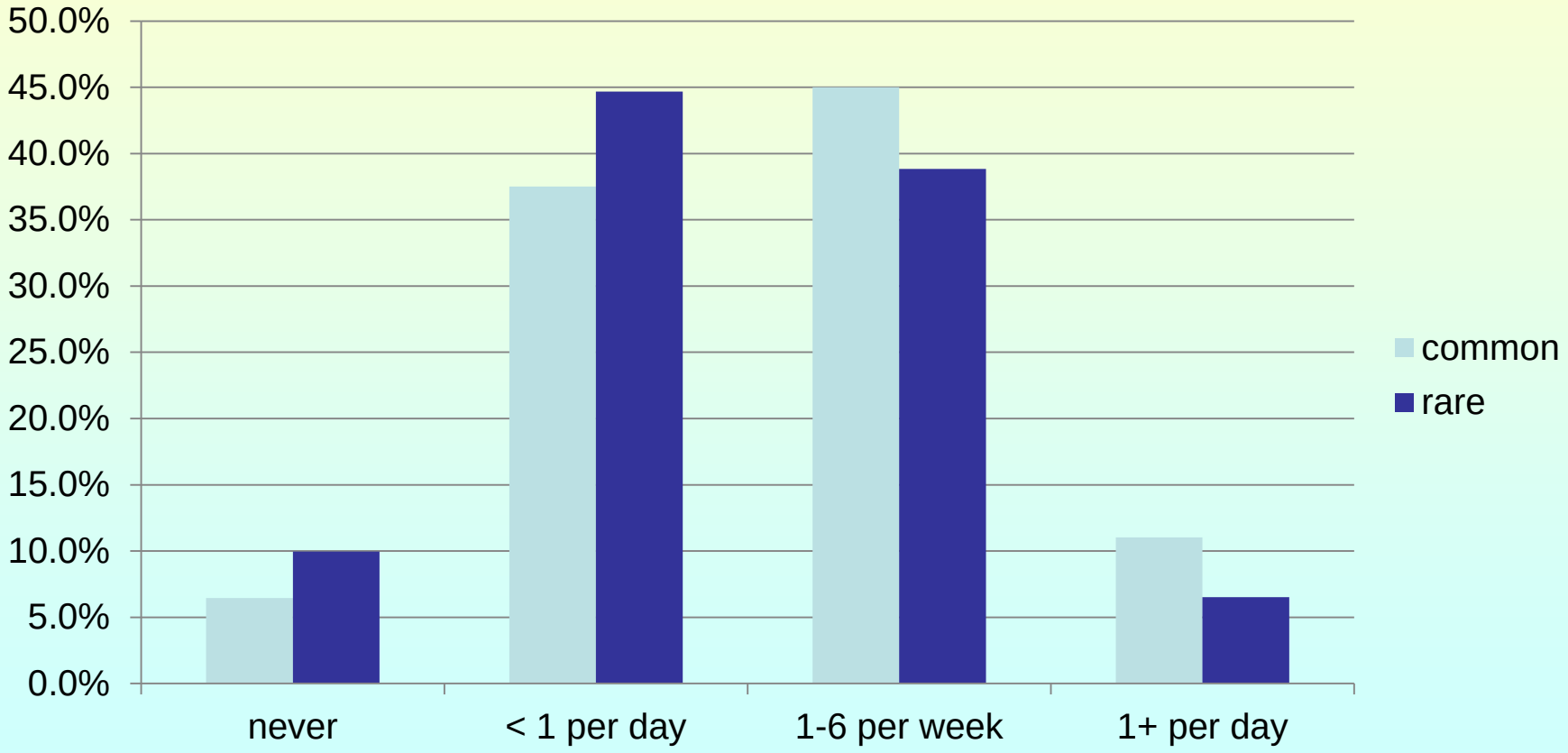
Women carrying rare allele of ADH1B tend to drink less prior to recognition of pregnancy



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Zuccolo et al, Human Molecular Genetics 2009

Results of observational analysis: Women who drank more prior to recognition of pregnancy tended to have children with higher Key stage 2 (age 11) scores

- **Average point change in KS2 score for increasing drinking by one category:**
- **Unadjusted 1.37 (0.13) $p < 0.00001$**
- **Adjusted 0.37 (0.12) $p=0.002$**

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Mendelian randomization (IV) results

- **Using the rare allele as an instrument for maternal alcohol intake estimates an average 1.96 (se=0.57, p=0.0006) points *lower* Key Stage 2 score per category of maternal drinking during 1st trimester**

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Conclusions

- Epidemiological of early life important
- But drawing causal inferences challenging
- Chance, bias and confounding are issues
- Traditional and novel approaches required

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