Are pre-adult exposures causally and importantly related to adult chronic disease?

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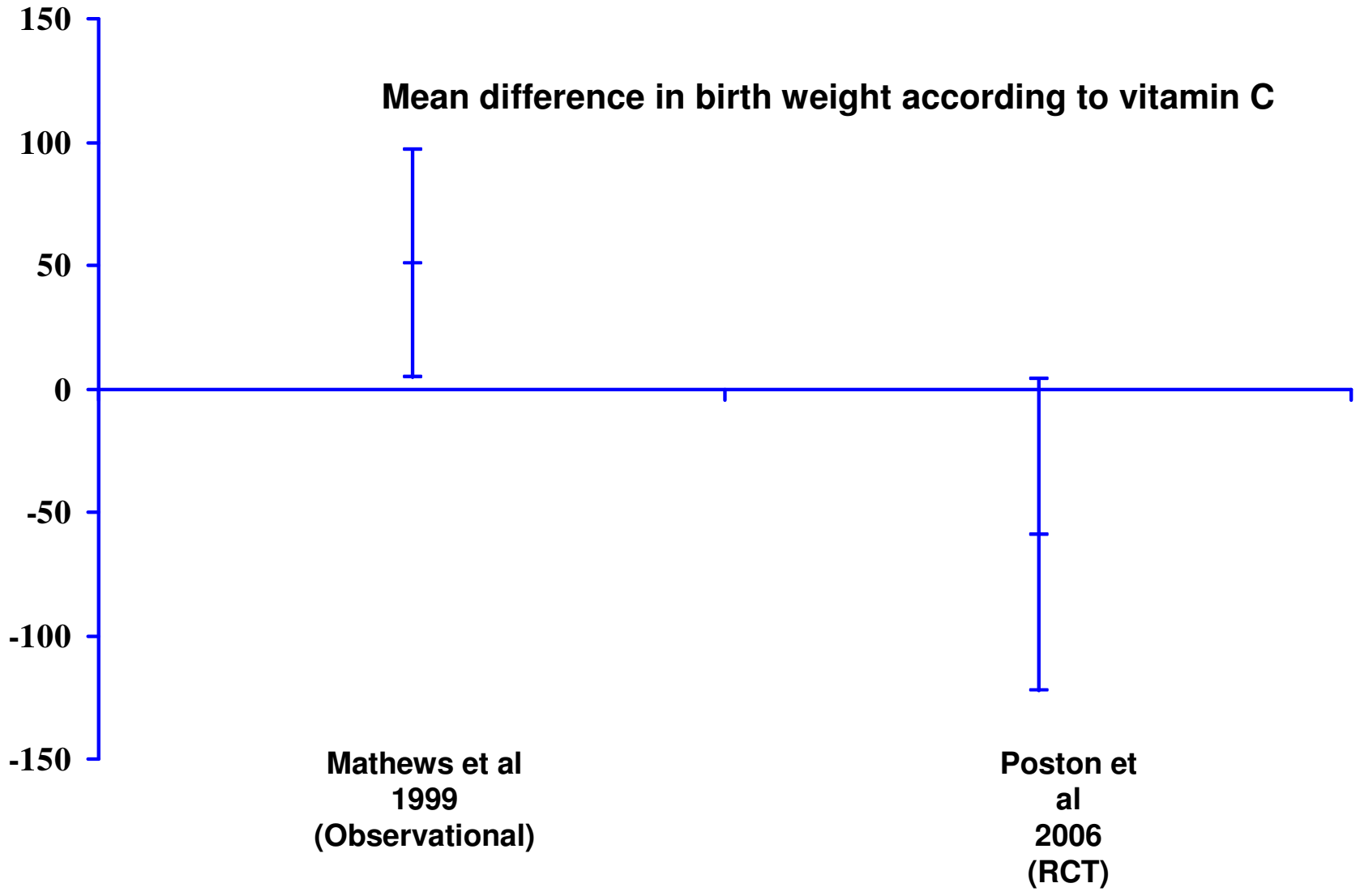
Difficulties

- Resources for very large sample sizes
- Selective loss to follow-up
- Retrospective report of exposure
- Change in exposure over life course
- Relevance to contemporary cohorts
- Confounding
- Identifying modifiable exposures

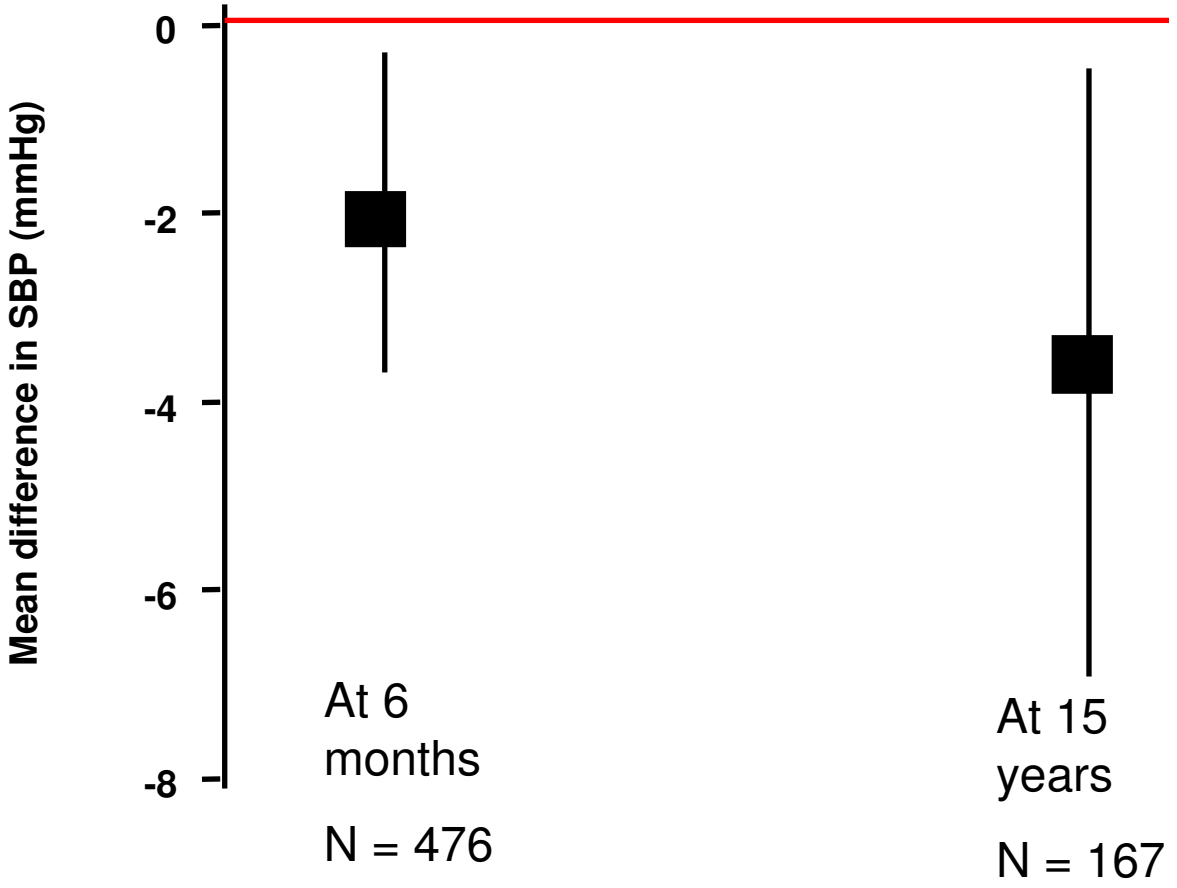
Association of maternal dietary vitamin C intake & birth weight



RCTs and pre-adult exposures for adult disease

- Rare
- Underpowered
- Loss to follow-up
- Contamination – revelation (unblinding) of randomised arm
- Relevance to later cohorts

The effect of randomisation to low sodium formula in infancy



Geleijnse JM, Hofman A, et al. Hypertension 1997; 29:913-17

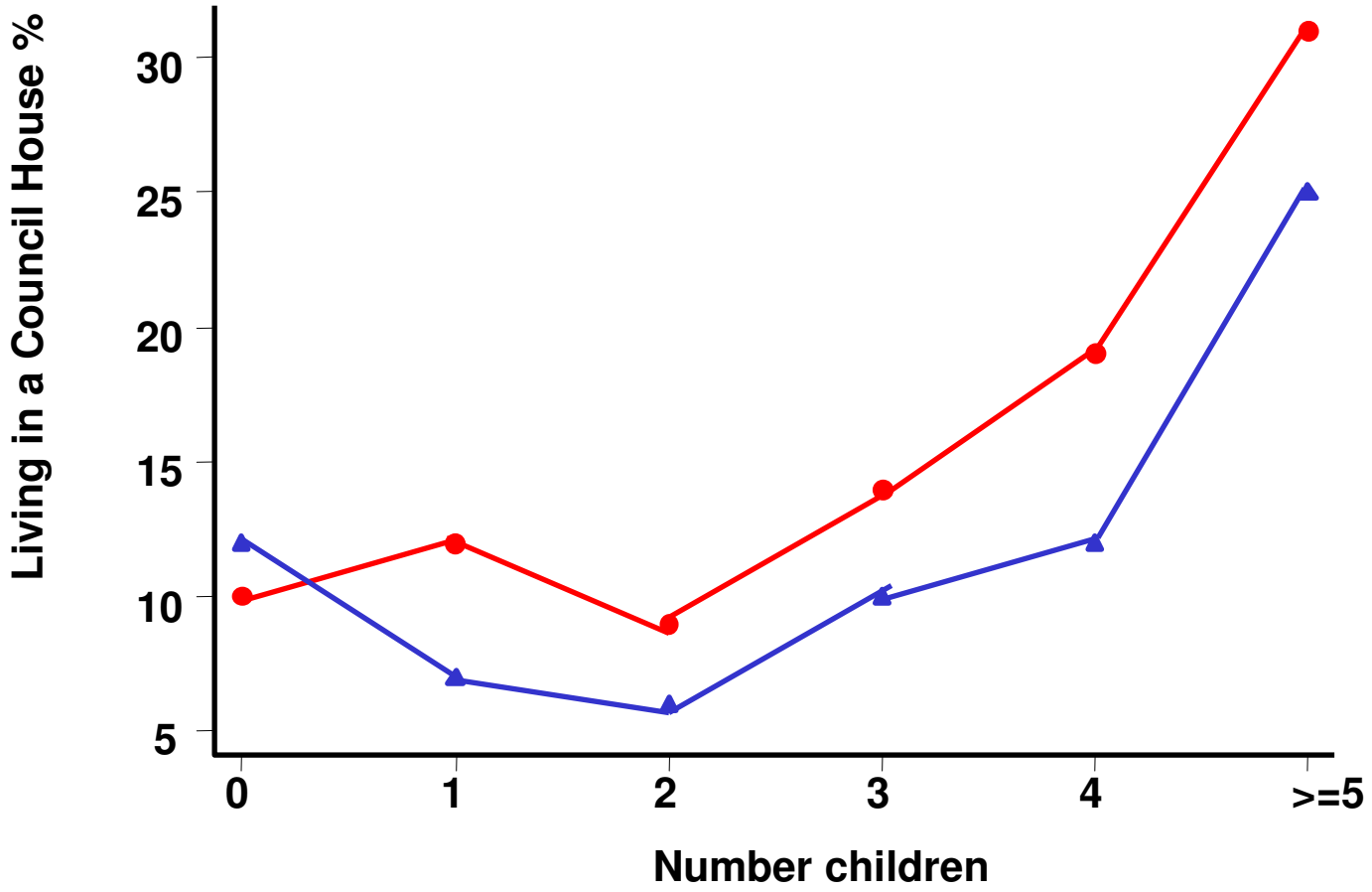
Alternative study designs

- Family based studies
- Mendelian randomisation

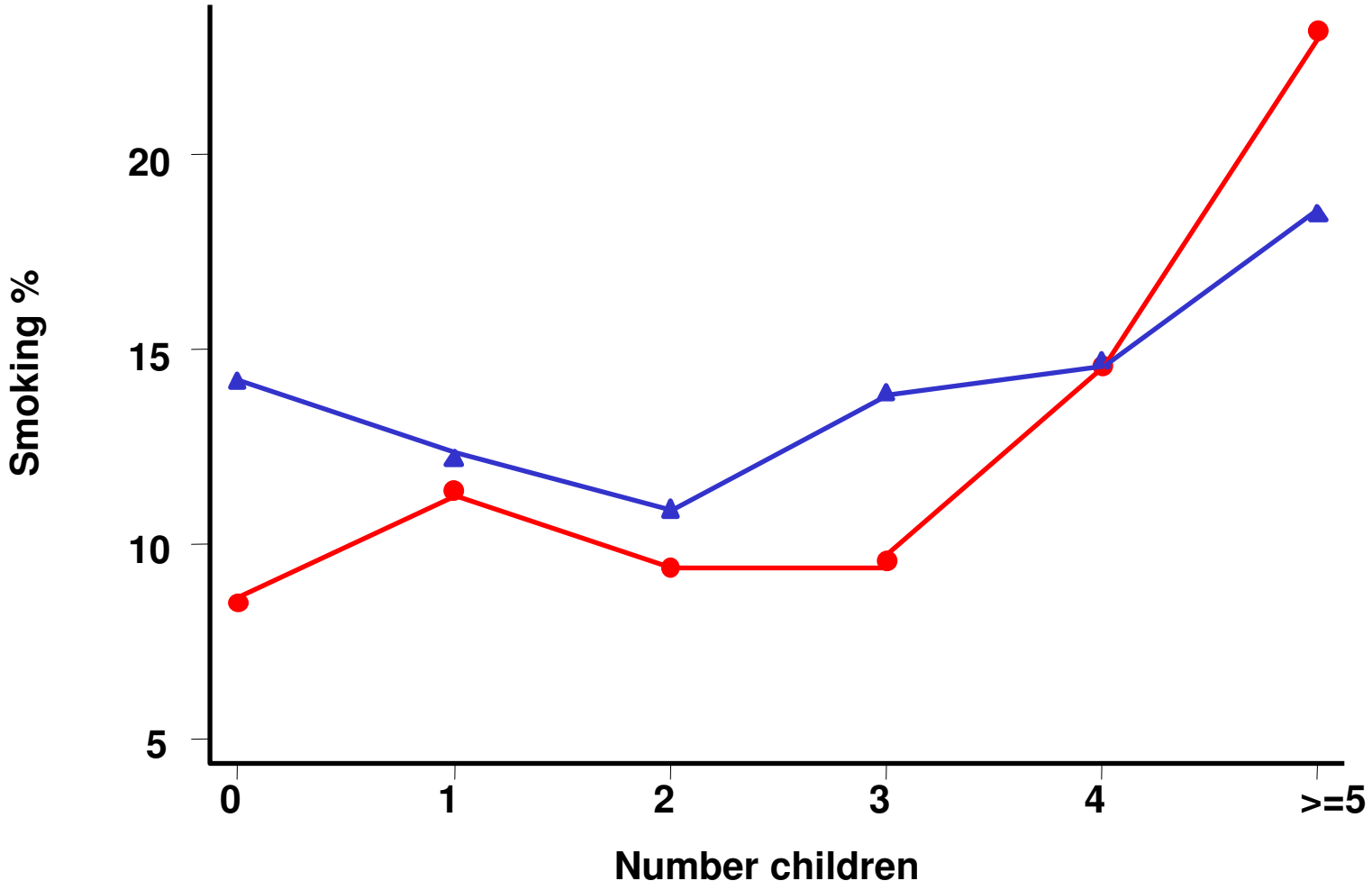
Why do women who have had more pregnancies have an increased risk of CHD?

Lawlor DA, et al. Circulation 2003

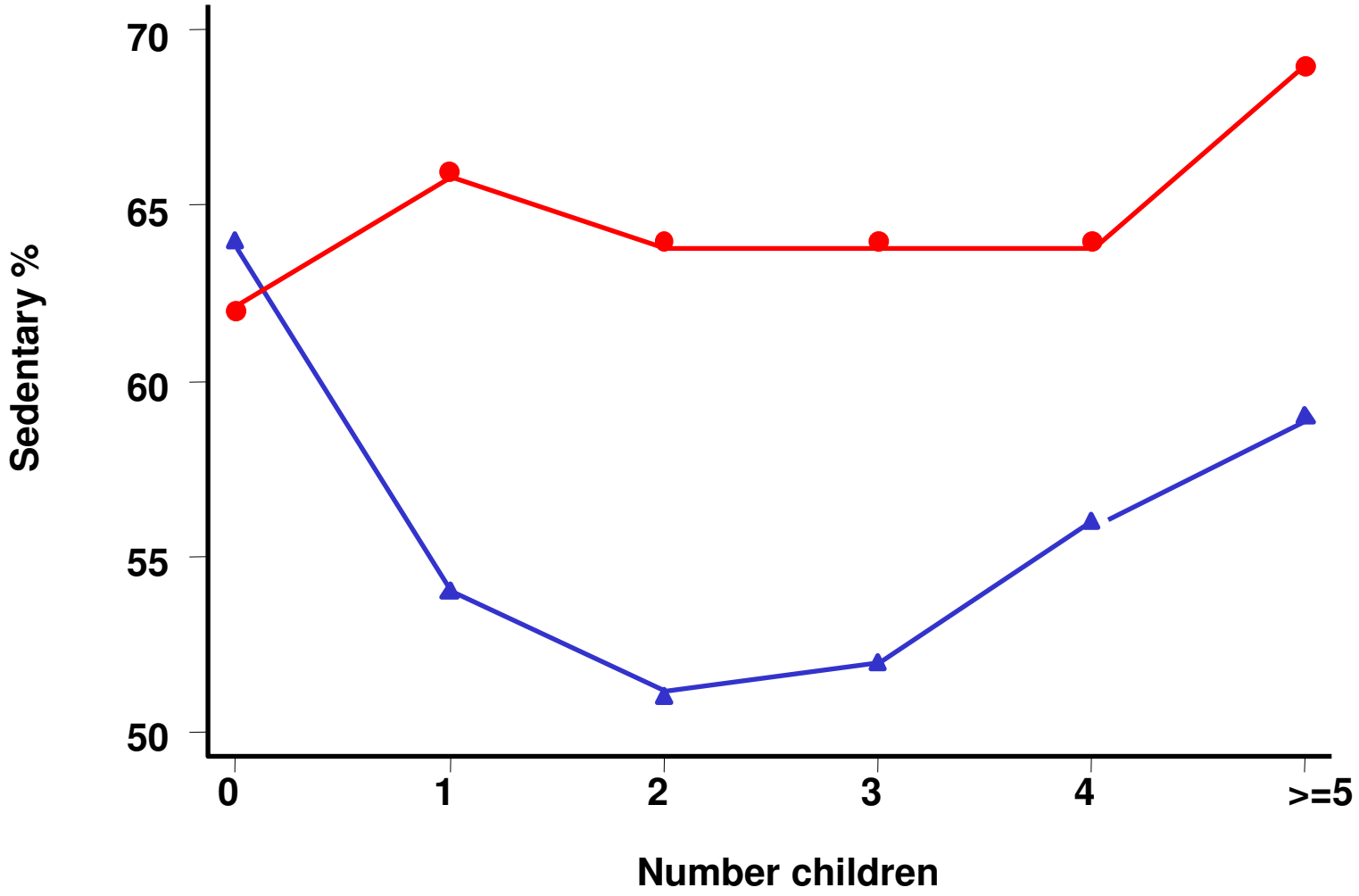
Living in council housing by number of children



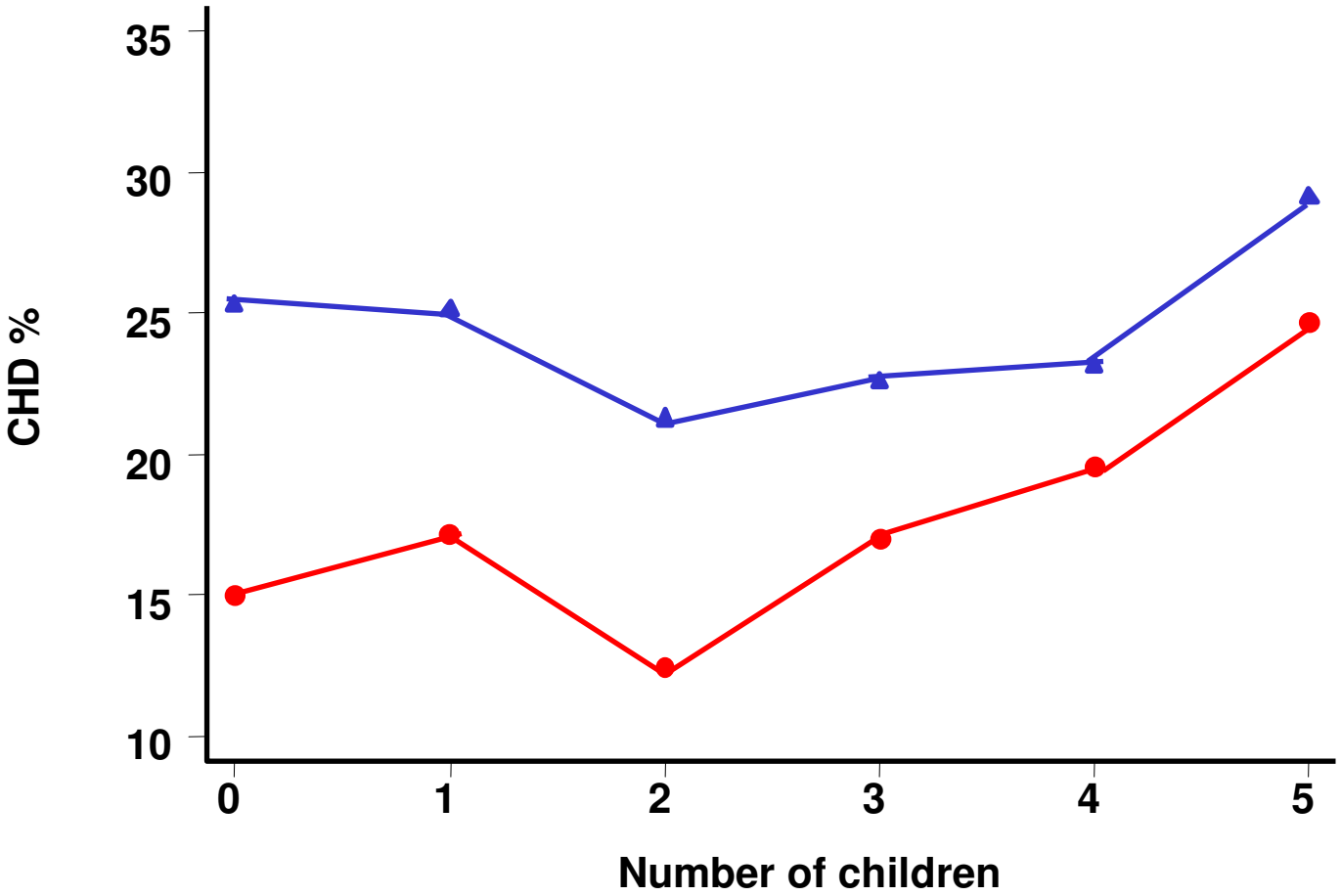
Smoking by number of children



Sedentary behaviour by number of children

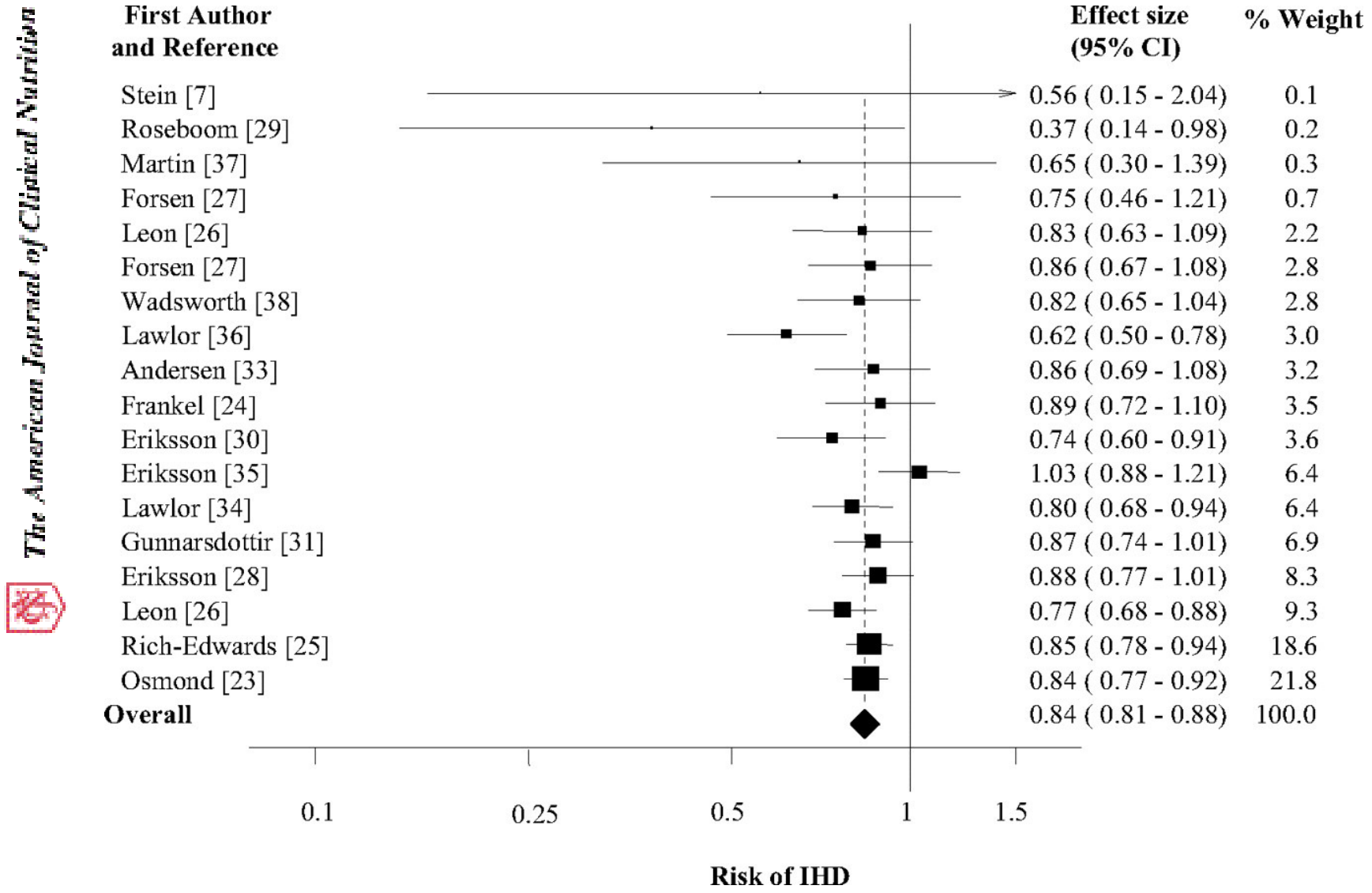


CHD by number of children



Intrauterine growth and CHD risk

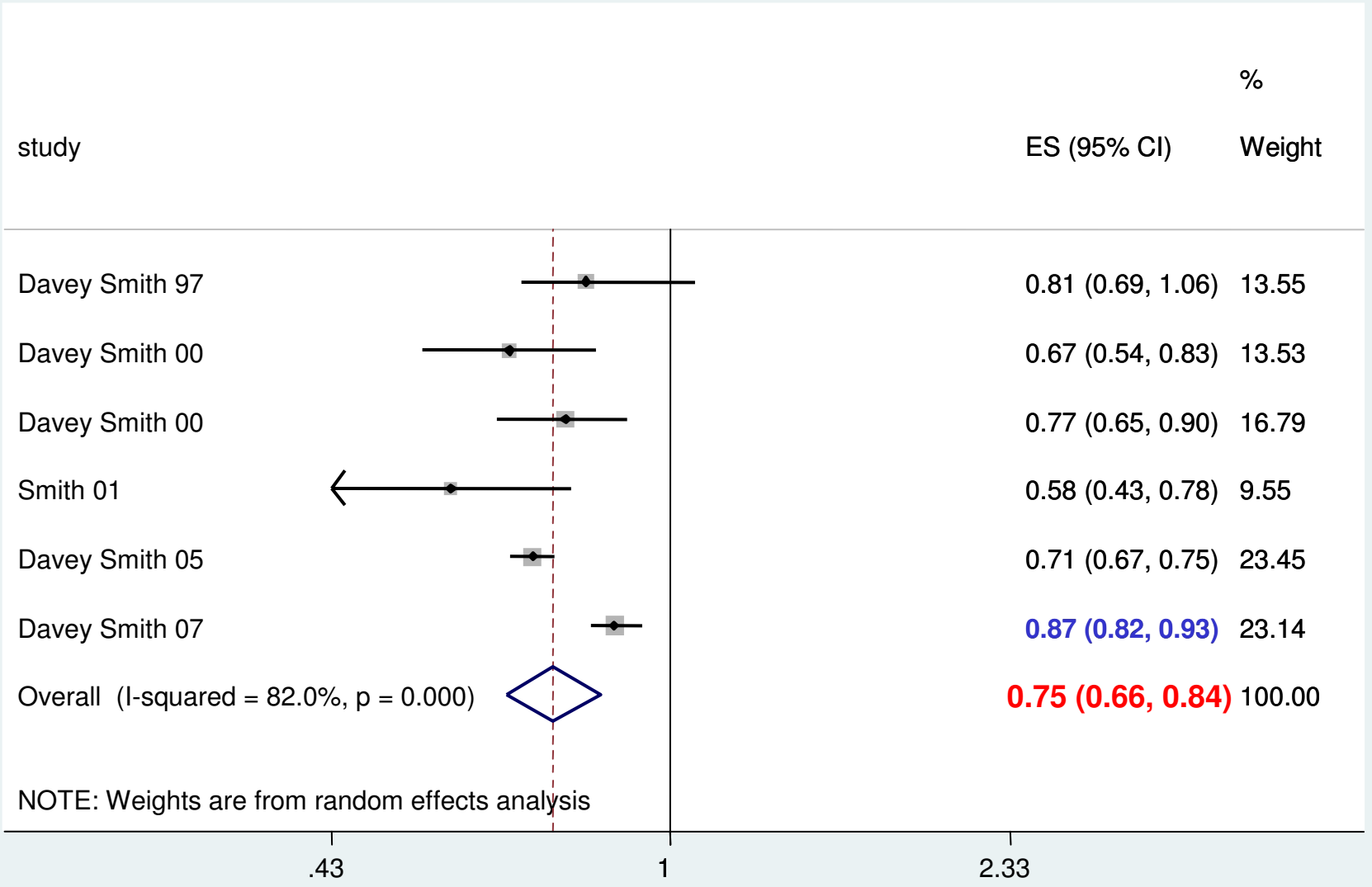
Relative risks for risk of CHD associated with birth weight



Huxley, R. et al. Am J Clin Nutr 2007;85:1244-1250

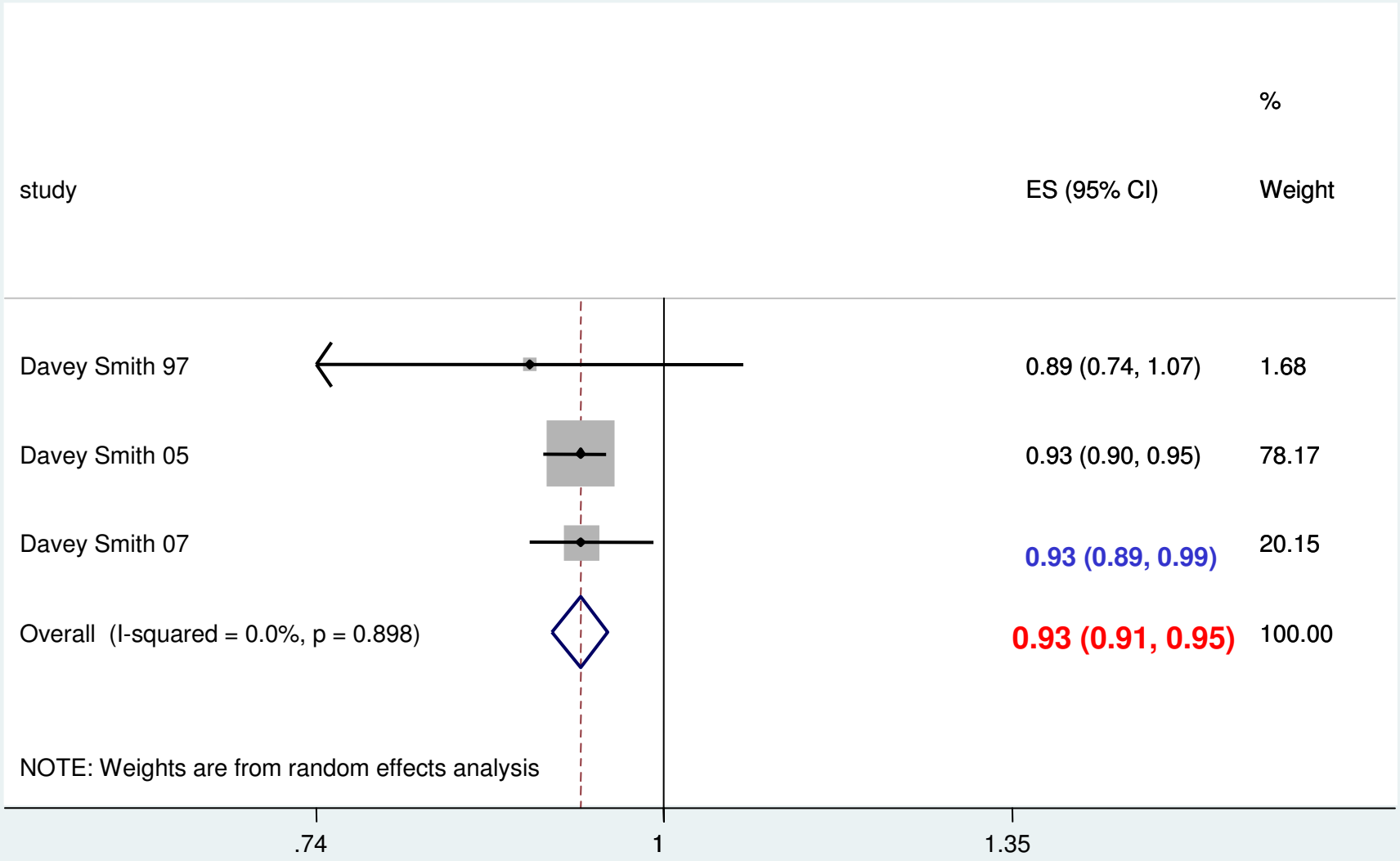
- Fetal undernutrition → ‘programming’
- Fetal insulin hypothesis: genetics
- Confounding: SEP, smoking

Offspring birth weight with mother's risk of CHD



Davey Smith G, Hypponen E, Power C, Lawlor DA. *AJE* 2007

Offspring birth weight with father's risk of CHD

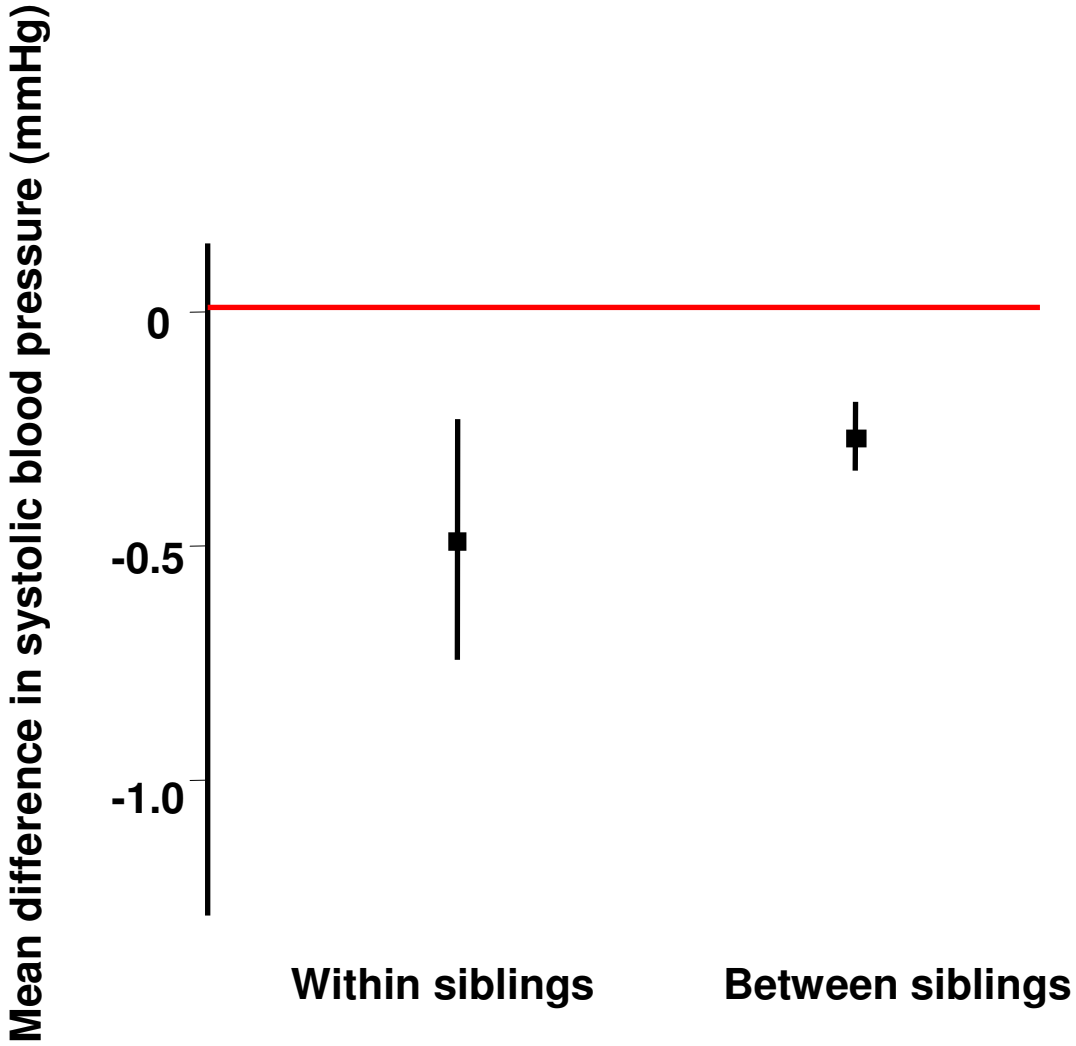


Davey Smith E, Hypponen E, Power C, Lawlor DA. *AJE* 2007

Swedish conscript examination data for 386, 485 men from 331, 089 families linked to birth registry data

Lawlor DA, Hubinette A, Tynelius P, Leon DA, Davey Smith G, Rasmussen F. *Circulation* 2007

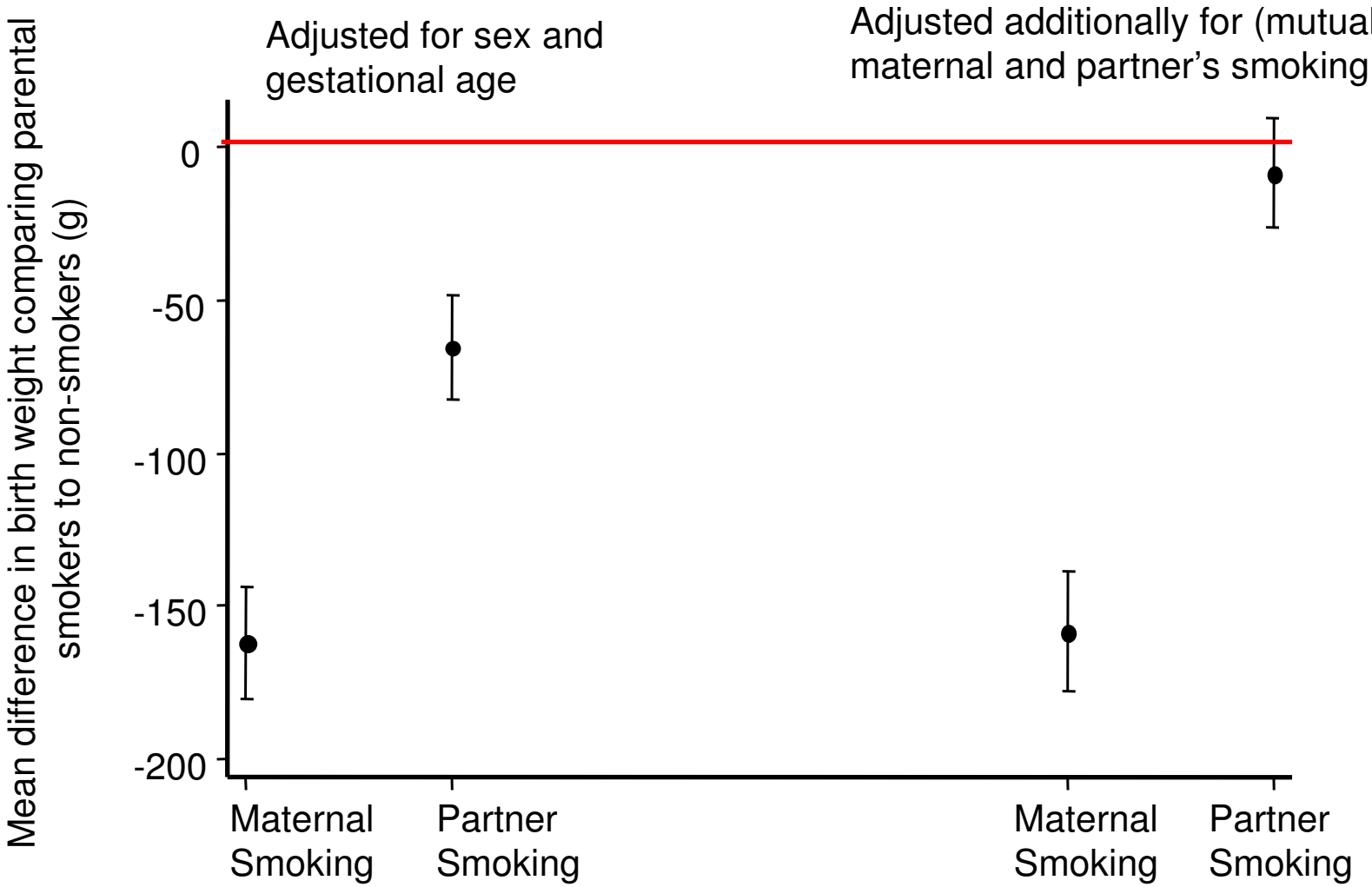
Mean difference in blood pressure at age 18 years for a 1kg greater birth weight



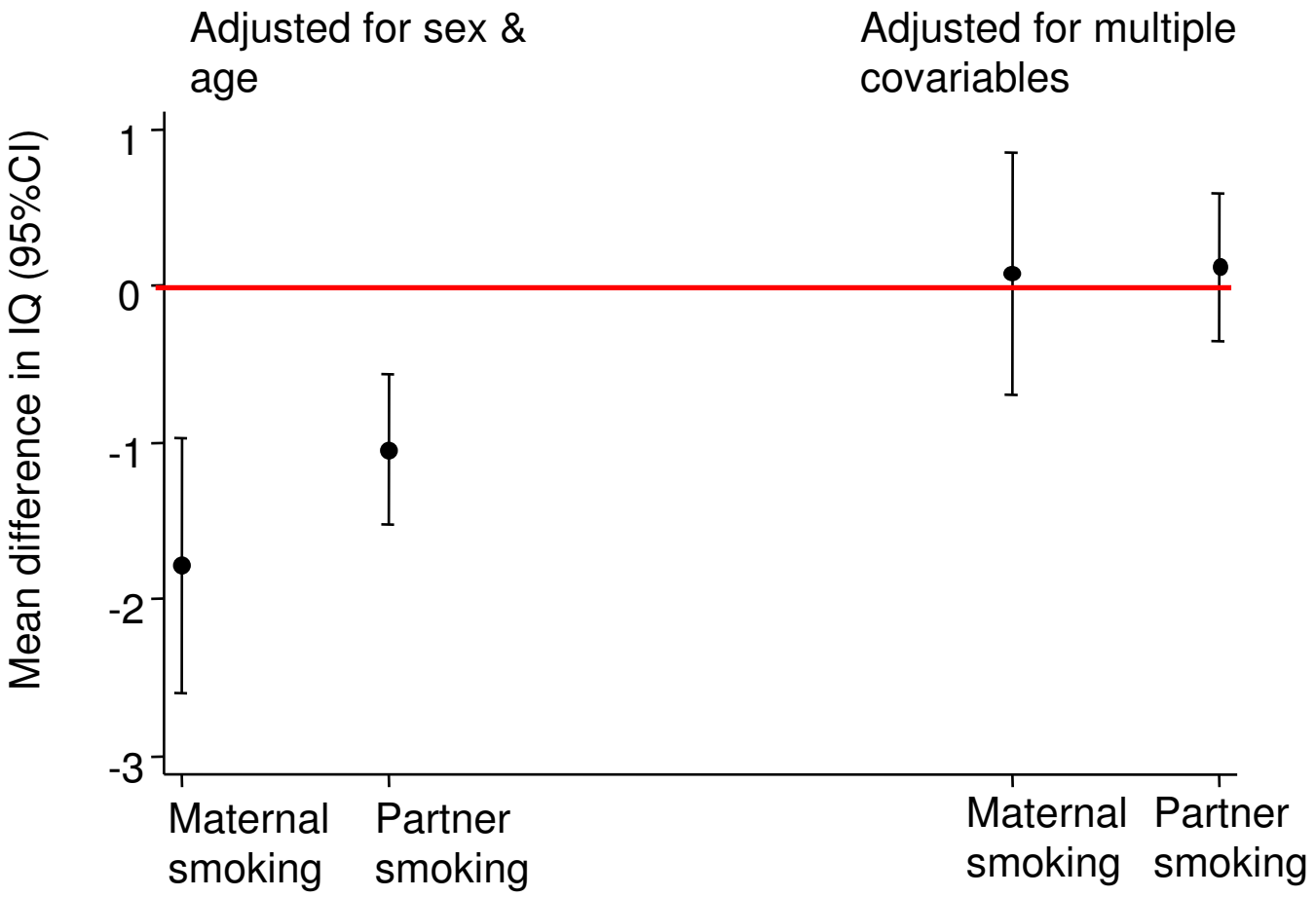
Other examples of testing maternal intrauterine effects

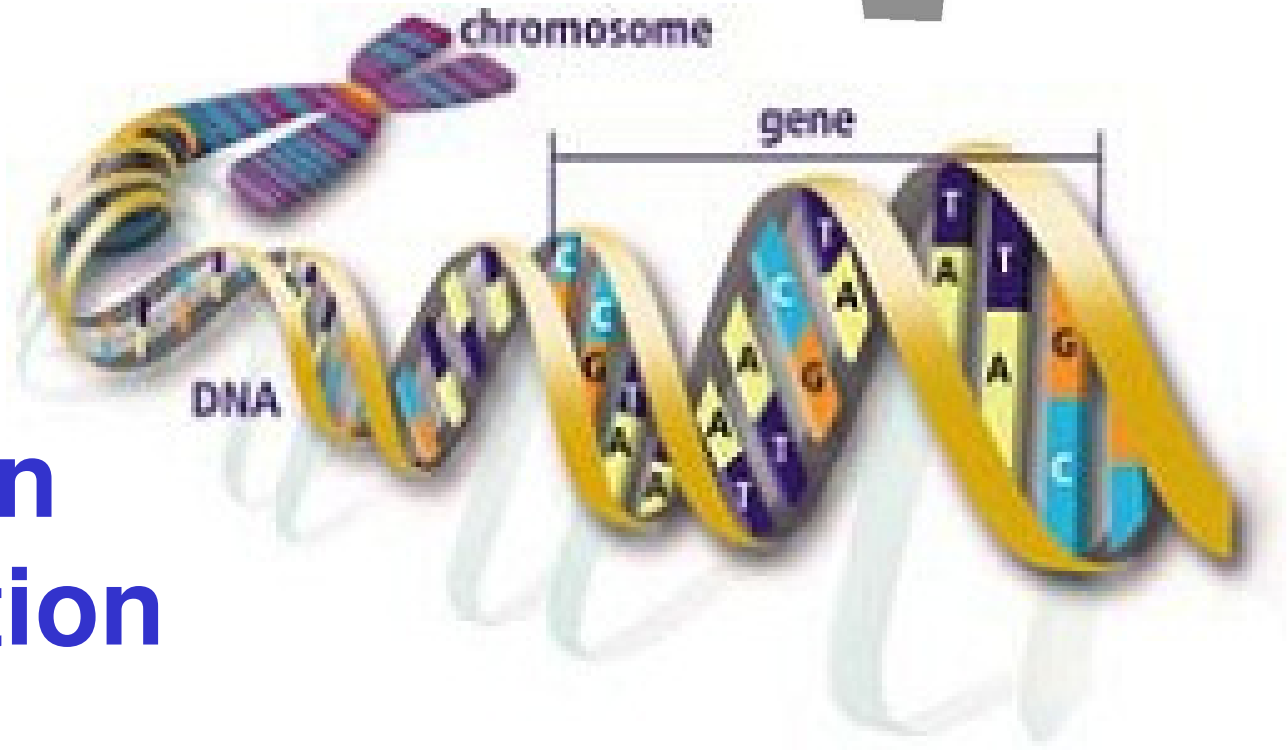
- Maternal gestational smoking and offspring blood pressure, fat mass, IQ
- Maternal BMI and intrauterine programming of offspring fat mass (developmental overnutrition)
- Maternal diet and offspring diet

Mean difference in birth weight by parental smoking



Mean difference in childhood IQ by parental smoking



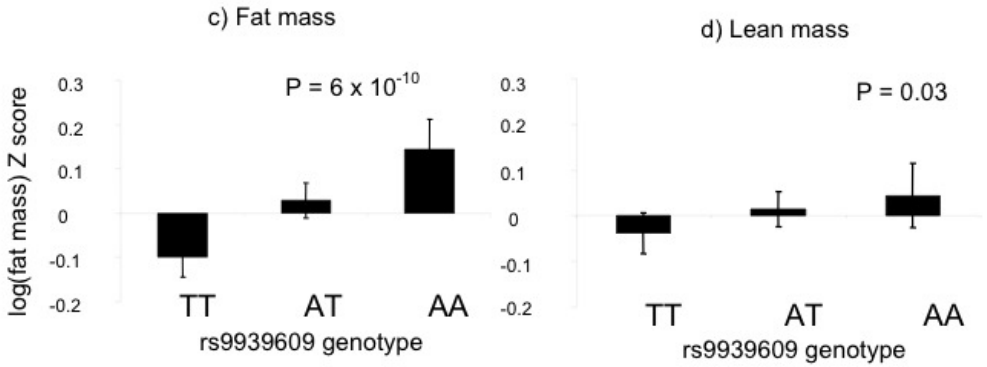


Mendelian randomisation

Does my bum look big in these genes? Absolutely, say scientists

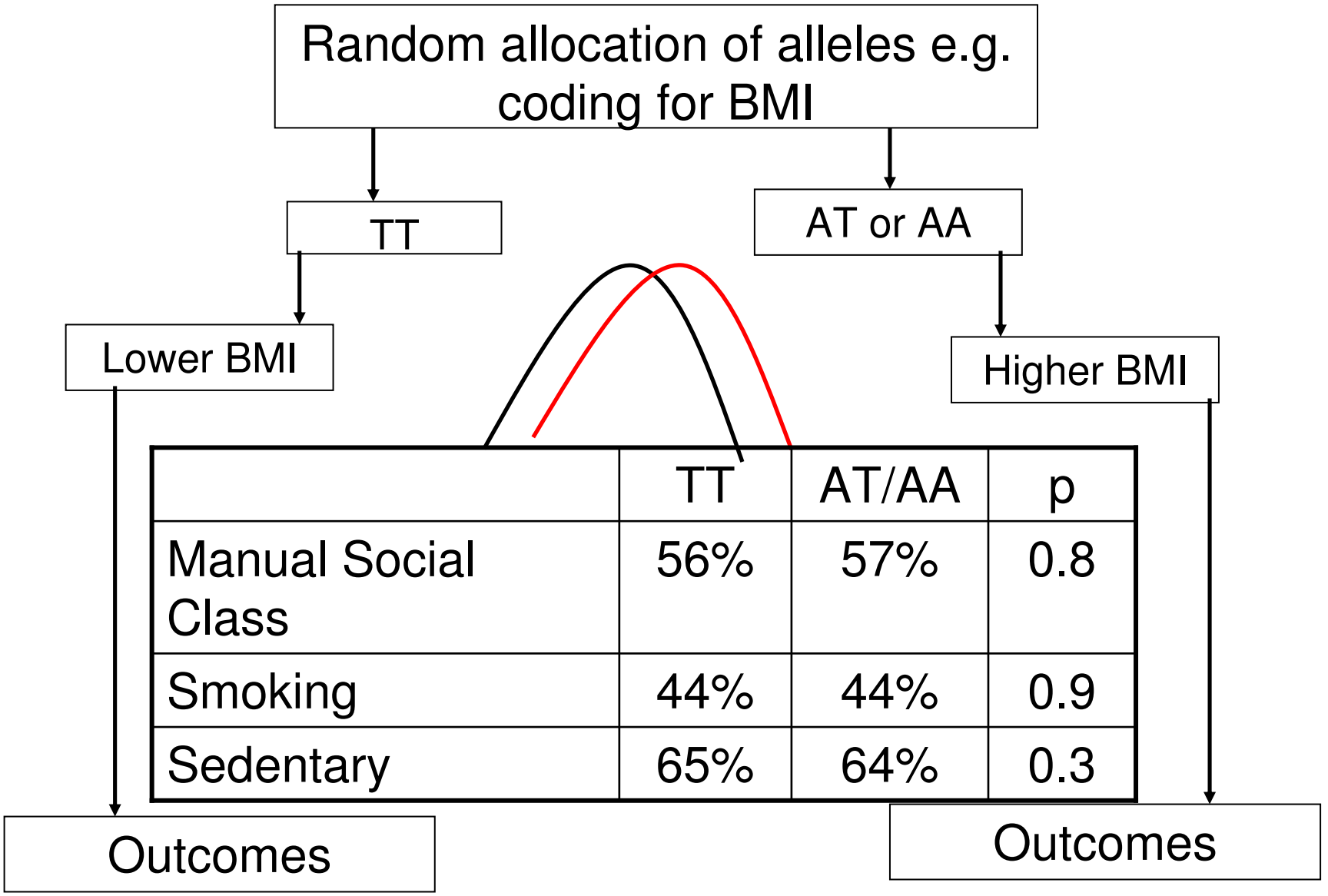
LYNDSAY MOSS
HEALTH CORRESPONDENT

and Oxford University, then tested a further 37,000 genetic samples to look for the varia-



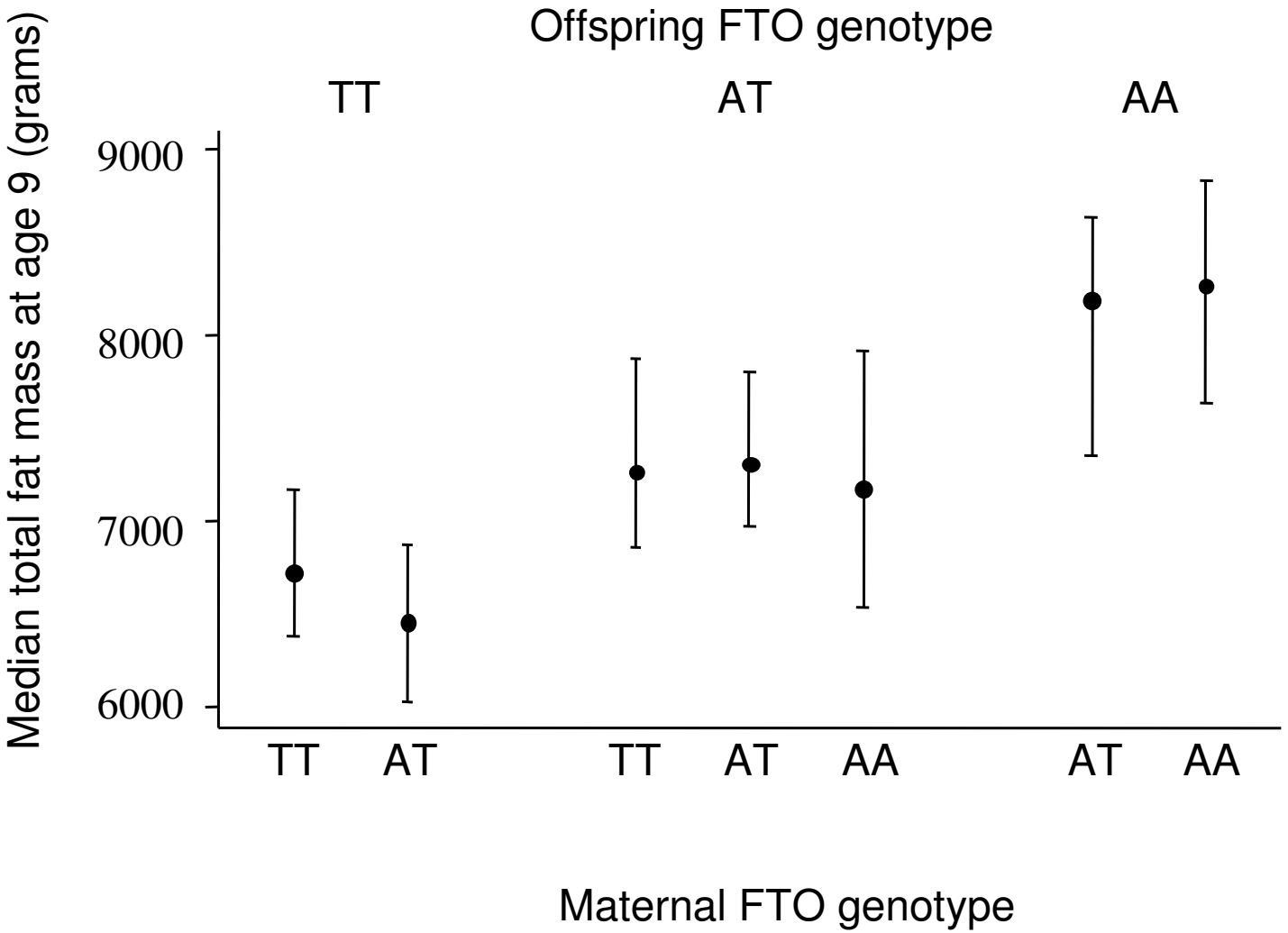
Frayling TM, Timpson NJ, Weedon MN et al. *Science* 2007

Nature's randomised controlled trials



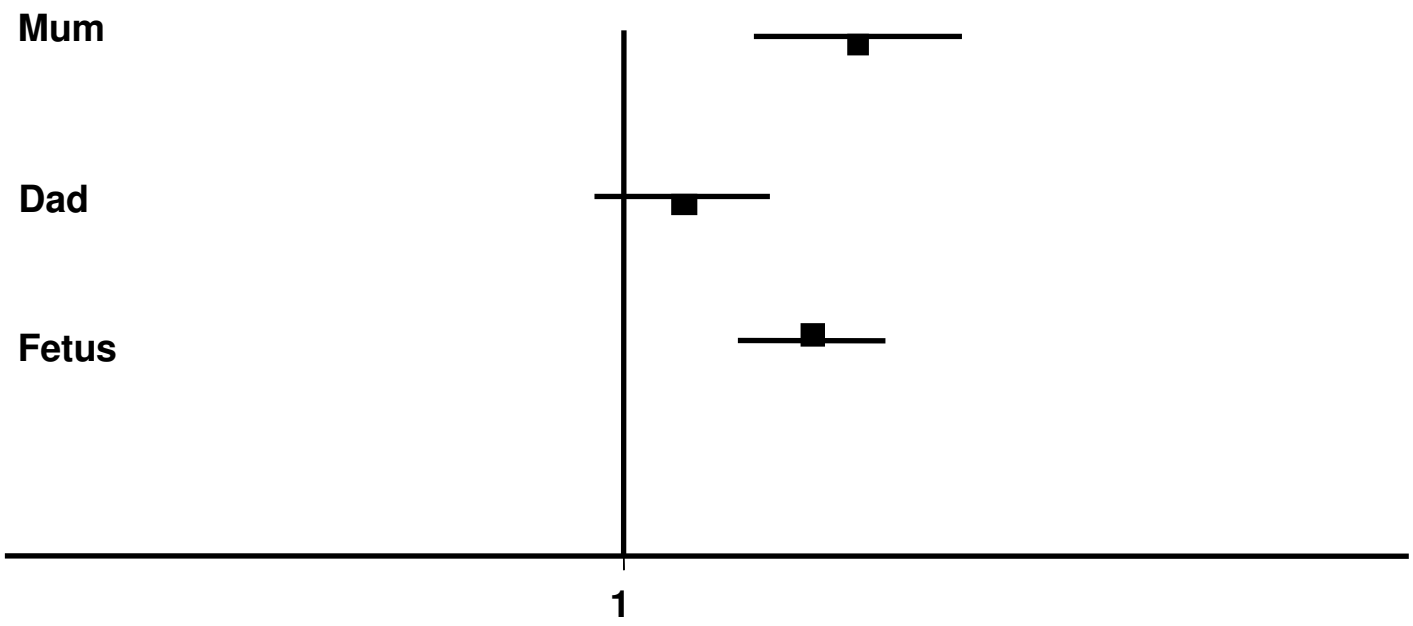
	TT	AT/AA	p
Manual Social Class	56%	57%	0.8
Smoking	44%	44%	0.9
Sedentary	65%	64%	0.3

Maternal and offspring *FTO* and offspring fat mass



Hazard ratio of neural tube defect by parental and fetal genotype

TT versus C/T or CC



Scholl To, et al Am J Clin Nutr 2000 & Botto LD, et al AJE 2000

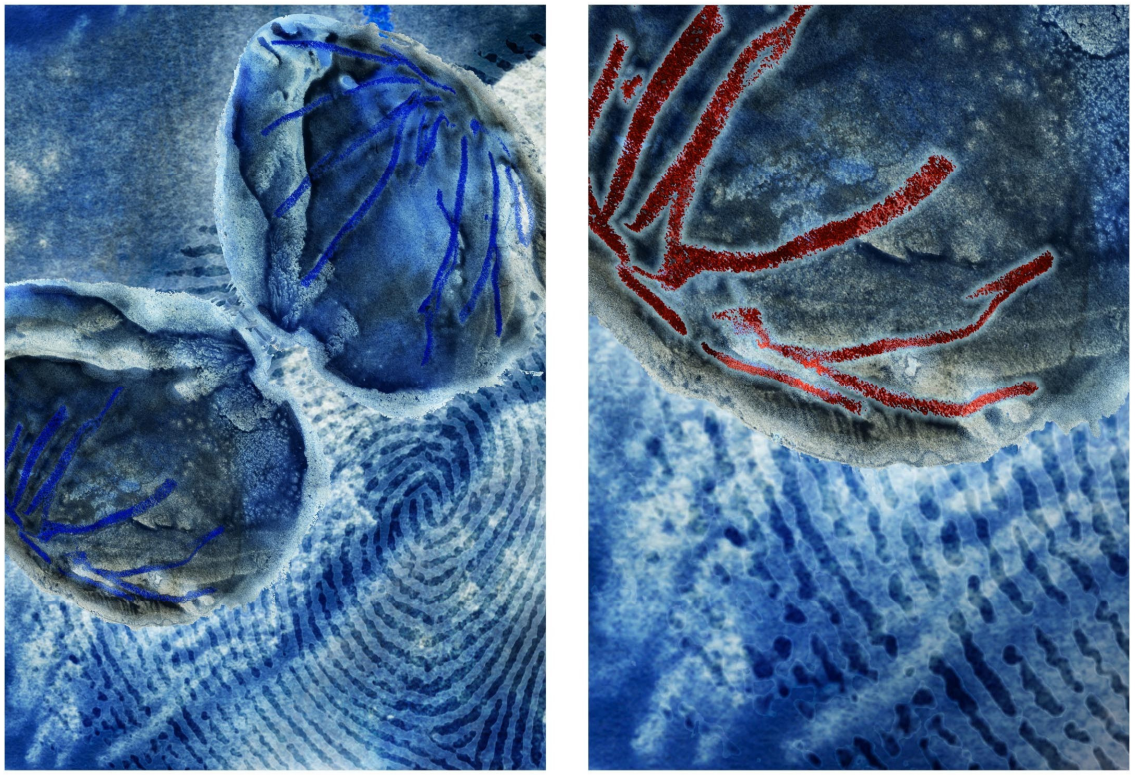
Importance even if causal

- Importance to contemporary population
- Mechanism e.g. does childhood BMI relate to CHD risk entirely through tracking to adult obesity?
- What interventions are feasible at different times of the life course?
- Are interventions differently effective at different times of the life course?

Conclusion

- Time to move forward from establishing association in developmental / life course epidemiology to asking (and answering) what should be done?
- Family based studies & Mendelian randomization offer potential to investigate causality and mechanisms

Family matters: using family based studies to determine the mechanisms underlying early life determinants of adult chronic diseases



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