Including multiple instrumental variables in Mendelian randomization analyses

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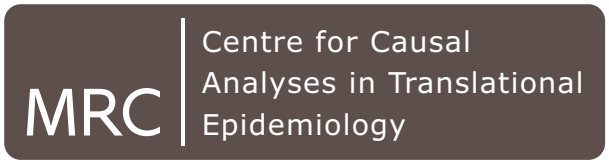


Outline

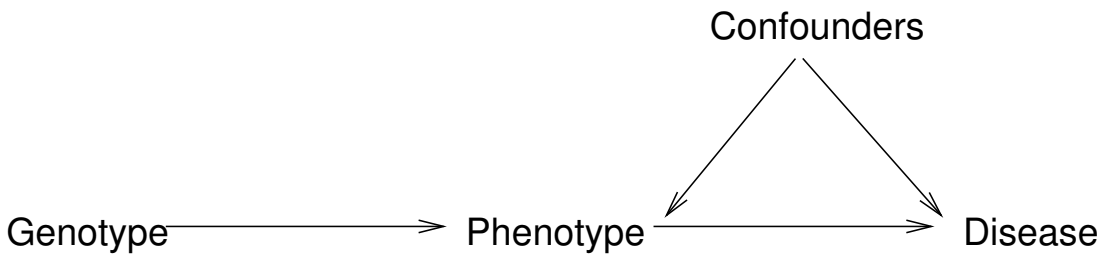
- Introduction to Mendelian randomization
- Multiple instruments example using ALSPAC data:
  - instrument strength
  - over-identification
  - allele scores
- Multiple instruments discussion

Introduction

Mendelian randomization approach:

- Difficult to adjust for all possible confounders
- Genotypes - instrumental variables
- Infer causal phenotype-disease association

(Davey Smith & Ebrahim, 2003)



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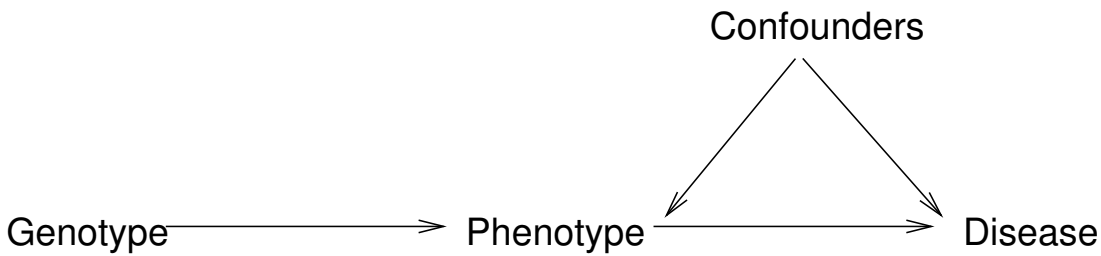

IV assumptions, genotype should be:

(i) independent of confounders

(ii) associated with phenotype

(iii) independent of disease given phenotype and confounders

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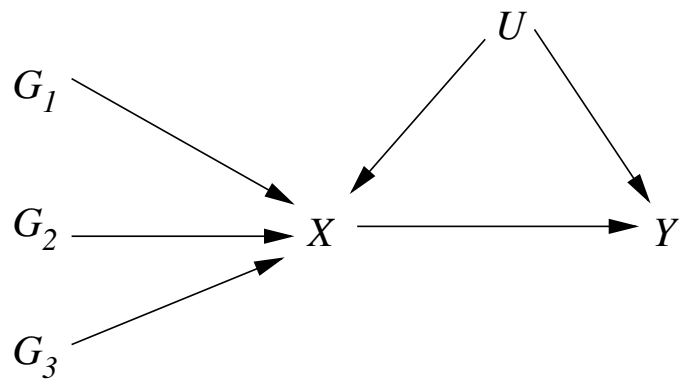
Solutions:

- Increase study sample size
- Stronger instrument
- **Multiple instruments**
- (Meta-analysis)

Multiple instruments

- Ideal situation (Didelez & Sheehan, 2007):



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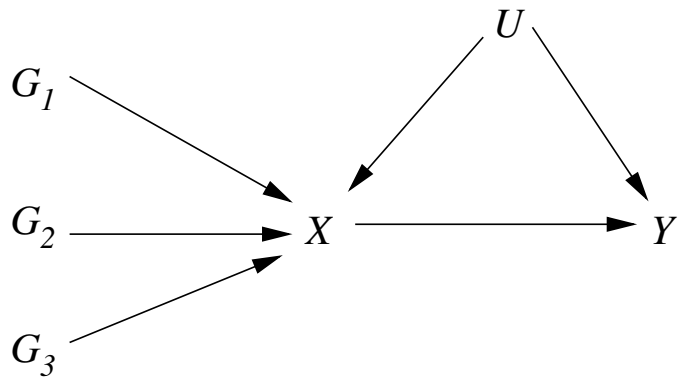

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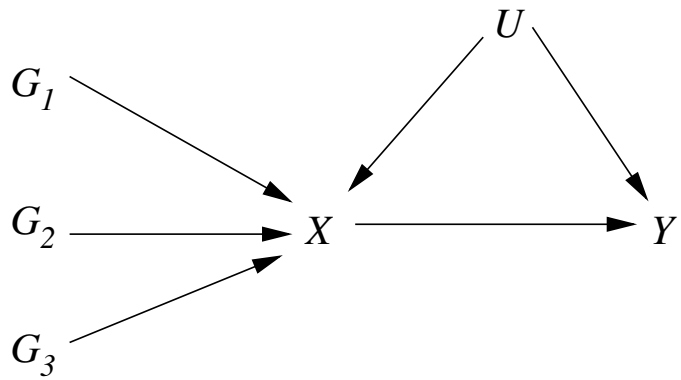

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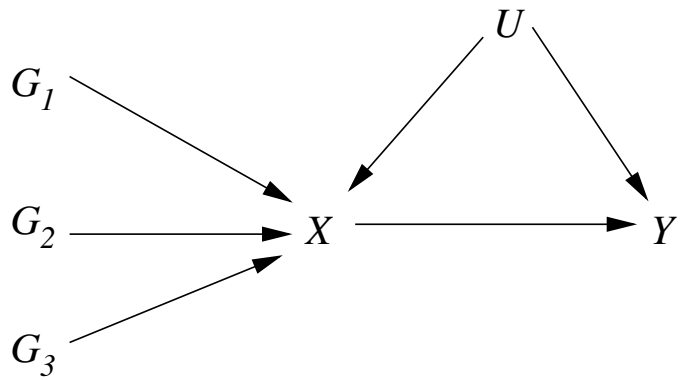

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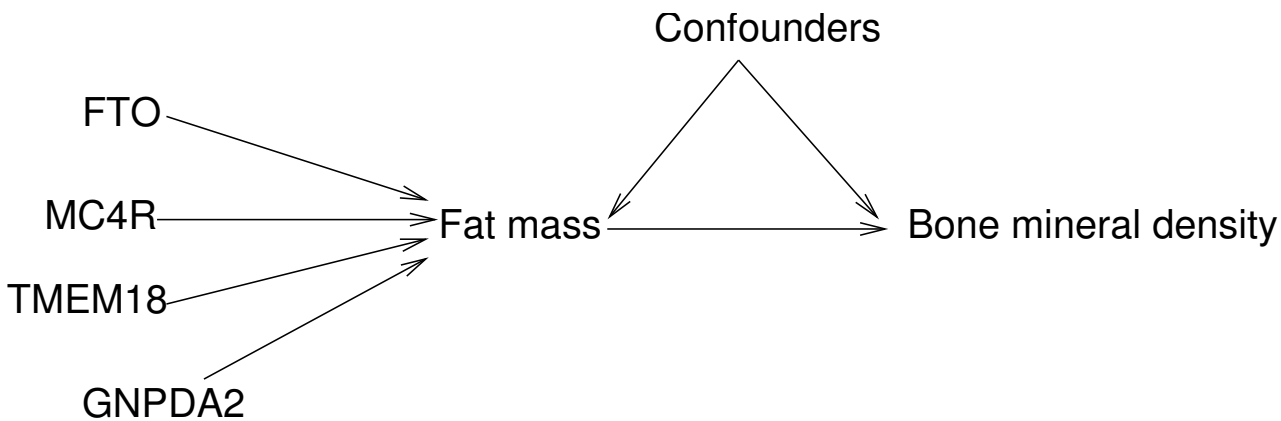

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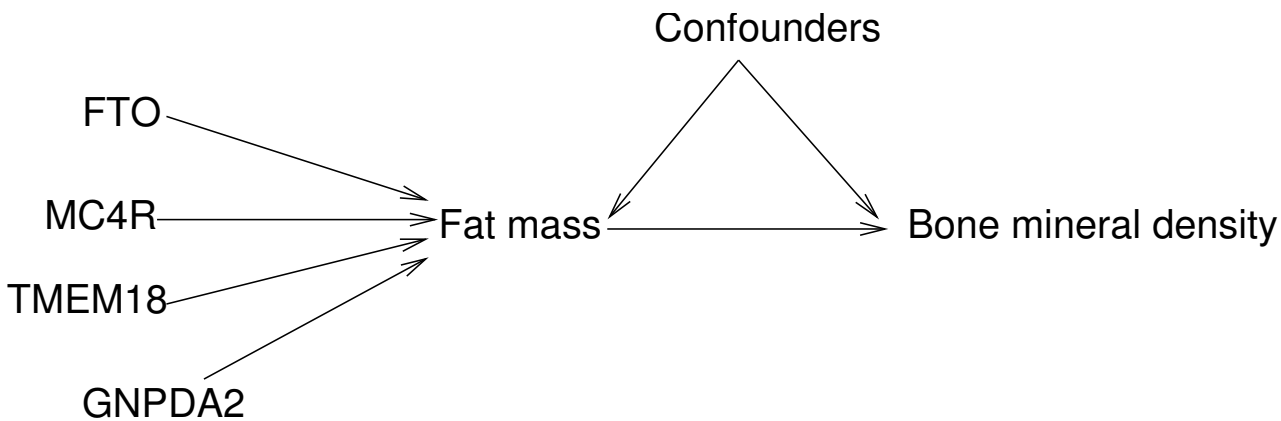

- FTO & MC4R: 0.2-0.4 kg/m^2 inc BMI
  OR: 1.1-1.3 for obesity (BMI $>$ 30 kg/m^2)

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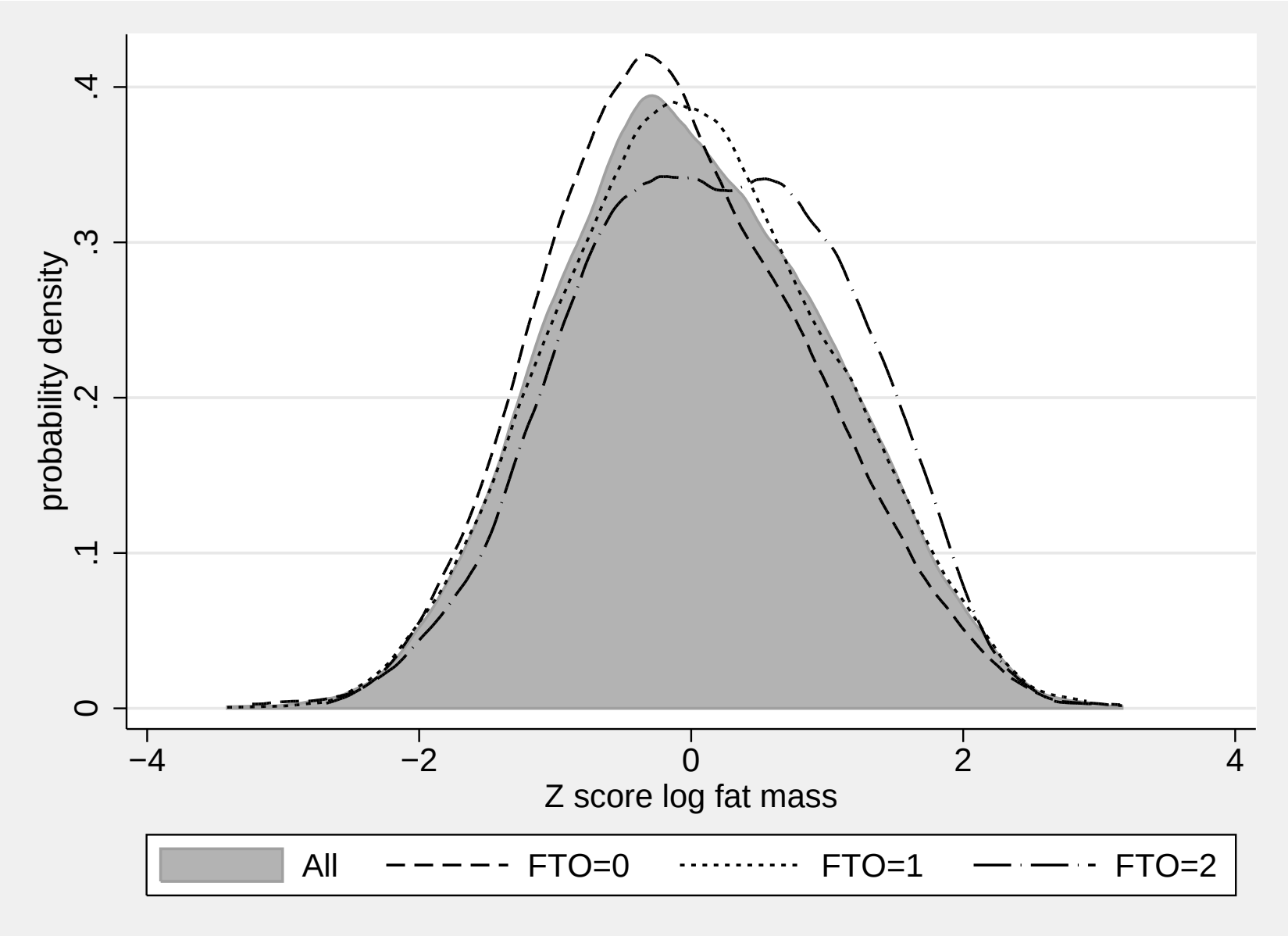
- Estimation:
  - TSLS
  - AR/LIML, LM, CLR (Mikusheva & Poi, 2006)

CDFs of BMD by FTO genotypes



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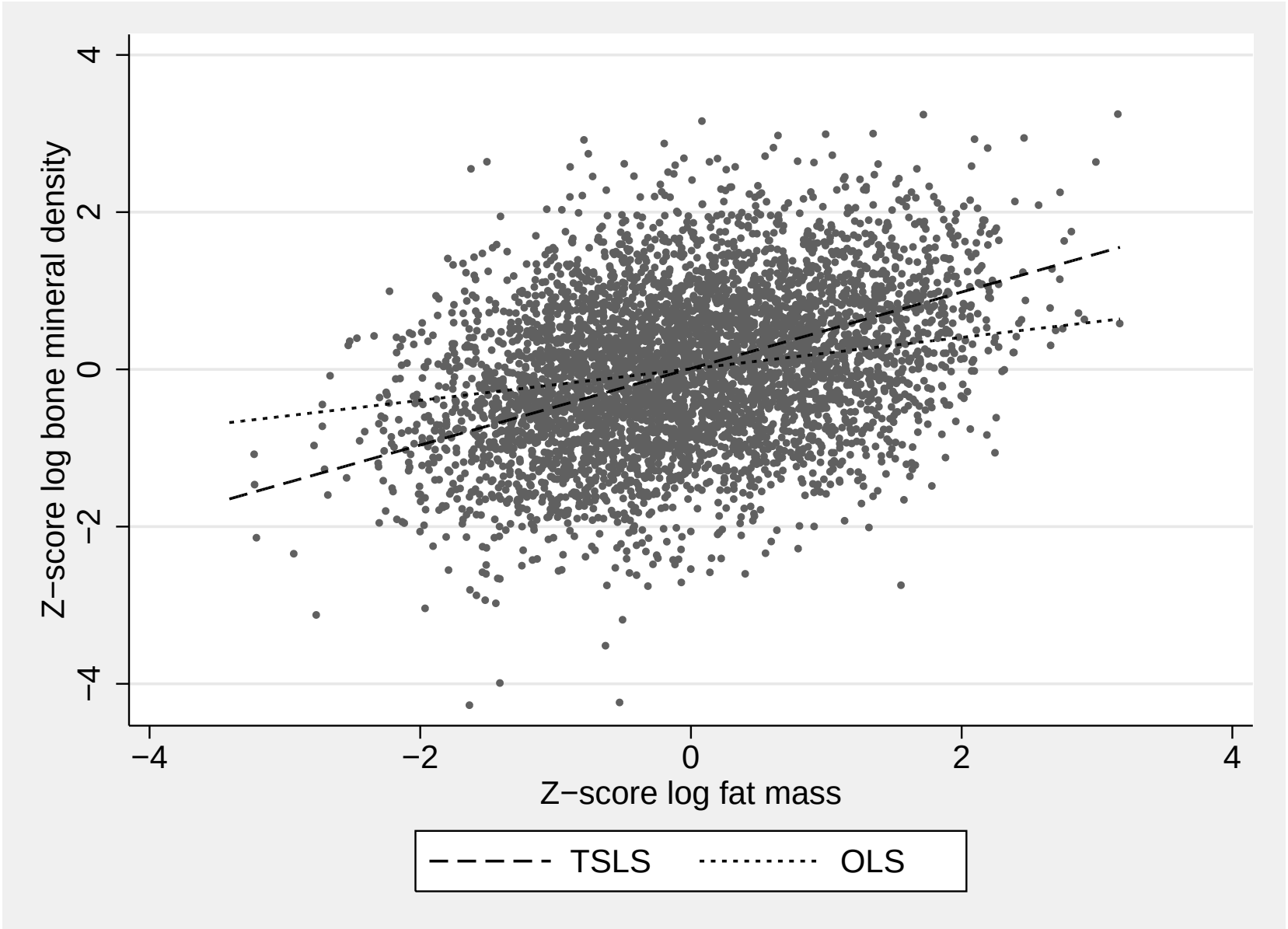
Allele sc.	1.40 (0.99, 1.98)	0.06	33.2	0.007	0.43	NA	4796

IV estimates of the causal assoc. between std. BMD & std. fat mass

Second stage regression



OLS: 1.22 (1.19, 1.26); IV allele score: 1.40 (0.99, 1.98)

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- This work in:
  Lawlor, Palmer, et al., Statistical Methods in Medical Research, submitted

Acknowledgements

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