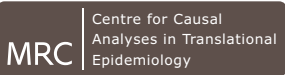


Including multiple instrumental variables in Mendelian randomization analyses

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26 August 2009



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
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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

Problem:

- ▶ MR analyses have low power:
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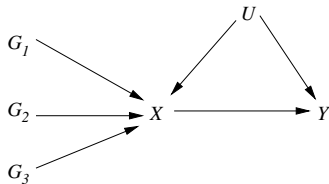
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Solutions:

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

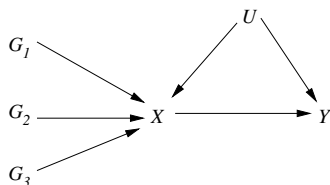
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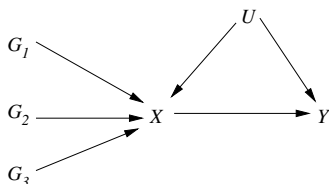
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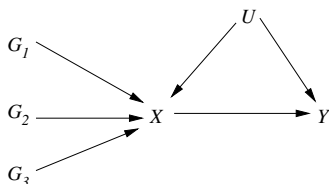
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- ▶ Over-identification: Sargan/Hansen test

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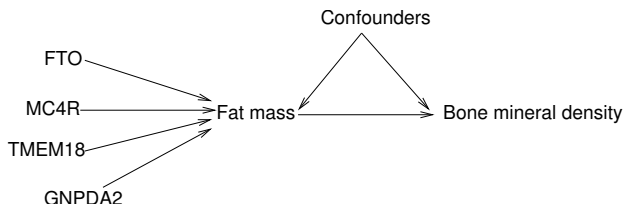
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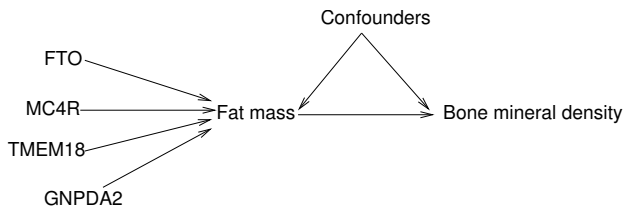
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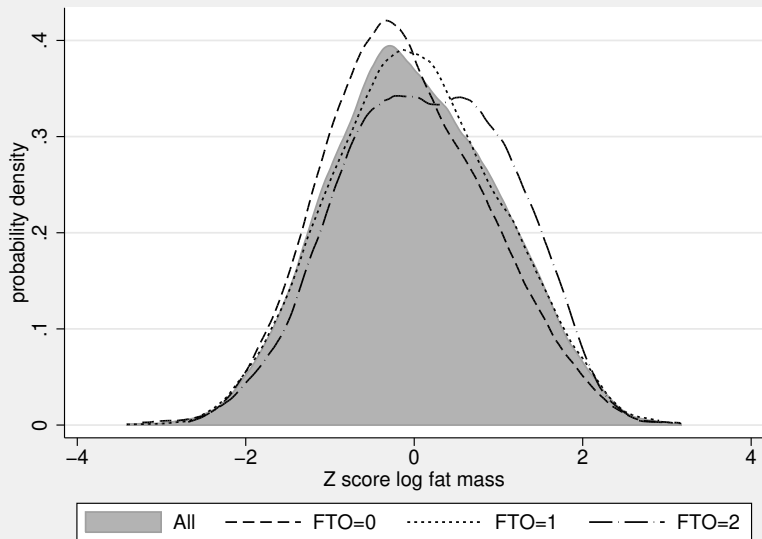
- ▶ FTO & MC4R: 0.2-0.4 kg/m² inc BMI
OR: 1.1-1.3 for obesity (BMI > 30 kg/m²)

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

CDFs of BMD by FTO genotypes



Model	Coef (95% CI)	<i>P</i>	<i>F</i>	R_p^2	DWH	Sargan	<i>N</i>
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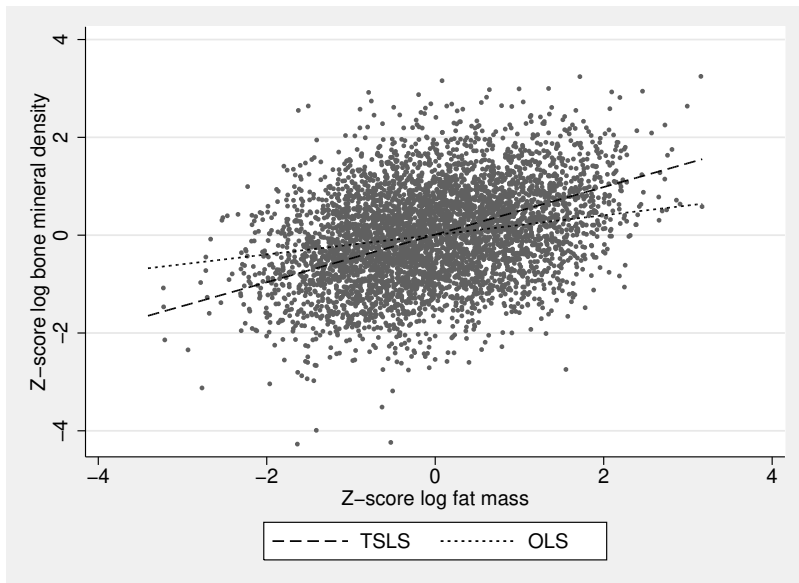
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Allele sc.	1.40 (0.99, 1.98)	0.06	33.2	0.007	0.43	NA	4796

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

MRC collaborative grant G0601625: Methods for Mendelian randomization

Collaborators: Nuala Sheehan, Vanessa Didelez, Sha Meng, Roger Harbord, John Thompson, Paul Clarke, Frank Windmeijer, Paul Burton, George Davey Smith.

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