Using allele scores to identify confounding by reverse causation:

studies of alcohol consumption as an exemplar

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OXFORD

Methods

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Hannah M Sallis [1,2,3,4]* Tom Palmer [1,2] Kate Tilling,[1,2] George Davey Smith [1,2] and Marcus R Munafò[1,4,5]

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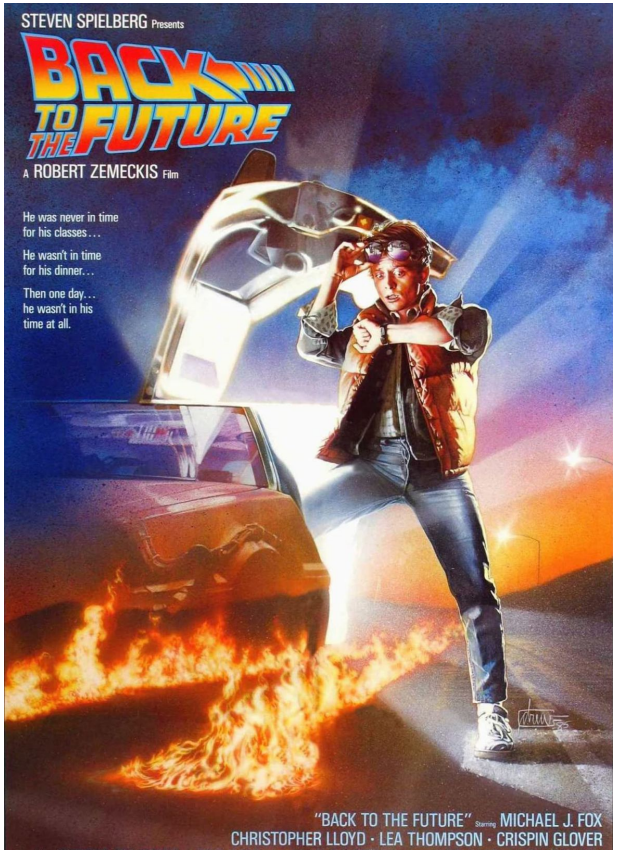
Outline

- Introduction
- Methods
- Results
- Discussion and possible complications

Introduction



International Journal of Obesity (2011) 35, 300–308

0307-0565/11
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ORIGINAL ARTICLE

C-reactive protein levels and body mass index: elucidating direction of causation through reciprocal Mendelian randomization

NJ Timpson[1], BG Nordestgaard[2,3], RM Harbord[1,4], J Zacho[2,3], TM Frayling[5,6], A Tybjærg-Hansen[3,7] and G Davey Smith[1]

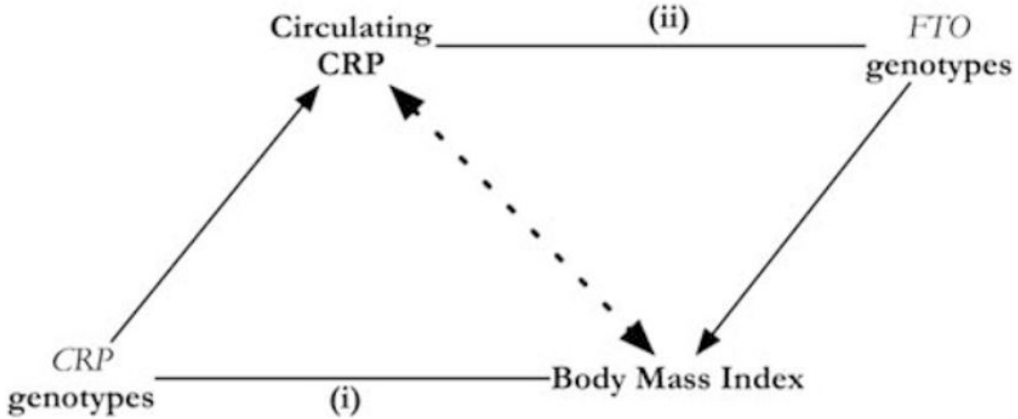
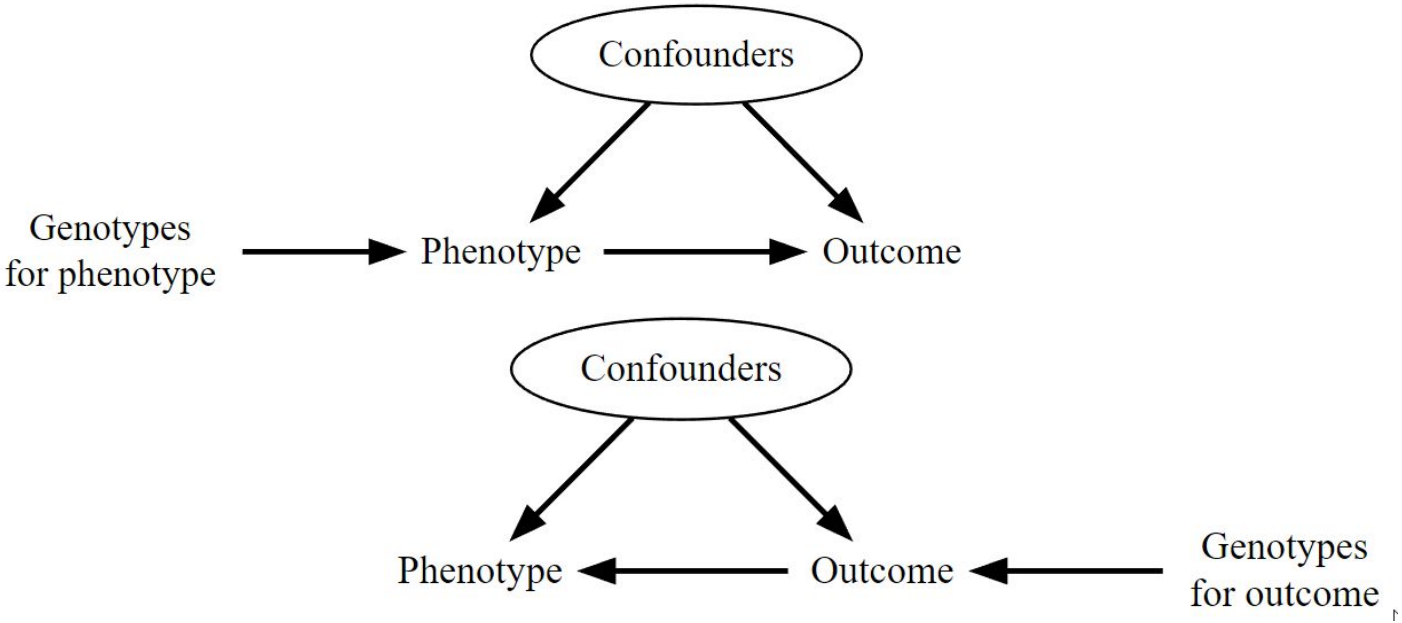
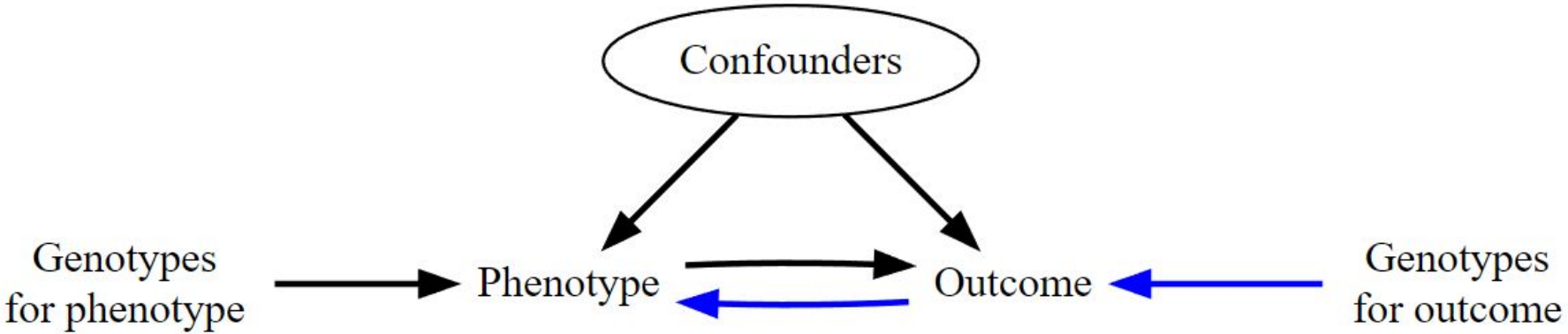


Figure 3 Graphical representation of the reciprocal Mendelian randomization framework used in main analyses. The dotted line represents the unknown direction of relationship between circulating CRP and BMI. Relationships (i) and (ii) denote the informative associations between *CRP* genotypes, *FTO* genotypes and circulating CRP and body mass index. Single-headed arrows represent the known (and assumed causal and largely nonconfounded) relationships between variation at the *CRP* and *FTO* loci and circulating CRP and body mass index, respectively.

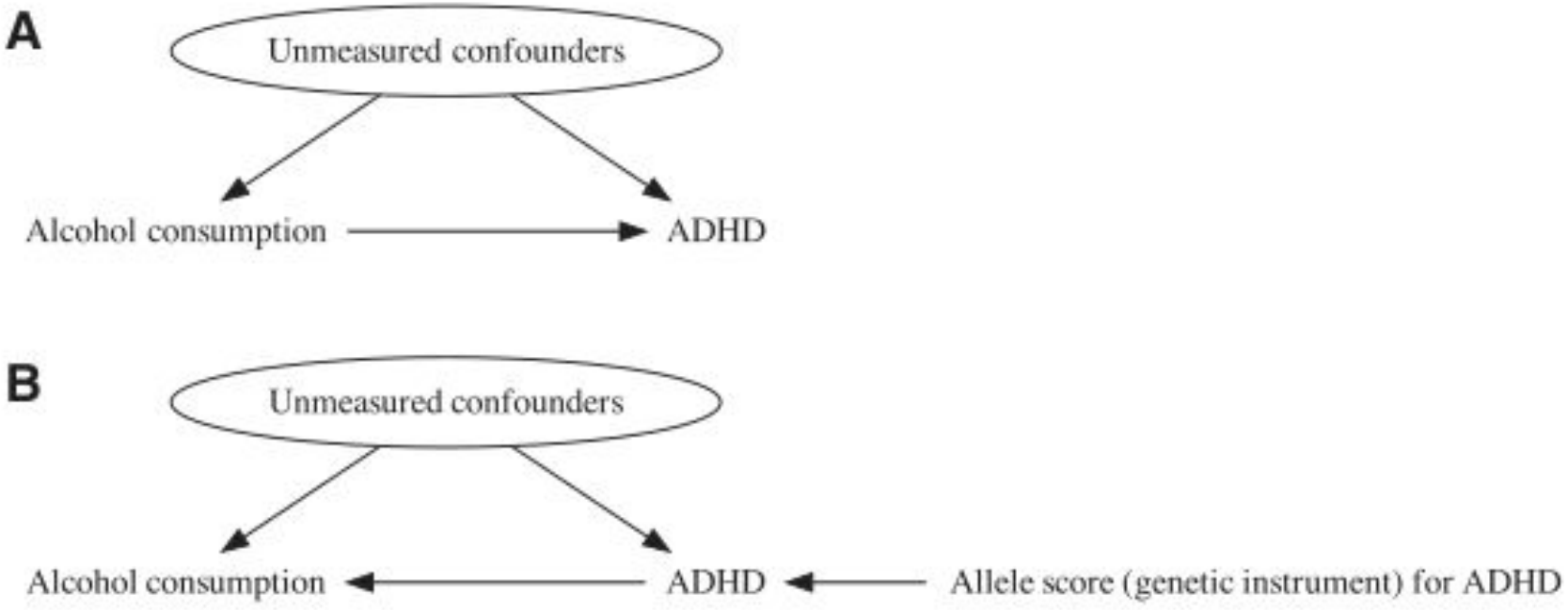
Figure 3 is 2 Mendelian randomization DAGs



Sometimes combined into a single figure



Methods: What we looked at

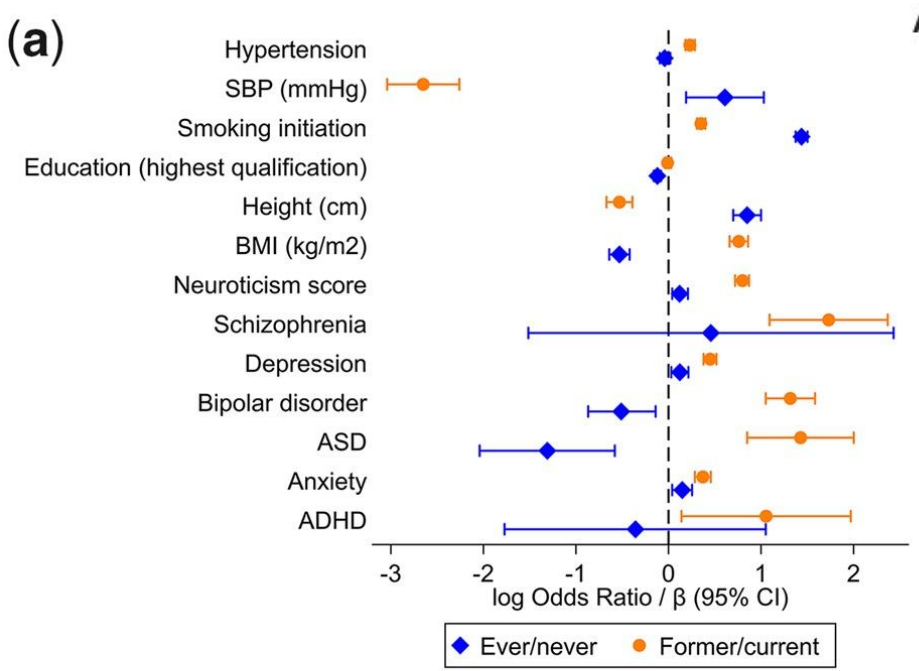


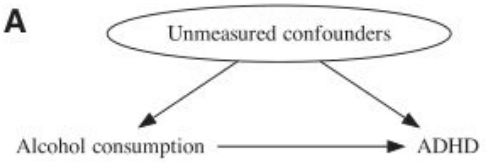
- A full bidirectional MR could present 4 estimates
  - Alc -> ADHD ; observational and MR
  - ADHD -> Alc ; observational and MR
- We hypothesised that reverse MR useful when instruments difficult to find for one of the exposures (e.g., cycling)
- Therefore we presented approx. 2 of those (instead of MR estimate, Causal Inference Test of 'outcome' ~ allele score, i.e., test of presence of causal effect)

- Phenotypes
  - Educational attainment, physical and mental health outcomes
  - Alcohol consumption
    - Drinking status: ever/never and former/current; units per week; extreme drinking > 50 units
  - Covariates: age, sex, highest educational qualification, total household income
  - Allele scores
    - Hits P < 5E-8 in GWAS not including UKB in discovery sample
    - Used plink v1.90
    - Weights from discovery GWAS

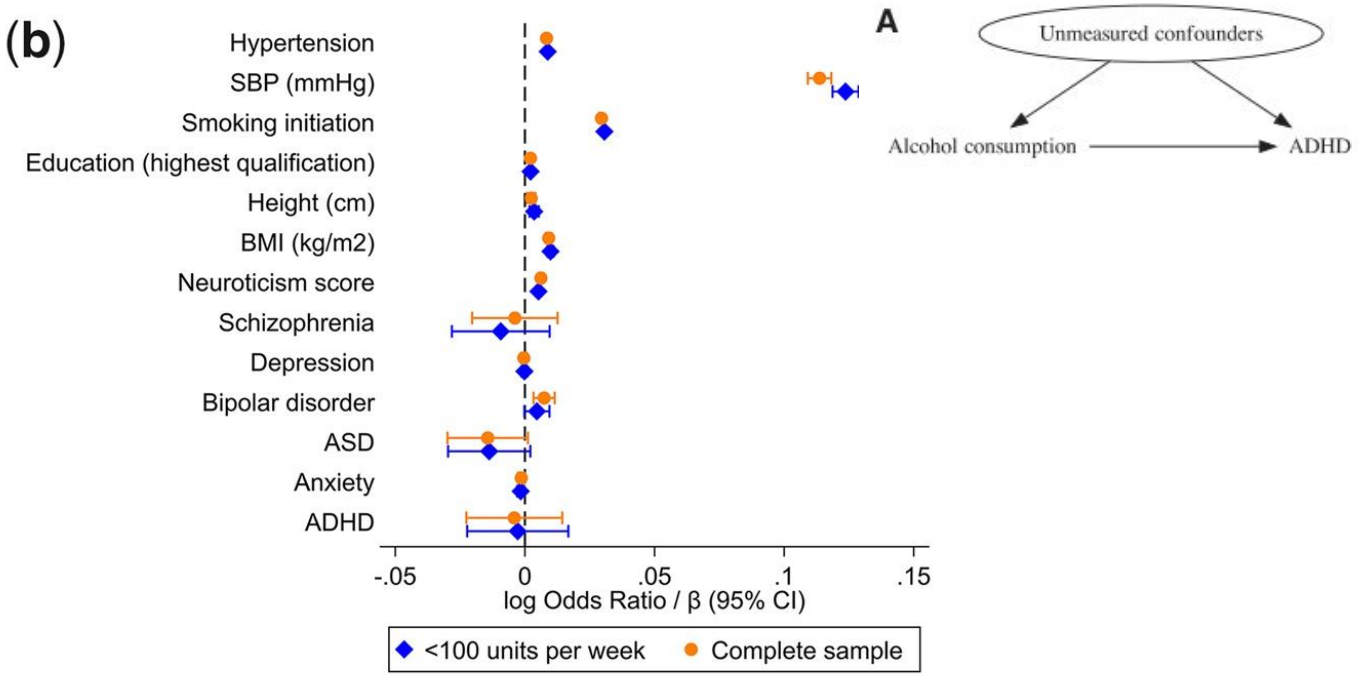
- Statistical models:
  - linear/logistic regression
  - Note IV estimation was not performed; instead Causal Inference Test of 'outcome' regressed on allele score
- Sample sizes ranged from 114,941–336,473 in observational analyses and 142,093–336,818 in genetic analyses

Results: Observational: outcome ~ alcohol estimates

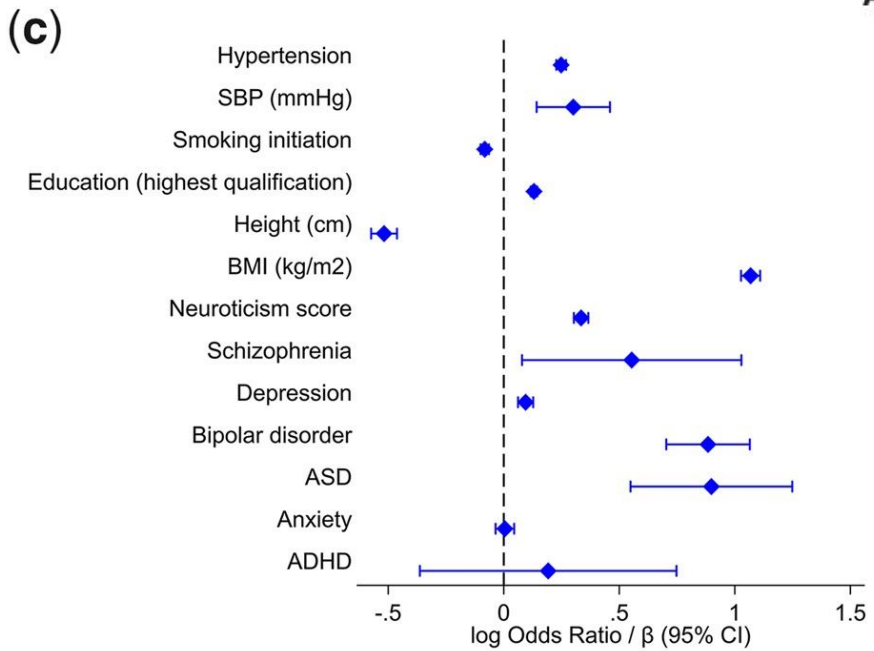


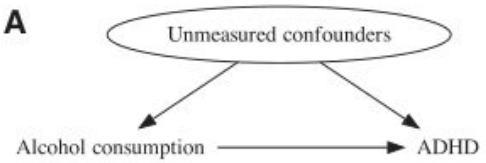


Observational: outcome ~ alcohol estimates

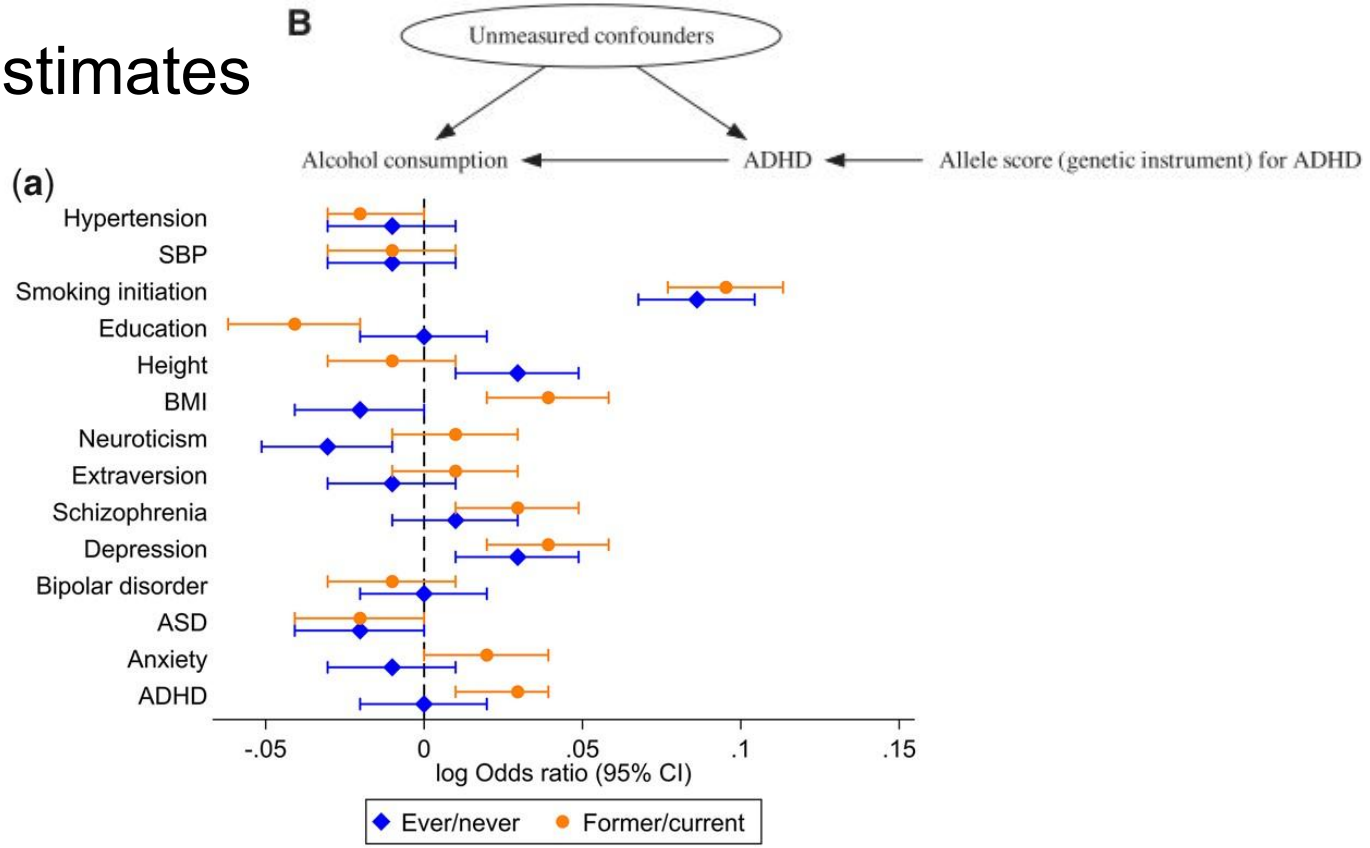


Observational: outcome ~ alcohol (extreme vs rest)

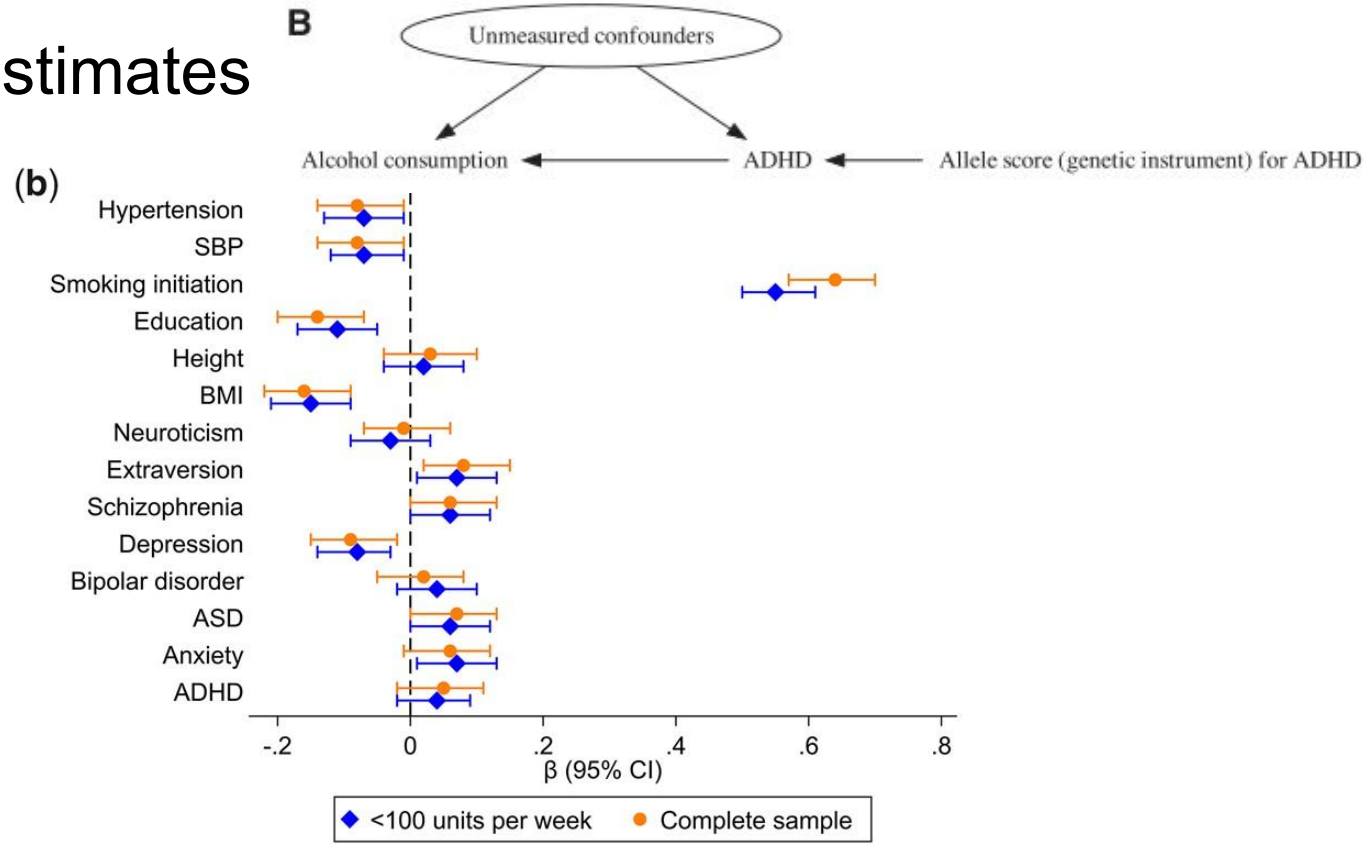




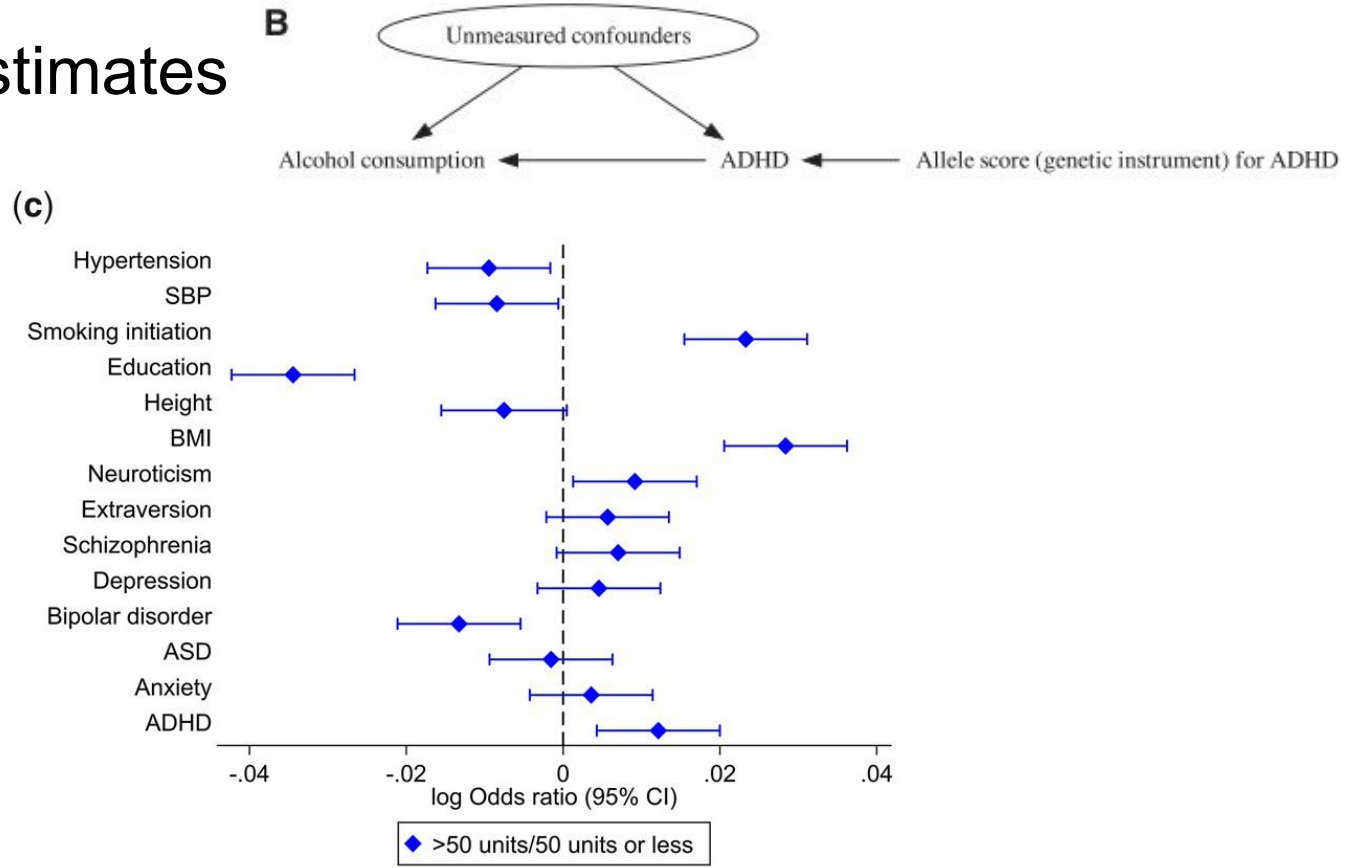
Allele score estimates



Allele score estimates



Allele score estimates



- Observational analyses indicated associations between alcohol consumption and a number of outcomes (neuroticism, body mass index, educational attainment)
- Analyses using allele scores suggested evidence of reverse causation for several of these relationships (physical health and educational attainment)

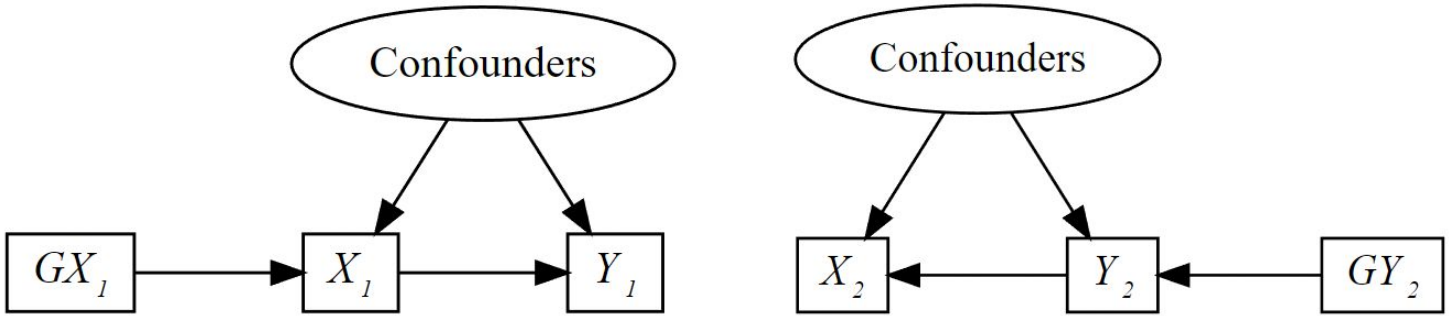
Discussion and possible complications

Key Messages

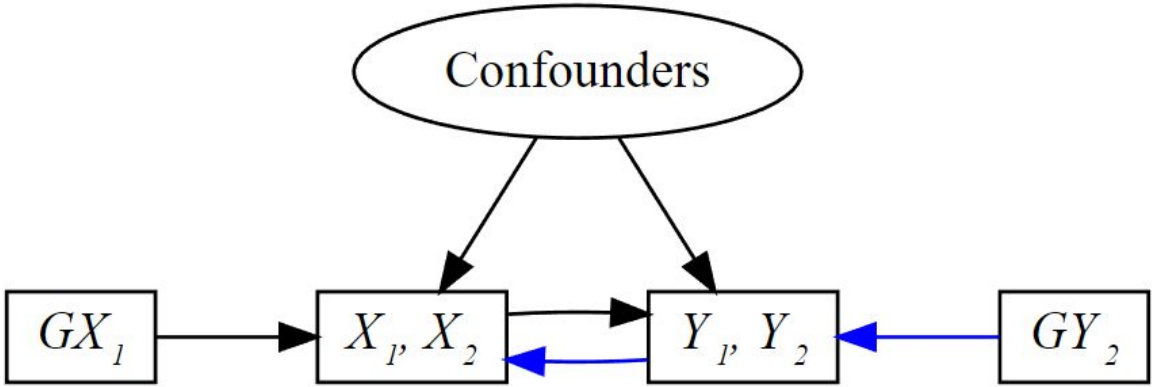
- Findings from conventional observational studies may be distorted by reverse causation.
- Reverse Mendelian randomization (MR) can be used to directly test reverse causation in observational epidemiological studies where bidirectional MR is not possible.
- Future extensions to this method could enable us to adjust observational estimates for reverse causation.
- Our findings suggest that observed associations suggesting beneficial effects of alcohol consumption may be largely due to confounding by reverse causation.

- Could have performed full bi-directional MR, as genotypes for alcohol consumption available
- Reverse MR useful when full bi-directional MR not possible

- Different true directions of effect at different time points, e.g. timepoints 1 and 2 separated by say puberty/menopause/a disease process??



You might accidentally try and fit



- Additionally, overlapping instrument sets for bi-directional Mendelian randomization analyses are problematic

Any questions

Code to draw Mendelian randomization DAGs

- https://remlapmot.github.io/mrdags/

R, DOT, and TikZ code to plot DAGs and SWIGs for Mendelian randomization analyses

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Introduction

This webpage shows some R code for generating figures, directed acyclic graphs (DAGs), and single world intervention graphs (SWIGs) for Mendelian randomization (MR) analyses.

On this page