Mendelian randomization with pharmaceutically modifiable biomarkers

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Overview

Background:
Mendelian randomization (MR) studies of biomarkers

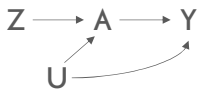
Objectives:

1. Describe the sources of bias that arise when using conventional methods to adjust for medication use.
2. Describe the causal estimands that can be targeted.
3. Demonstrate the use of g-methods to adjust for medication use.

Mendelian randomization (MR) is an increasingly popular application of instrumental variable analysis

Genetic variants used as proposed instruments

- Three instrumental conditions



Estimate the effect of a non-genetic exposure on outcome

- Even with unmeasured confounding

Exposures in MR studies

- Biomarkers that affect and are affected by medication use

LDL cholesterol and statins

Blood pressure and diuretics

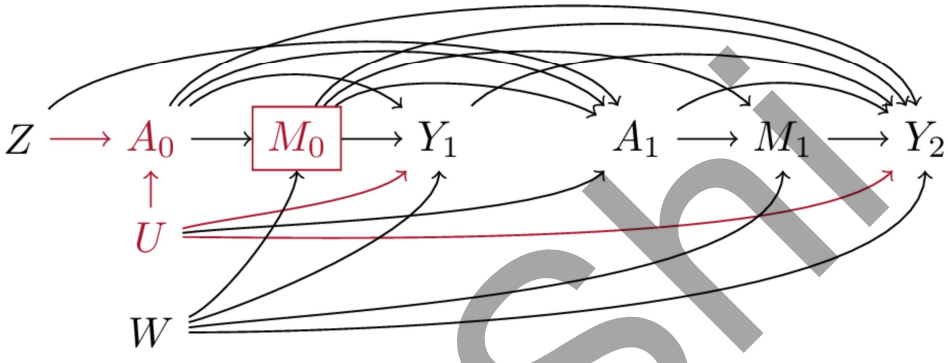
Blood glucose and metformin

- Adjusting for medication use or restricting to non-users introduces bias

Objective 1: Bias of conventional methods

Genetic variant (Z)
LDL cholesterol over time (A_k)
Statin use over time (M_k)

Coronary heart disease incidence (Y_{k+1})
LDL cholesterol-CHD confounders (U)
Statin-CHD confounders (W)



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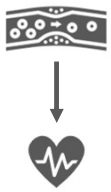
Objective 2: Potential causal estimands of interest

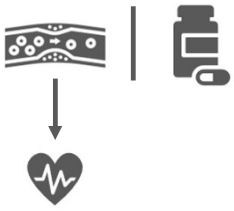
Total lifetime effect of LDL cholesterol



$\mathrm{E}[Y^{\bar{a}_K+1}] - \mathrm{E}[Y^{\bar{a}_K}]$

Unbiased

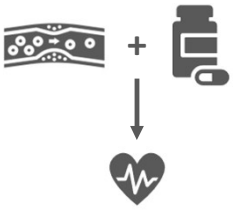
Lifetime effect of LDL cholesterol, **conditional on statin use**



$\mathrm{E}[Y^{\bar{a}_K+1}|M_k] - \mathrm{E}[Y^{\bar{a}_K}|M_k]$

Conditioning creates bias

Lifetime effect of a **joint intervention** on LDL cholesterol and statin use



$\mathrm{E}[Y^{\bar{a}_K+1,\bar{m}_K}] - \mathrm{E}[Y^{\bar{a}_K,\bar{m}_K}]$

Proposed approach

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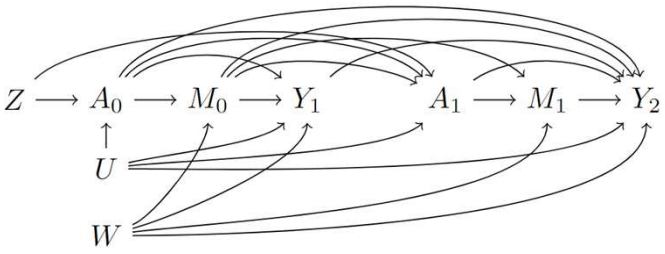
Proposed approach

G-methods to model an intervention on statin use

- Without conditioning on statin use
- Generate data under a hypothetical statin intervention (e.g., never take statins)
- Conduct MR analysis (to assess the effect of an LDL cholesterol intervention) in the counterfactual data
- Estimating lifetime effect of a joint intervention

Objective 3: Data simulations

Data on LDL cholesterol (A_k), statin use (M_k) and CVD (Y_{k+1}) generated according to the DAG:



Three scenarios:

1. A_k and M_k under the null
2. A_k only under the null
3. Neither under the null

Analysis

Conventional MR design

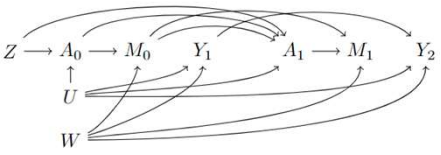
- 2SLS (single measurement of the exposure)
- Varying age of participants at start of follow-up

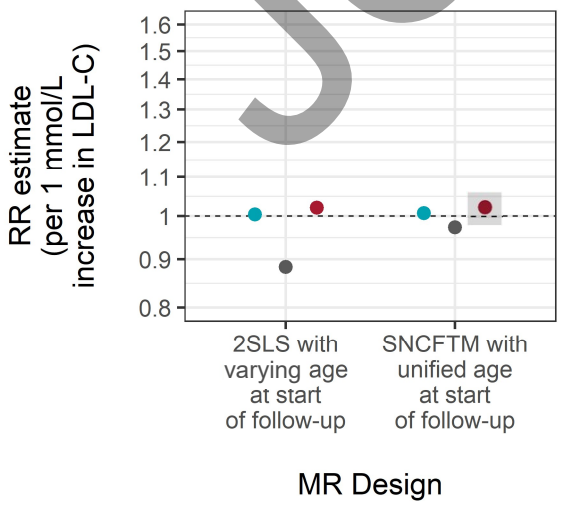
Ideal/proposed MR design

- G-estimation of SNCFTM[a] (longitudinal)
- Same age of participants at start of follow-up

[a] Shi et al. (BMC Medical Research Methodology 2021)

Simulation results for data generated under the null for A and M

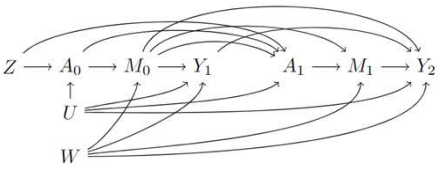


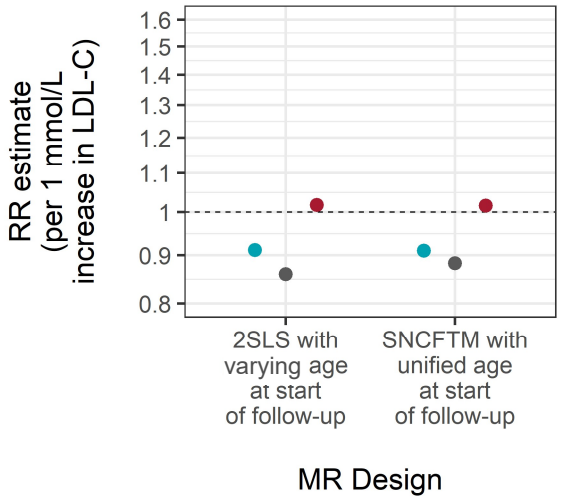


Analytical approach

- Unconditional → Unbiased
- Conditional on M at start of follow-up → Downward bias
- Counterfactual data under no medication use → Slightly upward biased

Simulation results for data generated under the null for A only

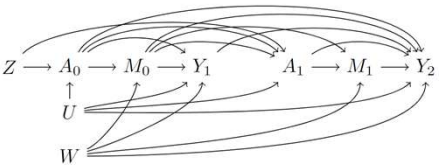


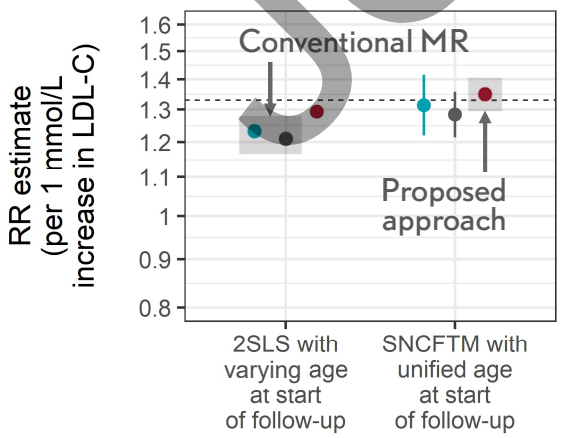


Analytical approach

- Unconditional → Combined effect of A+M
- Conditional on M at start of follow-up → Downward bias
- Counterfactual data under no medication use → Direct effect of A only

Simulation results for data generated not under the null for A or M





Analytical approach

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Conclusions

- Conditioning on variables downstream of the exposure can introduce bias
- Need to consider time-varying nature of the exposure in MR (and other IV) studies
- Combining g-methods and IV can mitigate bias of conventional approaches
- Future steps: real data analysis in the Million Veterans Program

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Questions

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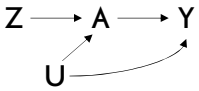
Supplementary Slides

Instrumental conditions



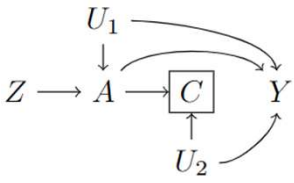
1. Relevance: the instrument (genetic variant) is associated with the exposure
2. Exclusion restriction: the instrument (genetic variant) does not affect the outcome except through its potential effect on the exposure
3. No confounding for Z: The instrument (genetic variant) and the outcome do not share common causes

To estimate a point effect, need a fourth assumption of homogeneity or monotonicity.

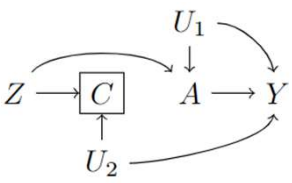
Selection bias in instrumental variable analyses

The instrumental conditions are violated in the presence of selection bias. For example, for a time-fixed exposure:

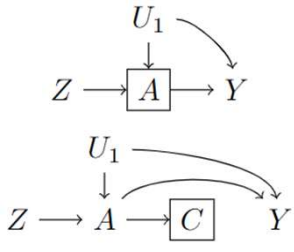
Loss to follow-up:



Misalignment of t_0:

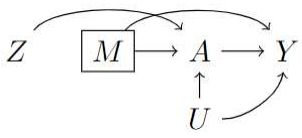


Conditioning on the exposure:

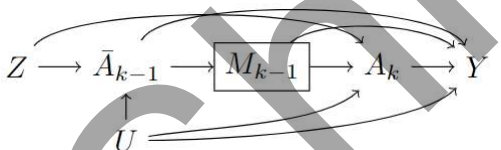


Mendelian randomization studies are often conditioning on variables downstream of the exposure without realizing it

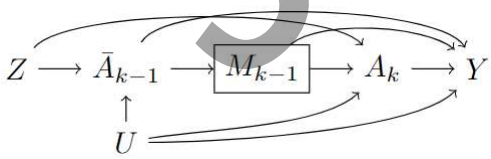
- Most MR studies are interested in the effects of a time-varying exposure, but
  - Consider only a single measure of the exposure in the analysis
  - Conceptualize the exposure as time-fixed
- Conditioning on a "pre-baseline" variable could introduce selection bias
  - If this variable is affected by prior exposure
- i.e., the DAG is not:



but rather more like:



Consider a MR study of LDL cholesterol and CVD



Z: LDL cholesterol-related genetic variant

$\bar{A}_{k-1}$: history of LDL cholesterol

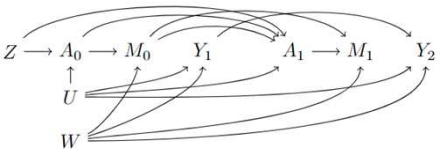
M_{k-1}: statin use at time $k-1$

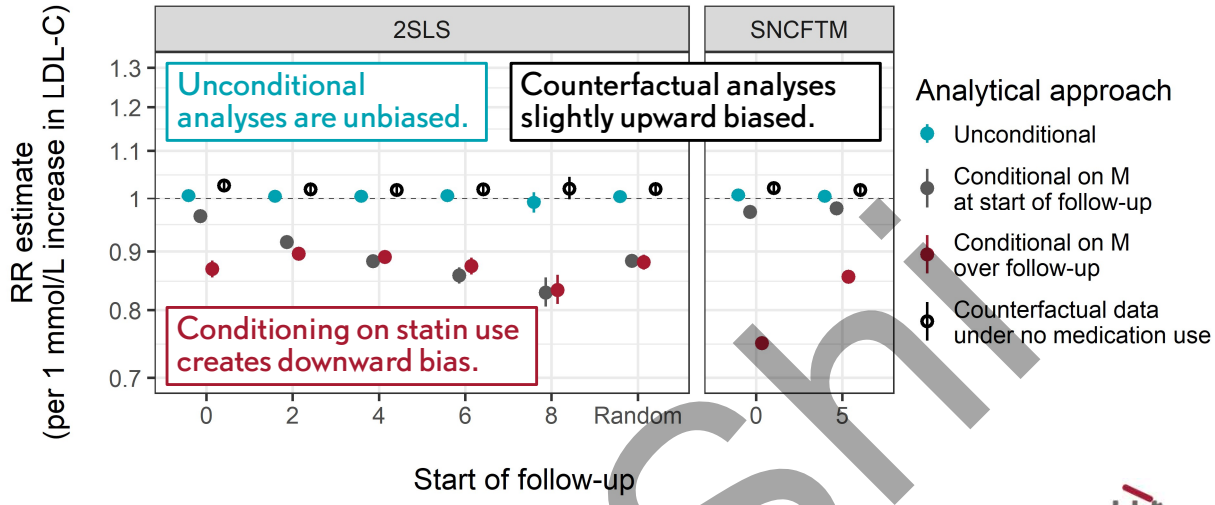
A_k: LDL cholesterol at time k

Y: CVD

A MR analysis of LDL cholesterol which conditions on statin use will introduce selection bias.

Simulation results for data generated under the null for A and M





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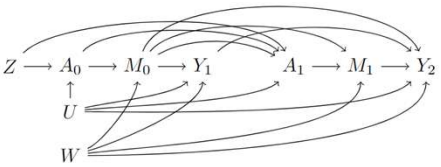
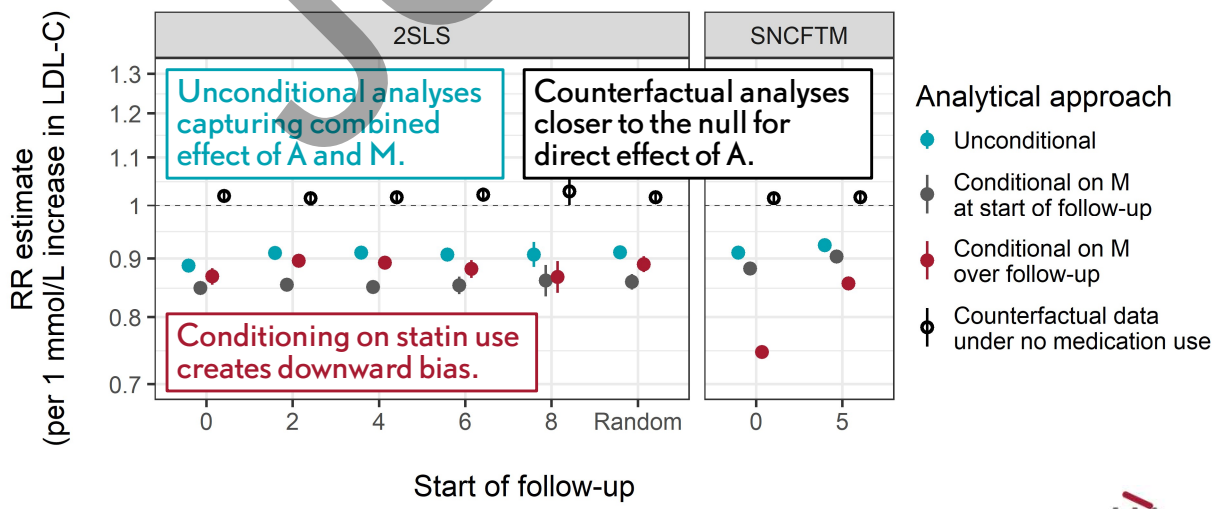
Simulation results for data generated under the null for A only





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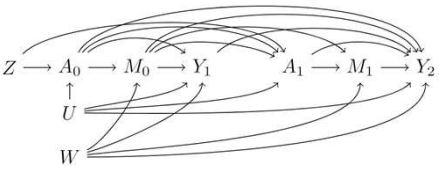
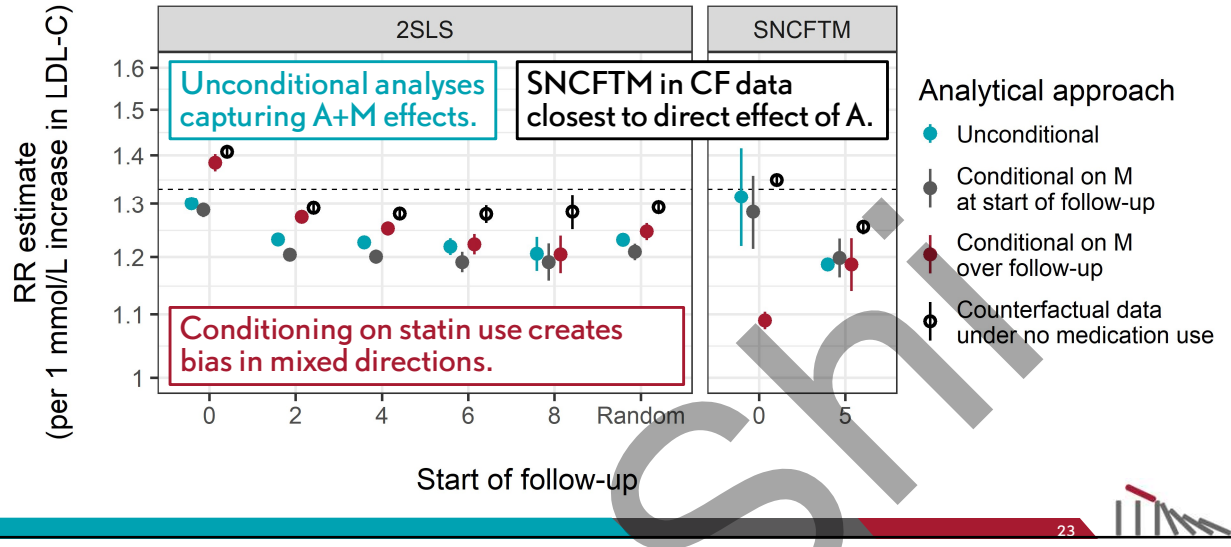
Simulation results for data generated not under the null for A or M





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