Emulating target trials for nutritional studies:

Instrumental variable methods

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Overview

Instrumental variable (IV) methods

Mendelian randomization (MR) as an application of IV

Alcohol intake and CVD

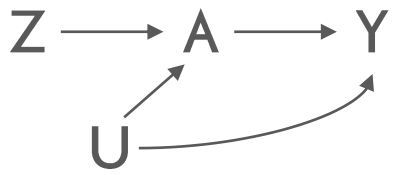
- Simple analogy between MR and randomized controlled trials
- Target trial emulation using MR
- Threats to emulation success

Instrumental variable conditions

Need a variable (i.e., an instrument, Z) that meets three conditions:

1. **Relevance**
   Associated with exposure
2. **Exclusion restriction**
   Does not affect outcome except through potential effect on exposure
3. **Independence**
   No common causes (or other sources of lack of exchangeability) with outcome

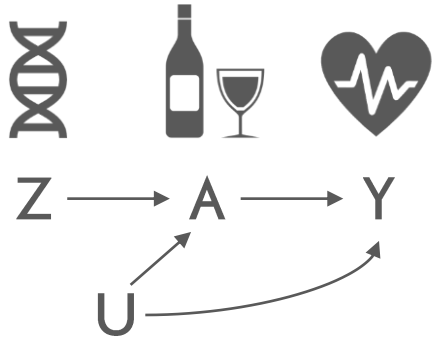
To estimate a point effect, need homogeneity or monotonicity



Canonical IV DAG

Mendelian randomization (MR) studies of nutritional factors as an application of IV

- Increasingly popular application of IV
- Genetic variants used as proposed instruments
- Leverage genetic data to estimate the effect of a non-genetic exposure on an outcome



Z: genetic variant(s) related to alcohol intake

A: alcohol intake

Y: coronary heart disease

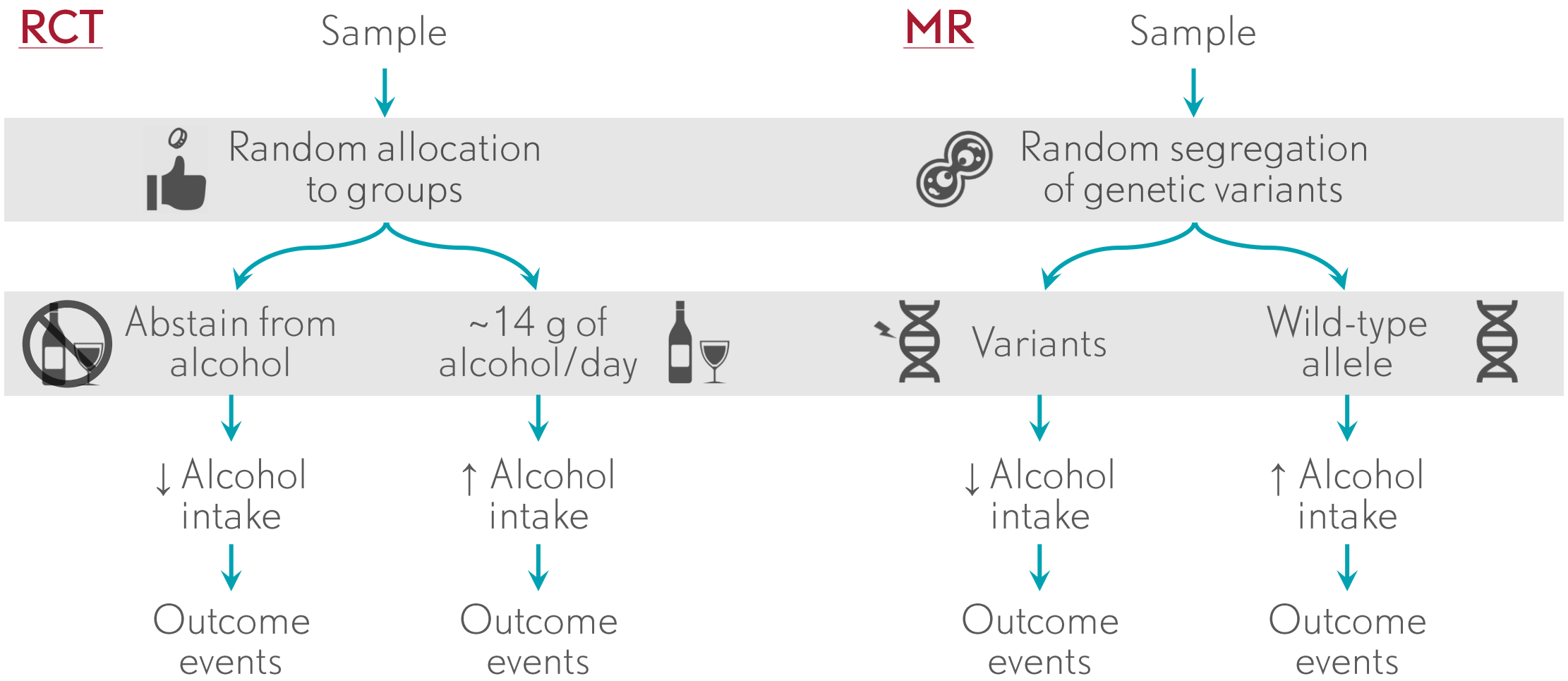
The appeal of MR studies

Identify causal effects even with unmeasured confounding

"Natural analogue" of a randomized controlled trial

Estimate the long-term ("lifetime") effects of exposures

A simplistic analogy between MR and RCTs



See Sanderson et al. (Nat Rev Methods Primers 2022), Larsson (Curr Opin Lipidol 2021), Smith & Ebrahim (BMJ 2005)

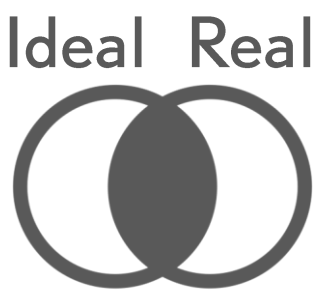
The appeal of MR studies

The New York Times

Does Moderate Drinking Protect Your Heart? A Genetic Study Offers a New Answer.

"Because the variants are distributed randomly in a population, they can serve in a study as the equivalent of randomly assigning people to abstain or to drink at varying levels."

Why explicitly emulate a target trial for MR studies?



Distinguish between the target trials:

- Ideally like to emulate
- Can realistically emulate using MR

Avoid methodological pitfalls

Inform the plans to use or avoid a MR approach

Consider a target trial for alcohol intake and CVD

Protocol component	Target trial specification	Target trial emulation
Eligibility criteria	• ≥50 years old • No history of CVD, alcohol/substance abuse • No intolerance or allergy to alcohol • No chronic kidney or liver disease	Same, plus • Must have available genetic data
Treatment strategies	1. Never drink 2. One standard serving (~14 g) daily of a preferred alcohol beverage	Same
Assignment procedures	Randomly assigned at baseline; unblinded	Randomly assigned at conception, assuming IV conditions hold

Consider a target trial for alcohol intake and CVD

Protocol component	Target trial specification	Target trial emulation
Follow-up period	**Start**: at randomization **End**: development of the outcome, loss to follow-up, or administrative end of follow-up	**Start**: time of eligibility criteria/outcome recording **End**: same
Outcome	Time to first occurrence of CVD event	Same
Causal contrasts of interest	Per-protocol effect	Same
Analysis plan	Per-protocol analysis accounting for time-varying adherence	Same

The follow-up period in the target trial vs. MR

Target trial

Unified "time zero"

(1) Randomization / treatment assigned
(2) Eligibility criteria applied
(3) Outcome recording begins

Time since start of follow-up

0

End of follow-up

Mendelian randomization

Misaligned "time zero"

(1) Randomization / treatment assigned at conception

(2) Eligibility criteria applied
(3) Outcome recording begins

Age

0

Unspecified period

Swanson et al. (Epidemiology 2017)

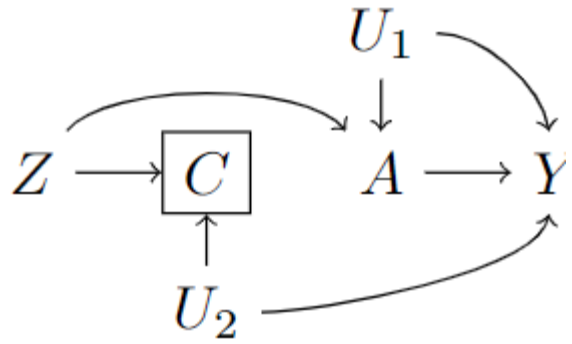
The follow-up period in the target trial vs. MR

Emulate RCTs with a lag between time of randomization and time of eligibility/outcome recording

- Lag time can be years or decades
- Average age of 50+ years for participants in MR studies of nutritional factors

Post-randomization selection may introduce bias

- Genetic factor (instrument) related to survival, eligibility, etc.
- Violation of instrumental conditions



Swanson et al. (Epidemiology 2017)

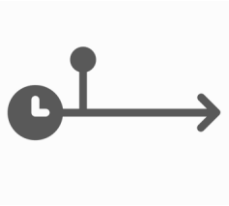
Analysis plan: (Adherence to a given) diet changes over time…

Target trial

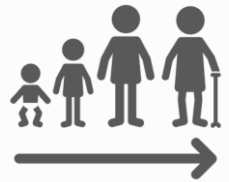
Expect per-protocol analysis to incorporate repeated measures of adherence

Estimate long-term effects of a given dietary intervention

Conventional Mendelian randomization



Generally conducted on a single measurement of "adherence"/ exposure



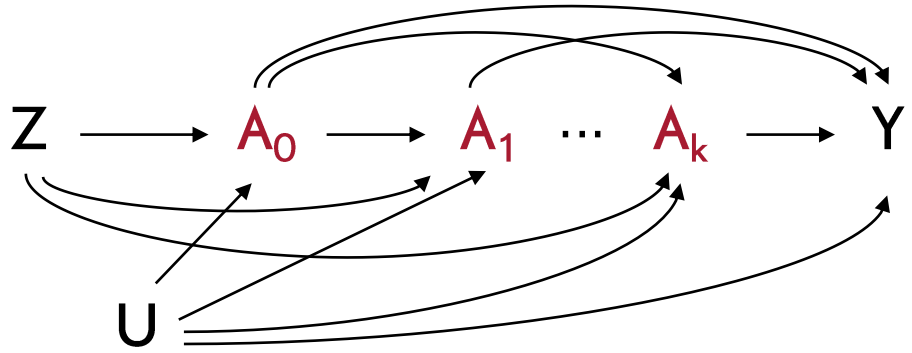
MR estimate often interpreted as a "lifetime effect"

- Requires strong, unverifiable assumptions about genetic effects over time†

† Labrecque and Swanson (AJE 2019)

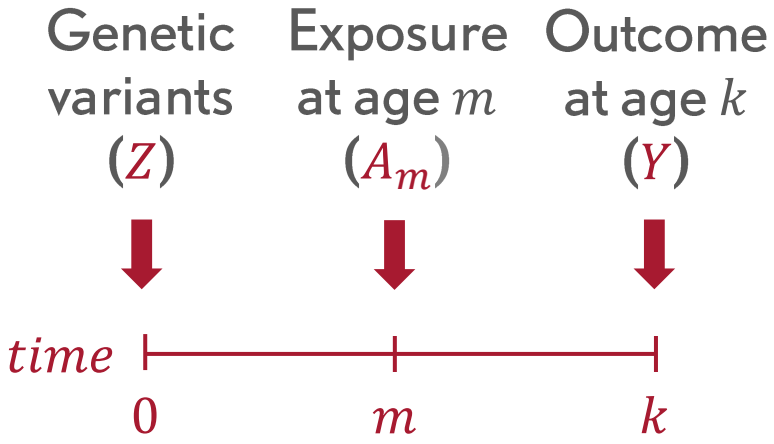
Analysis plan: (Adherence to a given) diet changes over time…

- Methods which can accommodate repeated measures of a time-varying exposure, e.g.
  - G-estimation of structural nested models†
- Be explicit about the causal estimand of interest
  - Multiple causal estimands can be targeted
  - Different assumptions needed

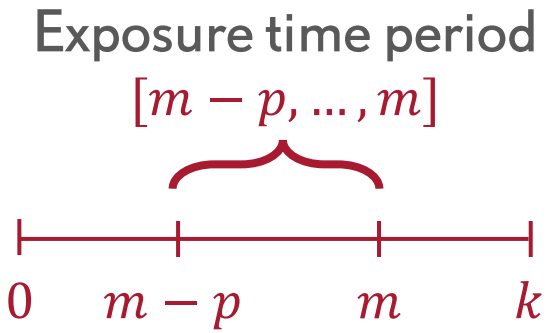


†Shi et al. (Epidemiology 2022), Shi et al. (BMC Med Res Methodol 2022)

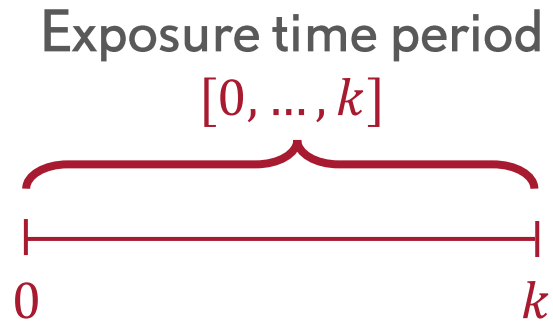
What types of causal estimands can we target?



Point effect:
e.g., effect of alcohol at age 50



Period effect:
e.g., effect of alcohol from age 50-60



Lifetime effect

Takeaways

Mendelian randomization (and IV methods) are an appealing alternative to confounding-adjustment methods

Given the complexities of studying nutritional factors, more explicit target trial emulation in MR studies can clarify:

- Sources of potential biases (e.g., misalignments in time zero)
- An appropriate analytical strategy that accommodates the time-varying nature of diet (e.g., g-estimation of SMMs)
- The causal estimand of interest

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Questions

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