Mendelian randomization with time-varying exposures

Challenges in timing, estimation and interpretation

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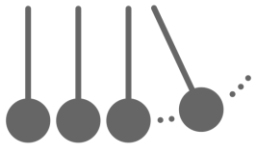
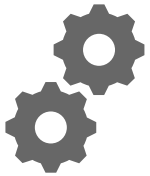
Overview

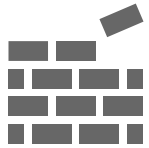
Mendelian randomization (MR) as an application of instrumental variable (IV) analysis and its limitations



Causal interpretations of MR estimates and their assumptions



Methods to incorporate repeated measures of an exposure in MR analyses



An application of structural models in a MR study and current works in progress

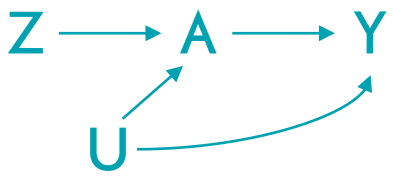
Instrumental variable methods for causal inference

Three broad classes of causal inference methods:

1. Confounding adjustment approaches
2. Frontdoor criterion
3. Instrumental variable (IV) methods

For IV methods, need a variable (i.e., an instrument, Z) that meets three conditions:

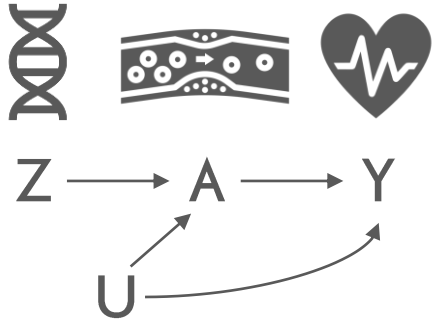
1. **Relevance**
   Associated with exposure



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

Mendelian randomization (MR) as an application of IV

- Increasingly popular application of instrumental variable analysis
- Genetic variants are 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 LDL cholesterol

A: LDL cholesterol

Y: coronary artery disease

The appeal of MR studies

Identify causal effects even with unmeasured confounding

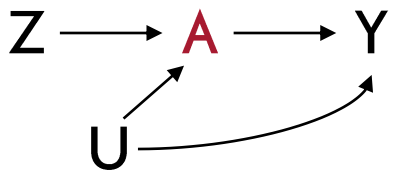
"Natural analogue" of a randomized controlled trial

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

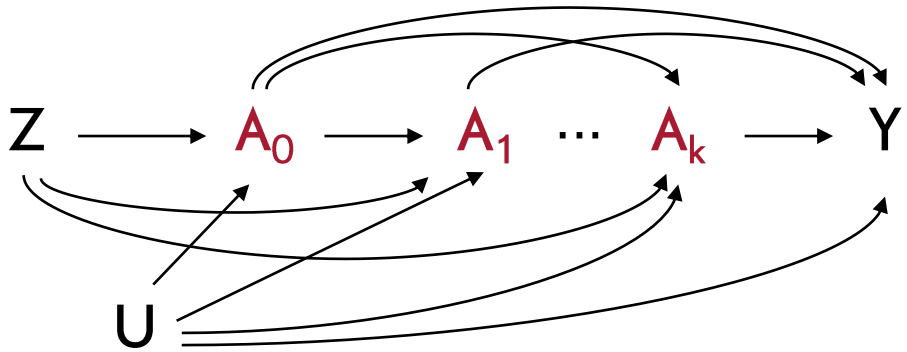
MR studies are generally concerned with the effects of time-varying exposures

- Examples: alcohol intake, blood pressure, LDL cholesterol, BMI, sleep duration, smoking
- Our IV DAG should reflect the fact that the exposure can change over time
- Time zero ($k = 0$) is at conception (when genes are assigned)

Time-fixed exposure



Time-varying exposure



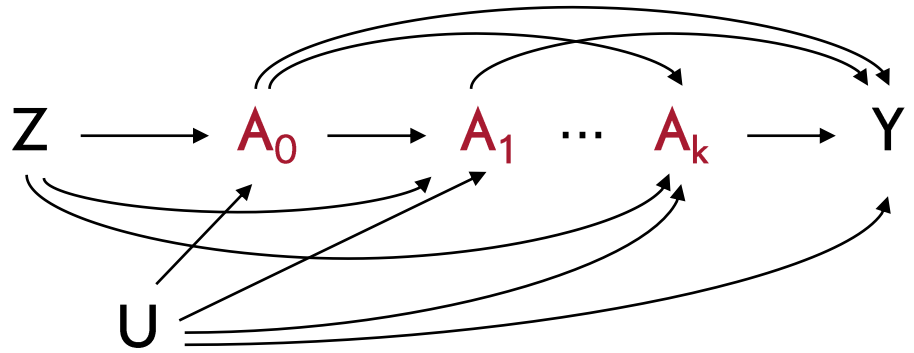
However, most MR studies ignore the time-varying nature of the exposure.

Why?

- Most biobanks only measure phenotypes are one time point
- Conventional IV methods (e.g., Wald estimator, two-stage least squares) weren't designed for time-varying exposures

How are most MR studies conducted in practice?

- A single measurement of the exposure is considered in the analysis
- The timing of this exposure measurement varies across individuals (e.g., for some, it's at $k = 40$, for others at $k = 45$, etc.)



- MR estimate is interpreted as the "lifetime effect" of the exposure on the outcome

How can we do better with MR?

- Define the types of causal estimands that can be targeted using Mendelian randomization
- Describe what additional assumptions are needed (if any) to identify these causal estimands using Mendelian randomization
- Propose methods to account for time-varying exposures in IV analyses

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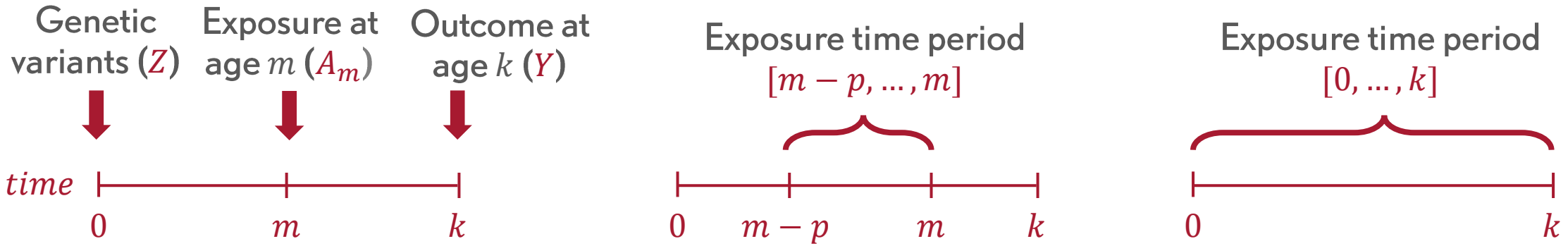
Causal estimands in Mendelian randomization studies and their assumptions

What types of causal estimands can we target?



Point effect:

$$\mathrm{E}[Y^{a_m}] - \mathrm{E}\left[Y^{a'_m}\right]$$

Period effect:

$$\mathrm{E}[Y^{a_{m-p},\ldots,a_{m-1},a_m}] - \mathrm{E}\left[Y^{a'_{m-p},\ldots,a'_{m-1},a'_m}\right]$$

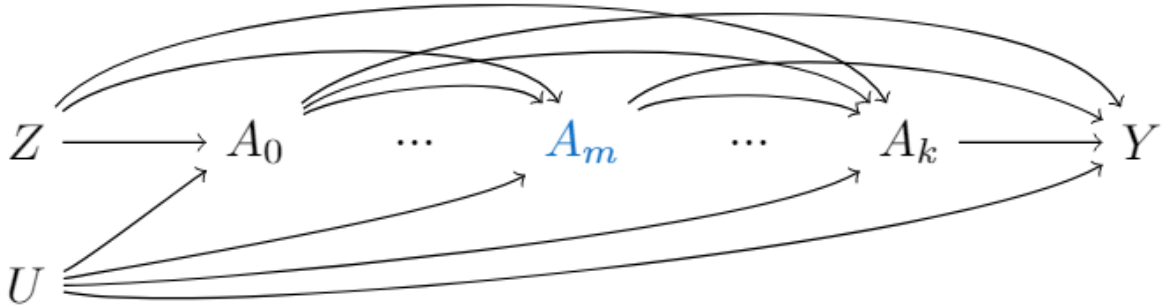
Lifetime effect:

$$[Y^{\bar{a}_k}] - \mathrm{E}\left[Y^{\bar{a}'_k}\right]$$

The exclusion restriction assumption for a point effect

$\mathrm{E}[Y^{a_m}] - \mathrm{E}[Y^{a'_m}]$

Recall our DAG for a time-varying exposure:



To estimate the point effect, Z must meet the three instrumental conditions for only A_m as the exposure

- Exclusion restriction assumption states "instrument does not affect outcome except through exposure"
- The only paths from Z to Y must go through A_m
- Presence of other exposure time points may violate this condition, e.g.

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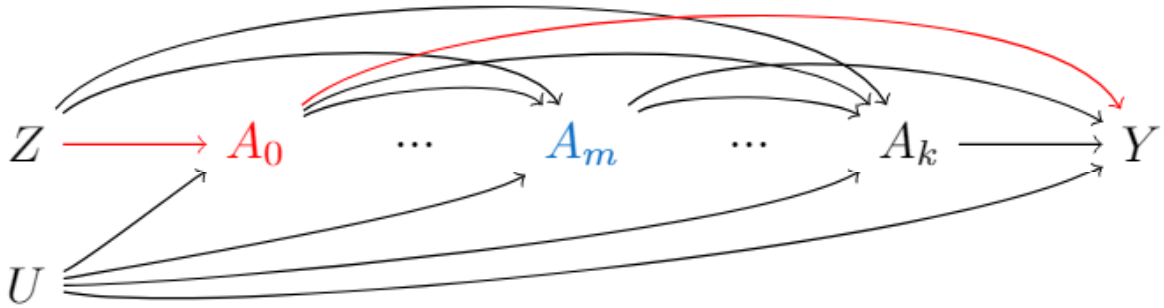

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  - Z affects A_0, and A_0 affects Y

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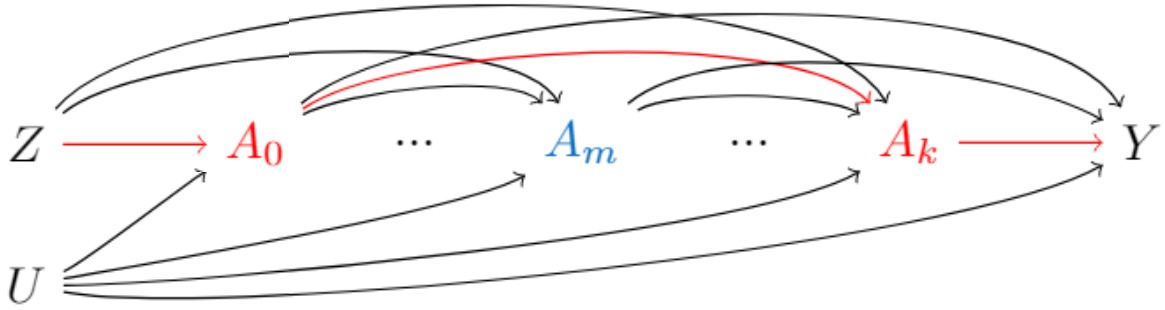

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- Exclusion restriction assumption states "instrument does not affect outcome except through exposure"
- The only paths from Z to Y must go through A_m
- Presence of other exposure time points may violate this condition, e.g.
  - Z affects A_0, and A_0 affects Y
  - Z affects A_0, A_0 affects another exposure time point (A_k), and A_k affects Y

The exclusion restriction assumption for a point effect

For the exclusion restriction assumption to hold, need all exposure time points other than A_m to be

- Unaffected by the instrument Z; or
- Have no effect on the outcome Y not through A_m

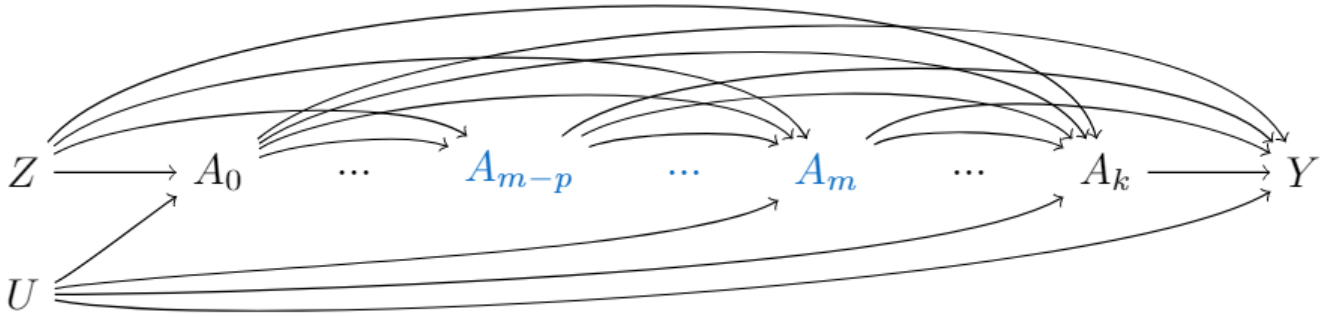
But…

- Genetic variants often have long-term effects on the exposure
- Critical windows of exposure can span years or decades for some outcomes

In general, wouldn't expect the exclusion restriction assumption to hold when identifying the point effects in MR studies.

The exclusion restriction assumption for a period effect

$$\mathrm{E}[Y^{a_{m-p},\ldots,a_{m-1},a_m}] - \mathrm{E}\left[Y^{a'_{m-p},\ldots,a'_{m-1},a'_m}\right]$$



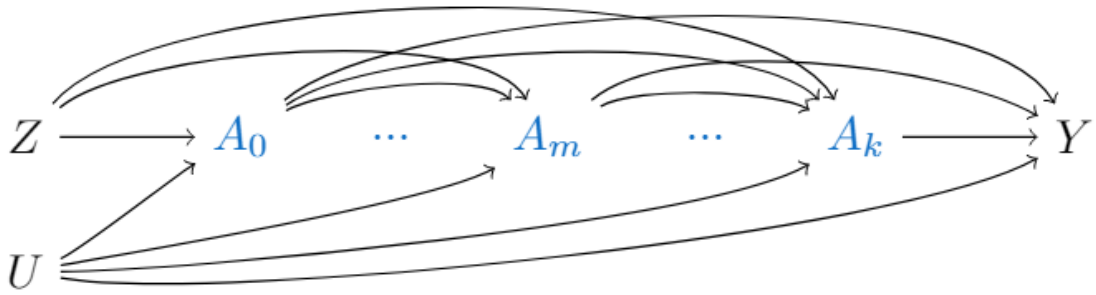
The exclusion restriction assumption must hold for the exposure during the time period $[m-p, \ldots, m]$, i.e., all exposure time points other than $(A_{m-p}, \ldots, A_{m-1}, A\_m)$ need to

- Be unaffected by the instrument Z; or
- Have no effect on the outcome Y not through $(A_{m-p}, \ldots, A_{m-1}, A_m)$

With a longer period, the number of arrows that need to be removed decreases.

The exclusion restriction assumption for a lifetime effect

$$\mathrm{E}[Y^{\bar{a}_k}] - \mathrm{E}\left[Y^{\bar{a}'_k}\right]$$

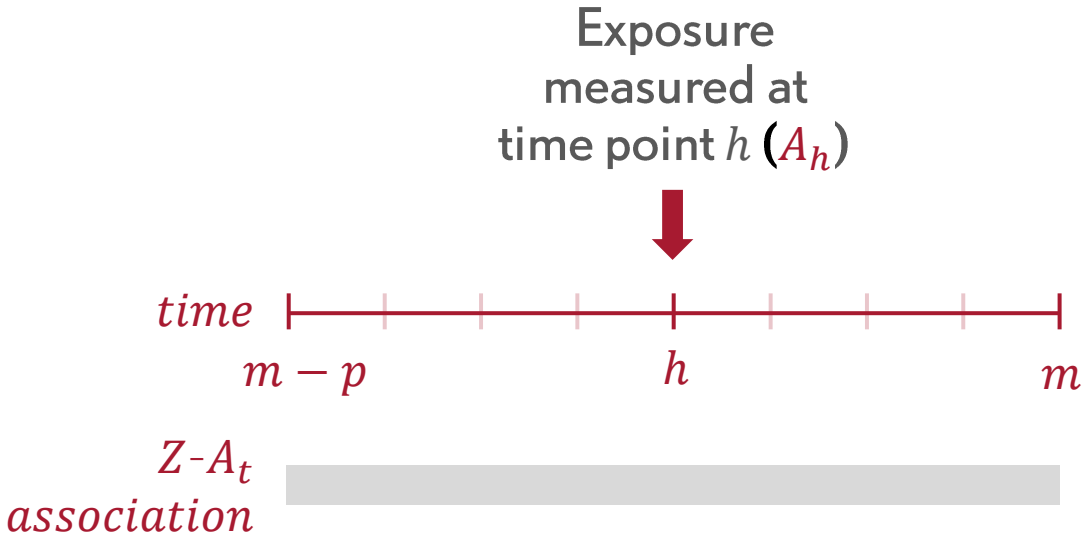


- Can consider the lifetime effect as a type of period effect in which the period spans from time $\mathbf{0}$ (i.e., at conception) until time $\boldsymbol{k}$ (i.e., the development of the outcome)
- No violation of the exclusion restriction assumption through exposure time points (because we are intervening on all exposure time points)

Additional assumptions for the period/lifetime effect

- The IV conditions (and homogeneity/monotonicity) may not be sufficient for identifying the period effect in MR studies
- Additional assumptions may be needed
  - The types of assumptions will depend on the number of exposure measurements that are considered in the IV analysis
  - The number of exposure measurements also affects the types of period effects that can be identified

Identification of the period/lifetime effect with the exposure measured at one time point



Can identify the effects of shifting the whole exposure trajectory during the period $(A_{m-p}, \ldots, A_m)$ by one unit:

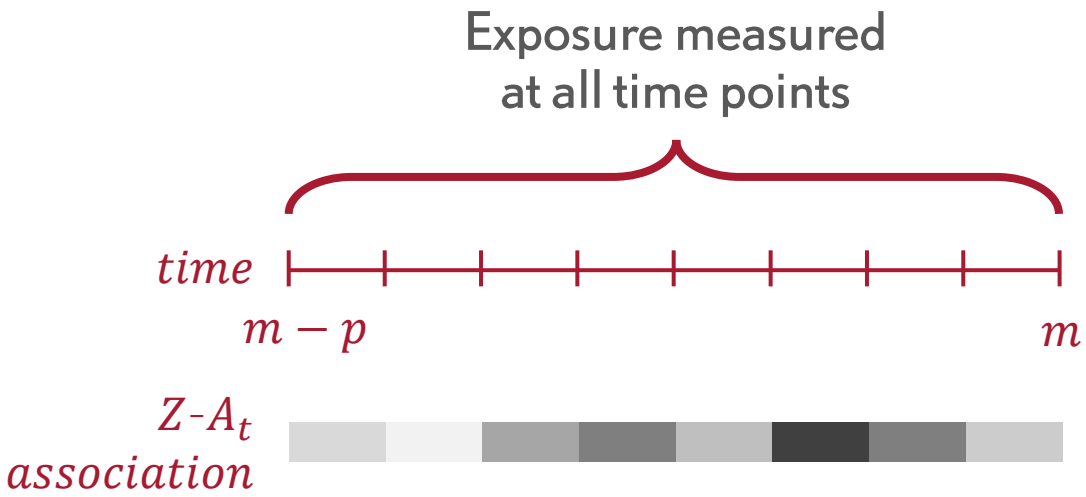
$$E[Y^{a_{m-p}+1,\ldots,a_{m-1}+1,a_m+1}] - E[Y^{a_{m-p},\ldots,a_{m-1},a_m}]$$

The magnitude of the association between the instrument and the exposure must stay constant during this period.

"If the relationship between $[Z]$ *and* A *changes over time, it cannot be adequately summarized by measuring it at 1 time point."*

(Labrecque and Swanson, AJE 2018)

Identification of the period/lifetime effect with the exposure measured at all relevant time points

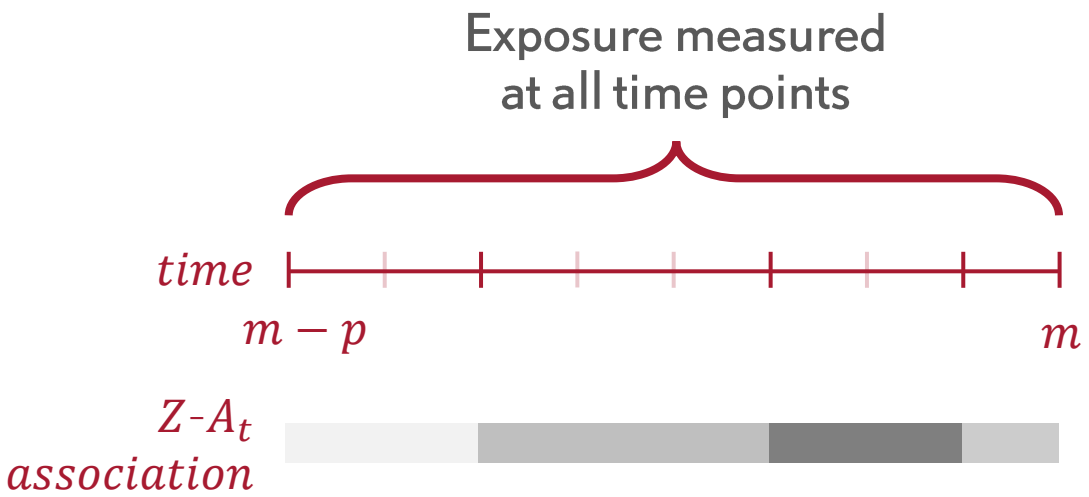


- Need multiple instruments with variation in their associations with the exposure association to disentangle effects of the exposure between time points
- Regardless, can identify the overall effect of shifting the exposure trajectory

Can identify controlled direct effects of each time point, e.g.

- What if we increase earlier exposures but keep later exposures constant?
- What if we decrease early exposures but increase later exposures?

Identification of the period/lifetime effect with the exposure measured at a subset of all time points



- Z-A_t association is constant from one measured exposure time point to the next to estimate the effect during that interval
- With variation in the instrument-exposure relationship, can identify controlled direct effects of each measured interval

2

Instrumental variable methods for time-varying exposures

Structural models for time-fixed outcomes

- Originally proposed to estimate the effects of time-varying exposures while adjusting for time-varying confounders
- Can be adapted for IV analyses but rarely used in practice

- Structural mean models are models for the causal effect
- For example, for a period effect:

$$\mathrm{E}\left[Y^{a_{m-p},\ldots,a_{m-1},a_m} - Y^{\bar{0}} | A_{m-p}, \ldots, A_m, Z\right] = \gamma\left(A_{m-p}, \ldots, A_m; \psi\right)$$

Model the period effect of interest…

…conditional on the exposures and the instruments…

…as some function (γ) of the exposures, indexed by ψ…

…where ψ represents the estimate for the causal effect(s) of interest

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$$\mathrm{E}\left[Y^{a_{m-p},\ldots,a_{m-1},a_m} - Y^{\bar{0}} | A_{m-p}, \ldots, A_m, Z\right] = \psi_1 A_{m-p} + \cdots + \psi_p A_{m-1} + \psi_p A_m$$

ψ_1 represents effect of increasing A_{m-p} by one unit, holding $A_{m-p+1}, \ldots, A_m$ constant

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Because of our homogeneity assumption,
this model cannot be dependent on Z
(i.e. no effect modification by Z)

G-estimation

Each structural model corresponds to an estimating equation that is a function of ψ^*:

$$U(\psi^*; Z_i) = H_i(\psi^*)(Z_i - E(Z))$$

Note: we use ψ^* to represent "proposed" values of ψ

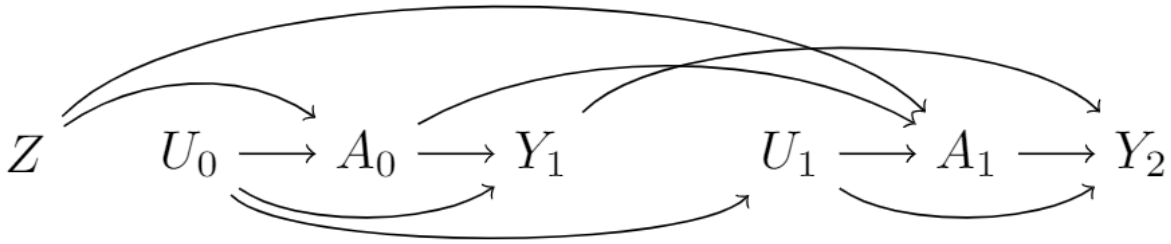
When ψ^* is equal to its true value (i.e. ψ), then the estimating equation (across all individuals i) will be equal to zero:

$$E[U(\psi; Z_i)] = 0$$

- For additive structural mean models (i.e. with continuous outcomes), there is a closed form solution to solve for ψ
- For multiplicative structural mean models, need to use a search algorithm (e.g. Newton Raphson) to solve for ψ

Structural models for failure time outcomes

We can also use structural models to model a failure-time outcome:



where Y_{k+1} is an indicator (1 : yes, 0: no) for developing the outcome by the end of the period k

Here, we indicate a time-fixed instrument (e.g., in Mendelian randomization studies) but we could also have a time-varying instrument.

Structural nested cumulative failure time models (SNCFTMs)

$$\exp[\gamma_k(\bar{A}_m;\psi)] = \begin{cases} \dfrac{\mathrm{E}\left[Y_k^{\bar{A}_m,\underline{0}} \middle| \bar{A}_m, Z, Y_m = 0\right]}{\mathrm{E}\left[Y_k^{\bar{A}_{m-1},\underline{0}} \middle| \bar{A}_m, Z, Y_m = 0\right]} & \text{if } Y_m = 0 \\ 1 & \text{if } Y_m = 1 \end{cases}$$

- Models the ratio of two counterfactual cumulative risks at time k under treatment strategies that differ only at time m for each time $m < k$
  - i.e., the conditional effect of a "blip" of treatment at time m on outcome at time k
- $\gamma_k(\bar{A}_m;\psi)$ is a blip function that is a function of treatment history through m, index by the parameter ψ
- The blip function cannot be a function of Z
- Example of a blip function: $\gamma_k(\bar{A}_m;\psi) = \psi A_m$

G-estimation of SNCFTMs

Solve the corresponding estimating equation

$$\mathrm{E}[U(\psi; Z)] = 0$$

where

$$U(\psi; Z) = \sum_{m=0}^{K} (1 - Y_m) \sum_{k=m+1}^{K+1} (Z - \mathrm{E}[Z|Y_m = 0]) H_{m,k}(\psi)$$

$$H_{m,k}(\psi) = \begin{cases} Y_k \exp\left(-\sum_{j=m}^{k-1} \gamma_j\left(\bar{A}_j; \psi\right)\right) & \text{if } Y_m = 0 \\ 1 & \text{if } Y_m = 1 \end{cases}$$

No closed form solution, so we use create a quadratic form of the estimating equation and use a search algorithm that finds the minimum (i.e., where $\psi = 0$) of this equation

Blipping down/up to obtain marginal counterfactual risks

- Our g-estimate $\hat{\psi}$ can be difficult to interpret (depending on the blip function)
- Can be used to calculate marginal counterfactual risks under a given treatment strategy

Blipping down:

- Estimate $\mathrm{E}[Y_k^{\bar{0}}]$
- "Remove" the effect (ψ) of each subject's nonzero treatments from the end of the study to the beginning of the study

Blipping up:

- Estimate $\mathrm{E}[Y_k^{g}]$
- "Adding" the effect of treatment to $\mathrm{E}[Y_g^{\bar{0}}]$ from the beginning of the study period to the end of the study period

Picciotto et al., JASA 2012

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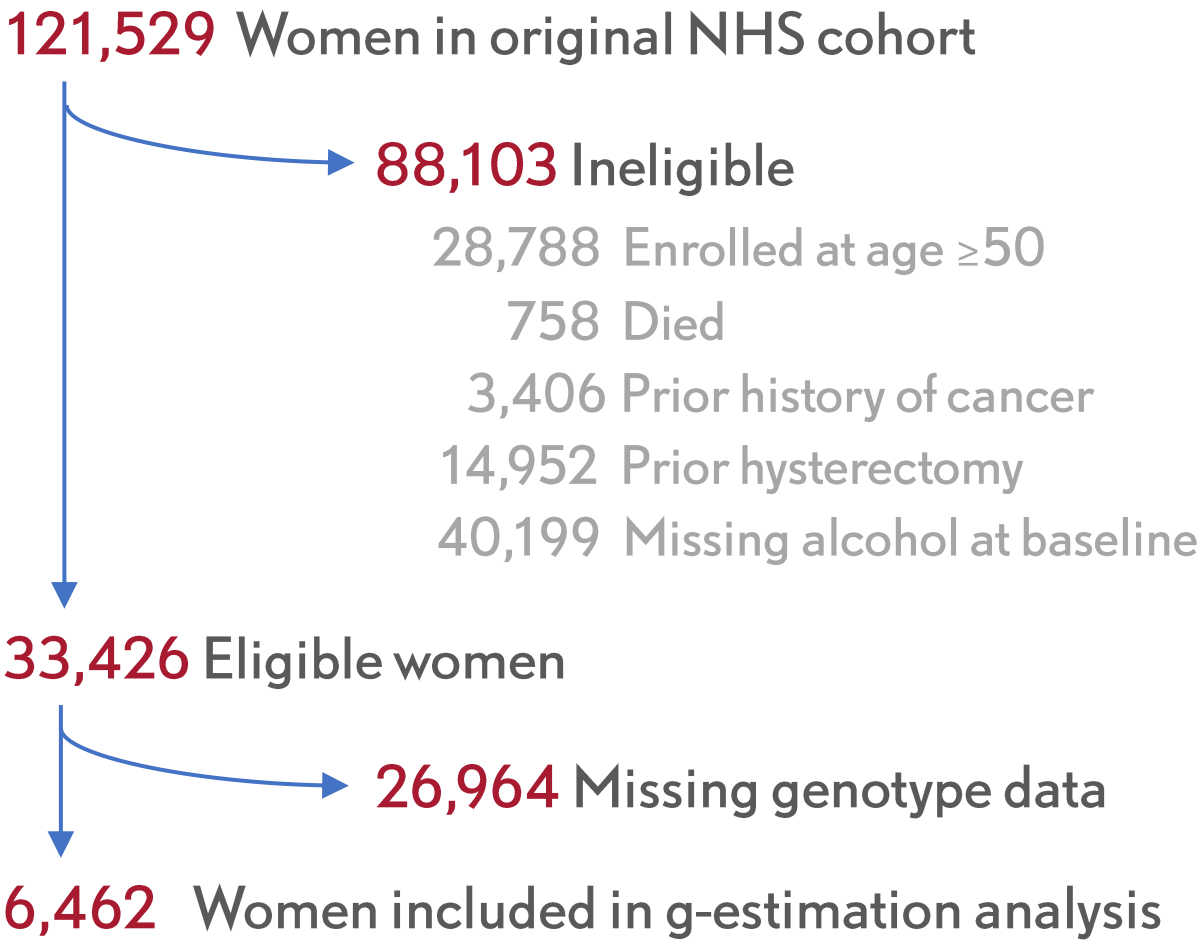
An application of g-estimation of SNCFTMs:

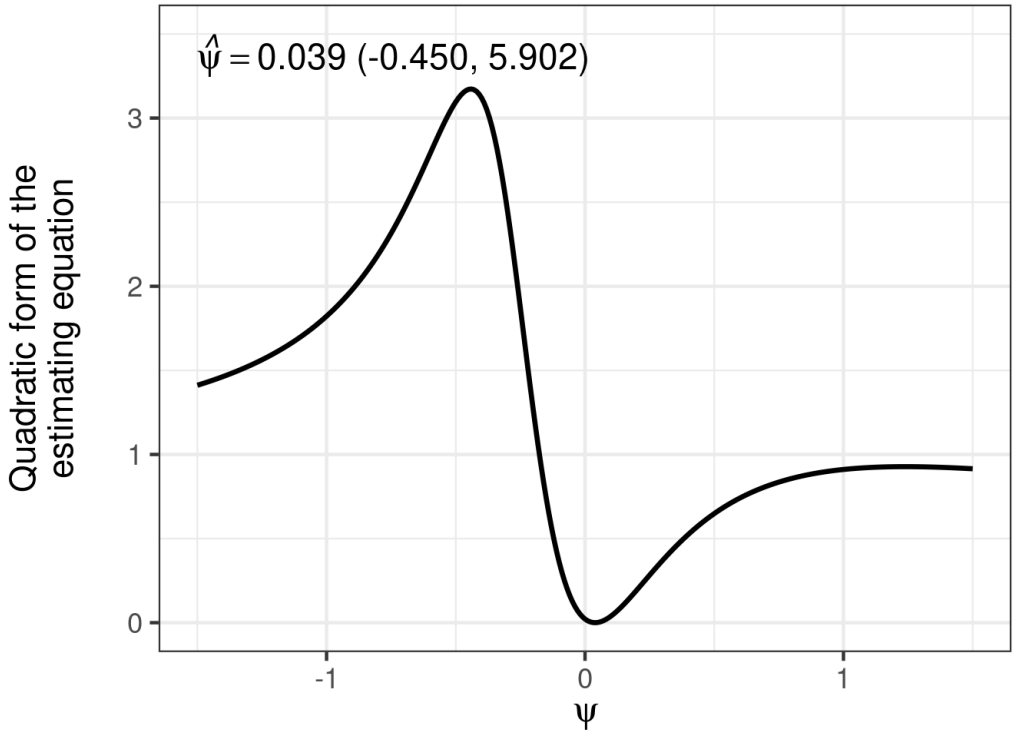
Alcohol intake and endometrial cancer risk in the Nurses' Health Study

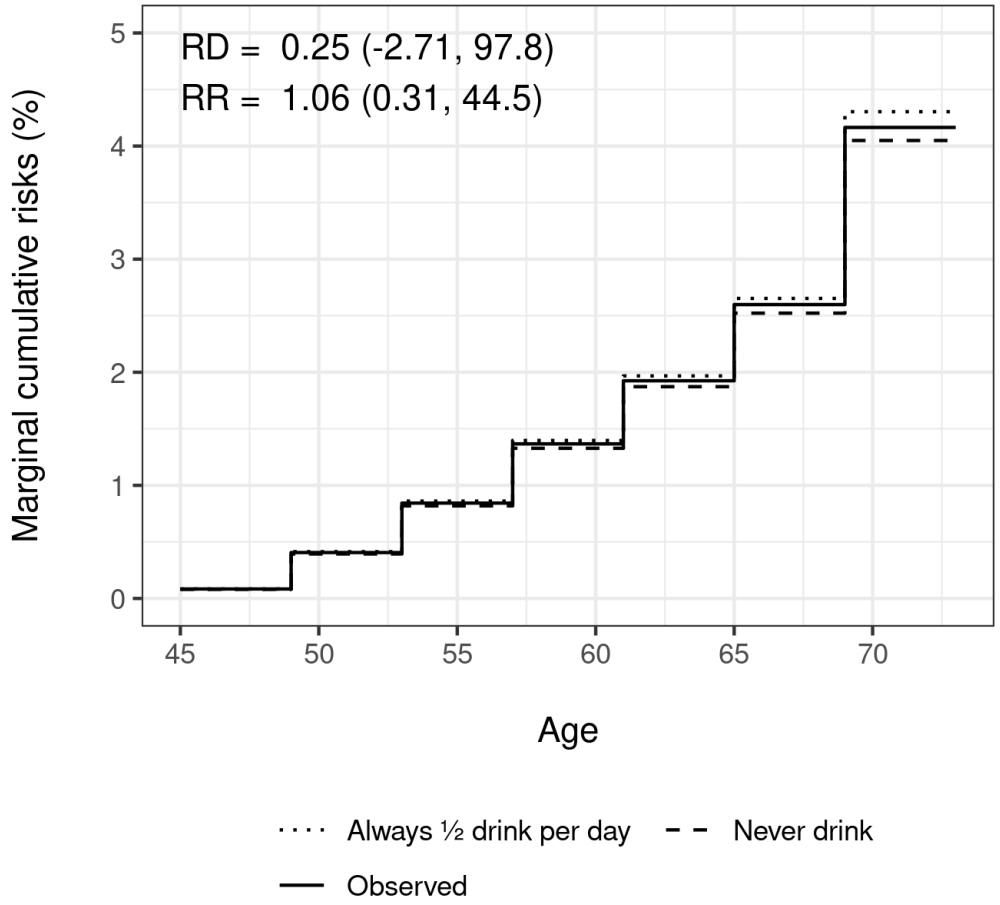
	Protocol of Target Trial	Deviations from the Target Trial in MR study
Eligibility criteria	Women aged 45-48 years; no history of cancer (except for non-melanoma skin cancer) or alcoholism; intact uterus	Additional criteria: women enrolled in Nurses' Health Study; alcohol intake must be measured at baseline
Treatment strategies	(1) Never drink (2) Always ½ drink/day, unless an absolute contraindication for moderate alcohol consumption arises	Can only compare static strategies (e.g., always ½ drink per day, regardless of contraindications for moderate alcohol consumption)
Assignment procedures	Randomly assigned to either strategy at baseline and are aware of the strategy they've been assigned to	Randomly assigned a weighted allele score that is related to their alcohol intake
Follow-up period	Starts at randomization and ends at development of endometrial cancer, incomplete follow-up, or 28 years after baseline (whichever occurs first)	Starts at the time of return of the first questionnaire after all eligibility criteria were met
Outcome	Endometrial cancer	N/A
Causal contrasts	Intention-to-treat effect Per-protocol effect	N/A
Analysis plan	ITT analysis Non-naïve per-protocol analysis	Gene-outcome associations G-estimation of SNCFTM via an instrument

Study population



Results


$\hat{\psi} = 0.039$ (-0.450, 5.902)
Quadratic form of the estimating equation
0
1
2
3
-1
0
1
ψ


RD = 0.25 (-2.71, 97.8)
RR = 1.06 (0.31, 44.5)
Marginal cumulative risks (%)
0
1
2
3
4
5
45
50
55
60
65
70
Age
Always ½ drink per day
Never drink
Observed

4

Current works in progress & potential future applications

Current works in progress & potential future applications

Selection bias in Mendelian randomization studies of biomarkers

- MR analyses of biomarkers (e.g., LDL cholesterol) often restrict to non-users of medications that modify levels of these biomarkers (e.g., statins)
- This can introduce selection bias and g-methods are needed to adequately adjust for this bias

More flexible blip functions for SNCFTMs

- Requires estimation of more psi parameters
- Allow for arbitrary risk curves (e.g., crossing curves)

Per-protocol analyses of trials using SNCFTMs

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