Interpretation of effect estimates in "Mendelian randomization" studies

The Future of Mendelian Randomization Studies 2021

Miguel Hernán and Joy Shi
CAUSALab, Department of Epidemiology
Harvard T.H. Chan School of Public Health

CAUSALab
A Center to Learn What Works

HARVARD
T.H. CHAN
SCHOOL OF PUBLIC HEALTH

If the goal is to estimate an effect, what exactly are we estimating in MR studies?

- Under a counterfactual framework of causal inference, we can define a per-protocol effect as:

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

- where
  - Y^{a} is the outcome that would have been observed had treatment A been set to the value a
- i.e., the difference in the mean counterfactual outcomes had everyone's treatment been set to a versus a'

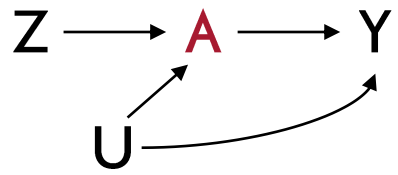
If the goal is to estimate an effect, what exactly are we estimating in MR studies?

- However, most MR studies interpret their estimates as a "lifetime effect"
- Doesn't correspond to the causal estimand for the per-protocol effect defined on the previous slide:

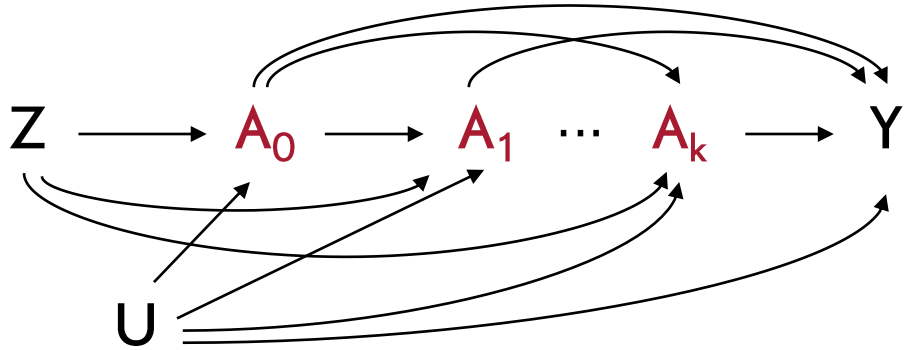
$$\mathrm{E}[Y^{a}] - \mathrm{E}[Y^{a'}]$$

- Why? Most MR studies are concerned with the effects of time-varying (not time-fixed) exposures
  - What causal estimands can we target?
  - What assumptions are needed?
  - How do the assumptions change depending on the number of exposure measurements we have?

Time-fixed exposure

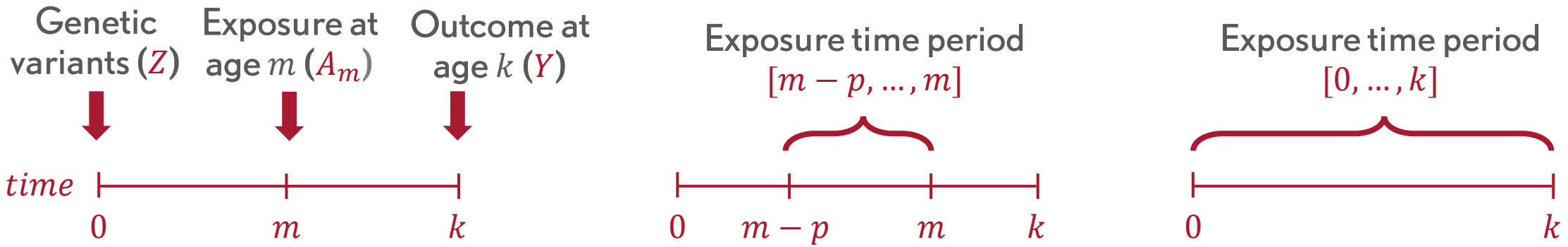


Time-varying exposure



(Vanderweele et al., Epidemiology 2014)

What types of causal estimands can we target?



Point effect:

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

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:

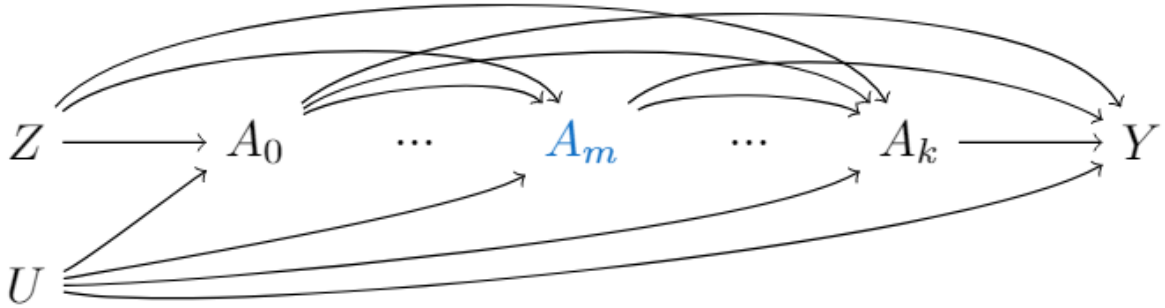
$$[Y^{\bar{a}_k}] - \mathrm{E}\left[Y^{\bar{a}'_k}\right]$$

(Shi et al., Epidemiology 2022;
Labrecque and Swanson, AJE 2019)

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:



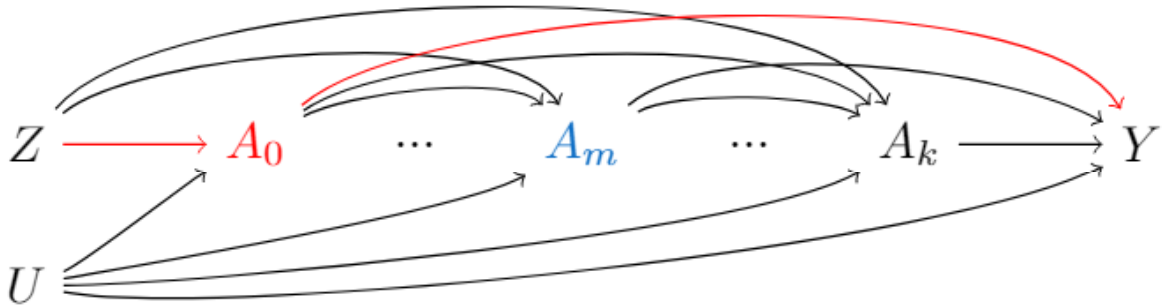
To estimate the point effect, Z must meet the three instrumental conditions for only A_m as the exposure

- 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.

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:



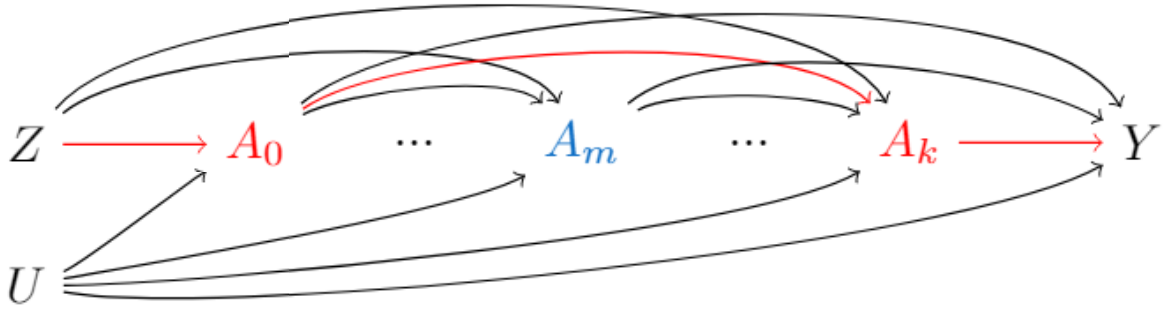
To estimate the point effect, Z must meet the three instrumental conditions for only A_m as the exposure

- 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.
  - Z affects A_0, and A_0 affects Y

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.
  - 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

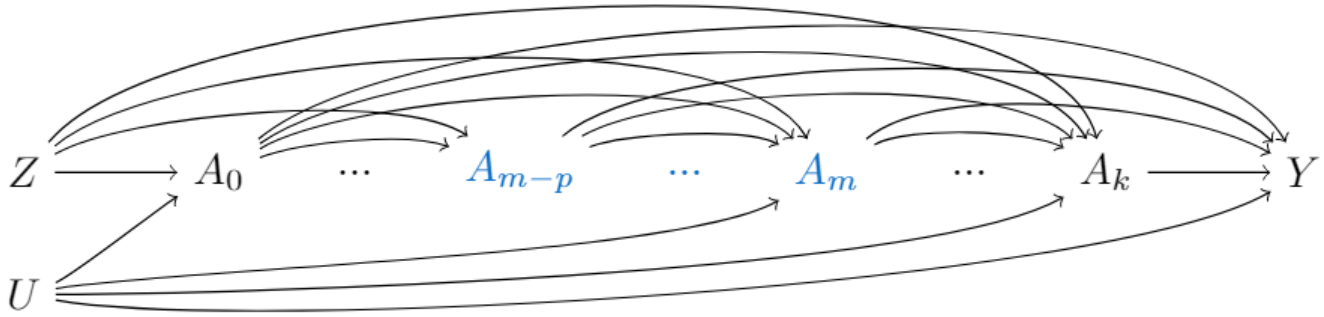
But…

- 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

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



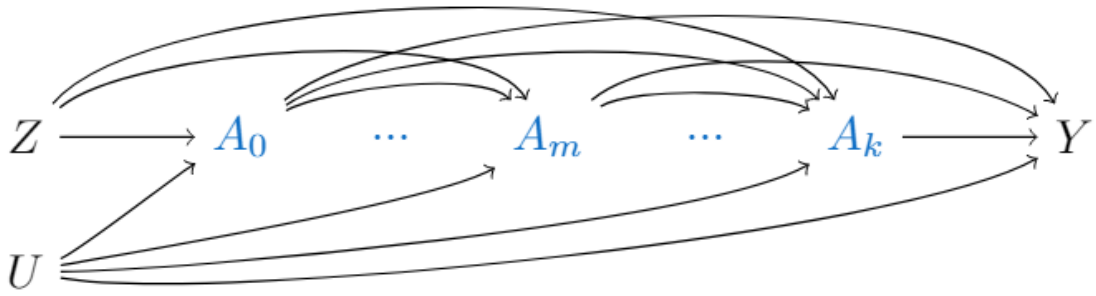
The exclusion restriction assumption must hold for the exposure during the time period $[m-p, \ldots, m]$, i.e., all exposure time points other than $(A_{m-p}, \ldots, A_{m-1}, A_m)$ need to

- 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

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

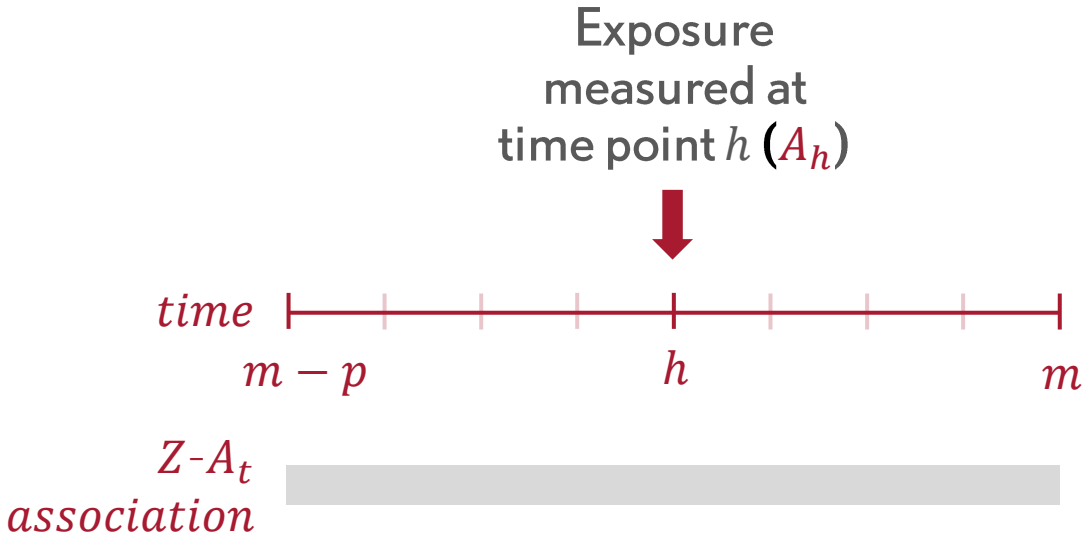


- Can consider the lifetime effect as a type of period effect in which the period spans from time 0 (i.e., at conception) until time k (i.e., the development of the outcome)
- No violation of the exclusion restriction assumption through exposure time points (because we are intervening on all exposure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

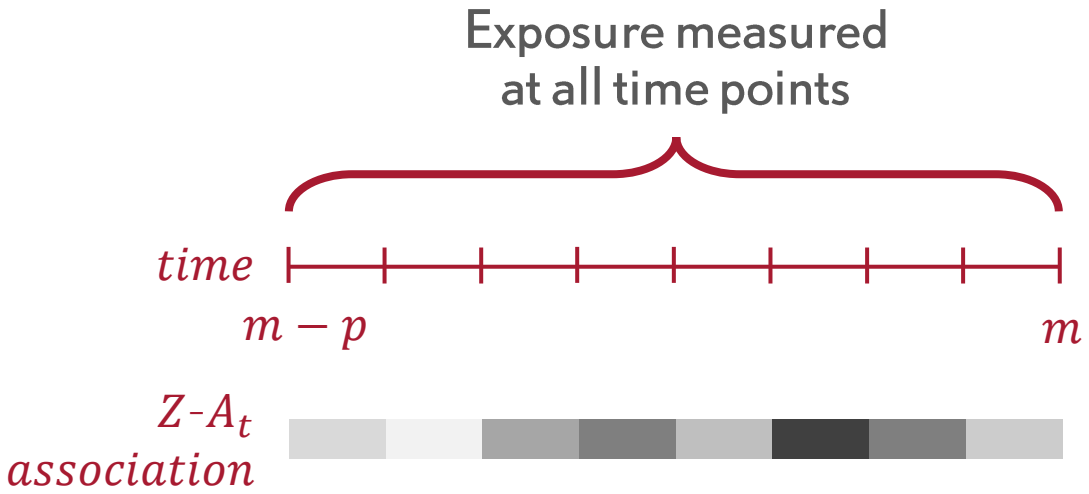
$$E[Y^{a_{m-p}+1,\ldots,a_{m-1}+1,a_m+1}] - E[Y^{a_{m-p},\ldots,a_{m-1},a_m}]$$

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 2019)

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



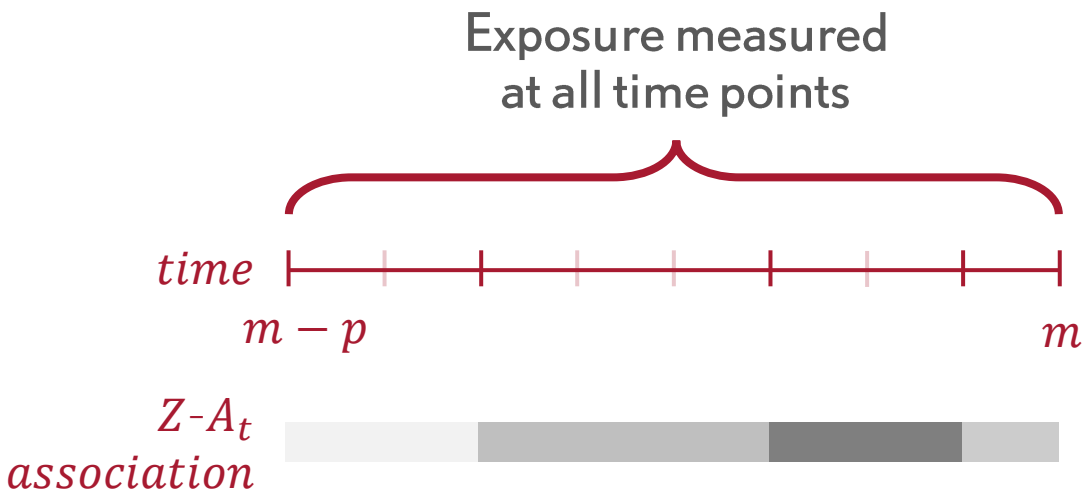
- Need multiple instruments with variation in their associations with the exposure association to disentangle effects of the exposure between time points
- Regardless, can identify the overall effect of shifting the exposure trajectory

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?

(Shi et al., Epidemiology 2022)

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

(Shi et al., Epidemiology 2022)

Summary

- Estimating analogues of the intention-to-treat and per-protocol effects in MR studies requires strong unverifiable assumptions
  - Complicated by the fact that MR studies are often interested in the effects of time-varying exposures
  - Different assumptions needed to target specific estimands (point effect, period effect, lifetime effect)
- If the goal is to test the null, IV estimation is not necessary
- Regardless of the goal, need clearly defined causal estimands and/or null hypotheses