Mendelian randomization:

Where are we now and where do we go from here?

Joy Shi, PhD
Instructor of Epidemiology
CAUSAL and 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

Disclosures

This research was supported by the U.S. Department of Veterans Affairs (VA) Office of Research and Development (ORD) Cooperative Studies Program (CSP) Epidemiology Center at the VA Boston Healthcare System through CSP #2032, by resources and the use of facilities at the VA Boston Healthcare System and VA Informatics and Computing Infrastructure (VINCI) (VA HSR RES 13-457).

The VA CAUSAL Methods Core is a collaboration between the Massachusetts Veterans Epidemiology, Research, and Information Center (MAVERIC) Division of Population Health and Data Sciences and the CAUSALab at the Harvard T.H. Chan School of Public Health.

CAUSALab
A Center to Learn What Works

Overview

- Mendelian randomization (MR) as an application of instrumental variable (IV) methods
  - What are we estimating with MR?
  - Who is being included in our MR analysis?
  - How do we obtain our MR estimate?
- How do we move forward with MR?

1

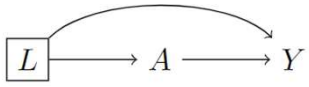
Mendelian randomization (MR) as an application of instrumental variable (IV) methods

CAUSALab
A Center to Learn What Works

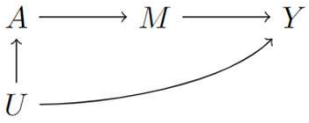
HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Three broad classes of methods for causal inference

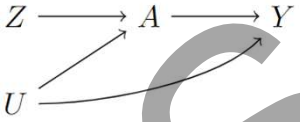
1. Confounding adjustment approaches (backdoor criterion)



2. Front-door criterion



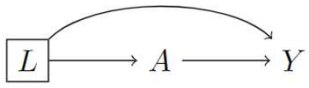
3. Instrumental variable methods



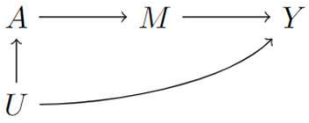
A: exposure
Y: outcome
L: measured common cause of A and Y
U: unmeasured common cause of A and Y
M: mediator
Z: instrument

Three broad classes of methods for causal inference

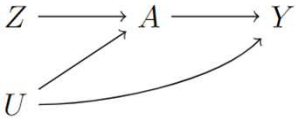
1. Confounding adjustment approaches (backdoor criterion)



2. Front-door criterion



3. Instrumental variable methods

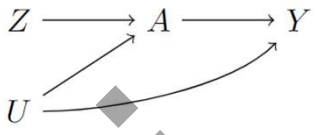


A: exposure
Y: outcome
L: measured common cause of A and Y
U: unmeasured common cause of A and Y
M: mediator
Z: instrument

IV and randomized trials

Consider a trial where:

- Participants are randomized to receive:
  - An invitation to one-time colonoscopy screening, *or*
  - No invitation
- Some (but not all) participants who receive the invitation undergo screening
- Followed for colorectal cancer mortality



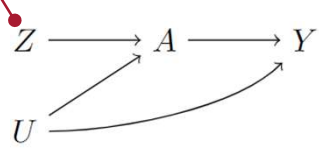
Z: randomization to invitation vs. no invitation
A: colonoscopy screening
Y: colorectal cancer mortality
U: unmeasured common cause of A and Y

IV and randomized trials

Consider a trial where:

- Participants are randomized to receive:
  - An invitation to one-time colonoscopy screening, *or*
  - No invitation
- Some (but not all) participants who receive the invitation undergo screening
- Followed for colorectal cancer mortality

Estimating the intention-to-treat effect (i.e., effect of Z on Y) is straightforward



…but we're probably not interested in the effect of the invitation on CRC mortality

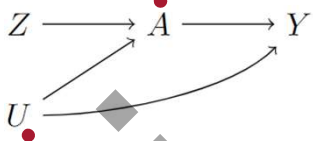
Z: randomization to invitation vs. no invitation
A: colonoscopy screening
Y: colorectal cancer mortality
U: unmeasured common cause of A and Y

IV and randomized trials

Consider a trial where:

- Participants are randomized to receive:
  - An invitation to one-time colonoscopy screening, *or*
  - No invitation
- Some (but not all) participants who receive the invitation undergo screening
- Followed for colorectal cancer mortality

We want the effect of colonoscopy screening on CRC mortality



…but estimating the per-protocol effect is complicated by confounding

Z: randomization to invitation vs. no invitation
A: colonoscopy screening
Y: colorectal cancer mortality
U: unmeasured common cause of A and Y

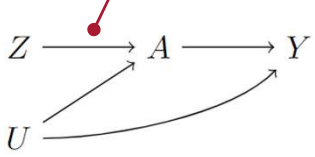
9

IV and randomized trials

We can learn something about the effect of A on Y under three conditions:

1. Relevance
   Z is associated with A

We expect receipt of invitation to be associated with being screened



Z: randomization to invitation vs. no invitation
A: colonoscopy screening
Y: colorectal cancer mortality
U: unmeasured common cause of A and Y

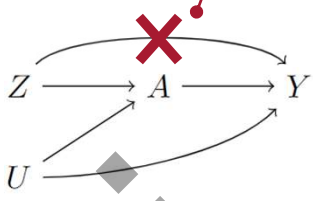
10

IV and randomized trials

We can learn something about the effect of A on Y under three conditions:

1. **Relevance**
   Z is associated with A
2. **Exclusion restriction**
   Z does not affect Y except through potential effect on A

We assume receipt (or not) of an invitation does not affect other behaviors that could, in turn, affect CRC mortality



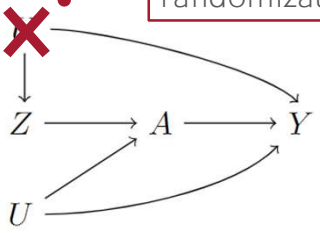
Z: randomization to invitation vs. no invitation
A: colonoscopy screening
Y: colorectal cancer mortality
U: unmeasured common cause of A and Y

IV and randomized trials

We can learn something about the effect of A on Y under three conditions:

1. **Relevance**
   Z is associated with A
2. **Exclusion restriction**
   Z does not affect Y except through potential effect on A
3. **Independence**
   No common causes (or other sources of lack of exchangeability) between Z and Y

Expect this to be true given randomization



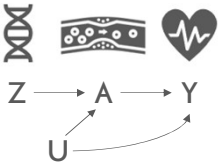
Z: randomization to invitation vs. no invitation
A: colonoscopy screening
Y: colorectal cancer mortality
U: unmeasured common cause of A and Y

In the observational setting, Mendelian randomization (MR) is an application of IV

- Increasingly popular application of instrumental variable analysis
- No randomization but, rather, use genetic variants as proposed instruments
- Leverage genetic data to estimate the effect of a non-genetic exposure on an outcome

In the observational setting, Mendelian randomization (MR) is an application of IV

- Increasingly popular application of instrumental variable analysis
- No randomization but, rather, use genetic variants as proposed instruments
- Leverage genetic data to estimate the effect of a non-genetic exposure on an outcome



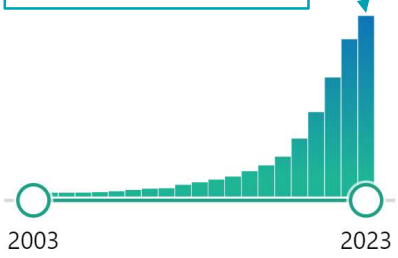
Z: genetic variant(s) related to LDL cholesterol

A: LDL cholesterol

Y: coronary artery disease

Mendelian randomization is everywhere…

1,847 publications as of 9/29 in 2023



> Orthop Surg. 2023 Sep 28. doi: 10.1111/os.13881. Online ahead of print.

Assessing the Casual Association between Sex Hormone Levels and Fracture Risk: A Two-Sample Mendelian Randomization Study

> Clin Epigenetics. 2023 Sep 28;15(1):154. doi: 10.1186/s13148-023-01572-z.

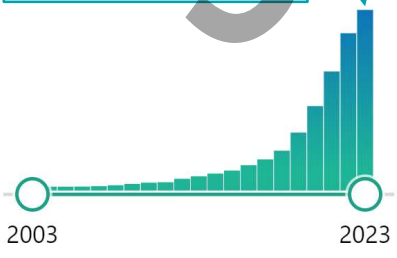
Effect of women's fertility and sexual development on epigenetic clock: Mendelian randomization study

> PLoS One. 2023 Sep 28;18(9):e0291086. doi: 10.1371/journal.pone.0291086. eCollection 2023.

Mendelian randomization study of gastroesophageal reflux disease and major depression

…and its applications are getting more and more… creative

1,847 publications as of 9/29 in 2023



> Orthop Surg. 2023 Sep 7. doi: 10.1111/os.13821. Online ahead of print.

The Genetic Causal Association between Educational Attainment and Risk of 12 Common Musculoskeletal Disorders: A Two-Sample Mendelian Randomization

> J Intell. 2023 Jan 31;11(2):29. doi: 10.3390/jintelligence11020029.

Can Intelligence Affect Alcohol-, Smoking-, and Physical Activity-Related Behaviors? A Mendelian Randomization Study

> World Allergy Organ J. 2023 Jun 15;16(6):100790. doi: 10.1016/j.waojou.2023.100790. eCollection 2023 Jun.

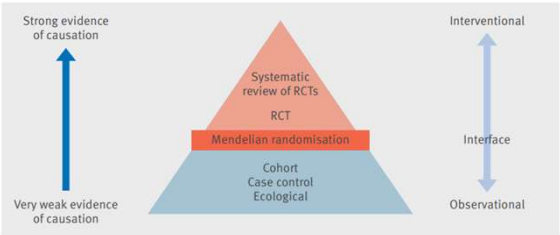
Socioeconomic status and asthma: A bidirectional Mendelian randomization study

Why the growing popularity?

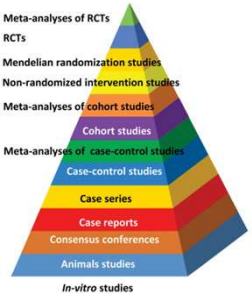
- Identify causal effects even in the presence of unmeasured confounding
- "Natural analogue" of a randomized controlled trial
- Increasing access to genetic data and software to implement (certain) MR approaches

Why the growing popularity?

- Identify causal effects even in the presence of unmeasured confounding
- "Natural analogue" of a randomized controlled trial
- Increasing access to genetic data and software to implement (certain) MR approaches



Davies et al. (BMJ 2018)



Zitterman (Anticancer Research 2018)

Mendelian randomization beyond the academic literature

June 21, 2021

MIND

Morning People May Be at Lower Risk of Depression Than Night Owls

Going to bed early and waking up early may help to provide some protection against depression, a new study suggests.

By Nicholas Bakalar

PRINT EDITION Early Risers May Have Less Risk of Depression | June 29, 2021, Page D6

"With Mendelian randomization, researchers can compare large groups of people based on genetic variants that are independent of other health or behavioral… Nature has, in essence, set up the randomized experiment for them."

Mendelian randomization beyond the academic literature

March 29, 2022

HEALTH

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

By studying the relationship between gene variants and alcohol consumption, scientists found no real cardiac benefit to drinking, even modestly.

By Gina Kolata

PRINT EDITION Drinking Moderately Does Not Confer Cardiac Benefits, Genetic Study Finds | March 30, 2022, Page A22

"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."

Mendelian randomization beyond the academic literature

June 19

OPINION

The Science of What We Eat Is Failing Us

Nutrition science needs a credibility revolution.

By Anupam B. Jena and Christopher M. Worsham

PRINT EDITION
June 20, 2023, Page A20

"Reliability still starts with randomization … Another way people can be accidentally randomized to health behaviors is through their genes."

"Although medical researchers are increasingly taking advantage of natural experiments … these methods remain undertaught and underused, particularly when it comes to diet. This important research needs a credibility revolution of its own."

Is Mendelian randomization the panacea for all causal inference woes?

In epidemiology, nothing is ever that straightforward.

In reality, what is the current state of MR?

1. What?
2. Who?
3. How?

2

What are we estimating with MR?

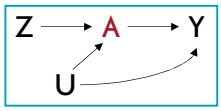
CAUSALab
A Center to Learn What Works

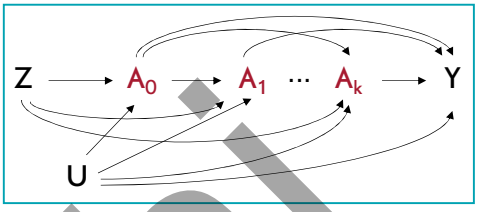
HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Consider some common exposures in MR studies

- E.g., alcohol intake, blood pressure, LDL cholesterol, BMI, sleep duration, etc.
  - Time-varying

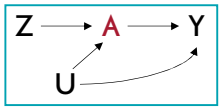
Consider some common exposures in MR studies

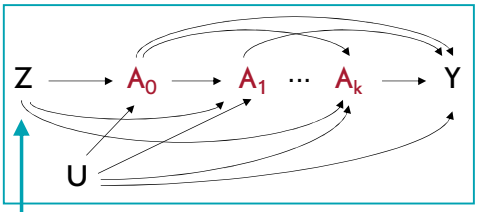
- E.g., alcohol intake, blood pressure, LDL cholesterol, BMI, sleep duration, etc.
  - Time-varying
- Not 

but more like 

Z: instrument
A: exposure
Y: outcome
U: unmeasured A-Y confounders

Consider some common exposures in MR studies

- E.g., alcohol intake, blood pressure, LDL cholesterol, BMI, sleep duration, etc.
  - Time-varying
- Not 

but more like 

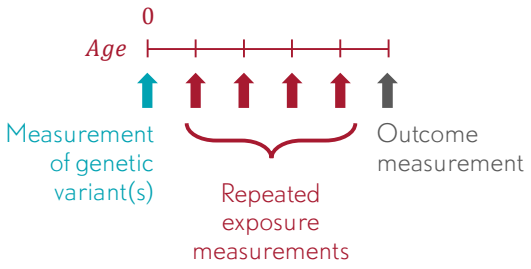
"Randomization" at conception

Exposures and outcome post-conception

Z: instrument
A: exposure
Y: outcome
U: unmeasured A-Y confounders

Mendelian randomization in practice

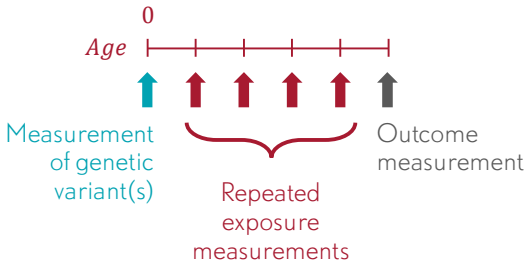
Ideally…



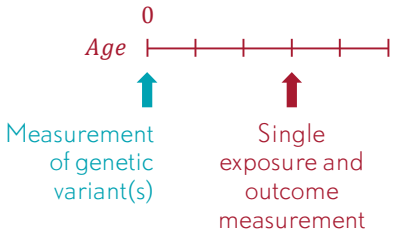
27

Mendelian randomization in practice

Ideally…



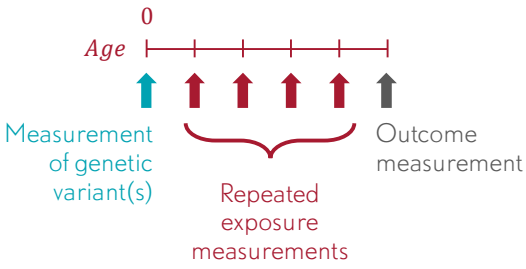
In practice…



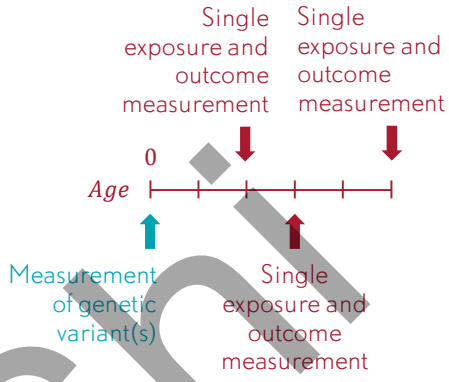
28

Mendelian randomization in practice

Ideally…



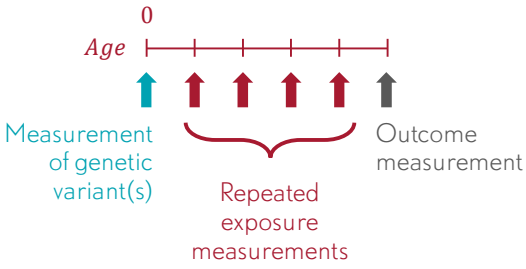
In practice…



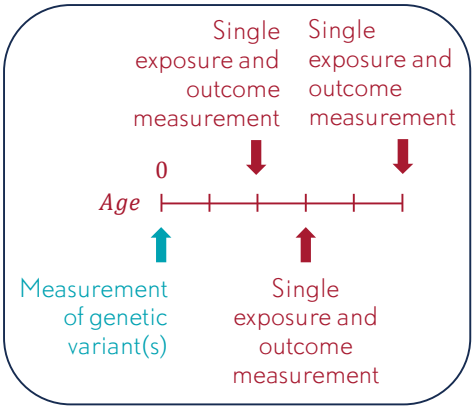
29

Mendelian randomization in practice

Ideally…



In practice…



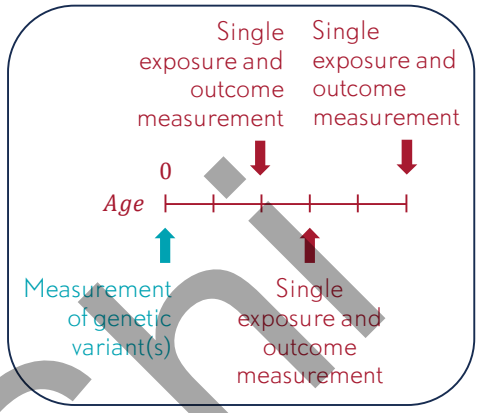
"Lifetime effect"

30

Mendelian randomization in practice

- Most biobanks don't have longitudinal follow-up
- "Lifetime effect" using a single exposure measurement—how is that justifiable?
  - "*The genetic variant remains fixed throughout life, providing for the assessment of a lifetime exposure.*" (Roberts, JACC 2023)

In practice…

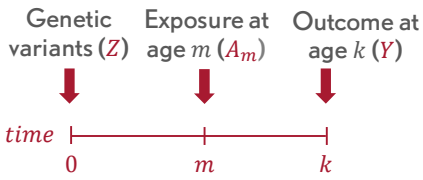


"Lifetime effect"

There are many causal estimands we could target in a MR study, and each require different (additional) assumptions

Shi et al. (Epidemiology 2021)

There are many causal estimands we could target in a MR study, and each require different (additional) assumptions

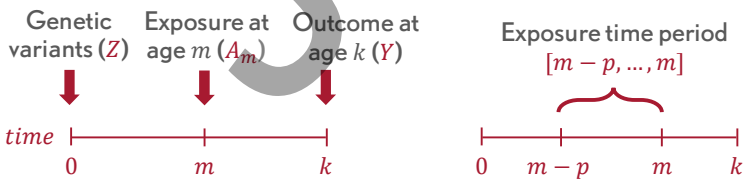


Point effect:

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

Shi et al. (Epidemiology 2021)

There are many causal estimands we could target in a MR study, and each require different (additional) assumptions



Point effect:

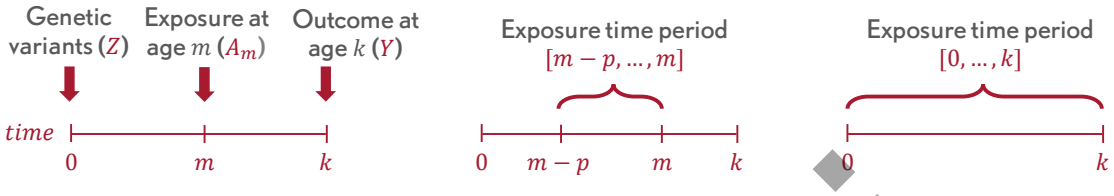
$$\mathrm{E}[Y^{a_m}] - \mathrm{E}[Y^{a'_m}]$$

Period effect:

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

Shi et al. (Epidemiology 2021)

There are many causal estimands we could target in a MR study, and each require different (additional) assumptions



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

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

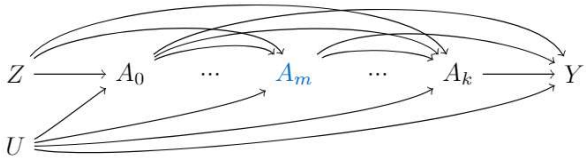
Lifetime effect:
$[Y^{\bar{a}_k}] - \mathrm{E}\left[Y^{\bar{a}'_k}\right]$

Shi et al. (Epidemiology 2021)

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:



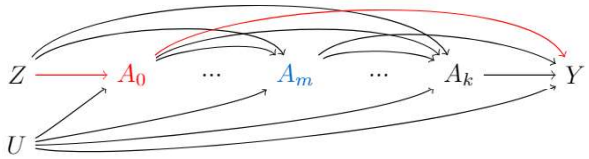
To estimate the point effect, Z must meet the three instrumental conditions for only A_m as the exposure

- 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:



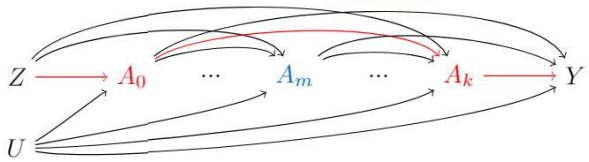
To estimate the point effect, Z must meet the three instrumental conditions for only A_m as the exposure

- 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

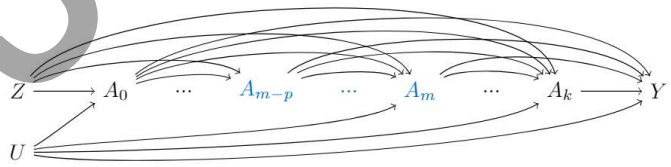
But…

- 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

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



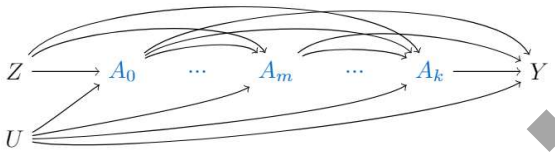
The exclusion restriction assumption must hold for the exposure during the time period $[m-p, \ldots, m]$, i.e., all exposure time points other than $(A_{m-p}, \ldots, A_{m-1}, A\_m)$ need to

- 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

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

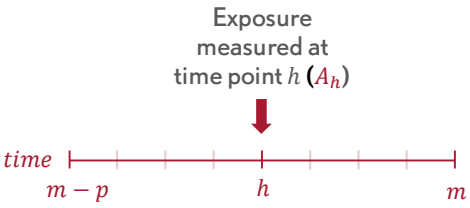


- Can consider the lifetime effect as a type of period effect in which the period spans from time 0 (i.e., at conception) until time k (i.e., the development of the outcome)
- No violation of the exclusion restriction assumption through exposure time points (because we are intervening on all exposure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

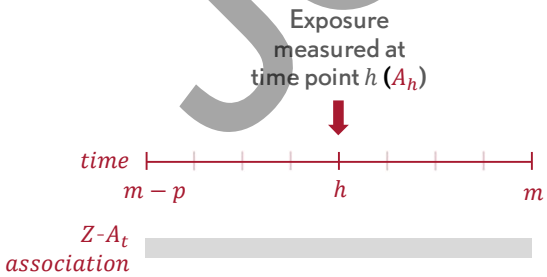
Additional assumptions for the period/lifetime effect

- 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



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:

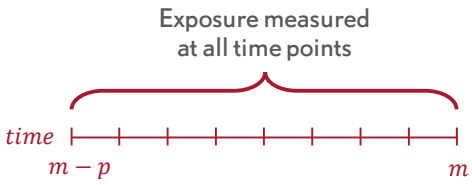
$$E[Y^{a_{m-p}+1,\ldots,a_{m-1}+1,a_m+1}] - E[Y^{a_{m-p},\ldots,a_{m-1},a_m}]$$

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

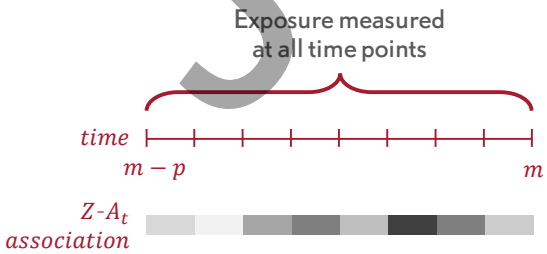
"If the relationship between $[Z]$ and A changes over time, it cannot be adequately summarized by measuring it at 1 time point."

(Labrecque and Swanson, AJE 2018)

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



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?

Takeaways

- **With a time-varying exposure, there is no "the" causal effect**
  - Be explicit about the causal estimand of interest
- **We need to be thinking about time**
  - When is exposure being measured?
  - When is the outcome being measured?
  - How do things change over time?

3

Who is being included in our MR analysis?

Most Mendelian randomization studies use a "2-sample" approach

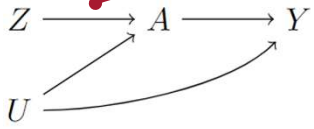
- "Meta-analyzing" publicly available summary statistics
- Based on the Wald estimator

Most Mendelian randomization studies use a "2-sample" approach

- "Meta-analyzing" publicly available summary statistics
- Based on the Wald estimator
- Let's return to our example of the colonoscopy screening trial:

Estimating the intention-to-treat effect (i.e., effect of Z on Y) is straightforward

Could also estimate the effect of Z on A (adherence)

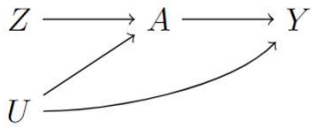


Z: randomization to invitation vs. no invitation
A: colonoscopy screening
Y: colorectal cancer mortality
U: unmeasured common cause of A and Y

Most Mendelian randomization studies use a "2-sample" approach

- "Meta-analyzing" publicly available summary statistics
- Based on the Wald estimator
- Let's return to our example of the colonoscopy screening trial:

$$\text{Effect of A on Y} = \frac{\text{Intention-to-treat effect}}{\text{Level of adherence}}$$



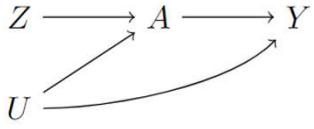
Z: randomization to invitation vs. no invitation
A: colonoscopy screening
Y: colorectal cancer mortality
U: unmeasured common cause of A and Y

51

Most Mendelian randomization studies use a "2-sample" approach

- "Meta-analyzing" publicly available summary statistics
- Based on the Wald estimator
- In the context of MR (ignoring the fact that the exposure is time-varying):

$$\text{Effect of A on Y} = \frac{\text{Gene-outcome association}}{\text{Gene-exposure association}}$$



Z: genetic variant
A: exposure
Y: outcome
U: unmeasured A-Y confounders

52

Two-sample MR

The Wald estimator:

$$\frac{\text{Gene}-\text{outcome association}}{\text{Gene}-\text{exposure association}}$$

In two-sample MR, the gene-outcome association is estimated in one study

The gene-exposure association is estimated in a second study

- Two samples assumed to represent the same underlying population
- Increased power
- Summary statistics from existing GWAS are leveraged (meta-analyzed)
- But GWAS are not designed to be used for MR
- Results in a very strange mix of participants who end up in the analysis

Consider a study of statins and CAD

What eligibility criteria might we consider in a target trial?

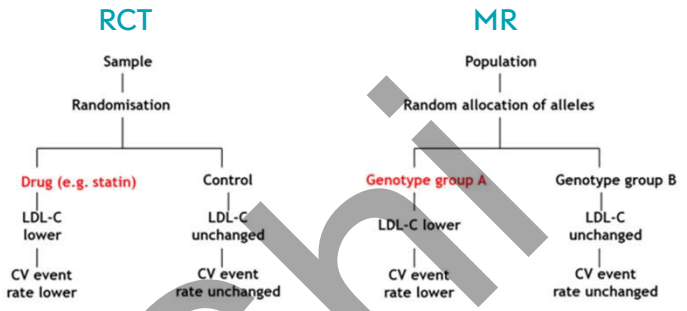
- No history of CAD
- No statin use in the past 12 months
- No history of contraindications to statin use (e.g., acute liver failure)
- etc.

Consider a study of statins and CAD

What eligibility criteria might we consider in a target trial?

- No history of CAD
- No statin use in the past 12 months
- No history of contraindications to statin use (e.g., acute liver failure)
- etc.

Now suppose we wanted use MR to answer this question:



Bennett and Holmes (Heart 2017)

How might we study statins and CAD using a 2-sample MR approach?

$$\frac{\text{Gene}-\text{outcome association}}{\text{Gene}-\text{exposure association}}$$

Global Lipids Genetics Consortium (GLGC):

- Existing GWAS which meta-analyzed data from 45 studies
- Excluded individuals known to be on lipid lowering medications

Allara et al. (Circulation: Genomic and Precision Medicine, 2019)

How might we study statins and CAD using a 2-sample MR approach?

$$\frac{\text{Gene}-\text{outcome association}}{\text{Gene}-\text{exposure association}}$$

UK Biobank:

- 367,703 participants
- Recruited between 2006 and 2010 and followed until March 31, 2017
- Individual-level data available to researchers
- Exclude people with CAD at baseline

Global Lipids Genetics Consortium (GLGC):

- Existing GWAS which meta-analyzed data from 45 studies
- Excluded individuals known to be on lipid lowering medications

Allara et al. (Circulation: Genomic and Precision Medicine, 2019)

57

Key elements of the target trial protocol are ill-defined

- Eligibility criteria
- Treatment strategies
- Treatment assignment
- Follow-up
- Outcomes
- Causal contrasts
- Statistical analysis plan

- UK Biobank (numerator) excludes individuals with the outcome; GLGC (denominator) does not
- GLGC (denominator) excludes individuals on lipid lowering medications; UK Biobank (numerator) does not

58

Key elements of the target trial protocol are ill-defined

- UK Biobank (numerator) excludes individuals with the outcome; GLGC (denominator) does not
- GLGC (denominator) excludes individuals on lipid lowering medications; UK Biobank (numerator) does not

Recall: recruited between 2006 and 2010 and followed until March 31, 2017

- End-of-follow-up binary outcome
- 7- to 11-year risk ratio?

59

What happens if we try to replicate these findings using VA data?

Proposed instruments:
Genetic variants in *HMGCR*, *PCSK9* and *LDLR* genes

Gene-LDL cholesterol associations:
Summary statistics obtained from GLGC

Gene-coronary artery disease associations:
Estimated in MVP

Analysis:
Inverse variance weighted 2-sample MR analysis, adjusted for sex, age at enrollment and ten genetic principal components

60

Comparison of two-sample MR estimates

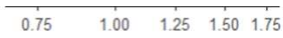
Dataset	Follow-up	Eligibility	n	Odds ratio (95 CI%) [a]
UKB	Start: 2006 to 2010 End: March 31, 2017	No history of CAD, European ancestry, age 40 to 69	367,703	

[a] Corresponding to a 39 ml/dL increase in LDL cholesterol
[b] No history of inflammatory muscle disease, chronic liver disease, abnormal liver function, chronic kidney disease or end-stage renal disease

61

Comparison of two-sample MR estimates

Dataset	Follow-up	Eligibility	n	Odds ratio (95 CI%) [a]
UKB	Start: 2006 to 2010 End: March 31, 2017	No history of CAD, European ancestry, age 40 to 69	367,703	
MVP	Start: 2011 to 2012 End: December 31, 2019	Same as above	34,927	



[a] Corresponding to a 39 ml/dL increase in LDL cholesterol
[b] No history of inflammatory muscle disease, chronic liver disease, abnormal liver function, chronic kidney disease or end-stage renal disease

62

Comparison of two-sample MR estimates

Dataset	Follow-up	Eligibility	n	Odds ratio (95 CI%) [a]
UKB	Start: 2006 to 2010 End: March 31, 2017	No history of CAD, European ancestry, age 40 to 69	367,703	
MVP	Start: 2011 to 2012 End: December 31, 2019	Same as above	34,927	
MVP	Start: 2011 to 2014 End: December 31, 2019	Same as above	97,967	

[a] Corresponding to a 39 ml/dL increase in LDL cholesterol
[b] No history of inflammatory muscle disease, chronic liver disease, abnormal liver function, chronic kidney disease or end-stage renal disease

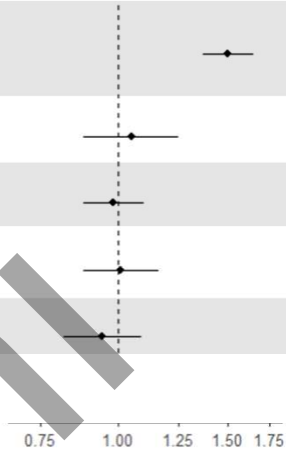
Comparison of two-sample MR estimates

Dataset	Follow-up	Eligibility	n	Odds ratio (95 CI%) [a]
UKB	Start: 2006 to 2010 End: March 31, 2017	No history of CAD, European ancestry, age 40 to 69	367,703	
MVP	Start: 2011 to 2012 End: December 31, 2019	Same as above	34,927	
MVP	Start: 2011 to 2014 End: December 31, 2019	Same as above	97,967	
MVP	Start: 2011 to 2014 End: after 5 years of follow-up	Same as above	97,967	

[a] Corresponding to a 39 ml/dL increase in LDL cholesterol
[b] No history of inflammatory muscle disease, chronic liver disease, abnormal liver function, chronic kidney disease or end-stage renal disease

Comparison of two-sample MR estimates

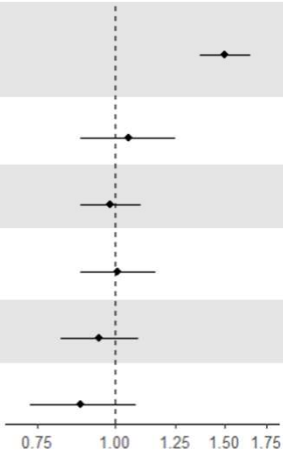
Dataset	Follow-up	Eligibility	n	Odds ratio (95 CI%) [a]
UKB	Start: 2006 to 2010 End: March 31, 2017	No history of CAD, European ancestry, age 40 to 69	367,703	
MVP	Start: 2011 to 2012 End: December 31, 2019	Same as above	34,927	
MVP	Start: 2011 to 2014 End: December 31, 2019	Same as above	97,967	
MVP	Start: 2011 to 2014 End: after 5 years of follow-up	Same as above	97,967	
MVP	Same as above	Same as above plus no contraindications [b]	86,758	



[a] Corresponding to a 39 ml/dL increase in LDL cholesterol
[b] No history of inflammatory muscle disease, chronic liver disease, abnormal liver function, chronic kidney disease or end-stage renal disease

Comparison of two-sample MR estimates

Dataset	Follow-up	Eligibility	n	Odds ratio (95 CI%) [a]
UKB	Start: 2006 to 2010 End: March 31, 2017	No history of CAD, European ancestry, age 40 to 69	367,703	
MVP	Start: 2011 to 2012 End: December 31, 2019	Same as above	34,927	
MVP	Start: 2011 to 2014 End: December 31, 2019	Same as above	97,967	
MVP	Start: 2011 to 2014 End: after 5 years of follow-up	Same as above	97,967	
MVP	Same as above	Same as above plus no contraindications [b]	86,758	
MVP	Same as above	Same as above plus no statin use in past year	48,825	



[a] Corresponding to a 39 ml/dL increase in LDL cholesterol
[b] No history of inflammatory muscle disease, chronic liver disease, abnormal liver function, chronic kidney disease or end-stage renal disease

Results: two-sample MR

- Very different results when trying to replicate UK Biobank findings in MVP data
  - Shorter duration of follow-up
  - MVP and GLGC probably represent very different underlying populations (Note: this is also probably true of the UK Biobank and GLGC)
- Refinements in the duration of follow-up and adding eligibility criteria shifted estimates downwards
  - But we could only apply these changes when estimating the gene-outcome association (don't have individual-level data on the gene-exposure association)

In two-sample MR, our study population is often unclear

- **"Like using the adherence observed in one trial to adjust the ITT effect in another trial"** (Swanson et al., Epidemiology 2017)
- **Researchers use two-sample MR because they have to, not because they want to**
  - Ideally would have individual-level data on instrument, exposure, outcome and covariates
  - Increasingly available through larger publicly available biobanks

4

How do we obtain our MR estimate?

Suppose we are in the ideal setting for an MR analysis

- Individual-level data on:
  - Genetic variants (meet all instrumental conditions)
  - Exposure (repeated measured across lifecourse)
  - Outcome (time-to-event)
- Near infinite sample size (no need to use two-sample methods)

Could we obtain the effect comparing two different exposure trajectories on our outcome of interest?

Suppose we are in the ideal setting for an MR analysis

- Individual-level data on:
  - Genetic variants (meet all instrumental conditions)
  - Exposure (repeated measured across lifecourse)
  - Outcome (time-to-event)
- Near infinite sample size (no need to use two-sample methods)

Could we obtain the effect comparing two different exposure trajectories on our outcome of interest?

Maybe but, again, under strong assumptions

IV methods for time-varying exposures are underdeveloped

- **Most MR methods are developed for time-fixed exposures and end-of-follow-up outcomes**
  - Most MR exposures are time-varying
  - Outcomes of interest are often survival outcomes

IV methods for time-varying exposures are underdeveloped

- Most MR methods are developed for time-fixed exposures and end-of-follow-up outcomes
  - Most MR exposures are time-varying
  - Outcomes of interest are often survival outcomes

Outcome type	Exposure type: Time-fix	Exposure type: Time-varying
End of follow-up	Wald estimator Two-stage least squares Two-sample approaches …	Multivariable MR G-estimation of structural models
Survival outcome	Additive Aalen models G-estimation of structural models	G-estimation of structural models

IV methods for time-varying exposures are underdeveloped

- Mathematically equivalent for continuous outcomes
- Assume linearity between exposure and outcome
- Structural models are more robust to mis-specification for binary outcomes

Outcome type	Exposure type: Time-fix	Exposure type: Time-varying
End of follow-up	Wald estimator Two-stage least squares Two-sample approaches …	Multivariable MR G-estimation of structural models
Survival outcome	Additive Aalen models G-estimation of structural models	G-estimation of structural models

Shi et al., (Epidemiology, 2022)

IV methods for time-varying exposures are underdeveloped

- Most MR methods ar
  end-of-follow-up outc
  - Most MR exposures ar
  - Outcomes of interest a
- Currently can only handle simple models, e.g.
  - Magnitude of effect is constant over time
  - Risk curves do not cross
- Computationally intensive and software to implement is not readily available

Outcome type	Exposure type: Time-fix	Exposure type: Time-varying
End of follow-up	Wald estimator Two-stage least squares Two-sample approaches …	Multivariable MR G-estimation of structural models
Survival outcome	Additive Aalen models G-estimation of structural models	G-estimation of structural models

Shi et al., (BMC Medical Research Methodology, 2021)

75

We still have some ways to go to make MR methods more flexible

- It's possible that there are some effects we could never identify with MR
  - Constrained by having only time-fixed instrument(s)
- Still an ongoing area of research in methods development
- In the interim, be explicit and critical of our model assumptions

76

5

How do we move forward with MR?

CAUSALab
A Center to Learn What Works

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Of course, there are other concerns

- Homogeneity/monotonicity for point estimation
- Treatment is often not well-defined
- Misalignments in time zero (Swanson et al., Epidemiology 2017)
- Survivor bias

Should we just abandon Mendelian randomization altogether?

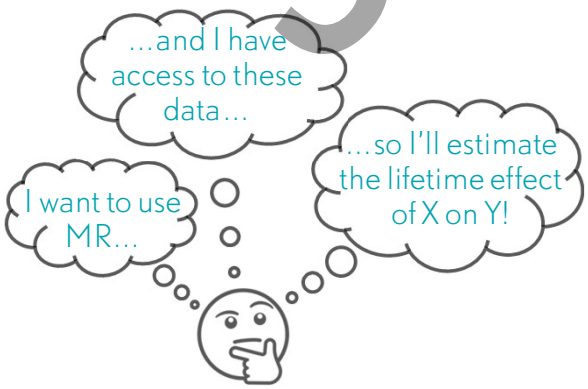
MR is probably here to stay, whether we like it or not

Mendelian randomization can be a helpful tool, but only if we use it with humility

1. Start with the question, not with the method

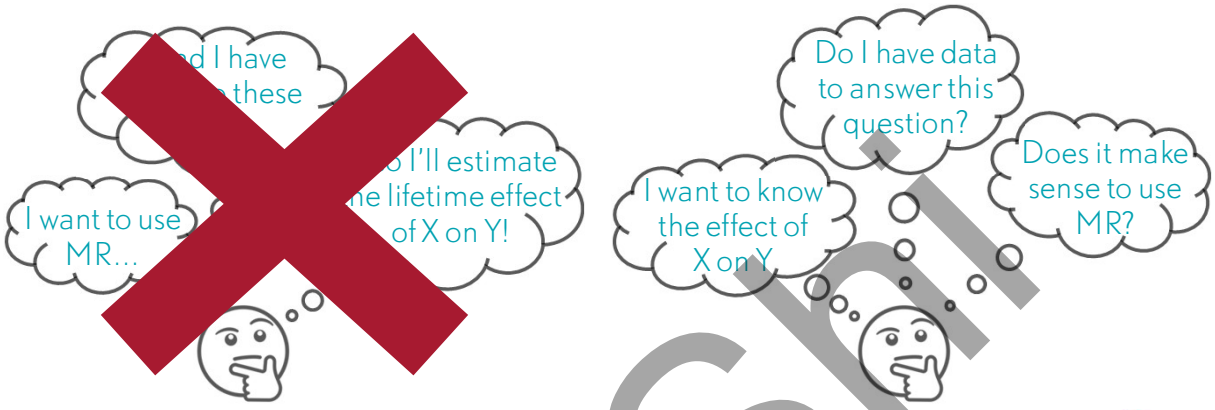
Mendelian randomization can be a helpful tool, but only if we use it with humility

1. Start with the question, not with the method



Mendelian randomization can be a helpful tool, but only if we use it with humility

1. Start with the question, not with the method



Mendelian randomization can be a helpful tool, but only if we use it with humility

1. Start with the question, not with the method
2. Check our assumptions and be explicit about them
   - ⚠ MR relies on more assumptions than we think
   - 🔍 Falsification tests and bounds are underutilized

Mendelian randomization can be a helpful tool, but only if we use it with humility

1. Start with the question, not with the method
2. Check our assumptions and be explicit about them
   - MR relies on more assumptions than we think
   - Falsification tests and bounds are underutilized
3. Interpret our estimates cautiously
   - Is this hypothesis-generating? (e.g., genome-wide MR)
   - Who do these estimates apply to?

Mendelian randomization can be a helpful tool, but only if we use it with humility

1. Start with the question, not with the method
2. Check our assumptions and be explicit about them
   - MR relies on more assumptions than we think
   - Falsification tests and bounds are underutilized
3. Interpret our estimates cautiously
   - Is this hypothesis-generating? (e.g., genome-wide MR)
   - Who do these estimates apply to?
4. Triangulate MR estimates with those obtained via other methods
   - But make sure that they're targeting the same causal estimand

Acknowledgements

- Sonja Swanson
- Miguel A. Hernán
- Elizabeth W. Diemer
- CAUSALab
- VA-CAUSAL Methods Core (CSP #2032)

CAUSALab | A Center to Learn What Works

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

85