Designing Your MR Study: SSGG MR Shortcourse Lecture 4

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MR Study Overview

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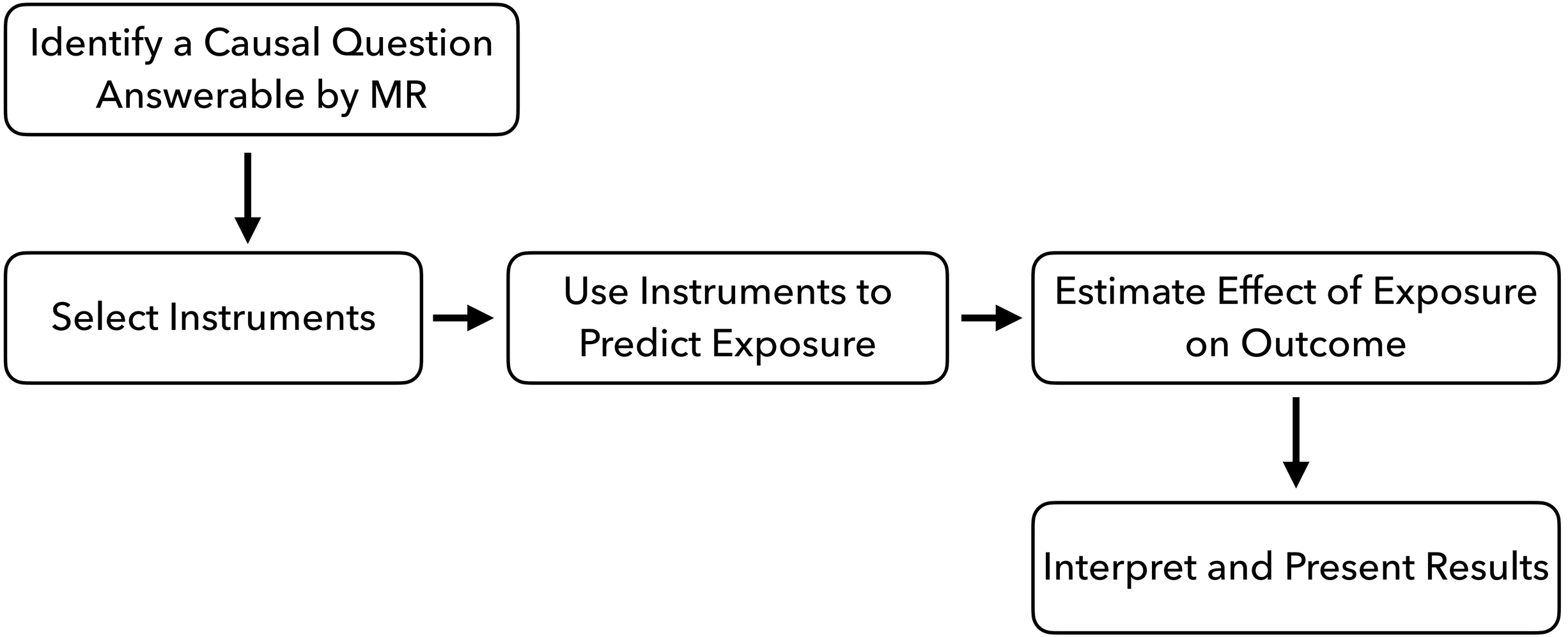


Outline

Identify a Causal Question Answerable by MR

Select Instruments

Use Instruments to Predict Exposure

Estimate Effect of Exposure on Outcome

Interpret and Present Results

Part 1: Data Selection:

- One sample vs two sample
- Individual level vs summary stats
- Considerations for GWAS summary statistics

Outline

Identify a Causal Question Answerable by MR

Part 2: Instrument Selection

- Combatting Winner's Curse
- Combatting Horizontal Pleiotropy
- Drug Target/Pathway MR

Select Instruments → Use Instruments to Predict Exposure → Estimate Effect of Exposure on Outcome → Interpret and Present Results

Outline

Identify a Causal Question Answerable by MR

Part 3: Choosing a Question and Interpreting Results

- Interpreting Effect Estimates
- Exposure Specificity
- Scientific Considerations

Select Instruments → Use Instruments to Predict Exposure → Estimate Effect of Exposure on Outcome

Interpret and Present Results

Part 1: Data Selection

- One sample vs two sample
- Individual level data vs summary statistics
- Considerations for GWAS summary statistics

One vs Two Sample MR

- In one sample MR (1SMR), variant-exposure associations and variant-outcome associations are measured in the same individuals.
- Int two sample MR (2SMR), these are measured in different individuals.
- In some cases, there is partial overlap between exposure and outcome samples.

One vs Two Sample MR

One Sample MR

- Estimates biased towards population association (unless we account for overlapping samples).
- No risk of population differences.

Two Sample MR

- Estimates unbiased or biased towards zero.
- Must assume that variant-exposure associations are the same in both populations.

Weak Instrument Bias

- In 2SMR (with no overlap), weak instrument bias is towards zero.
- For both IVW regression and two stage least squares,

$$E[\hat{\beta}_{MR} - \beta] \approx \rho c \frac{1}{\kappa}$$

  ρ: population correlation of X and Y, c: proportional to sample overlap proportion, κ: average instrument strength, estimated by F-stat minus 1.

- With complete sample overlap, bias is towards the (confounded) population correlation.

Accounting for Sample Overlap

- Some methods have reduced weak instrument bias (e.g. dIVW, MR-RAPS)
  - These will still be biased unless sample overlap is accounted for.

- Some methods can explicitly account for sample overlap (GRAPPLE, CAUSE, MR-BEE, MR-APSS, etc.)

- These methods accept a parameter, for residual correlation.
  - Residual correlation can be estimated directly from the data without knowing true overlap proportion.
  - Two methods: intercept from cross-trait LD-score regression or compute correlation of “non-significant” z-scores.

Population Considerations

- If using 2SMR, we need to assume that the marginal instrument-exposure association is the same in the exposure and outcome samples.

- This could fail if:
  - LD patterns differ between the two populations
  - There are gene-environment interactions
  - There is effect modification by covariates that differ between the two populations (e.g. sex, age, etc).

Population Considerations

- It is usually not a good idea to perform MR using samples from different continental populations.
  - LD differences, GxE, and effect modification could all be substantial.

- Some phenotypes may be more prone to gene-environment interactions or effect modification than others:
  - E.g. social/behavioral phenotypes like educational attainment and smoking.

- If there are major covariate differences between populations, effect interpretations will rely strongly on the no effect-modification assumption.

Example: Sex

- Suppose we are interested in the effect of birthweight on age at menarch.
- Age at menarche is a female-specific trait so the outcome population is entirely female.
- The exposure sample should either also be all female, or we need to argue that that variant-birthweight associations are the same in males and females.

Individual Level v Summary Statistic Data

- When individual level data is available, some more robust/flexible analyses are possible.

- Individual data also allows more control over how summary stats are calculated, even if a summary stat method is used.

- Individual-level outcome data can allow:
  - Use of semi-parametric or family-based methods
  - Estimates of effect-modification/sub-group effects
  - Sample splitting and cross-fitting (more coming on this)

Considerations When Using Summary Stats

- Summary statistics are often the most practical choice.
  - Individual level data may not be available or available only for small samples.
  - Using individual level data may be computationally prohibitive.

- If using summary statistics, pay close attention to methods used to compute them.
  - Biases in summary statistics can propagate to MR estimates.

Sources of Bias in GWAS Summary Statistics

- Uncorrected population stratification
- Dynastic effects (genetic nurture)
- Cross-trait assortative mating
- Adjustment for heritable covariates (due to colliding)

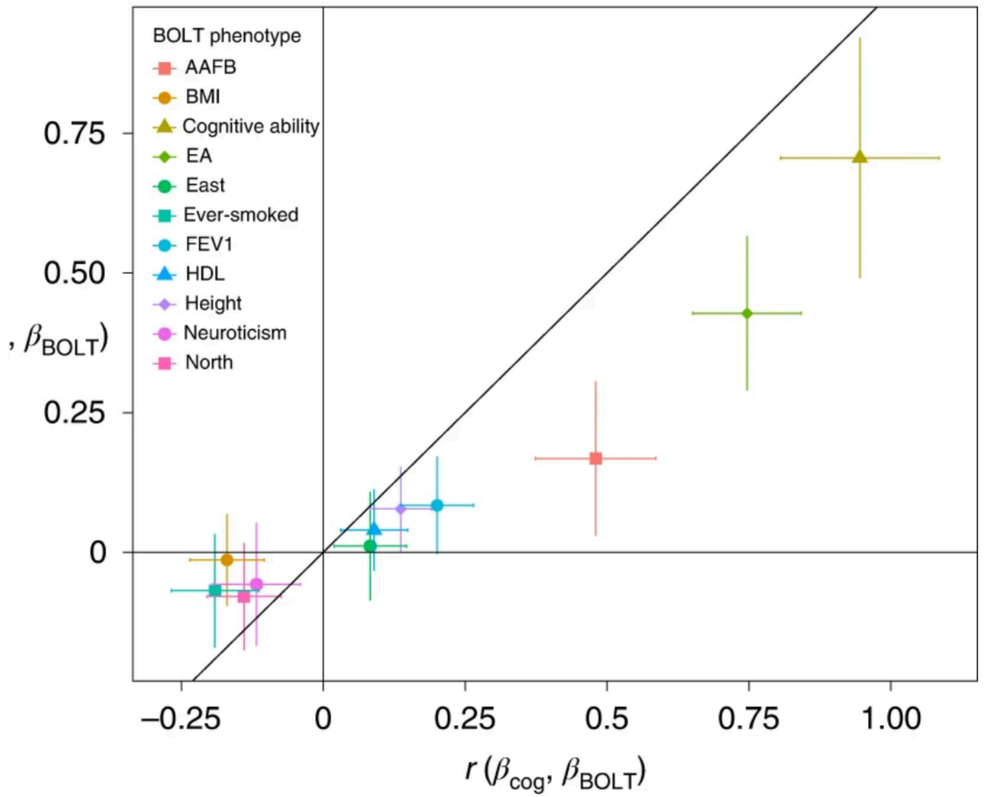
Confounding Bias in GWAS

- Population structure, genetic nurture, and cross-trait assortative mating all result in spurious associations between variants and GWAS traits.
  - “Spurious” = not a measure of a direct genetic effect.
- Most GWAS adjust for PCs which account for some population structure.
- However, in some cases, confounding may persist (e.g. Sohail et al. 2019).
- Family-based GWAS can resolve bias due to population structure and genetic nurture.

GWAS Confounding and MR

- GWAS confounding can result in biased MR results when the same confounding factors affect multiple traits.

Genetic correlation between cognition and other traits



Genetic correlation from family-based estimates

from Young et al (2022)

Genetic correlation from population estimates

Phenotypes that Proxy SES

- Some phenotypes strongly proxy SES or population structure.
  - Educational attainment, frequency of sunburn in childhood, pollution exposure, …
- We should be wary of MR using these phenotypes as exposures.
- We may need to obtain family-based GWAS estimates to really believe the results.

Phenotypes that Proxy SES

- Some phenotypes strongly proxy SES or population structure.
  - Educational attainment, frequency of sunburn in childhood, pollution exposure, …
- We s… …res.
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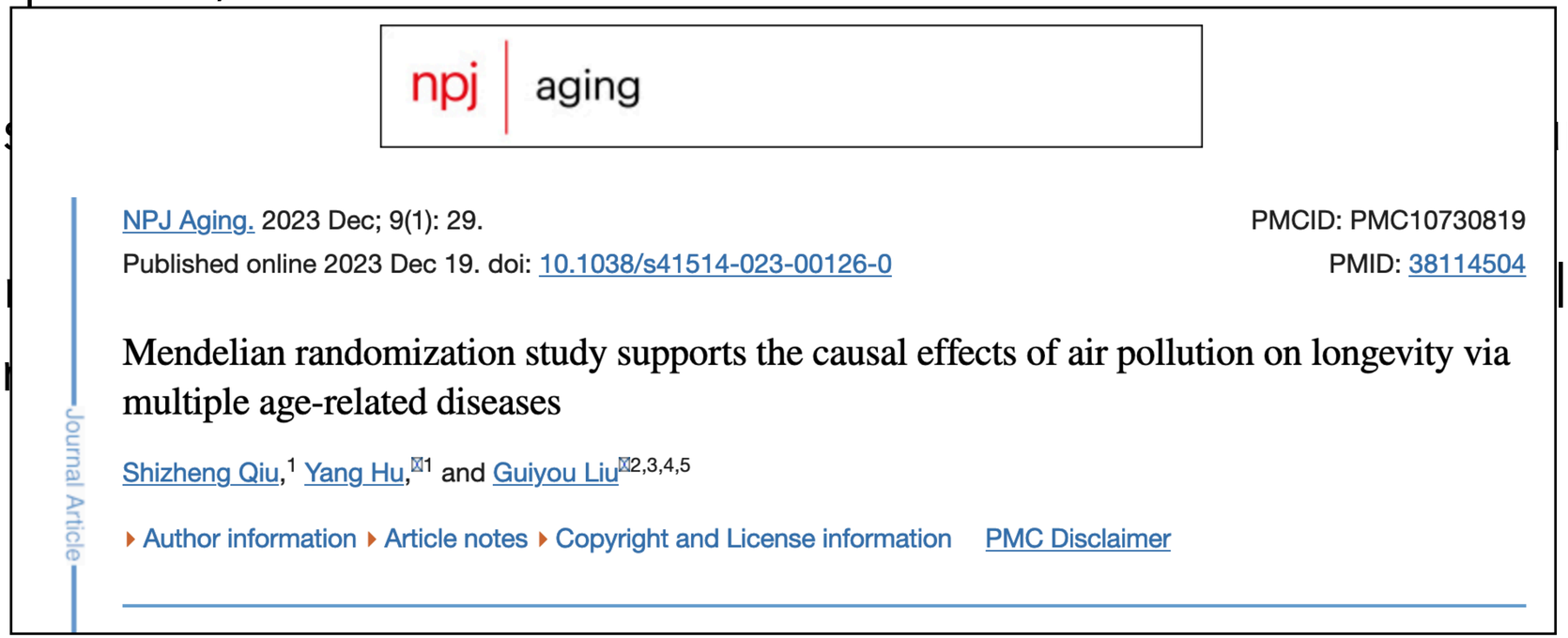


npj | aging

Journal Article

NPJ Aging. 2023 Dec; 9(1): 29.
Published online 2023 Dec 19. doi: 10.1038/s41514-023-00126-0
PMCID: PMC10730819
PMID: 38114504

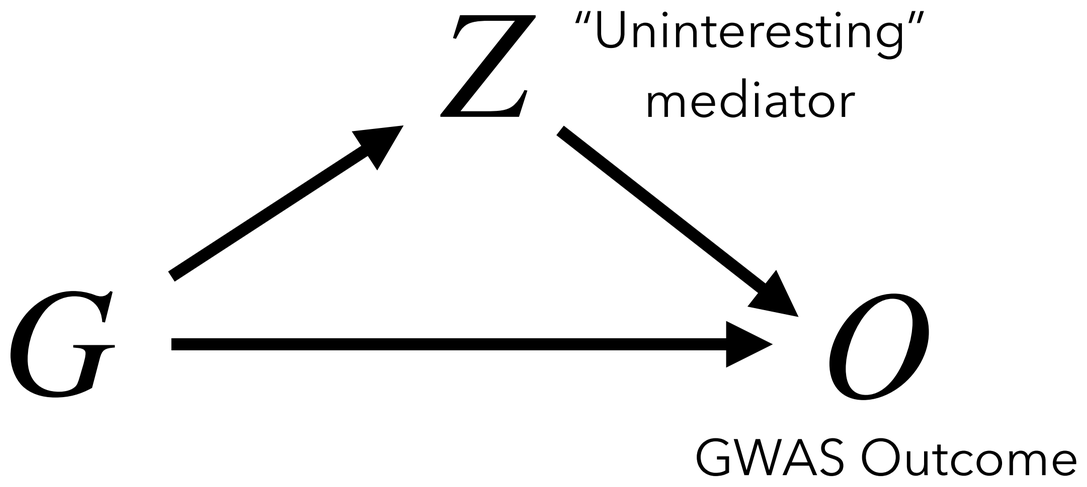
Mendelian randomization study supports the causal effects of air pollution on longevity via multiple age-related diseases

Shizheng Qiu,[1] Yang Hu,[✉1] and Guiyou Liu[✉2,3,4,5]

Covariate Adjustment and Colliding

- Some GWAS will condition on covariates that they believe have a large effect on the outcome, to eliminate variants mediated by these covariates.

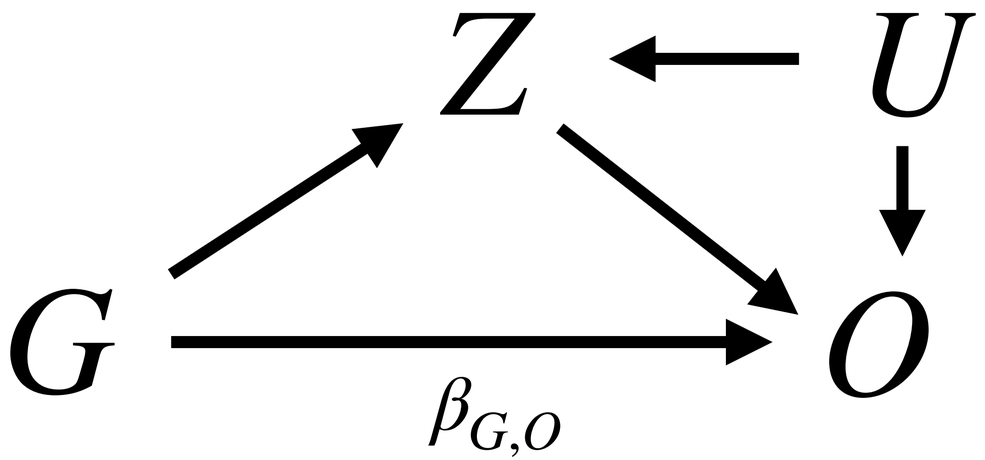
- For example, many GWAS of lung cancer condition on smoking status (Bosse and Amos 2017), many GWAS of waist to hip ratio condition on BMI (Shungin et al 2015, Pullit et al 2019)



Covariate Adjustment and Colliding

- However, adjusting for Z introduces collider bias if Z is heritable and there is a common cause of Z and the GWAS outcome.

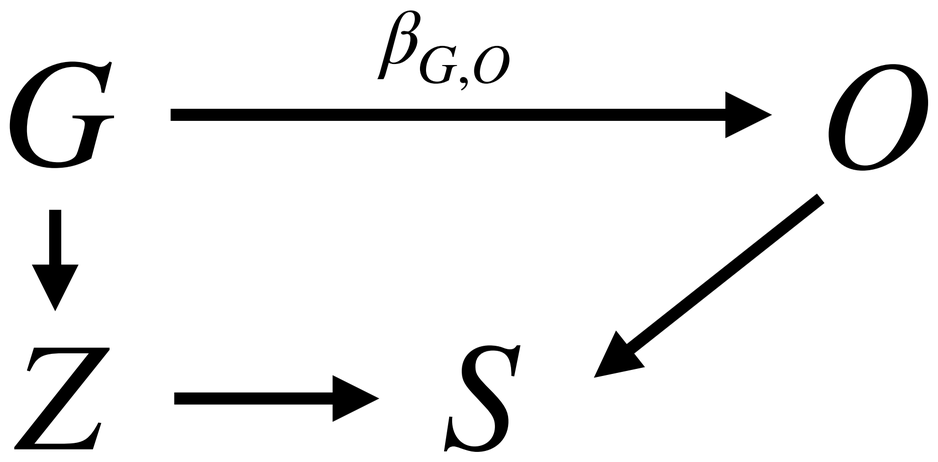
- In the graph below, the association between G and O conditional on Z is different from $\beta_{G,O}$ because Z is a collider.



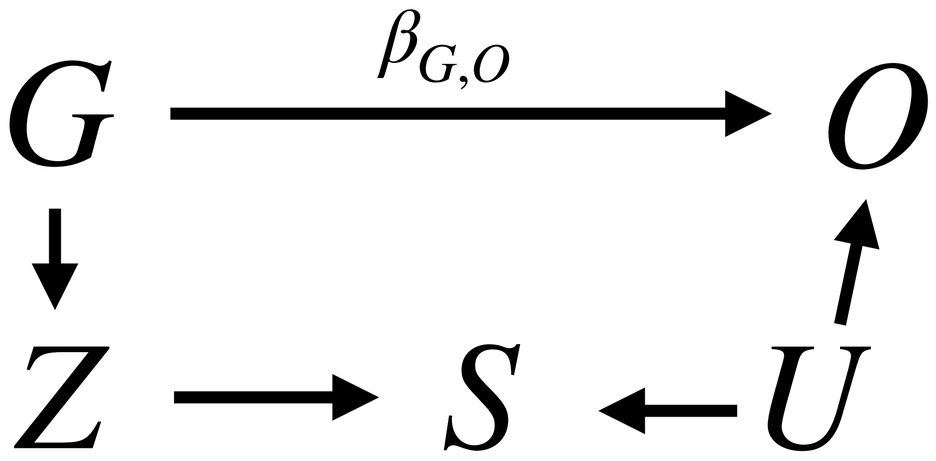
Selection Bias and Colliding

- Collider bias can also occur if selection into the GWAS sample depends on the GWAS trait (or a causal parent) as well as other heritable traits.

- In the graphs below, variants associated with Z will look associated with O even if $\beta_{G,O}$ is zero.



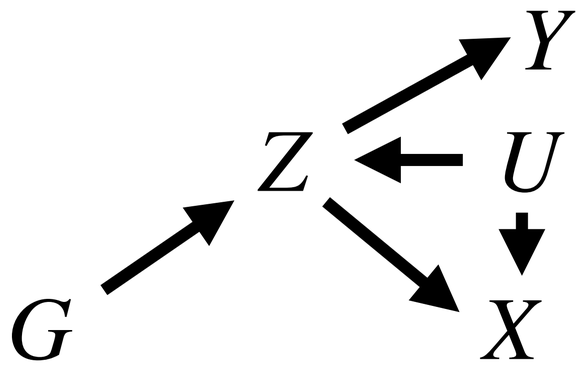
Selection into GWAS



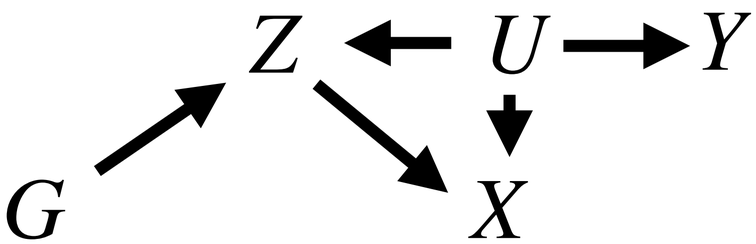
Selection into GWAS

Collider Bias and MR

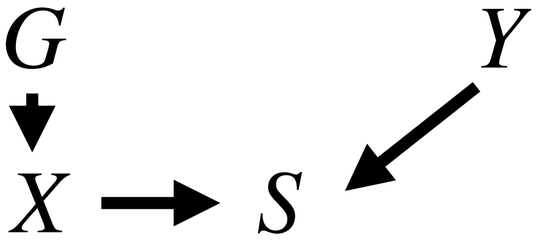
- Collider bias in GWAS estimates can lead to biased MR results.



Bias if $G - X$ association is adjusted for Z and $G - Y$ association is unadjusted.



Bias if both $G - X$ and $G - Y$ associations are adjusted for Z.



Bias if selection occurs in the outcome GWAS sample.

Part 2: Instrument Selection

- Combatting Winner's Curse
- Combatting Horizontal Pleiotropy
- Drug Target/Pathway MR

Winner's Curse

- Instruments are usually selected based on the strength of the variant-exposure association in order to avoid weak instrument bias.
- If this selection is done in the same data that are used for MR estimation, $G - X$ associations will be biased away from zero due to winner's curse.
- If there is no sample overlap, this will bias the MR estimate towards zero.
  - With sample overlap, bias is towards the observational association.

Combating Winner's Curse

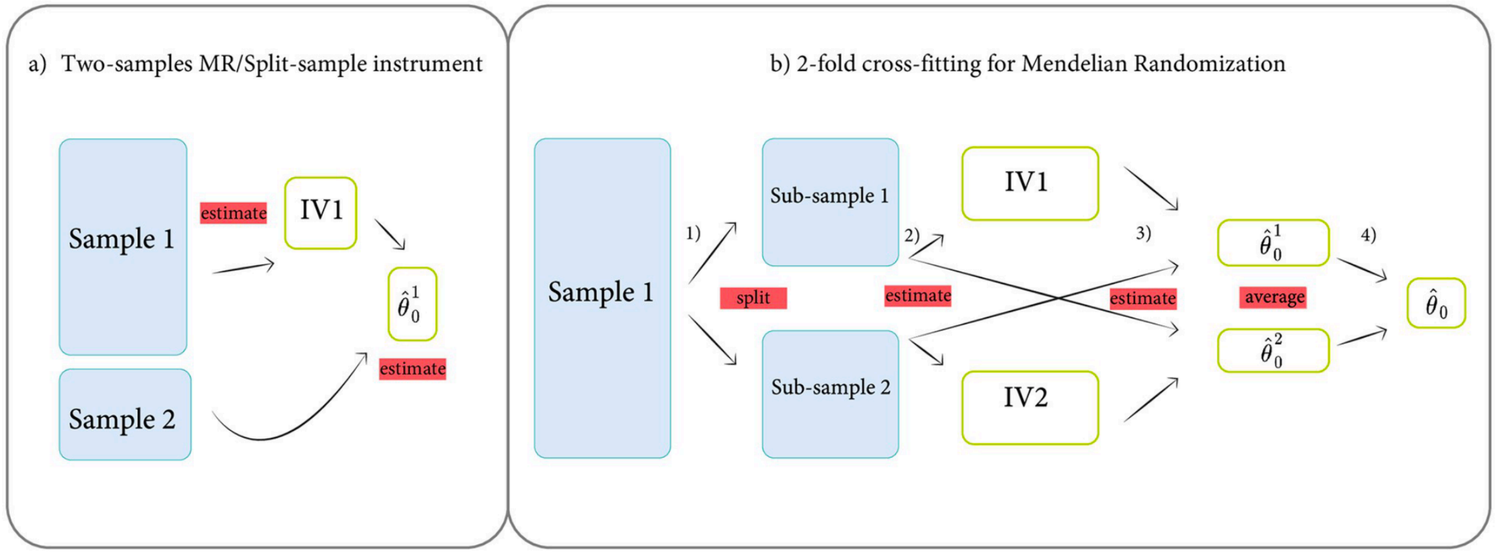
- One commonly suggested strategy is "three sample" MR.
  - Select instruments using an exposure data set that does not overlap with the data that will be used for analysis.

- Cons of this strategy:
  - Additional data sets may not exist
  - It is inefficient, the additional data set could be used to improve precision of the exposure association estimates.

Combating Winner's Curse

- Ma et al (2023) use a randomization approach (add a little error to each $\hat{\gamma}$ and adjust the variance of the final estimator).

- Denault et al (2022) use cross-fitting. This requires individual level data but solves both sample overlap and winner's curse problems.



Combatting Horizontal Pleiotropy

- Instrument selection is sometimes also used to combat horizontal pleiotropy.
  - Idea: Use a test or additional data to identify variants with HP and exclude them.

- Tests:
  - Steiger filtering: Identify and remove variants more strongly associated with the outcome than the exposure. (Hemani et al 2017)
  - Outlier tests: e.g. HEIDI test used by MR-PRESSO, Filtering based on contribution to Q-statistic (Verbanck et al 2017, Bowden et al 2019)

Pros and Cons of Outlier Removal

- Removing outliers can improve the MR estimate if a large majority of instruments are valid and there are just a few invalid outliers.

- If there is a lot of heterogeneity, or there is correlated horizontal pleiotropy, removing outliers can make things worse by removing the wrong variants.

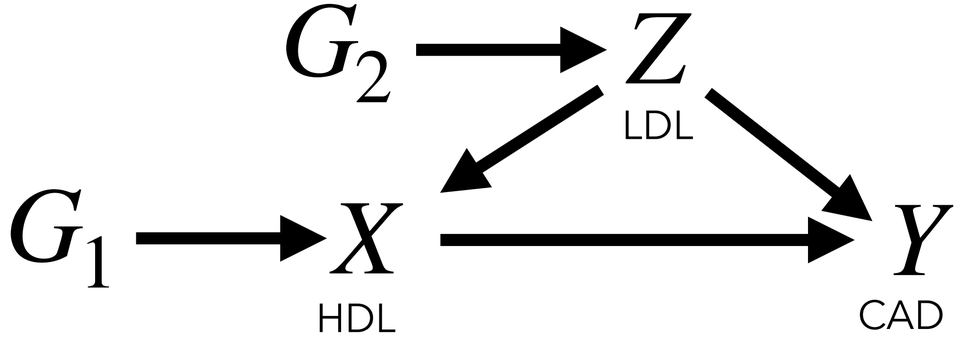
- It is a good idea to compare results from removing outliers with alternative methods of managing horizontal pleiotropy (Lecture 2).

Combatting Horizontal Pleiotropy

- Variants may also be removed if they are associated with a potential heritable confounder (e.g. Voight et al. 2012)

- However, this method could result in information loss if many variants affect both X and the heritable confounder(s).

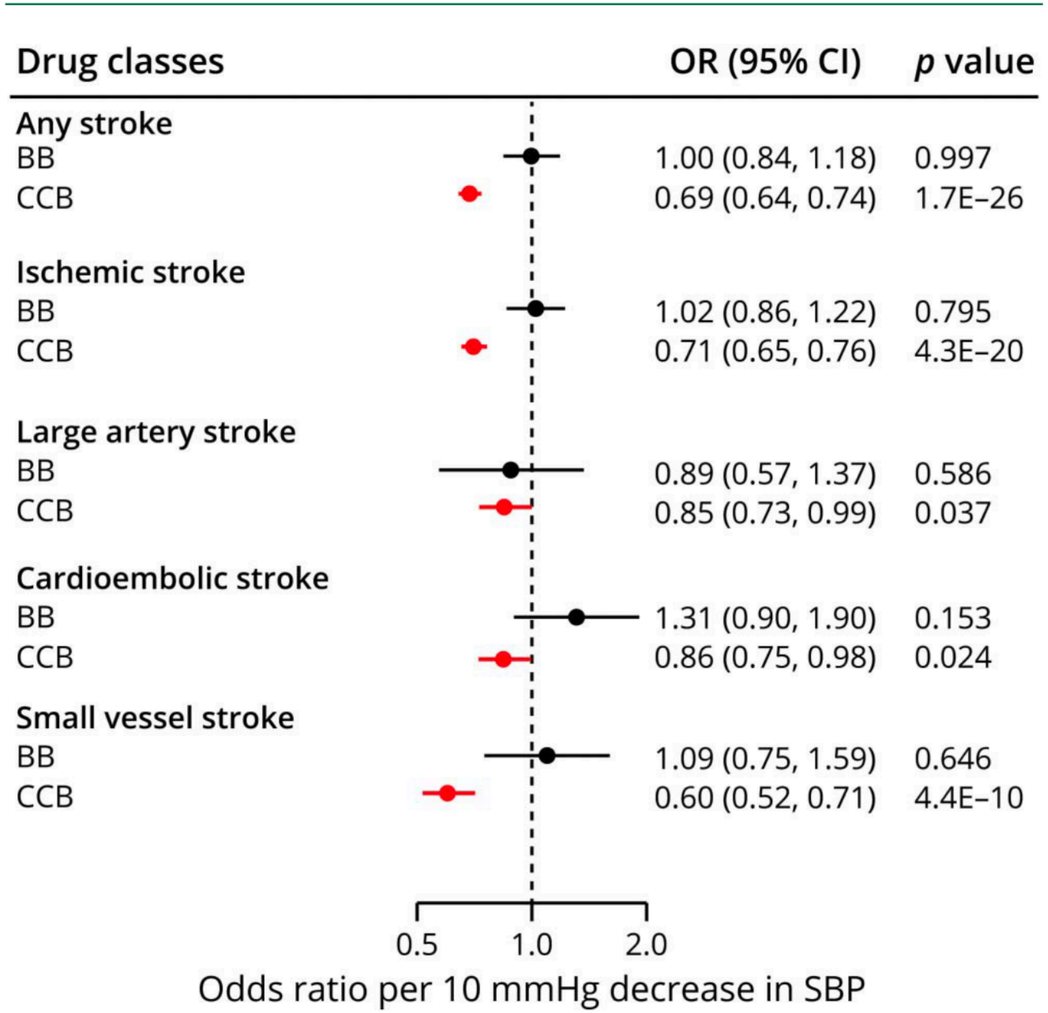
- An alternative strategy is multivariable MR, adjusting for known heritable confounders.



Drug Target/Pathway MR

- In some cases, we may be interested in predicting the effects (or side effects) of a specific drug or modification to a specific pathway.
- Drug target MR attempts to measure this by selecting only variants that affect genes in the targeted pathway.
- For example, Gill et al. (2019) and Georgakis et al 2020 identify variants in promoters or enhancers of genes targeted by beta blockers or calcium channel blockers that affect systolic blood pressure.
  - They then assume that these variants affect other traits through the same mechanisms that the corresponding drugs would act.

Drug Target/Pathway MR



Georgakis et al 2020

Part 3: Choosing a Question and Interpreting Results

- Interpreting Effect Estimates
- Exposure Specificity
- Scientific Considerations

What is MR Estimating?

- In the idealized MR scenario, Y and X are both continuous and the true causal relationship of X on Y is linear.

$$X_i = G_i^\top \gamma + e_x$$
$$Y_i = \beta X_i + e_y$$

- If all instruments are valid, then MR estimates β.

Complications to the model

- Effect heterogeneity for variant-exposure effects
- Effect heterogeneity in the exposure-outcome effect
- Binary outcomes with associations measured via logistic regression
- Binary exposures with associations measured via logistic regression
- Nonlinear causal relationships

Effect Heterogeneity

- Effect heterogeneity = different effect for different individuals.
- Heterogeneity in variant-exposure effects does not alter the MR estimate
  - Unless we are using 2SMR and average effects differ between samples.
- If there is heterogeneity in the exposure-outcome effect,
  - MR estimates the average causal effect in the outcome sample.
  - If we can assume the effect is in the same direction for everyone, then the direction of the MR effect is meaningful even if the outcome sample is non-representative.

Binary Outcome

- If Y is binary and $G - Y$ associations are measured by logistic regression, the 2SMR estimate approximates a population-averaged causal odds ratio for a small change in X.

- This odds ratio is marginal over all covariates, including the exposure itself.

- In 1SMR in a case-control study for the outcome, the variant-exposure association can't be computed in the full sample:
  - Case-control selection could distort the variant-exposure association (selection bias).
  - $\hat{\gamma}$ should be estimated in the controls only, relying on the assumption that the G-X association is similar in cases and controls.

Binary Exposure

- If X is binary and $\hat{\gamma}$ are estimated from logistic regression, then $\hat{\gamma}$ is approximately proportional to a linear effect on the liability scale.
  - Logistic regression summary statistics can also be converted to liability scale estimates (Gillett et al 2018)

- We could interpret the MR estimate as an effect of increased genetic liability for X on Y. (Burgess and Labrecque 2018).

Binary Exposure

- It is usually not sensible to interpret the MR estimate as an effect of binary X status.
  - For example, if X is rare or absent in the outcome population, we couldn't be measuring a causal effect X status.

- If X is a dichotomization of an underlying continuous variable (e. g. hypertension), it is better to use the continuous exposure.

Non-Linear Relationships

- If the true relationship between X and Y is non-linear then MR estimates a weighted average of derivatives.
  - The average is over the distribution of exposure values in the outcome sample.
  - See Burgess et al (2017), Section 8.1

- If the relationship is monotonic, then MR still provides a valid test of the null (zero causal effect for all values of X).

Exposure Specificity

- In many cases, the measured exposure you are interested in and a related variable share nearly all genetic causes.
- Examples:
  - Multiple metabolites in the same chemical pathway
  - Levels of gene expression or a biomarker in multiple tissues
  - Current and historical levels of the exposure
- MR may not be able to distinguish between these exposures, even if they are measured.
- It is important to keep in mind that an effect measured by MR may not measure the effect of intervening on exactly the measured exposure.

Units

- In order to determine the units of the estimated effect, we need to figure out the unit the exposure was originally measured in, if using GWAS results.
- If the exposure was normalized before analysis, we need to find the standard deviation of the exposure in the GWAS sample.
- In some cases, GWAS units are not what we would have chosen
  - The exposure may have been transformed oddly or differently in multiple sub-studies of a meta analysis.
- In some cases we may need to focus only on sign of an effect and hypothesis testing.

Final Thoughts

- It is possible to obtain an MR estimate in a formulaic fashion without thinking too hard about the problem or data contexts.
  - The MR field is currently awash in large numbers of applied papers of various quality.
- Careful analysis and careful, accurate interpretations are necessary to obtain useful results.
- Sensitivity analyses are important for evaluating robustness of conclusions.
- The STROBE MR guidelines (https://www.strobe-mr.org/) collect many of the considerations from this and previous lectures into a checklist.
  - These guidelines are a good place to start but not sufficient to guarantee a good analysis.

Questions?

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