



MENDELIAN RANDOMIZATION AND MR-DoC2

HGEN619

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Introduction to mendelian randomization

Sensitivity analysis in MR

Mixing with the DoC model

Bi-directional MR-DoC, MR-DoC2

INTRODUCTION TO MENDELIAN RANDOMIZATION

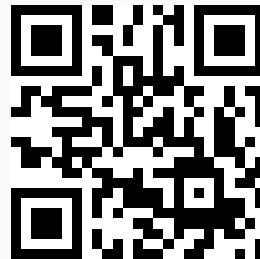


- Problems with observational data
- Randomized controlled trials
- Mendelian Randomization (MR):
 - How it works
 - Core assumptions
 - Calculating causal effect estimates
- MR example
- Limitations of MR



Lot's of slides borrowed from David Evans' talk^a

^aEvans, June 2021, "Introduction to Mendelian Randomization - Part 1," (Boulder 2021).



THE PROBLEM WITH INFERRING CAUSALITY IN OBSERVATIONAL STUDIES

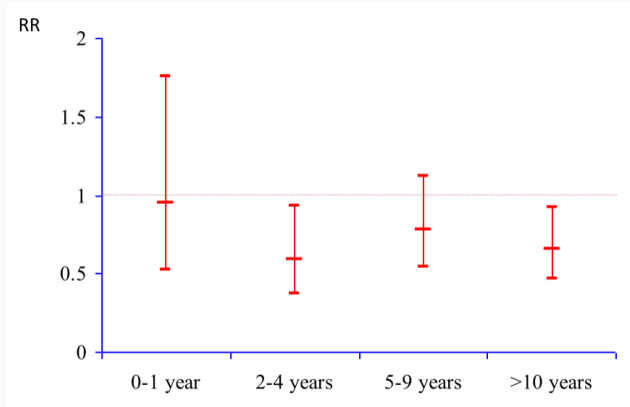
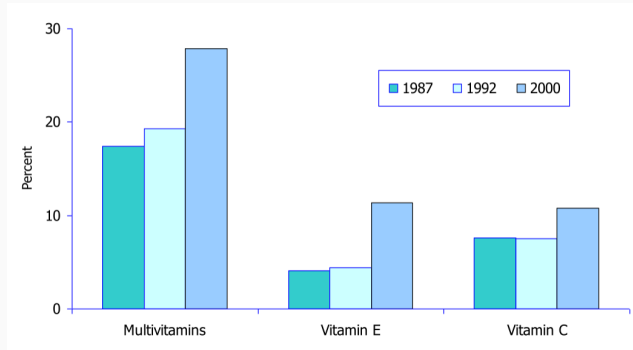


Figure 1: CHD risk according to duration of current Vitamin E supplement use compared to no use

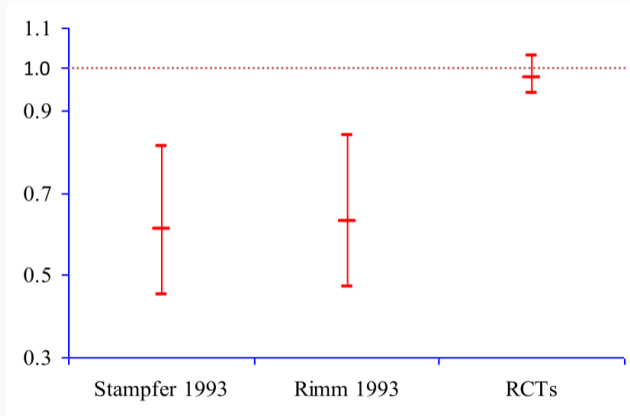
USE OF VITAMIN SUPPLEMENTS BY US ADULTS, 1987-2000



2

²Millen, (2004), "Use of Vitamin, Mineral, Nonvitamin, and Nonmineral Supplements in the United States," *J Am Diet Assoc.*

VITAMIN E SUPPLEMENT USE AND RISK OF CORONARY HEART DISEASE



3

³Stampfer, (1993), "Vitamin E Consumption and the Risk of Coronary Disease in Women," *N Engl J Med*; Eric B. Rimm, Meir J. Stampfer, Alberto Ascherio, Edward Giovannucci, Graham A. Colditz, and Walter C. Willett, "Vitamin E Consumption and the Risk of Coronary Heart Disease in Men"; Eidelman, (2004), "Randomized Trials of Vitamin E in the Treatment and Prevention of Cardiovascular Disease," *Arch Intern Med*.

MANY OTHER EXAMPLES



- VITAMIN C, VITAMIN A, HRT,
- MANY DRUG TARGETS.....
- WHAT'S THE EXPLANATION?



Reduces Vitamin E levels

- Childhood SES^a
- Manual social class
- No car access
- State pension only
- Smoker
- Obese

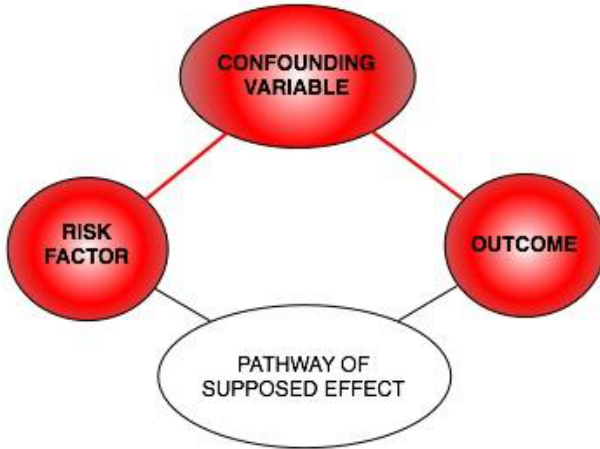
Increases Vitamin E levels

- Daily alcohol
- Exercise
- Low fat diet
- Height
- Leg length

^aLawlor, (2004), "Those Confounded Vitamins," *Lancet*.



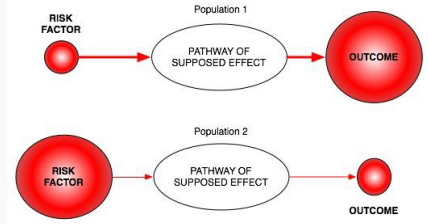
- Confounding

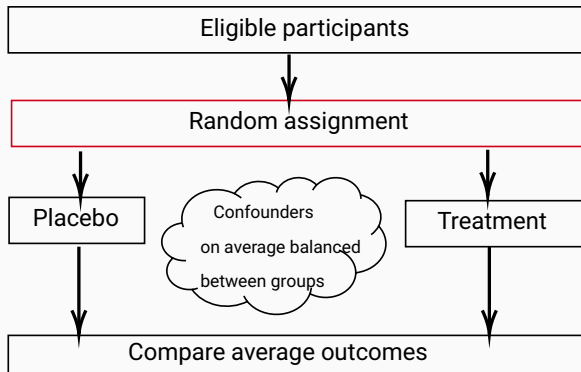


- Reverse causation



- Bias





⁴Camelia, 2017, "Mendelian Randomization," (VIPBG 2017).

⁵Camelia, 2017, "Mendelian Randomization," (VIPBG 2017).



Randomized Controlled Trials (RCTs):

- Not always ethical or practically feasible eg anything toxic
- Expensive, requires experimentation in humans
- Impractical for long follow up times
- Should only be conducted on interventions that show very strong observational evidence in humans

Observational studies:

- Association between environmental exposures and disease measured in observational designs (non-experimental) eg case-control studies or cohort studies
- Reliably assigning causality in these types of studies is **very limited**

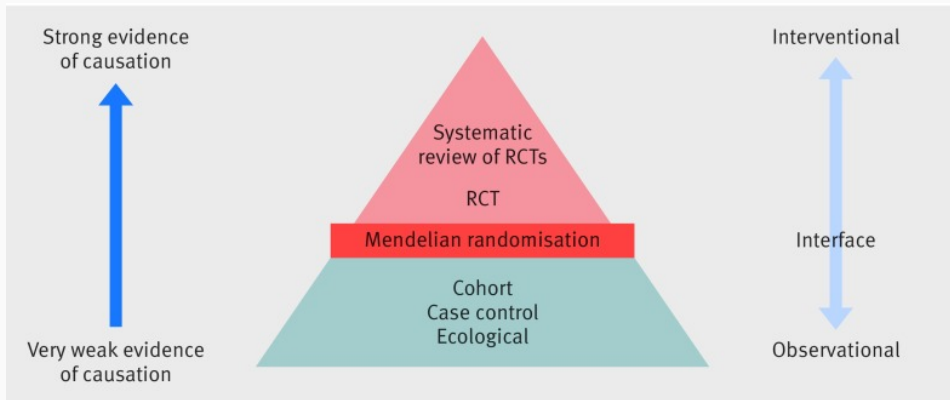


Figure 2: Mendelian randomisation studies sit at the interface of experimental and observational studies. Their findings can be used to provide more reliable evidence to guide interventional research and provide information about potential public health interventions when a randomised controlled trial may not be feasible.



Philip G Wright



- Known for first description of the parameter identification problem
- The instrumental variables method^a
- Could supply and demand be derived from price/volume data? As price confounds both supply & demand, Wright deduced that to resolve them, he needed an “instrument” – Something affecting only one of demand or supply. With this, he could compute the curves he needed.
- Wright hit upon variation in rainfall. Rain didn’t alter demand, but by increasing grass production, did impact butter supply. And thus the need to model food supply saw the first instrumental model conceived in 1938!
- Sewell Wright’s dad!

^aTimothy Bates [@timothycbates], October 2022, “Using a Modern SEM-based IV Model & Wanted to Learn Who Invented Them. Turns Out Likely Sewell Wright’s (SEM) Dad! In a Situation Similar to “Student” Wright Had a Commercial Need,” *Twitter*, (2022).



- Traditional Observational Epidemiological Studies
- Behavior Genetics and the Social Sciences
- Molecular Studies
- Pharmacogenomics

HOW DOES MENDELIAN RANDOMIZATION WORK?



- Assess causal relationship between two variables
- Estimate magnitude of causal effect

How does it do this?

- By harnessing Mendel's laws of inheritance

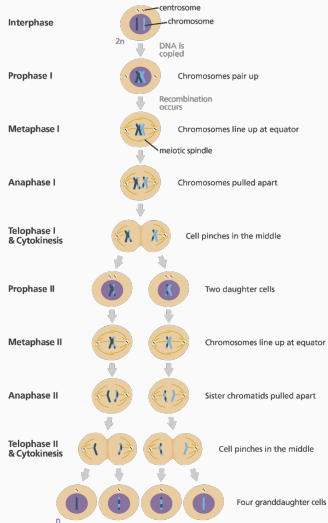


Gregor Mendel



Mendel's Laws of Inheritance

1. Segregation: alleles separate at meiosis and a randomly selected allele is transmitted to offspring
 2. Independent assortment: alleles for separate traits are transmitted independently of one another
- Mendel in 1862

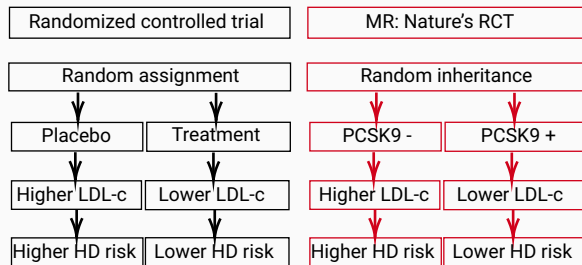


- Two cell divisions
- Produces four daughter cells
- Produces haploid cells
- Daughter cells are non-identical
- Produces sex cells
- Crossing-over occurs
- Homologous chromosomes pair up
 - and are separated at random (independent segregation)



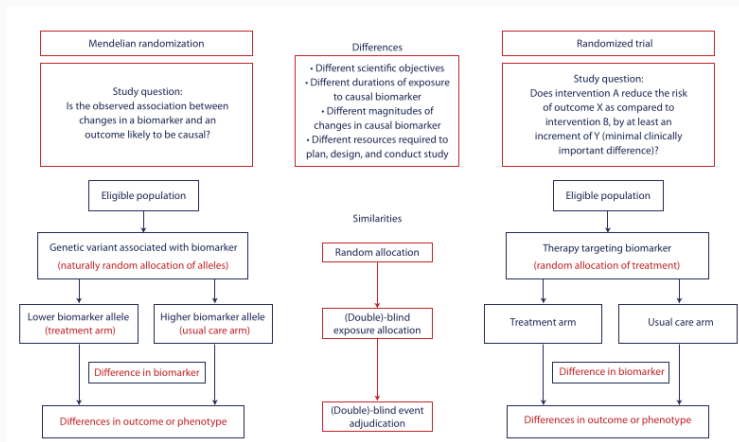
The genotype only affects the disease status indirectly and is assigned randomly (given the parents' genes) at meiosis, independently of the possible confounding factors. It is well known in the econometrics and causal literature, and slowly being recognized in the epidemiological literature that these properties define an instrumental variable (IV)⁷

⁷ Didelez, (2007), "Mendelian Randomization as an Instrumental Variable Approach to Causal Inference," *Stat Methods Med Res.*



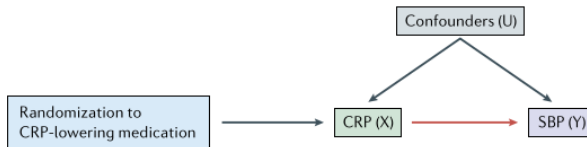
⁸ Minica Camelia, "Mendelian Randomization"; Costet, (2008), "PCSK9 and LDL Cholesterol," *Trends Biochem Sci*.

⁹ Minica Camelia, "Mendelian Randomization"; Costet, (2008), "PCSK9 and LDL Cholesterol," *Trends Biochem Sci*.





a An RCT to test whether lowering CRP lowers SBP



b An MR study to test whether lowering CRP lowers SBP

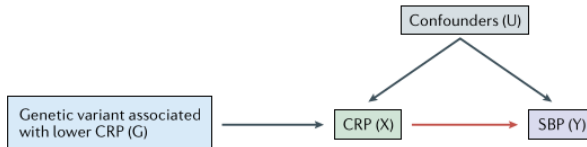


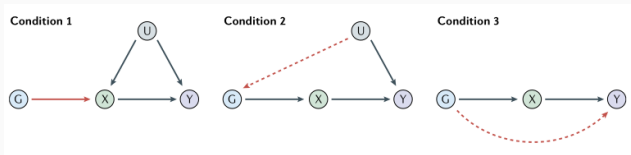
Figure 3: Illustration of a randomized control study and instrumental variable estimation. A randomized controlled trial (RCT) (panel a) and a Mendelian randomization (MR) study (panel b) to estimate the effect of lowering C-reactive protein (CRP) on systolic blood pressure (SBP). The arrows highlighted in red show the causal effect of interest.

¹¹Sanderson, (2022), "Mendelian Randomization | Nature Reviews Methods Primers," *Nature Reviews Methods Primers*.

¹²Sanderson. (2022). "Mendelian Randomization | Nature Reviews Methods Primers," *Nature Reviews Methods Primers*.



- Uses genetic variants as instrumental variables¹³
- Helps understand causation, but has strong assumptions¹⁴
 1. G (instrument) is robustly associated with X (“relevance”);
 2. G does not share common causes (C) with Y (Outcome) (“independence” or “exchangeability”); and
 3. G affects Y exclusively through its effect on X (“exclusion restriction”).
 4. No bidirectional causation between X and Y



¹³Richmond, (2022), “Mendelian Randomization,” *Cold Spring Harb Perspect Med*.

¹⁴Eleanor Sanderson, M. Maria Glymour, Michael V. Holmes, Hyunseung Kang, Jean Morrison, Marcus R. Munafò, Tom Palmer, C. Mary Schooling, Chris Wallace, Qingyuan Zhao, and George Davey Smith, “Mendelian Randomization | Nature Reviews Methods Primers.”



- Depends on instruments sufficiently predictive of exposure¹⁵
- Psychiatric disorders polygenicity, weak instrument bias
- Cause is (typically) assessed in one direction

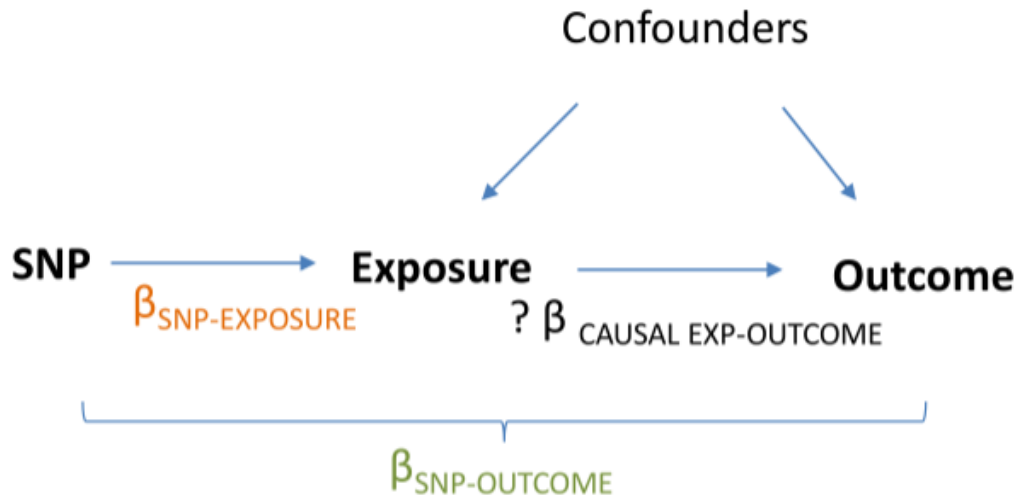
Table 4. Extensions to the basic Mendelian randomization (MR) approach

Method	Description	Directed acyclic graphs (DAGs)	Applications
Bidirectional or reciprocal MR (Timpson et al. 2011)	Used to evaluate the causal direction(s) of effect between two traits X and Y, with the use of valid instruments G_X and G_Y	$G_1 \longrightarrow X \longrightarrow Y$ $G_2 \longrightarrow Y \longrightarrow X$	Body mass index (BMI) and vitamin D (Vimalaswaran et al. 2013)

¹⁵Rebecca C. Richmond and George Davey Smith, "Mendelian Randomization."



- Robustness to confounding due to Mendel's laws:
 - Law of segregation: inheritance of an allele is random and independent of environment etc
 - Law of independent assortment: genes for different traits segregate independently (assuming not in LD)
- The direction of causality is known – always from SNP to trait
- Genetic variants are **potentially** very good instrumental variables
- Using genetic variants as IVs is a special case of IV analysis, known as Mendelian randomization





- Stage 1: regress exposure on instrument and get predicted values
- Stage 2: use predicted exposure to predict the outcome



Stage 1

$$X_i = \beta_0 + \beta_1 * GV_i + \epsilon_i$$

- Regress exposure on GV & obtain **predicted** values

Stage 2

$$Y_i = g_0 + g_1 * \hat{X}_i + \epsilon_i$$

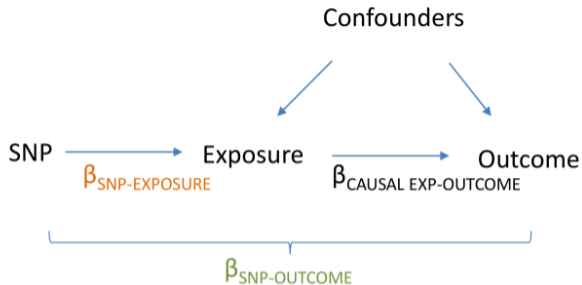
- Regress outcome on predicted exposure

g_1 difference in outcome per unit change in (genetically-predicted) exposure

- needs to be done in one sample

¹⁶Minica Camelia, "Mendelian Randomization."

¹⁷Minica Camelia, "Mendelian Randomization."

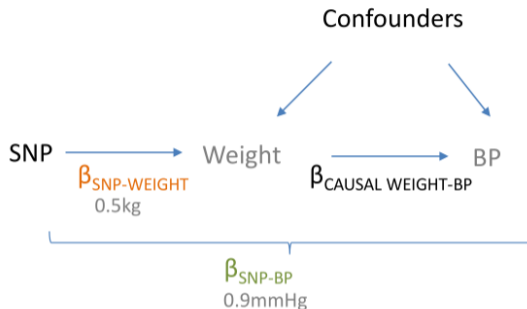


Causal effect by
Wald Estimator* :

$$\frac{\hat{\beta}_{\text{SNP-OUTCOME}}}{\hat{\beta}_{\text{SNP-EXPOSURE}}}$$

$$\beta_{\text{SNP-OUTCOME}} = \beta_{\text{CAUSAL EXP-OUTCOME}} \times \beta_{\text{SNP-EXPOSURE}}$$

- can be used in different samples



**Causal effect by
Wald Estimator* :**

$$\frac{\hat{\beta}_{\text{SNP-OUTCOME}}}{\hat{\beta}_{\text{SNP-EXPOSURE}}}$$

= change in outcome
per unit change in exposure

BP and weight:

$$\frac{0.9 \text{ mmHg/allele}}{0.5 \text{ kg/allele}}$$

$$= 1.8 \text{ mmHg/kg}$$



- Also known as two-sample MR, SMR, or MR with summary data etc
- Advantages:
 - The data is readily available, non-disclosive, free, open source
 - The exposure and outcome might not be measured in the same sample
 - The sample size of the outcome variable, key to statistical power, is not limited by requiring overlapping measures of the exposure
- Disadvantages:
 - Some extensions of MR not possible, e.g. non-linear MR, use of GxE for negative controls, various sensitivity analyses

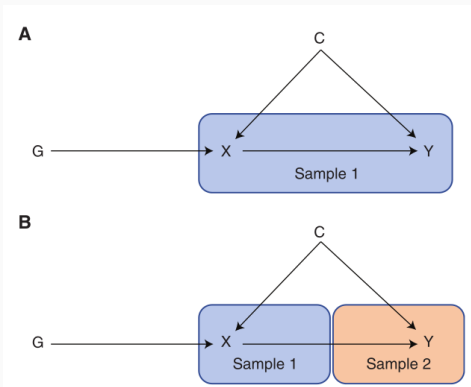


Figure 4: (A) One-sample MR uses a data set in which genotype, exposure, and outcome have been assessed. (B) Two-sample MR uses a genetic data set in which the exposure has been measured (to derive SNP-exposure estimates, sample 1) and a second genetic data set in which the outcome has been measured (to derive SNP-outcome estimates, sample 2).

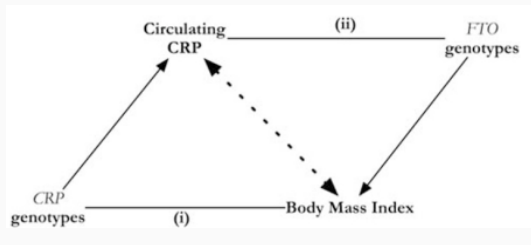
AN EXAMPLE USING MENDELIAN RANDOMIZATION



- C-Reactive Protein (CRP) is a biomarker of inflammation
- It is associated with BMI, metabolic syndrome, CHD and a number of other diseases
- It is unclear whether these observational relationships are causal or due to confounding or reverse causality
- This question is important from the perspective of intervention and drug development



- Only achieved by running twice^a



^aTimpson, (2011), "C-Reactive Protein Levels and Body Mass Index," *Int J Obes (Lond)*.

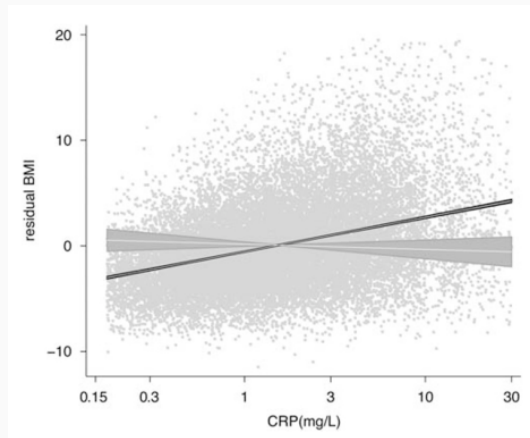
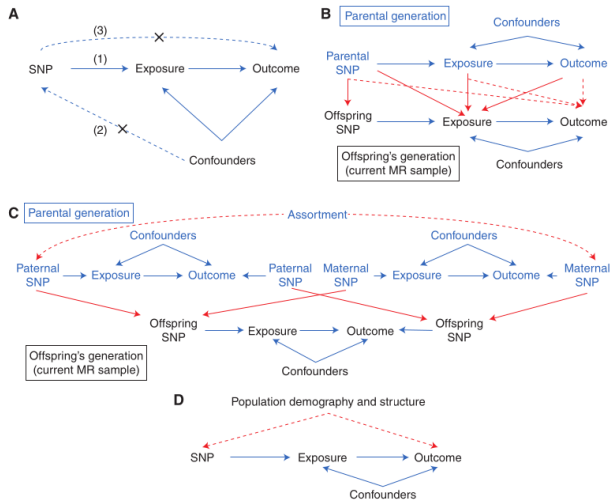


Figure 5: Comparison of linear relationships between residual BMI and circulating CRP observationally and when estimated using the CRP locus rs3091244 as an instrument for log-transformed CRP



1. Population stratification
2. The existence of instruments
3. Power and “weak instrument bias”
4. Pleiotropy



The solid blue arrows represent relationships within an individual (e.g., the effects of offspring single-nucleotide polymorphisms [SNPs] on offspring exposure). The red lines represent the effects of relationships between individuals (e.g., the direct effects of parents' phenotypes on their children). B, dynastic effects; C, cross-trait assortative mating (educated females and tall men); D, population structure^a

^aHwang, (2021), "Integrating Family-Based and Mendelian Randomization Designs," *Cold Spring Harb Perspect Med*.



- Power:
 - Genetic variants explain very small amounts of phenotypic variance in a given trait
 - VERY large sample sizes are generally required
- Weak instruments:
 - Genetic variants that are weak proxies for the exposure.
 - Results in biased causal estimates from MR
- Different impact of the bias from weak instruments:
 - **Single Sample MR:** to the confounded estimate
 - **Two-Sample MR:** to the null

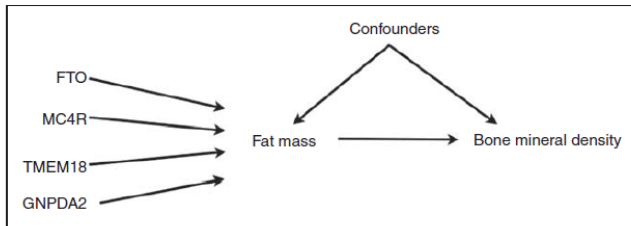


Figure 1. DAG for a Mendelian randomisation analysis using four genetic variants as instrumental variables for the effect of fat mass on bone mineral density.

- Allelic scores¹⁹
- Testing multiple variants individually
- Meta-analyze individual SNPs

¹⁹Palmer, (2012), "Using Multiple Genetic Variants as Instrumental Variables for Modifiable Risk Factors," *Stat Methods Med Res.*



mRnd: Power calculations for Mendelian Randomization

Input

Calculate:

☒ Power
☐ Sample size

Provide:

Sample size

1000

α

0.05

Type-I error rate

β_{yz}

0

The regression coefficient β_{yz} for the true underlying causal association between the exposure (X) and outcome (Y) variables

β_{OLS}

0

The regression coefficient β_{OLS} for the observational association between the exposure (X) and outcome (Y) variables

Continuous outcome **Binary outcome** Binary outcome derivations Citation About

Two-stage least squares

Power	0.05	
NCP	0.00	Non-Centrality-Parameter
F-statistic	11.10	The strength of the instrument

Power or sample size calculations for two-stage least squares Mendelian Randomization studies using a genetic instrument Z (a SNP or allele score), a continuous exposure variable X (e.g. body mass index [BMI, $\frac{kg}{m^2}$]) and a continuous outcome variable Y (e.g. blood pressure [mmHg]).

YZ association

Power	0.05	
NCP	0.00	Non-Centrality-Parameter

Power or sample size calculations for the regression association of a genetic instrument Z (e.g. a BMI SNP), with a continuous outcome variable Y (blood pressure).

Working Example

If we are interested in calculating the minimum required sample size for performing a Mendelian Randomization (MR) study ascertaining the causal effects of body mass index (BMI) on systolic blood pressure (SBP) in children, the required parameters for this online calculator could be taken from, for example, results from a published observational epidemiology study reporting associations between BMI and SBP and a SNP instrument that is reliably associated with BMI.

In an observational study reporting the association of BMI and SBP in children^[1], the regression coefficients for the association between BMI and SBP (averaged coefficients for boys and girls) was observed to be $1.41 \frac{mmHg}{SD}$ (no confounder-adjustment) and $1.30 \frac{mmHg}{SD}$ [4] (adjusted for confounders). The SD for SBP in this sample (from the paper's online supplementary data) was 10.8, with an SD (standard deviation) of 1 for BMI.

Assume that the causal effect of BMI on SBP is $1.30 \frac{mmHg}{SD}$ [4] and that the population regression coefficient of BMI on SBP, including the effects of confounders, is $1.41 \frac{mmHg}{SD}$. Also assume that for the MR study we have a genetic instrument that explains $R_{zz}^2 = 0.01$ of variation in BMI (based on a α FTO SNP which explains $\sim 1\%$ of the variation in BMI^[2]). Then we can calculate the power of an MR study using the

²⁰Brion, (2013), "Calculating Statistical Power in Mendelian Randomization Studies," *Int J Epidemiol*.



- Genetic variant influences more than one trait
- Horizontal vs Vertical pleiotropy
 - It has a central role in the genetic architecture^a
 - Using MR-PRESSO found pleiotropy in over 48% of significant MR,^b with large distortions on MR estimates.

^a Jordan, (2019), "HOPS," *Genome Biology*.

^b Verbanck, (2018), "Detection of Widespread Horizontal Pleiotropy in Causal Relationships Inferred from Mendelian Randomization Between Complex Traits and Diseases," *Nat Genet*.

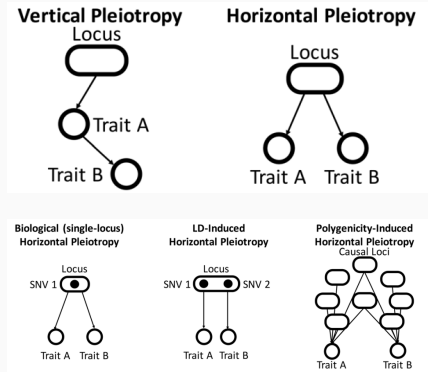
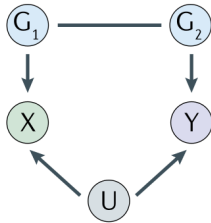


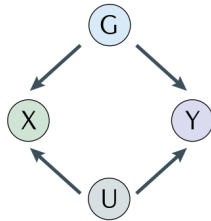
Figure 6: (LD) and polygenicity are expected to contribute to horizontal pleiotropy



a Distinct causal variants



b Shared causal variant, horizontal pleiotropy



c Shared causal variant, vertical pleiotropy

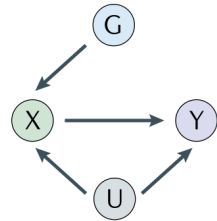


Figure 7: a | An example of distinct causal variants that violate the instrumental variable assumption IV2. G_1 and G_2 represent two genetic variants and the link between them is non-directional, reflecting linkage disequilibrium. b,c | Examples of a shared causal variant are a violation of assumption IV2 (panel b) and a situation that satisfies the IV assumptions (panel c).

SENSITIVITY ANALYSIS IN MR



- Inverse variance weighted MR (unbiased estimator, but no pleiotropy assumption)
 - Heterogeneity tests
 - Multivariable MR
 - MR Egger



- There is one underlying 'true' effect
- All deviations of sample effects from the 'true' effect are due to chance
- For N studies, each study i contributes more to the meta-analysis if its standard error is lower

$$w_i = \frac{1}{\text{var}(\beta_i)}$$

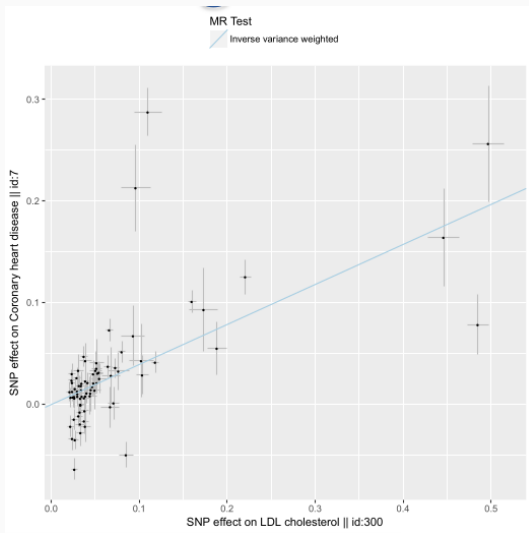
$$\beta_{\text{pooled}} = \frac{\sum_{i=1}^N (w_i * \beta_i)}{\sum_{i=1}^N (w_i)}$$

$$\text{se}_{\text{pooled}} = \sqrt{\frac{1}{\sum_{i=1}^N (w_i)}}$$

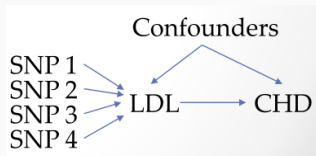


$$\chi^2_{df=1} = \frac{\beta_{\text{pooled}}^2}{\text{se}_{\text{pooled}}^2} = \frac{\left(\sum_{i=1}^N w_i * \beta_i\right)^2}{\sum_{i=1}^N w_i}$$

$$Z = \frac{\beta_{\text{pooled}}}{\text{se}_{\text{pooled}}} = \frac{\sum_{i=1}^N w_i * \beta_i}{\sqrt{\sum_{i=1}^N w_i}}$$



- IVW is equivalent to a weighted regression of SNP-outcome effects on SNP-exposure effects passing through the origin
- The weights are the inverse of the variance of the individual causal effect estimates
- The slope is the estimate of the causal effect



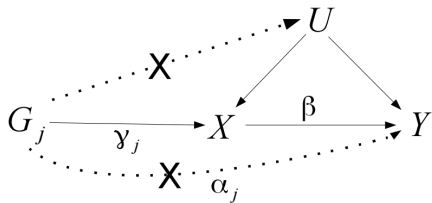


What is the problem?

- Mendelian Randomization (MR) uses genetic variants to test for causal relationships between phenotypic exposures and disease-related outcomes
- Due to the proliferation of GWAS, it is increasingly common for MR analyses to use large numbers of genetic variants
- Increased power but greater potential for **pleiotropy**
- Pleiotropic variants affect biological pathways other than the exposure under investigation and therefore can lead to biased causal estimates and false positives under the null



Single Variants



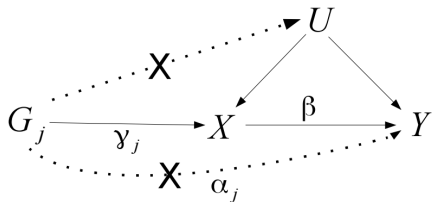
$$\text{Wald} = \frac{\text{Beta-GY}}{\text{Beta-GX}}$$

- Causal estimate using Wald method:

$$\frac{\beta\gamma_j}{\gamma_j} = \beta$$



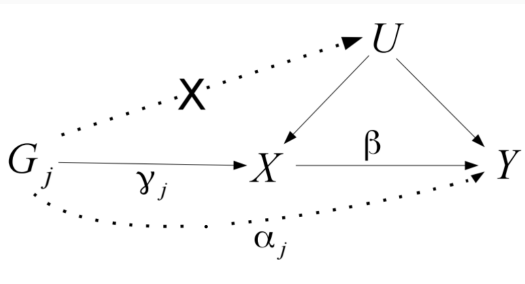
Multiple Variants



- Causal estimate using IVW from summarised data:
$$\frac{\sum_{j=1}^J \hat{\gamma}_j^2 \sigma_{Yj}^{-2} \hat{\beta}_j}{\sum_{j=1}^J \hat{\gamma}_j^2 \sigma_{Yj}^{-2}} = \beta$$

(Approximates TSLS)

where $\hat{\beta}_j = \frac{\hat{\gamma}_j}{\hat{\gamma}_j}$ is the ratio method estimate for variant j , and σ_{Yj} is the standard error in the regression of the outcome on the j th genetic variant, assumed to be known.



$$Y_i = \Gamma_j G_{ij} + \epsilon'_{ij}{}^Y$$

$$= (\alpha_j + \beta \gamma_j) G_{ij} + \epsilon'_{ij}{}^Y.$$

Single variant Wald estimate: $\beta_j = \beta + \frac{\alpha_j}{\gamma_j}$

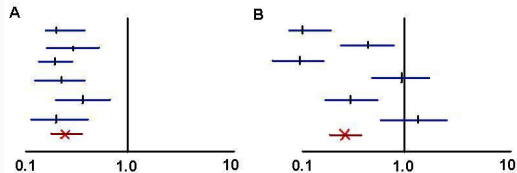
Multiple variant:

$$\beta + \frac{\sum_{j=1}^J \gamma_j \sigma_{Yj}^{-2} \alpha_j}{\sum_{j=1}^J \gamma_j^2 \sigma_{Yj}^{-2}} = \beta + \text{Bias}(\alpha, \gamma)$$



- We expect that each SNP represents an independent study, and each should give an unbiased (if imprecise) estimate of the causal effect of x on y
- Heterogeneity, where effect estimates are more different than expected due to standard errors, arises because at least some of the instruments are invalid
- Cochran's Q statistic

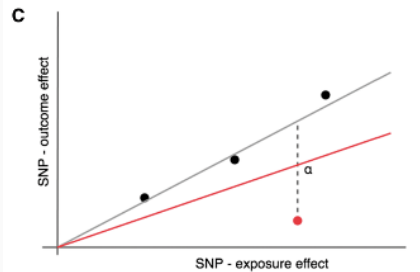
$$Q = \sum_{k=1}^K w_k (\hat{\beta}_k - \hat{\beta}_{IVW})^2$$



- n=6 instruments
- Expect $Q = 5$ if there is no heterogeneity
- Q is chi-square distributed with n-1 degrees of freedom



- Some SNPs might contribute to the majority of the heterogeneity
- If we assume these are the invalid instruments then the IVW estimate excluding them should be less biased
- However, beware of:
 - Cherry picking, remove outliers will artificially provide a more precise estimate
 - What if the outlier is the only valid instrument, and all the others are invalid?





- We are testing for whether X_1 has an influence on Y^a
- We know that some instruments for X_1 also have influences on X_2
- This opens up the possibility of horizontal pleiotropy biasing our estimate
- What is the X_1 - Y association adjusting for X_2 ?

^aEleanor Sanderson, M. Maria Glymour, Michael V. Holmes, Hyunseung Kang, Jean Morrison, Marcus R. Munafò, Tom Palmer, C. Mary Schooling, Chris Wallace, Qingyuan Zhao, and George Davey Smith, "Mendelian Randomization | Nature Reviews Methods Primers."

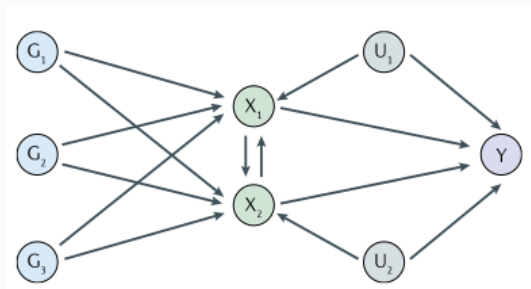


Figure 8: Multivariable Mendelian randomization (MR) for three genetic variants (G_1 , G_2 , G_3), two exposures (X_1 , X_2) and an outcome Y . Confounders U_1 and U_2 are assumed to be unknown.



- IVW fixed effects estimate assumes all SNPs are valid instruments, and averages across them all
- IVW random effects model allows all SNPs to be drawn from a different distribution – the estimate is the same but the standard error is larger if there is any heterogeneity

MR EGGER REGRESSION

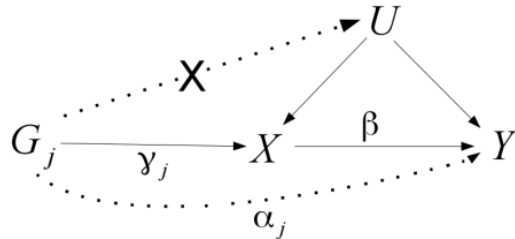


- In Mendelian Randomization when multiple genetic variants are being used as IVs, Egger regression can:
- Identify the presence of 'directional' pleiotropy (biasing the IV estimate)
- provide a less biased causal estimate (in the presence of pleiotropy)
- However, MR Egger lacks power



Relaxing MR's assumptions

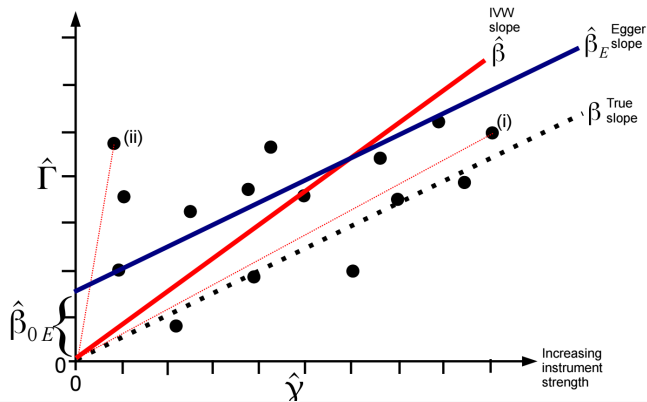
We explore the condition that the correlation between the genetic associations with the exposure (the γ_j parameters) and the direct effects of the genetic variants on the outcome (the α_j parameters) is zero. We refer to the condition that the distributions of these parameters are independent as *InSIDE* (Instrument Strenght Independent of Direct Effect). It can be viewed as a weaker version of the exclusion restriction assumption.



$$\begin{aligned}
 Y_i &= \Gamma_j G_{ij} + \epsilon_{ij}^{'Y} \\
 &= (\alpha_j + \beta \gamma_j) G_{ij} + \epsilon_{ij}^{'Y}
 \end{aligned}$$



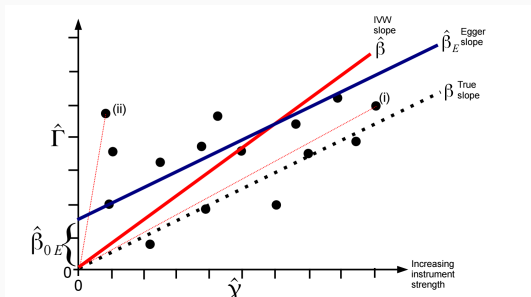
SNP – exposure association





- Intercept not constrained to zero

$$\hat{\Gamma}_j = \beta_{0E} + \beta_E \hat{\gamma}_j$$



- Egger's test assesses whether the intercept term is significantly different from zero. The estimated values of the intercept can be interpreted as the average pleiotropic effect across all genetic variants. An intercept term different from zero indicates direct pleiotropy



- IVW MR the most powerful option, but assumes the absence of horizontal genetic pleiotropy
- MR Egger, Weighted Median and Modal based estimators relax the strict requirement of no horizontal pleiotropy, but at the cost of decreased statistical power
- Crucial to perform sensitivity analyses and obtain metrics regarding the likely reliability of the MR estimates

MIXING WITH THE DoC MODEL



- We've seen:
 - Causal inference, gold standard: randomized controlled trial
 - Not always feasible, ethics²²
 - ▶ E.g. exposure to trauma → substance abuse
- Mendelian randomization,²³ helps with these cases.
- However, pleiotropy can bias the estimates
- Now we will see that pleiotropy can be controlled for if we use a twin design
- But first we need to show proof that we can find equivalence from tsIs in SEM

²²Ohlsson, (2020), "Applying Causal Inference Methods in Psychiatric Epidemiology," *JAMA Psychiatry*.

²³Katikireddi, (2018), "Assessing Causal Relationships Using Genetic Proxies for Exposures," *Addiction*.



- SEM solutions have been shown to recover exact estimates as 2SLS^a
 - less convergence in weak instruments
 - slightly worse performance in ML-SEM

^aMaydeu-Olivares, (2019), "Instrumental Variables Two-Stage Least Squares (2SLS) Vs. Maximum Likelihood Structural Equation Modeling of Causal Effects in Linear Regression Models," *Structural Equation Modeling: A Multidisciplinary Journal*.

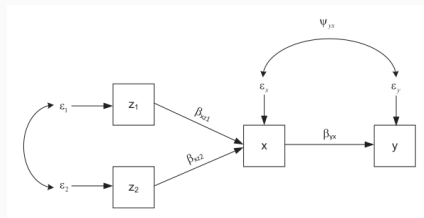


Figure 9: Instrumental Variables Regression (IVR) model that enables drawing causal inferences on the target regression model

QUICK DEMONSTRATION IN UMX()



```
library(umx)
df = umx_make_MR_data(nSubjects = 10000, Vqtl = .02, bXY= .1)

m1 = sem::tsls(formula = Y ~ X, instruments = ~ qtl, data = df)
coef(m1)
```

```
(Intercept)          X
      0.00228      0.15807
```

```
m1 = umxMR(Y~X, instruments= ~qtl, data = df)
```

	name	Estimate	SE	type
7	phi2	0.192	0.075	Factor Cov
3	eY_to_Y	1.000	0	Factor loading
4	eX_to_X	1.000	0	Factor loading
6	eY_with_eY	0.913	0.032	Factor Variance
8	eX_with_eX	0.999	0.014	Factor Variance
1	X_to_Y	0.158	0.075	Manifest path
2	qtl_to_X	0.181	0.014	Manifest path
9	one_to_X	-0.196	0.017	Mean
10	one_to_Y	0.002	0.01	Mean
11	one_to_qtl	1.007	0.007	Mean
5	qtl_with_qtl	0.494	0.007	Residual

QUICK DEMONSTRATION IN UMX()



```
df = umx_make_MR_data(10e4)

m2 <- umxRAM("myMR", data = df, autoRun = FALSE,
  umxPath(v.m. = c("qtl", "X", "Y")),
  umxPath("qtl", to = "X"),
  umxPath("X", to = "Y")
  # umxPath("X", with = "Y") # Due to OpenMx rules, will be deleted!
)
m2 <- umxModify(m2, "X_with_Y", free = TRUE, value = .2)
```

```
m1 = umxMR(Y~X, instruments= ~qtl, data = df)
```

	name	Estimate	SE	type
7	phi2	0.192	0.075	Factor Cov
3	eY_to_Y	1.000	0	Factor loading
4	eX_to_X	1.000	0	Factor loading
6	eY_with_eY	0.913	0.032	Factor Variance
8	eX_with_eX	0.999	0.014	Factor Variance
1	X_to_Y	0.158	0.075	Manifest path
2	qtl_to_X	0.181	0.014	Manifest path
9	one_to_X	-0.196	0.017	Mean
10	one_to_Y	0.002	0.01	Mean
11	one_to_qtl	1.007	0.007	Mean
5	qtl_with_qtl	0.494	0.007	Residual

GENETIC VARIANT OR POLYGENIC SCORE?



- The use of instrumental PS is common in Mendelian randomization studies^a.
- PS as an instrument is mathematically equivalent to a weighted mean of the results from individual SNPs.^b

^aBurgess, April 2020, "Guidelines for Performing Mendelian Randomization Investigations," (2020).

^bDudbridge, (2021), "Polygenic Mendelian Randomization," *Cold Spring Harb Perspect Med*.

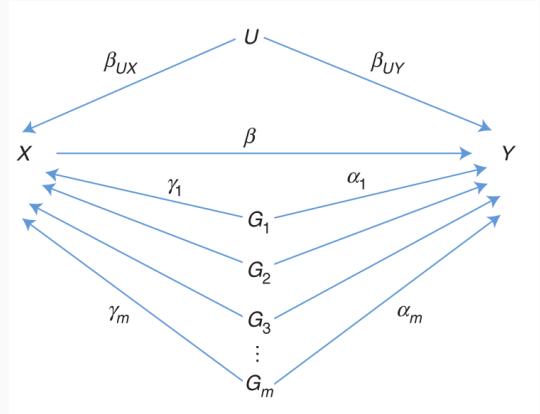


Figure 10: DAG showing m single-nucleotide polymorphisms (SNPs) G_j used as instrumental variables for the association of exposure X with outcome Y in the presence of confounder U . Each SNP has an effect γ_j on X and a direct pleiotropic effect α_j on Y . Under linear models for X and Y , the total effect of SNP j on Y is shown next



- the total effect of SNP j on Y : $\Gamma_j = \alpha_j + \beta\gamma_j$
- PS which is the weighted sum of genotypes over many SNPs:

$$S = \sum_{j=1}^m \gamma_j G_j$$

- where G_j is a numerical coding of the genotype of SNP $_j$, typically the number of effect alleles carried
- The ratio estimate for the polygenic score S is:

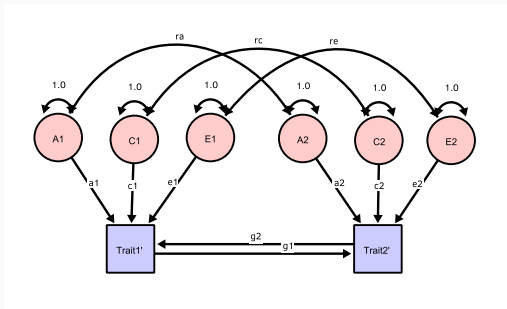
$$\begin{aligned} \frac{\text{cov}(S, Y)}{\text{cov}(S, X)} &= \frac{\sum \gamma_j \text{cov}(G_j, Y)}{\sum \gamma_j \text{cov}(G_j, X)} \\ &= \frac{\sum \gamma_j \Gamma_j \text{var}(G_j)}{\sum \gamma_j \Gamma_j \text{var}(G_j)} \\ &= \sum_j \frac{\gamma_j^2 \text{var}(G_j)}{\sum_k \gamma_k^2 \text{var}(G_k)} \frac{\Gamma_j}{\gamma_j} \end{aligned}$$

- polygenic score approach is in fact equivalent to an average MR ratio approach
- or, PS as an instrument is mathematically equivalent to a weighted mean of the results from individual SNPs.^a

^aIbid.



Model specification



a

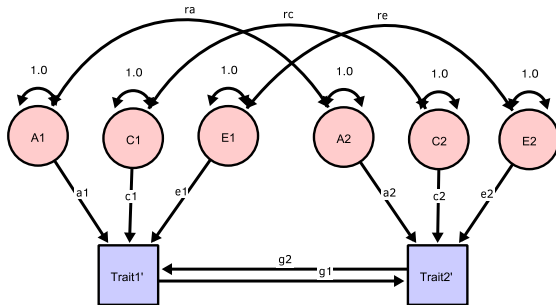
^aHeath, (1993), "Testing Hypotheses About Direction of Causation Using Cross-Sectional Family Data," *Behav Genet*.

Path diagram representing a Bidirectional DoC for one twin.

- causal paths are estimated affording information from the cross-twin cross-trait correlations.
- Cross-twin covariance between additive genetic effects is 0.5 (not shown) for DZ twins, as DZs are expected to share 50% of the genetic effects.
- Standard SEM symbology is used.



Model specification



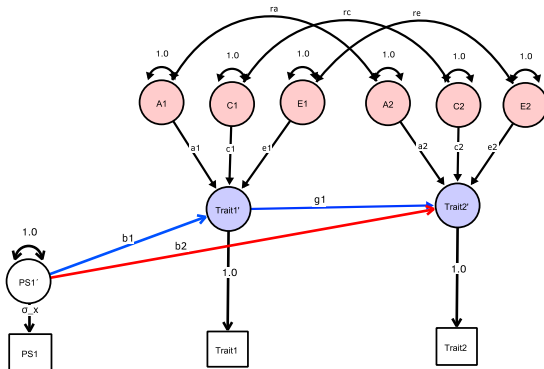
Problems

- Not identified as depicted
- Bias at the phenotypic level^a
- Bias due to E confounding^b
- Better detection of cause with different variance component proportions for each phenotype^c

^aGillespie, (2003), "Direction of Causation Modeling Between Cross-Sectional Measures of Parenting and Psychological Distress in Female Twins," *Behav Genet*.

^bRasmussen, (2019), "A Major Limitation of the Direction of Causation Model," *Twin Res Hum Genet*.

^cMaes, (2021), "Using Multimodel Inference/Model Averaging to Model Causes of Covariation Between Variables in Twins," *Behav Genet*.



- Shown to recover exact values as a 2SLS-MR or 2sample-MR^a
- Not identified as shown

^aMinică, (2018), "Extending Causality Tests with Genetic Instruments," *Behav Genet*.

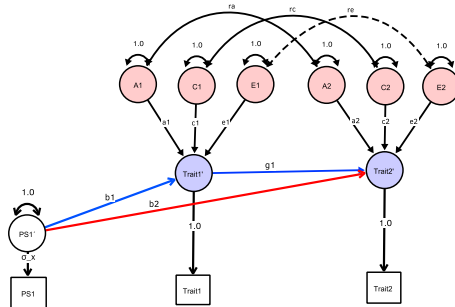


x	aX	cX	eX	aY	cY	eY	ra	rc	re	b1	b2	g1	ld
fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	No
fr	fr	fr	fr	fr	fr	fr	fr	fr	0	fr	fr	fr	Yes
fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	0	fr	Yes
fr	fr	fr	fr	fr	fr	fr	fr	0	fr	fr	fr	fr	Yes
fr	fr	0	fr	fr	0	fr	fr	0	fr	fr	fr	fr	No
fr	fr	fr	fr	fr	0	fr	fr	0	fr	fr	fr	fr	Yes
fr	fr	0	fr	fr	fr	fr	fr	0	fr	fr	fr	fr	No

MR-DoC - IDENTIFIED CASES

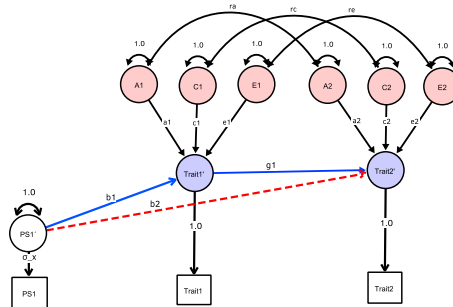


x	aX	cX	eX	aY	cY	eY	ra	rc	re	b1	b2	g1	Id
fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	No
fr	fr	fr	fr	fr	fr	fr	fr	fr	0	fr	fr	fr	Yes
fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	0	fr	Yes
fr	fr	fr	fr	fr	fr	fr	fr	0	fr	fr	fr	fr	Yes
fr	fr	0	fr	fr	0	fr	fr	0	fr	fr	fr	fr	No
fr	fr	fr	fr	fr	0	fr	fr	0	fr	fr	fr	fr	Yes
fr	fr	0	fr	fr	fr	fr	fr	0	fr	fr	fr	fr	No



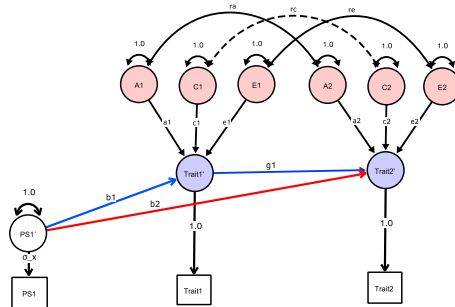


x	aX	cX	eX	aY	cY	eY	ra	rc	re	b1	b2	g1	Id
fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	No
fr	fr	fr	fr	fr	fr	fr	fr	fr	0	fr	fr	fr	Yes
fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	0	fr	Yes
fr	fr	fr	fr	fr	fr	fr	fr	0	fr	fr	fr	fr	Yes
fr	fr	0	fr	fr	0	fr	fr	0	fr	fr	fr	fr	No
fr	fr	fr	fr	fr	0	fr	fr	0	fr	fr	fr	fr	Yes
fr	fr	0	fr	fr	fr	fr	fr	0	fr	fr	fr	fr	No





x	aX	cX	eX	aY	cY	eY	ra	rc	re	b1	b2	g1	Id
fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	No
fr	fr	fr	fr	fr	fr	fr	fr	fr	0	fr	fr	fr	Yes
fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	0	fr	Yes
fr	fr	fr	fr	fr	fr	fr	fr	0	fr	fr	fr	fr	Yes
fr	fr	0	fr	fr	0	fr	fr	0	fr	fr	fr	fr	No
fr	fr	fr	fr	fr	0	fr	fr	0	fr	fr	fr	fr	Yes
fr	fr	0	fr	fr	fr	fr	fr	0	fr	fr	fr	fr	No





x	aX	cX	eX	aY	cY	eY	ra	rc	re	b1	b2	g1	Id
fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	No
fr	fr	fr	fr	fr	fr	fr	fr	fr	0	fr	fr	fr	Yes
fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	fr	0	fr	Yes
fr	fr	fr	fr	fr	fr	fr	fr	0	fr	fr	fr	fr	Yes
fr	fr	0	fr	fr	0	fr	fr	0	fr	fr	fr	fr	No
fr	fr	fr	fr	fr	0	fr	fr	0	fr	fr	fr	fr	Yes
fr	fr	0	fr	fr	fr	fr	fr	0	fr	fr	fr	fr	No

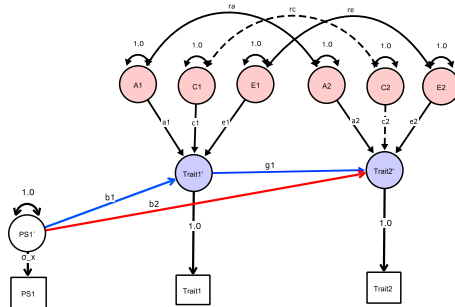


Fig. 4 Path diagrammatic representation of the MR-DoC model in DZ twins. The parameter α equals the standard deviation of the observed instrument, i.e., PGS in the circle is standardized. The model as depicted is not identified (see Table 1)

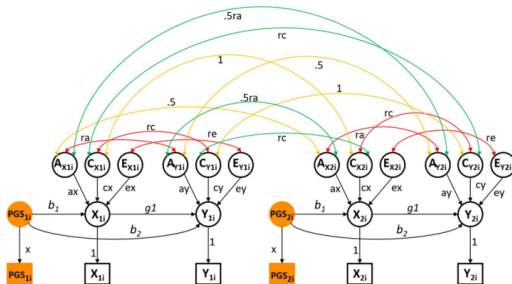
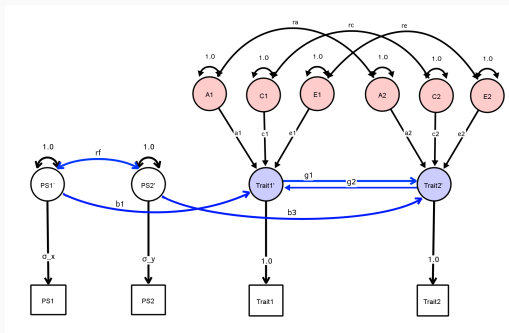


Figure 11: MR-DoC extension. Some confounding, not bidirectional. Not identified as depicted.

BI-DIRECTIONAL MR-DoC, MR-DoC2

Model specification



Modified MR-DOC

- Path diagram of the MR-DoC2 model for an individual.
- The model includes the effects of additive genetic (A), common environment (C) and specific environment (E) factors for both X and Y, and their effects may correlate (parameters r_a , r_c and r_e).

²⁵Dolan, 2020, "Introducing Polygenic Risk Scores into the Twin Design," (Boulder 2020).

²⁶Dolan, 2020, "Introducing Polygenic Risk Scores into the Twin Design," (Boulder 2020).



- Which parameters drive power?

Revisiting limitations

- Do we need phenotypes with distinct inheritance patterns
- What about measurement error at the phenotypic level?
- How robust it is regarding pleiotropy

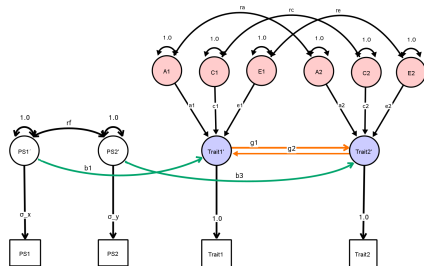
WHICH PARAMETERS DRIVE POWER?²⁸



Table 8: Variance explained in statistical power (non-centrality parameter; NCP) by model parameters.

	g1 = 0	g2 = 0	g1 = g2 = 0
g1	0.517	0.000	0.289
g2	0.000	0.517	0.289
b1	0.365	0.000	0.181
b3	0.000	0.365	0.181
ra	0.000	0.000	0.000
rc	0.000	0.000	0.000
re	0.002	0.002	0.000
rf	0.041	0.041	0.000
ay	0.002	0.000	0.001
ax	0.000	0.002	0.001
cy	0.002	0.000	0.001
cx	0.000	0.002	0.001
Total R2	0.929	0.929	0.945

- Distinct inheritance patterns from phenotypes - not needed
- b1, b2, g1, and g2 are what drives power
- slightly better power without C variance



²⁷Van der Sluis, (2008), "Power Calculations Using Exact Data Simulation," *Behav Genet*.

²⁸Van der Sluis, (2008), "Power Calculations Using Exact Data Simulation," *Behav Genet*.



θ	Design 1 (ACE)	Design 2 (AE)	Design 3 (AE)
b1	$\sqrt{0.025}, \sqrt{0.05}$	$\sqrt{0.025}, \sqrt{0.05}, \sqrt{0.075}$	$-\sqrt{0.075}, -\sqrt{0.03}, \sqrt{0.03}, \sqrt{0.075}$
b3	$\sqrt{0.025}, \sqrt{0.05}$	$\sqrt{0.025}, \sqrt{0.05}, \sqrt{0.075}$	$-\sqrt{0.075}, -\sqrt{0.03}, \sqrt{0.03}, \sqrt{0.075}$
g1	$\sqrt{0.020}, \sqrt{0.05}$	$\sqrt{0.020}, \sqrt{0.04}, \sqrt{0.06}$	$-\sqrt{0.050}, -\sqrt{0.020}, \sqrt{0.050}, \sqrt{0.020}$
g2	$\sqrt{0.020}, \sqrt{0.05}$	$\sqrt{0.020}, \sqrt{0.04}, \sqrt{0.06}$	$-\sqrt{0.050}, -\sqrt{0.020}, \sqrt{0.050}, \sqrt{0.020}$
ra	0.25, 0.50	0.0, 0.25, 0.50	0.3
rc	0.25, 0.50	0	0
re	0.25, 0.50	0.0, 0.25, 0.50	0.3
rf	0.25, 0.50	0.0, 0.25, 0.50	0.3
ax	$\sqrt{0.10}, \sqrt{0.25}$	$\sqrt{0.10}, \sqrt{0.25}$	$\sqrt{0.5}$
ay	$\sqrt{0.10}, \sqrt{0.25}$	$\sqrt{0.10}, \sqrt{0.25}$	$\sqrt{0.3}$
cx	$\sqrt{0.10}, \sqrt{0.25}$	0	0
cy	$\sqrt{0.10}, \sqrt{0.25}$	0	0
Total cells	$2^{12}=4096$	$3^7 \cdot 2^2 = 8748$	$4^4=256$

Parameter levels on the three factorial designs, with respective total number of cells for each design simulation. Also, ex was specified as $\sqrt{1 - ax^2 - cx^2}$ and ey as $\sqrt{1 - ay^2 - cy^2}$.



- Power simulations typically involve simulating many datasets corresponding to one true model and calculating the proportion of simulations where a given effect is significant.

Exact data simulation

1. choosing a set of parameter values for the model shown in the figure;
 2. exact data simulation, with arbitrary $N=1,000$ MZ pairs and $N=1,000$ DZ twin pairs;
 3. fitting the true model using ML estimation in OpenMx;
 4. fitting the false model by fixing one or more parameters to zero and refitting the model; and
 5. calculating the NCP and the power to reject the false model restrictions.
- **Regressing the NCP on the parameters to work out which ones are important wrt power.**

²⁹ibid.

³⁰ibid.

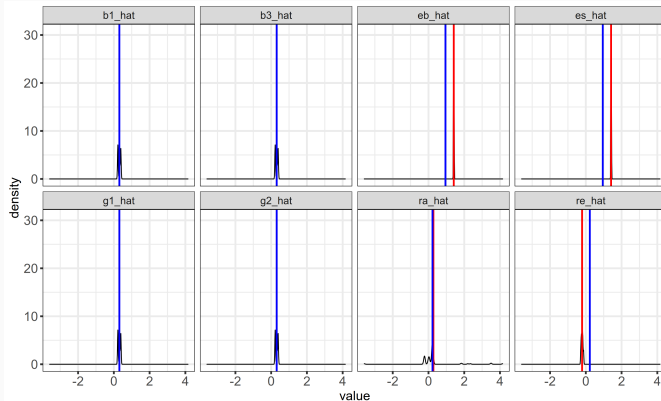


Reliability

$$relB = \text{var}(B) / \{\text{var}(B) + \text{var}(\text{error}B)\}$$

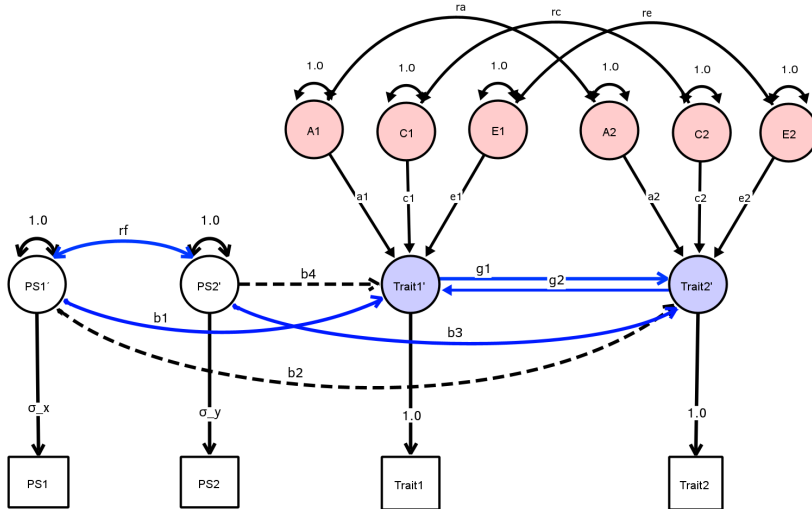
$$relS = \text{var}(S) / \{\text{var}(S) + \text{var}(\text{error}S)\}$$

- power reduces
- but no bias in estimation of b1, b3, g1, g2

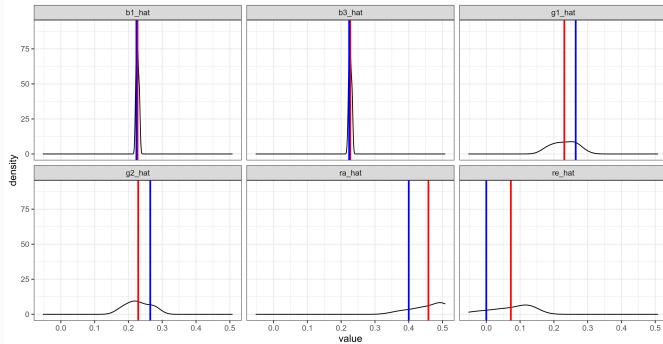


$\theta = \{b1 = c(\text{sqrt}(.05), \text{sqrt}(.1), \text{sqrt}(.15)), b3 = c(\text{sqrt}(.05), \text{sqrt}(.1), \text{sqrt}(.15)), g1 = c(\text{sqrt}(.05), \text{sqrt}(.1), \text{sqrt}(.15)), g2 = c(\text{sqrt}(.05), \text{sqrt}(.1), \text{sqrt}(.15)), \text{abs} = .05, \text{ass} = 0.05, \text{cbs} = 0.05, \text{css} = 0.05, \text{ra} = .224, \text{rc} = .224, \text{re} = .224, \text{rf} = .224, \text{reliability} = c(0, .1, .2, .3, .4)\}$

OTHER TYPES OF PLEIOTROPY NOT INCLUDED IN THE MODEL



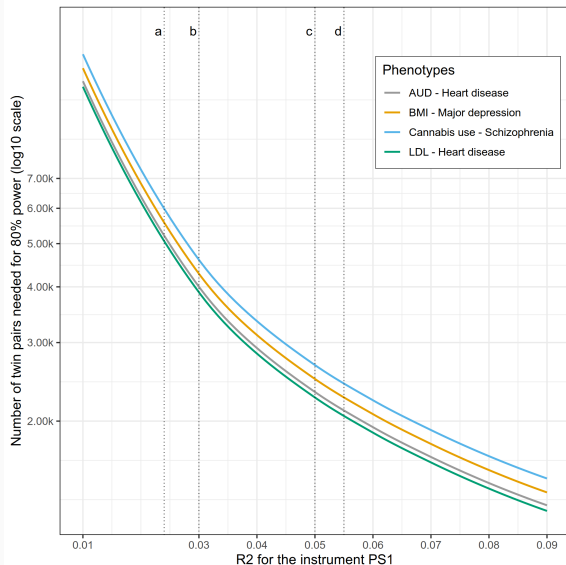
NOT ROBUST TO PLEIOTROPY (b_2 AND $b_4 \neq 0$)



The red lines indicate the observed mean of the distribution of the estimated v while the blue lines indicated the simulated value for the parameter. If the red line is on the right of the blue line, then the parameter is overestimated and if the red line is on the left of the blue line the parameter is underestimated.

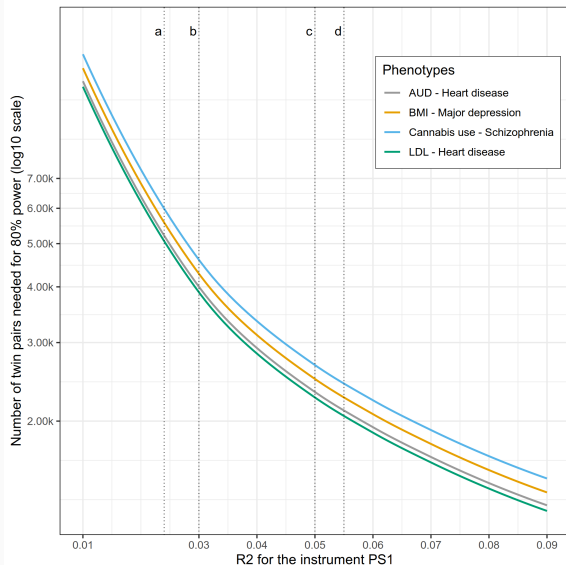
Results from simulation with 1024 replications, with variation on the factor level of b_2 and b_4 (0 , $\sqrt{.001}$, $\sqrt{.002}$, $\sqrt{.003}$, $\sqrt{.004}$).

REASONABLE SAMPLE SIZES IN RELEVANT SCENARIOS



A and C variances for the groups:

1. alcohol use (a^2 49%, c^2 10%) (Verhulst et al., 2015) and heart disease (a^2 22%, c^2 0%) (Wu et al., 2014);
2. BMI (a^2 72%, c^2 3%) (Rokholm et al., 2011) and major depression (a^2 37%, c^2 1%) (Scherrer et al., 2003);
3. cannabis use (a^2 51%, c^2 20%) (Verweij et al., 2010) and schizophrenia (a^2 81%, c^2 11%) (Sullivan et al., 2003);
4. dyslipidemia (LDL) (a^2 60%, c^2 28%) (Zhang et al., 2010) and heart disease (a^2 22%, c^2 0%) (Wu et al., 2014).



A and C variances for the groups:

1. alcohol use (a^2 49%, c^2 10%) (Verhulst et al., 2015) and heart disease (a^2 22%, c^2 0%) (Wu et al., 2014);
 2. BMI (a^2 72%, c^2 3%) (Rokholm et al., 2011) and major depression (a^2 37%, c^2 1%) (Scherrer et al., 2003);
 3. cannabis use (a^2 51%, c^2 20%) (Verweij et al., 2010) and schizophrenia (a^2 81%, c^2 11%) (Sullivan et al., 2003);
 4. dyslipidemia (LDL) (a^2 60%, c^2 28%) (Zhang et al., 2010) and heart disease (a^2 22%, c^2 0%) (Wu et al., 2014).
- Vertical lines were added to represent R2 for four PSs reported in recent papers: a, smoking (Pasman et al., 2022); b, BMI (Furlong and Klimentidis, 2020); c, LDL (Kuchenbaecker et al., 2019); d, attention deficit hyperactivity disorder (ADHD) (Demontis et al., 2019).

Behavior Genetics

<https://doi.org/10.1007/s10519-022-10122-x>

ORIGINAL RESEARCH



MR-DoC2: Bidirectional Causal Modeling with Instrumental Variables and Data from Relatives

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Abstract

Establishing causality is an essential step towards developing interventions for psychiatric disorders, substance use and many other conditions. While randomized controlled trials (RCTs) are considered the gold standard for causal inference, they are unethical in many scenarios. Mendelian randomization (MR) can be used in such cases, but importantly both RCTs and MR assume unidirectional causality. In this paper, we developed a new model, MRDoC2, that can be used to identify bidirectional causation in the presence of confounding due to both familial and non-familial sources. Our model extends the MRDoC model (Minică et al. in *Behav Genet* 48:337–349, <https://doi.org/10.1007/s10519-018-9904-4>, 2018), by simultaneously including risk scores for each trait. Furthermore, the power to detect causal effects in MRDoC2 does not require the phenotypes to have different additive genetic or shared environmental sources of variance, as is the case in the direction of causation twin model (Heath et al. in *Behav Genet* 23:29–50, <https://doi.org/10.1007/BF01067552>, 1993).

Keywords Causality · Pleiotropy · Twin design · Mendelian randomization

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Tour on MR

- Requires fulfilling of strong assumptions
- Pleiotropy being the hardest one to fulfill

MR-DoC2

- Can complement MR within twin studies framework with a bidirectional causal model
- Improves on some limitations of classic DoC and MR

Future directions

- Apply MR-DoC2 to real data



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- **THANK YOU**