Bidirectional Causal Modeling With Instrumental Variables and Data From Relatives

Seminar - The University of Tennessee Health Science Center (UTHSC)

Luis Castro-de-Araujo¹

Virginia Institute for Psychiatric and Behavioral Genetics

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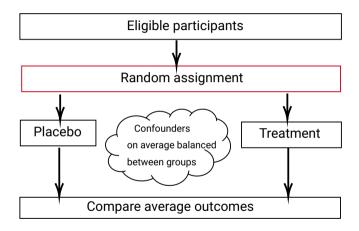


Outline

- Introduction
- Mendelian randomization
- Equivalence to SEM
- Twin study design
- MRDoC2 paper



Causal inference, gold standard: randomized controlled trial²





Introduction

- Causal inference, gold standard: randomized controlled trial
- Not always feasible, ethics³
 - E.g. exposure to trauma → substance abuse
- Mendelian randomization,⁴ helps with these cases.

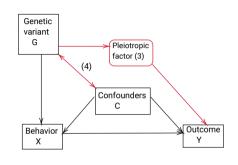


³Ohlsson, (2020), "Applying Causal Inference Methods in Psychiatric Epidemiology," *JAMA Psychiatry*.

⁴Katikireddi, (2018), "Assessing Causal Relationships Using Genetic Proxies for Exposures," Addiction.

Mendelian randomization⁵

- Uses genetic variants as instrumental variables
- Helps understand causation, but has strong assumptions
 - G (instrument) is robustly associated with X ("relevance");
 - 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





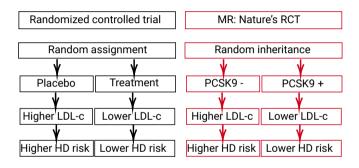
Mendelian Randomization⁶

- Depends on intruments sufficiently predictive of exposure
- 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 (Vimaleswaran et al. 2013)

Analogy RCT - Mendelian Randomization⁷





Two-stage least squares (2SLS)

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



Two-stage least squares (2SLS)⁸

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
 - g₁ difference in outcome per unit change in (genetically-predicted) exposure



Structural equation modeling - equivalence to 2SLS

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





^a Maydeu-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*.

Genetic variant or polygenic score?

- The use of instrumental PS is common in Mendelian randomization studies⁹.
- PS as an instrument is mathematically equivalent to a weighted mean of the results from individual SNPs.¹⁰

The twin-design case

 Use of structural equation modeling to complement mendelian randomization, inspired by Direction of Causation (DoC) model¹¹

¹¹Minică, (2018), "Extending Causality Tests with Genetic Instruments," Behav Genet.



⁹Burgess, April 2020, "Guidelines for Performing Mendelian Randomization Investigations," (2020).

¹⁰Dudbridge, (2021), "Polygenic Mendelian Randomization," Cold Spring Harb Perspect Med.

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The twin-design case

- Use of structural equation modeling to complement mendelian randomization, inspired by Direction of Causation (DoC) model¹¹
- Same paper shows proof of equivalence to 2SLS

¹¹Minică, (2018), "Extending Causality Tests with Genetic Instruments," Behav Genet.

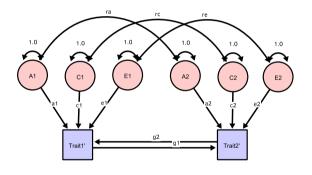


⁹Burgess, April 2020, "Guidelines for Performing Mendelian Randomization Investigations," (2020).

 $^{^{10}}$ Dudbridge, (2021), "Polygenic Mendelian Randomization," Cold Spring Harb Perspect Med.

Classic Direction of Causation model - reciprocal causation¹²

Model specification



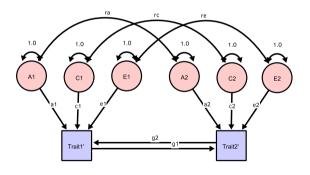
Path diagram representing a Bidirectional DoC for one twin.

- 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.



Classic Direction of Causation

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

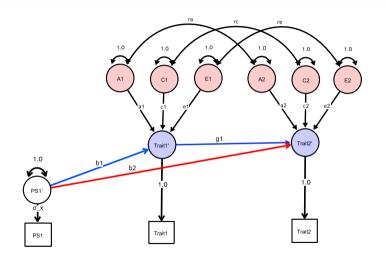


^aGillespie, (2003), "Direction of Causation Modeling Between Cross-Sectional Measures of Parenting and Psychological Distress in Female Twins," *Behav Genet*.

^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*.

MR-DoC model¹³

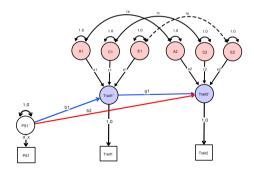




X	аX	cX	eX	aΥ	cY	eΥ	ra	rc	re	b1	b2	g1	Id
	fr												
													Yes Yes
fr	0	fr	fr	fr	fr	Yes							
fr	fr	0	fr	fr	0	fr	fr	0	fr	fr	fr	fr	No
fr	fr	fr	fr	fr	0	fr	fr	0	fr	fr	fr	fr	Yes
fr	fr	0	fr	fr	fr	fr	fr	0	fr	fr	fr	fr	No

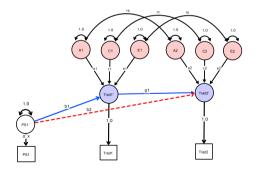


x	aX	cX	eX	aY	cY	eY	ra	rc	re	b1	b2	g1	Id
fr fr	fr 0	fr fr	fr fr	fr fr	No Yes								
fr	fr	fr	0	fr	Yes								
fr	0	fr	fr	fr	fr	Yes							
fr	fr	0	fr	fr	0	fr	fr	0	fr	fr	fr	fr	No
fr	fr	fr	fr	fr	0	fr	fr	0	fr	fr	fr	fr	Yes
fr	fr	0	fr	fr	fr	fr	fr	0	fr	fr	fr	fr	No



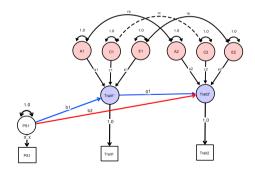


x	aX	cX	eX	aY	cY	eY	ra	rc	re	b1	b2	g1	Id
fr	No												
fr	0	fr	fr	fr	Yes								
fr	0	fr	Yes										
fr	0	fr	fr	fr	fr	Yes							
fr	fr	0	fr	fr	0	fr	fr	0	fr	fr	fr	fr	No
fr	fr	fr	fr	fr	0	fr	fr	0	fr	fr	fr	fr	Yes
fr	fr	0	fr	fr	fr	fr	fr	0	fr	fr	fr	fr	No



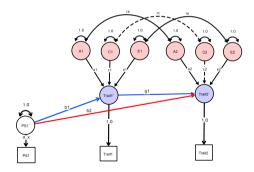


x	aX	cX	eX	aΥ	cY	eY	ra	rc	re	b1	b2	g1	Id
fr	No												
fr	0	fr	fr	fr	Yes								
fr	0	fr	Yes										
fr	0	fr	fr	fr	fr	Yes							
fr	fr	0	fr	fr	0	fr	fr	0	fr	fr	fr	fr	No
fr	fr	fr	fr	fr	0	fr	fr	0	fr	fr	fr	fr	Yes
fr	fr	0	fr	fr	fr	fr	fr	0	fr	fr	fr	fr	No





х	аX	cX	eX	aY	cY	eY	ra	rc	re	b1	b2	g1	ld
fr	No												
fr	0	fr	fr	fr	Yes								
fr	0	fr	Yes										
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-DoC¹⁴

Fig. 4 Path diagrammatic representation of the MR-DoC model in DZ twins. The parameter x 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)

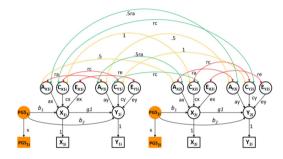
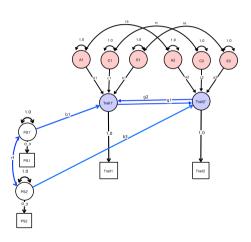


Figure 1: MR-DoC extension. Some confounding, not bidirectional. Not identified as depicted.

MR-DoC2¹⁵

Model specification

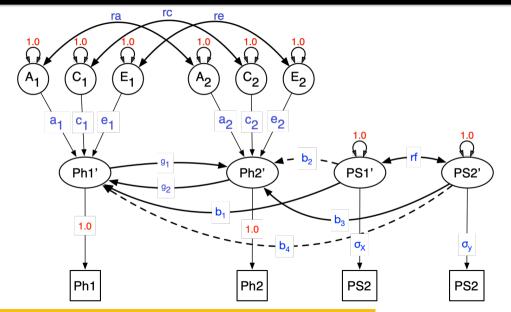


Modified MR-DOC

- 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 ra, rc and re).



MR-DoC2





Results

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

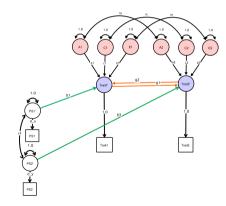


Which parameters drive power?¹⁶

Table 6: 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
су	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



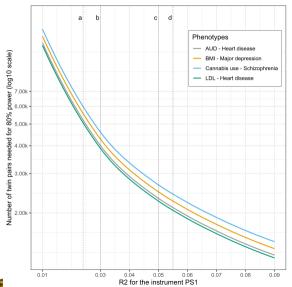


Factorial design simulation - factors

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
су	$\sqrt{0.10}$, $\sqrt{0.25}$	0	0
Total cells	2 ¹² =4096	3 ⁷ *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 as $\sqrt{1-ax^2-cx^2}$ and ey as $\sqrt{1-ay^2-cy^2}$.

Reasonable sample sizes in relevant scenarios

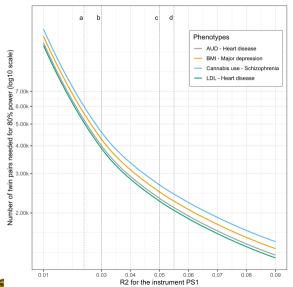


A and C variances for the groups:

- alcohol use (a² 49%, c² 10%) (Verhulst et al., 2015) and heart disease (a² 22%, c² 0%) (Wu et al., 2014);
- BMI (a² 72%, c² 3%) (Rokholm et al., 2011) and major depression (a² 37%, c² 1%) (Scherrer et al., 2003);
- cannabis use (a² 51%, c² 20%) (Verweij et al., 2010) and schizophrenia (a² 81%, c² 11%) (Sullivan et al., 2003);
- 4. dyslipidemia (LDL) (a 2 60%, c 2 28%) (Zhang et al., 2010) and heart disease (a2 22%, c 2 0%) (Wu et al., 2014).



Reasonable sample sizes in relevant scenarios



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- dyslipidemia (LDL) (a² 60%, c² 28%) (Zhang et al., 2010) and heart disease (a2 22%, c² 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).



Online biorXiv, BeGe¹⁷

MR-DoC2: bidirectional causal modeling with instrumental variables and data from relatives

Luis FS Castro-de-Araujo, Madhurbain Singh, Yi (Daniel) Zhou, Philip Vinh, Brad Verhulst,

Conor V Dolan, Michael C Neale

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Abstract

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Establishing causal associations is an essential step towards developing interventions for psychiatric, substance use and many other disorders. While randomized controlled trials (RCTs) are considered the gold standard for causal inference, they are unethical in many scenarios. Mendelian randomization (MR) can instead be used, but both methods focus on





Conclusion

MR-DoC2

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

Future directions

Apply MR-DoC2 to real data



Acknowledgements

Team

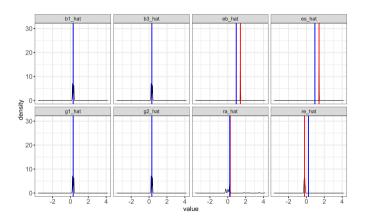
- Madhur Singh.
- Daniel Zhou.
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- Brad Verhulst.
- Conor V Dolan.
- Michael C Neale.
- NIH grant no R01 DA049867 and 5T32MH-020030

Contact





Revisiting limitations: Error at the phenotypic level



Reliability

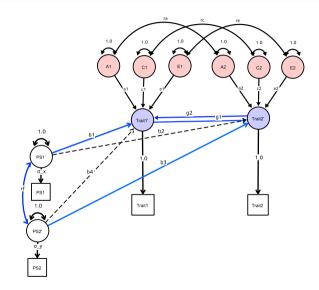
```
relB = var(B) / {var(B) + var(errorB)}
relS = var(S) / {var(S) + var(errorS)}
```

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

 θ = {b1 = c(sqrt(.05), sqrt(.1), sqrt(.15)), b3 = c(sqrt(.05), sqrt(.1), sqrt(.15)), g1 = c(sqrt(.05), sqrt(.1), sqrt(.15)), g2 = c(sqrt(.05), sqrt(.1), sqrt(.15)), abs=.05, ass = 0.05, cbs=0.05, css=0.05, ra=.224, re=.224, r

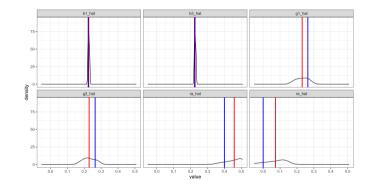


Other types of pleiotropy not included in the model





Not robust to pleiotropy (b2 and b4 !=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 b2 and b4 (0, $\sqrt{.001}$, $\sqrt{.002}$, $\sqrt{.003}$, $\sqrt{.004}$).



Power simulations¹⁸

 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 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;
- 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.

