Bidirectional Causal Modeling With Instrumental Variables and Data From Relatives

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

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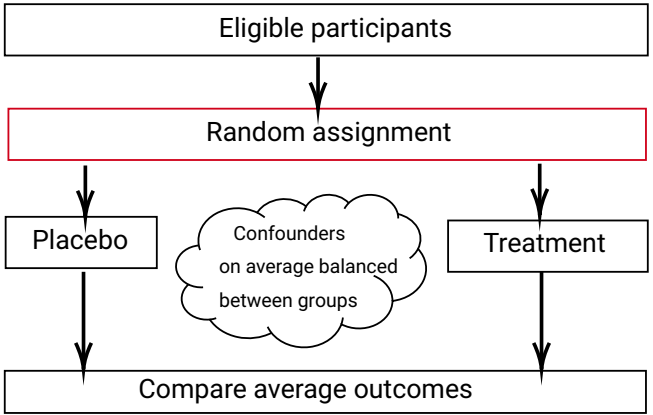
Outline

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

Causal inference, gold standard: randomized controlled trial[2]



[2] Camelia, 2017, "Mendelian Randomization," (VIPBG 2017).

Introduction

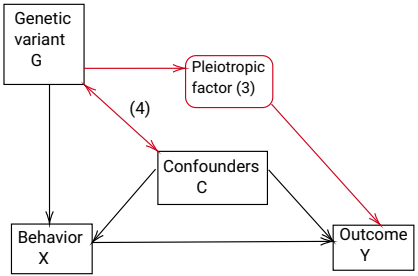
- Causal inference, gold standard: randomized controlled trial
- Not always feasible, ethics[3]
  - E.g. exposure to trauma $\rightarrow$ substance abuse
- Mendelian randomization,[4] helps with these cases.

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

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

Mendelian randomization[5]

- Uses genetic variants as instrumental variables
- Helps understand causation, but has strong assumptions
  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



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

Mendelian Randomization[6]

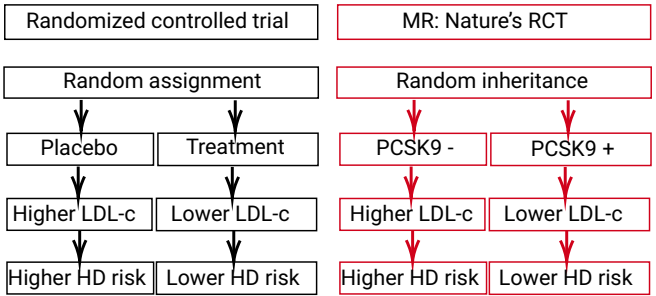
- Depends on intruments sufficiently predictive of exposure
- Psychiatric disorders polygenicity, weak instrument bias
- Cause is (typically) assessed in one direction

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	$G_1 \rightarrow X \rightarrow Y$ $G_2 \rightarrow Y \rightarrow X$	Body mass index (BMI) and vitamin D (Vimaleswaran et al. 2013)

[6] Ibid.

Analogy RCT - Mendelian Randomization[7]



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

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

[8] Minica Camelia, "Mendelian Randomization."

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 studies[9] .
- 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) model[11]

[9] Burgess, April 2020, "Guidelines for Performing Mendelian Randomization Investigations," (2020); Dudbridge, (2021), "Polygenic Mendelian Randomization," *Cold Spring Harb Perspect Med*.

[10] Frank Dudbridge, "Polygenic Mendelian Randomization."

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

Genetic variant or polygenic score?

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The twin-design case

- Use of *structural equation modeling* to complement *mendelian randomization*, inspired by Direction of Causation (DoC) model[11]
- Same paper shows proof of equivalence to 2SLS

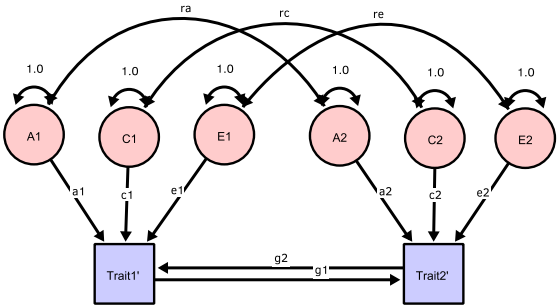
[9] Burgess, April 2020, "Guidelines for Performing Mendelian Randomization Investigations," (2020); Dudbridge, (2021), "Polygenic Mendelian Randomization," *Cold Spring Harb Perspect Med*.

[10] Frank Dudbridge, "Polygenic Mendelian Randomization."

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

Classic Direction of Causation model - reciprocal causation[12]

Model specification



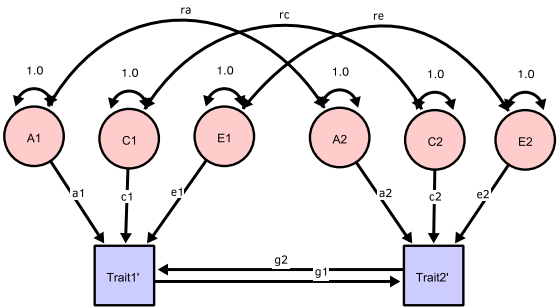
Path diagram representing a Bidirectional DoC for one twin.

- 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.

[12] Heath, (1993), "Testing Hypotheses About Direction of Causation Using Cross-Sectional Family Data," *Behav Genet*.

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]

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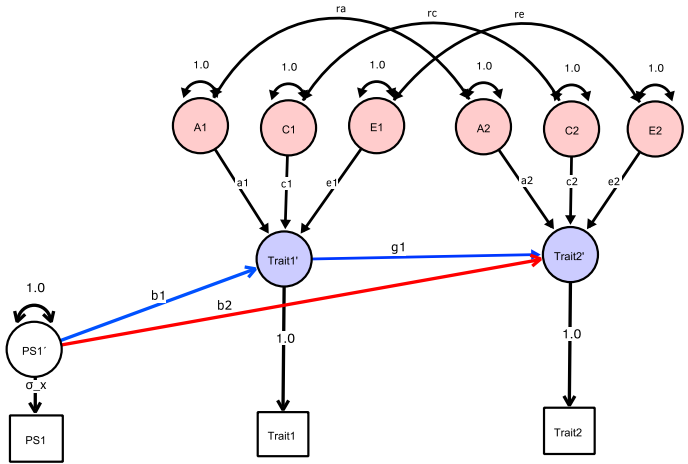
[a] Gillespie, (2003), "Direction of Causation Modeling Between Cross-Sectional Measures of Parenting and Psychological Distress in Female Twins," *Behav Genet*.

[b] Rasmussen, (2019), "A Major Limitation of the Direction of Causation Model," *Twin Res Hum Genet*.

[c] Maes, (2021), "Using Multimodel Inference/Model Averaging to Model Causes of Covariation Between Variables in Twins," *Behav Genet*.

MR-DoC model[13]



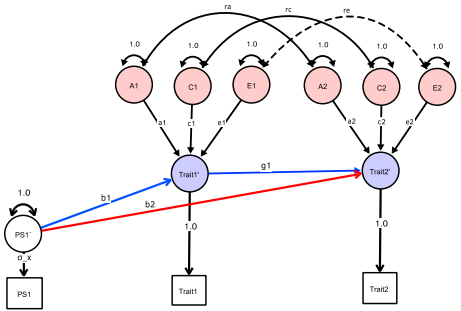
[13] Camelia C. Minică, Conor V. Dolan, Dorret I. Boomsma, Eco de Geus, and Michael C. Neale, "Extending Causality Tests with Genetic Instruments."

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

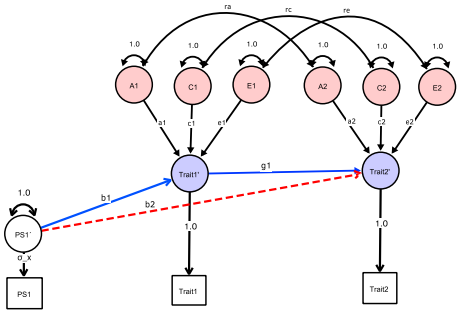
MR-DoC - identified cases

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



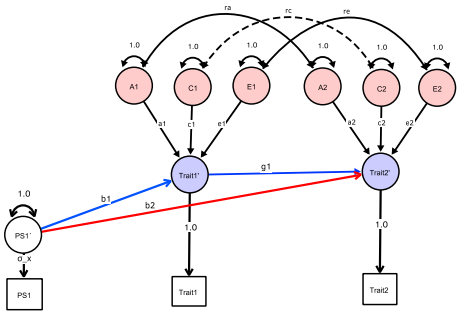
MR-DoC - identified cases

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



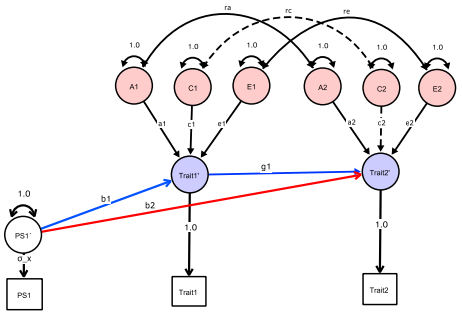
MR-DoC - identified cases

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



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



MR-DoC[14]

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)

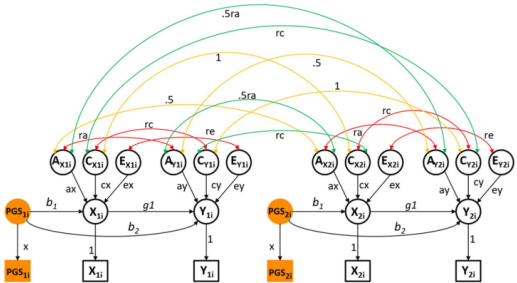
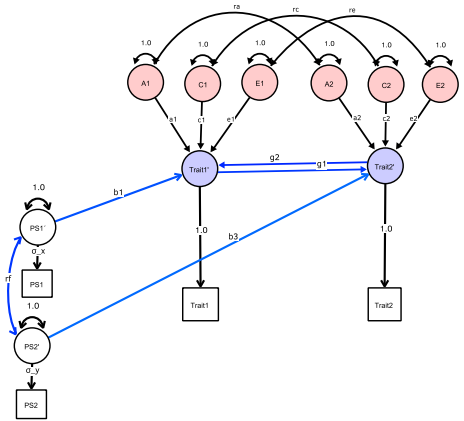


Figure 1: MR-DoC extension. Some confounding, not bidirectional. Not identified as depicted.

[14] Ibid.

MR-DoC2[15]

Model specification

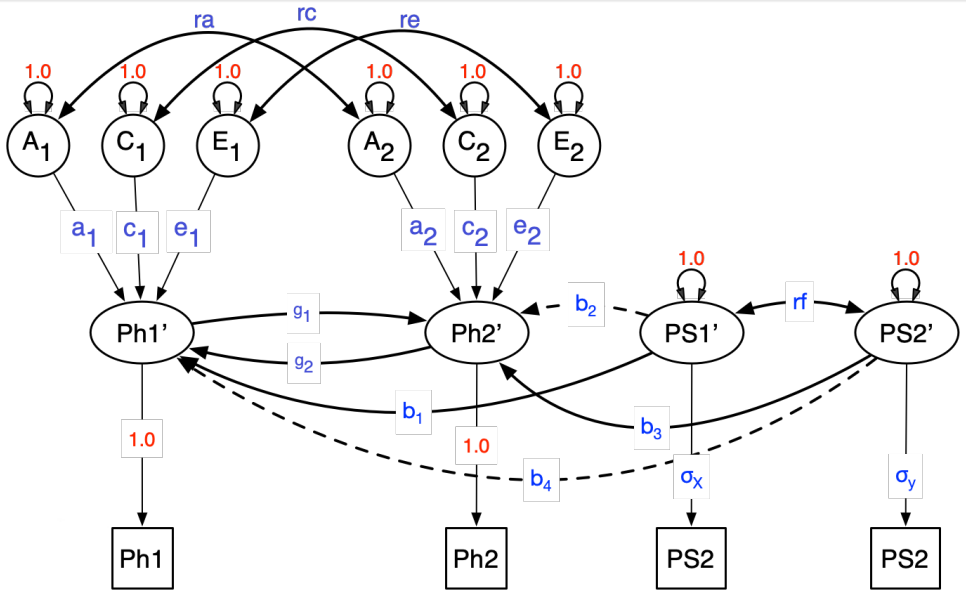


Modified MR-DOC

- 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).

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

MR-DoC2


ra
rc
re
1.0
1.0
1.0
1.0
1.0
1.0
A1
C1
E1
A2
C2
E2
a1
c1
e1
a2
c2
e2
1.0
1.0
Ph1'
g1
g2
Ph2'
b2
PS1'
rf
PS2'
b1
b3
1.0
1.0
b4
σX
σy
Ph1
Ph2
PS2
PS2

Results

- Which parameters drive power?

Revisiting limitations

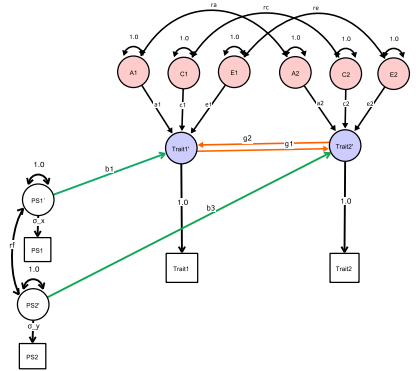
- Do we need phenotypes with distinct inheritance patterns
- What about measurement error at the phenotypic level?
- How robust it is regarding pleiotropy

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
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



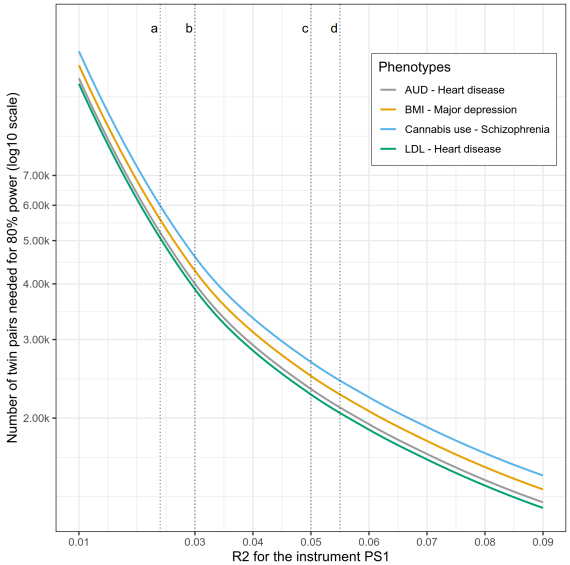
[16] Van der Sluis, (2008), "Power Calculations Using Exact Data Simulation," *Behav Genet*.

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
cy	$\sqrt{0.10}$, $\sqrt{0.25}$	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 $\sqrt{1 - ay^2 - cy^2}$.

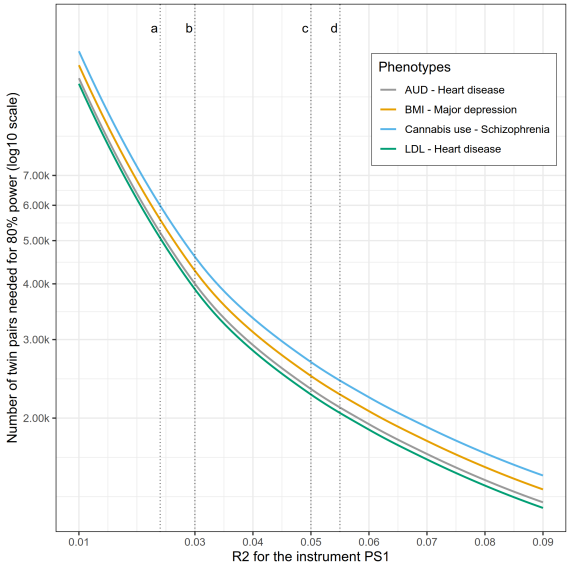
Reasonable sample sizes in relevant scenarios



A and C variances for the groups:

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 (a2 22%, c^2 0%) (Wu et al., 2014).

Reasonable sample sizes in relevant scenarios



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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).

- 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, BeGe[17]

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

doi: https://doi.org/10.1101/2022.03.14.484271

Abstract

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

[17] Castro-de-Araujo, March 2022, "MR-DoC2," (2022).

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

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- Conor V Dolan.
- Michael C Neale.
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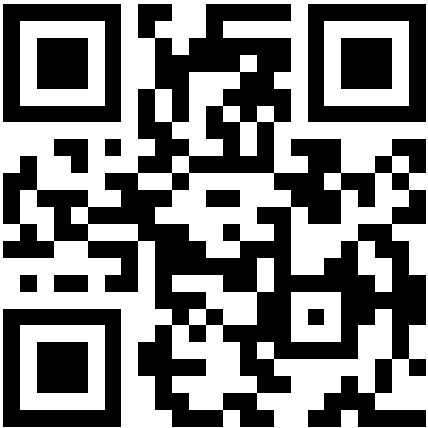
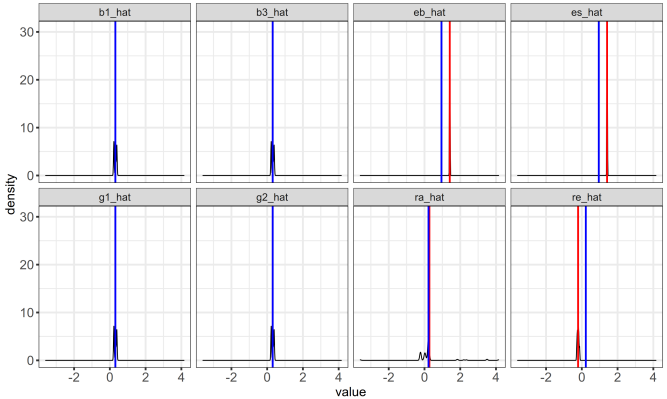
Contact



Revisiting limitations: Error at the phenotypic level



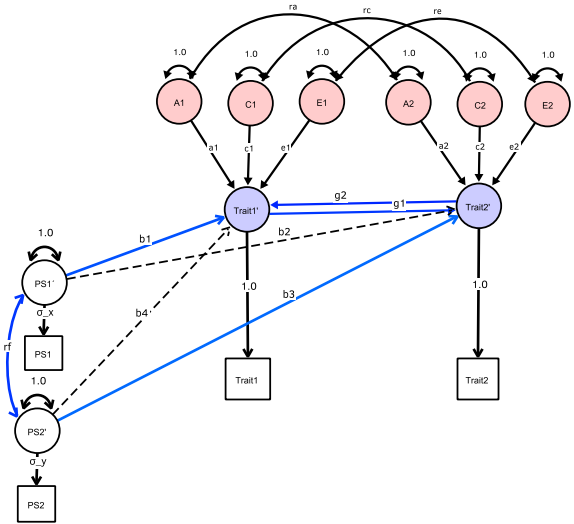
θ = {b1 = c(sqrt(.05), sqrt(.1), sqrt(.15)), b3 = c(sqrt(.05), sqrt(.1), sqrt(.15)), g1 = c(sqrt(.05), sqrt(.1), sqrt(.15)), g2 = c(sqrt(.05), sqrt(.1), sqrt(.15)), abs= .05, ass = 0.05, cbs=0.05, css=0.05, ra=.224, rc=.224, re=.224, rf=.224, reliability =c(.0, .1, .2, .3, .4)

Reliability

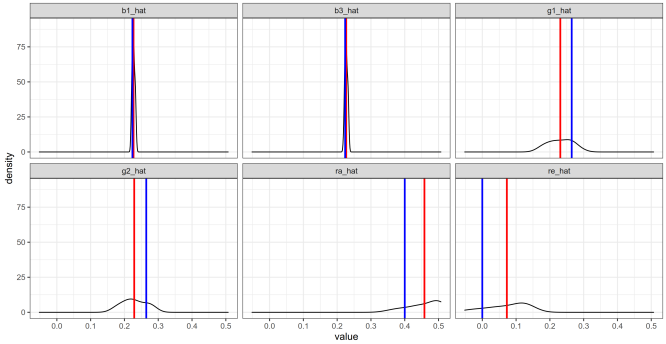
```
relB = var(B) / {var(B) + var(errorB)}
relS = var(S) / {var(S) + var(errorS)}
```

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

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 simulations[18]

- 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;
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.**

[18] Sophie van der Sluis, Conor V. Dolan, Michael C. Neale, and Danielle Posthuma, "Power Calculations Using Exact Data Simulation."