Causal inference with MR-DoC and genetically informed CLPM

VIPBG Seminar

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18 April 2023

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Mendelian Randomization

MR-DoC

Bi-directional MR-DoC, MR-DoC2

Temporal precedence in causal inference, CLPM

Longitudinal model

Mendelian Randomization

- Problems with observational data
- Randomized controlled trials
- Mendelian Randomization (MR):
  - How it works
  - Core assumptions

The Problem with Inferring Causality in Observational Studies[2]

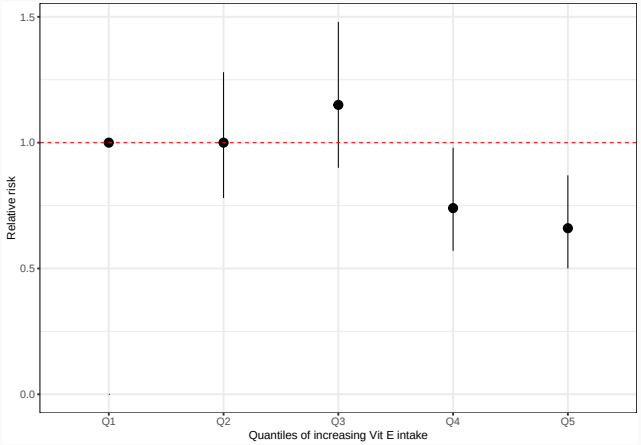


Figure 1: Age-Adjusted Relative Risks of Major Coronary Heart Disease, According to Quintile Group for Total Vitamin E Intake and Intake of Vitamin E from Dietary Sources

[1] Stampfer, (1993), "Vitamin E Consumption and the Risk of Coronary Disease in Women," *N Engl J Med*.

USE OF VITAMIN SUPPLEMENTS BY US ADULTS, 1987-2000[4]

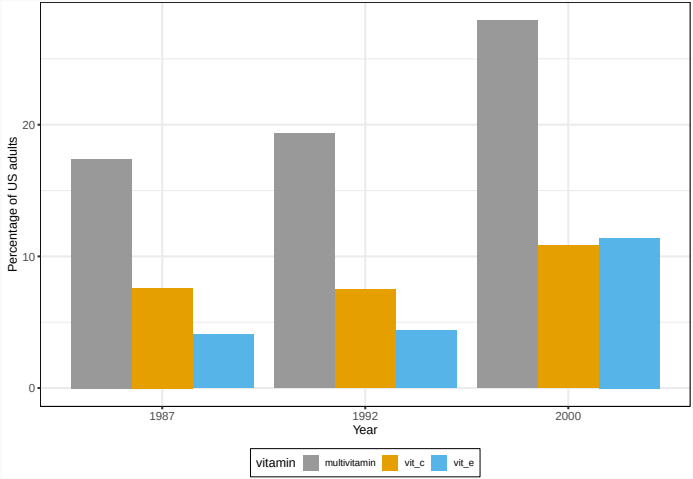
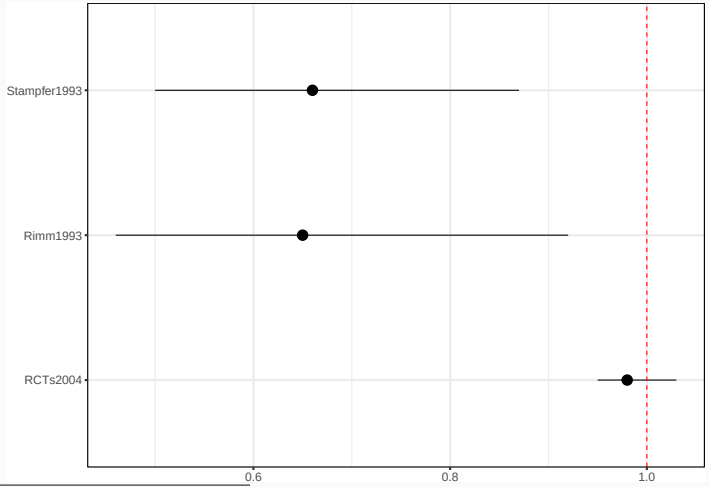


Figure 2: Use of vitamin supplements by US adults, 1987-2000. National Health Interview Surveys

[3] Millen, (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[6]



[5]M. J. Stampfer, C. H. Hennekens, J. E. Manson, G. A. Colditz, B. Rosner, and W. C. Willett, "Vitamin E Consumption and the Risk of Coronary Disease in Women"; Rimm, (1993), "Vitamin E Consumption and the Risk of Coronary Heart Disease in Men," *N Engl J Med*; Eidelman, (2004), "Randomized Trials of Vitamin E in the Treatment and Prevention of Cardiovascular Disease," *Arch Intern Med*.

[6]M. J. Stampfer, C. H. Hennekens, J. E. Manson, G. A. Colditz, B. Rosner, and W. C. Willett, "Vitamin E Consumption and the Risk of Coronary Disease in Women"; Rimm, (1993),

MANY OTHER EXAMPLES

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

Vitamin E levels and confounding risk factors:

Reduces Vitamin E levels

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

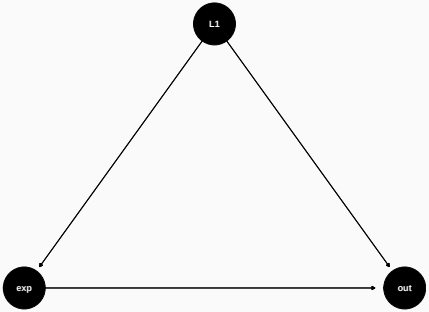
Increases Vitamin E levels

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

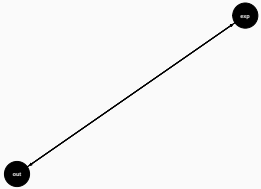
[a] Lawlor, (2004), "Those Confounded Vitamins," *Lancet*.

Classic limitations of observational studies

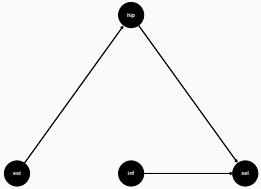
- Confounding



- Direction of causation is uncertain

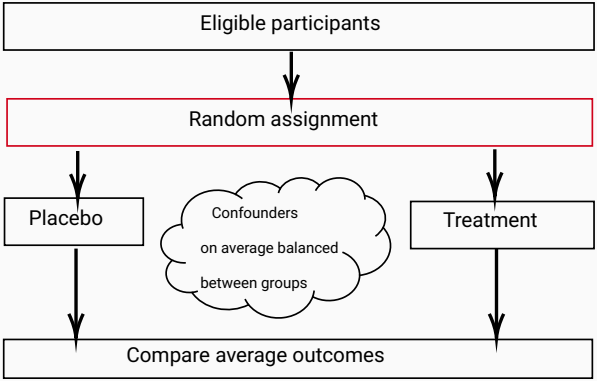


- Other biases, e.g. selection bias[a]



[a] Hernán, (2004), "A Structural Approach to Selection Bias," *Epidemiology*.

Causal inference, gold standard: randomized controlled trial[8]



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

[8] Camelia, 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***

The Wide Applicability of MR

- 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?

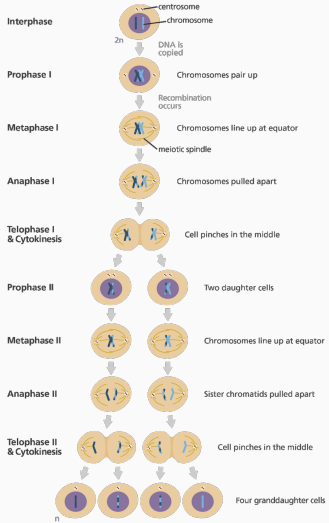
- By harnessing Mendel's laws of inheritance

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

Meiosis



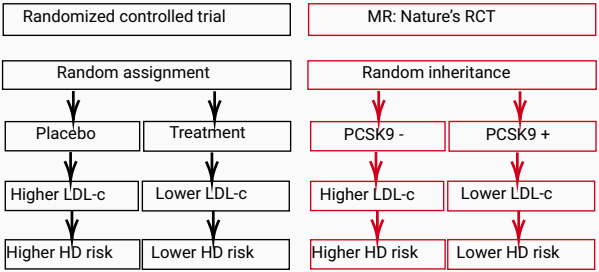
- Two cell divisions
- Produces four daughter cells
- Produces haploid cells
- Daughter cells are non-identical
- Produces sex cells
- Crossing-over occurs
- Homologous chromosomes pair up
  - and are separated at random (independent segregation)

ADD DISCUSSION FROM THE AUTOR HERE

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)[9]

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

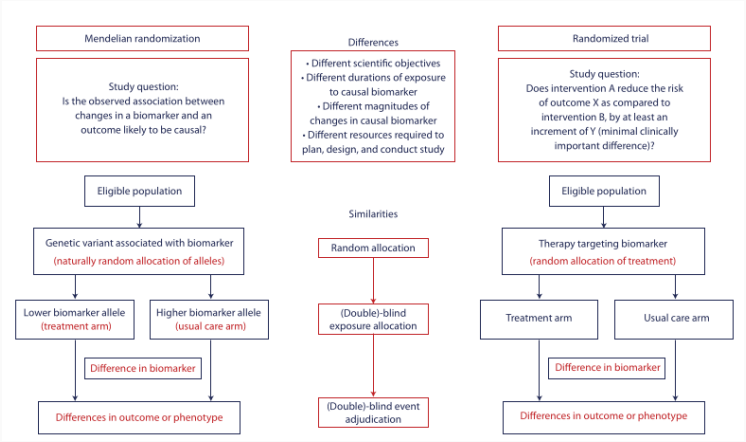
Analogy RCT - Mendelian Randomization[11]



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

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

Similarities MR - RCT



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[12] Ference, (2021), "Using Mendelian Randomization to Improve the Design of Randomized Trials," *Cold Spring Harb Perspect Med*.

Similarities MR - RCT[14]

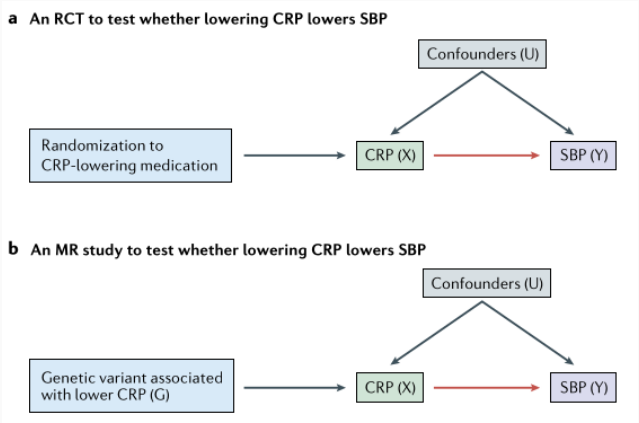

Figure 3: Illustration of a randomized control study and instrumental variable estimation. A randomized controlled trial (RCT) (panel a) and a Mendelian randomization (MR) study (panel b) to estimate the effect of lowering C-reactive protein (CRP) on systolic blood pressure (SBP). The arrows highlighted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

[13] Sanderson, (2022). "Mendelian Randomization | Nature Reviews Methods Primers." *Nature Reviews Methods Primers*

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!

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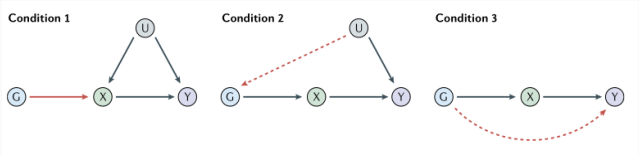
[a] Timothy Bates [@timothycbates], October 2022, "Using a Modern SEM-based IV Model & Wanted to Learn Who Invented Them. Turns Out Likely Sewell Wright's (SEM) Dad! In a Situation Similar to "Student" Wright Had a Commercial Need," *Twitter*, (2022).

- Uses genetic variants as instrumental variables[15]
- Helps understand causation, but has strong assumptions[16]
  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



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

[16]Eleanor 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 intruments sufficiently predictive of exposure[17]
- 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)

[17]Rebecca C. Richmond and George Davey Smith, "Mendelian Randomization."

Why are genetic associations special?

- 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

MR-DoC

Pleiotropy is pervasive

- 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*.

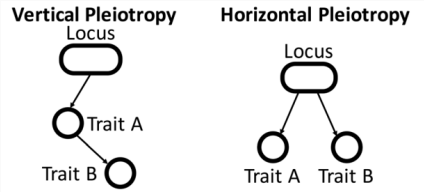


Figure 4: (LD) and polygenicity are expected to contribute to horizontal pleiotropy

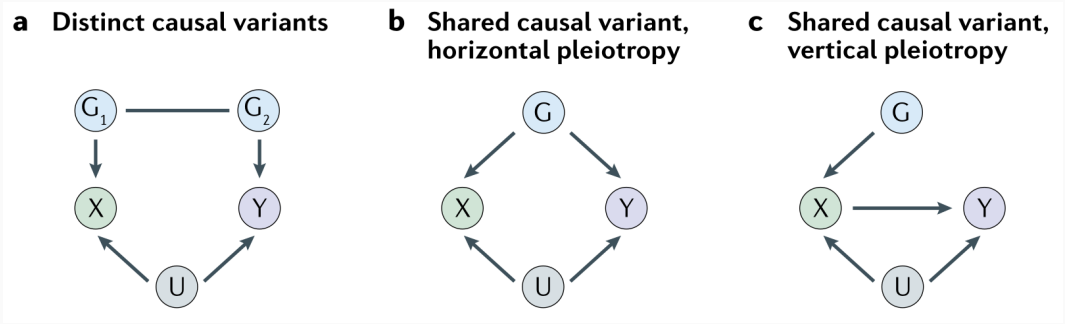


Figure 5: a | An example of distinct causal variants that violate the instrumental variable assumption IV2. G1 and G2 represent two genetic variants and the link between them is non-directional, reflecting linkage disequilibrium. b,c | Examples of a shared causal variant are a violation of assumption IV2 (panel b) and a situation that satisfies the IV assumptions (panel c).

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

[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*.

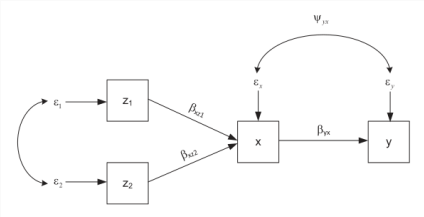


Figure 6: Instrumental Variables Regression (IVR) model that enables drawing causal inferences on the target regression model

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

- 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]

[a] Burgess, (2020), "Guidelines for Performing Mendelian Randomization Investigations," *Wellcome Open Research*.

[b] Dudbridge, (2021), "Polygenic Mendelian Randomization," *Cold Spring Harb Perspect Med*.

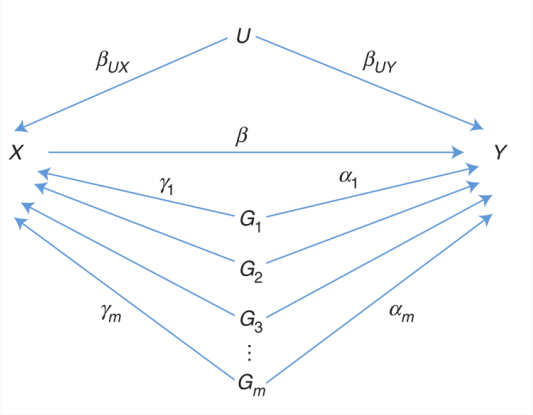


Figure 7: DAG showing m single-nucleotide polymorphisms (SNPs) Gj used as instrumental variables for the association of exposure X with outcome Y in the presence of confounder U. Each SNP has an effect yj on X and a

Genetic variant or polygenic score?

- 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

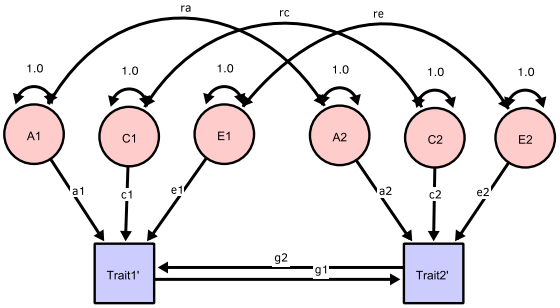
$$\begin{aligned}\frac{\text{cov}(S, Y)}{\text{cov}(S, X)} &= \frac{\sum \gamma_j \,\text{cov}\left(G_j, Y\right)}{\sum \gamma_j \,\text{cov}\left(G_j, X\right)} \\ &= \frac{\sum \gamma_j \Gamma_j \,\text{var}\left(G_j\right)}{\sum \gamma_j \Gamma_j \,\text{var}\left(G_j\right)} \\ &= \sum_j \frac{\gamma_j^2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

- 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]

[a] Ibid.

Classic Direction of Causation model - reciprocal causation[19]

Model specification



Path diagram representing a Bidirectional DoC for one twin.

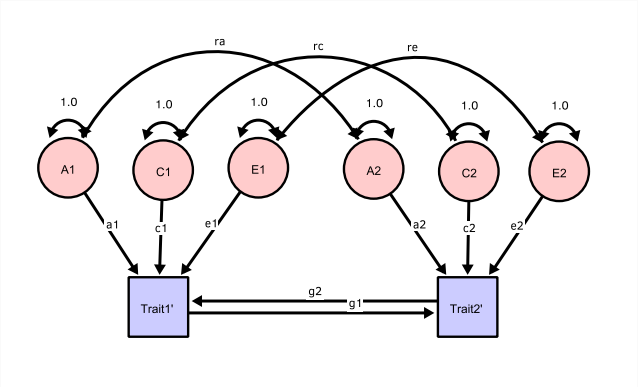
- causal paths are estimated affording information from the cross-twin cross-trait correlations.
- Cross-twin covariance between additive genetic effects is 0.5 (not shown) for DZ twins, as DZs are expected to share 50% of the genetic effects.
- Standard SEM symbology is used.

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

[19] 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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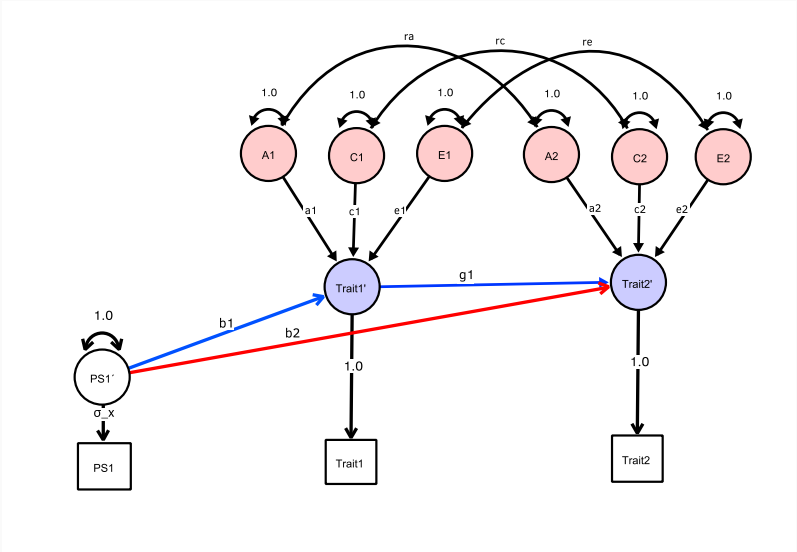
[a] Gillespie, (2003), "Direction of Causation Modeling Between Cross-Sectional Measures of Parenting and Psychological Distress in Female Twins," *Behav Genet*.

[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[21]



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

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
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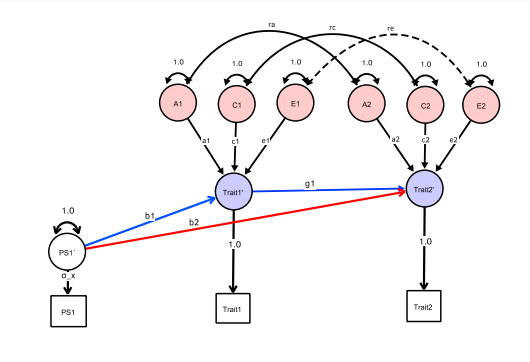

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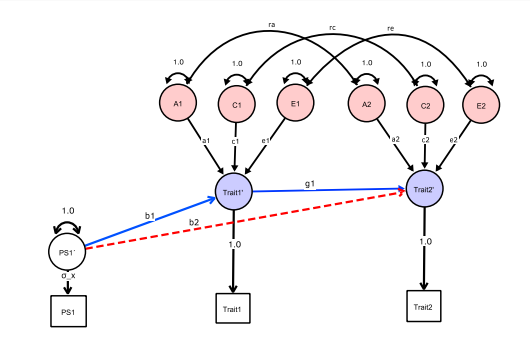

x	aX	cX	eX	aY	cY	eY	ra	rc	re	b1	b2	g1	Id
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fr	fr	fr	fr	fr	fr	fr	fr	fr	0	fr	fr	fr	Yes
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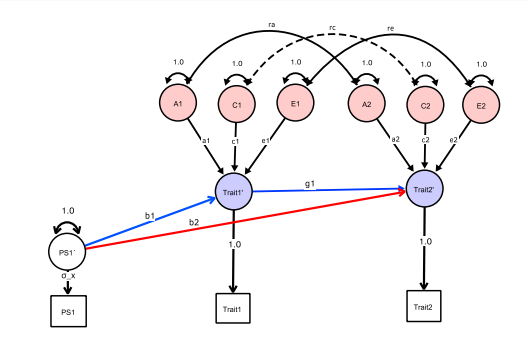
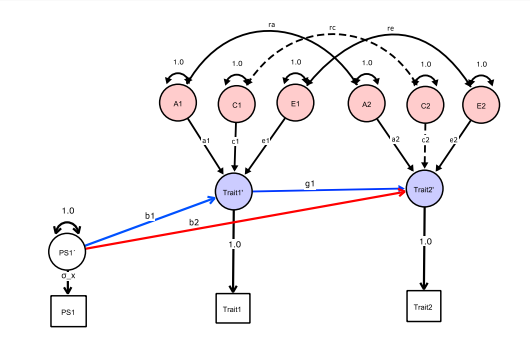
fr	fr	0	fr	fr	0	fr	fr	0	fr	fr	fr	fr	No
fr	fr	fr	fr	fr	0	fr	fr	0	fr	fr	fr	fr	Yes
fr	fr	0	fr	fr	fr	fr	fr	0	fr	fr	fr	fr	No



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



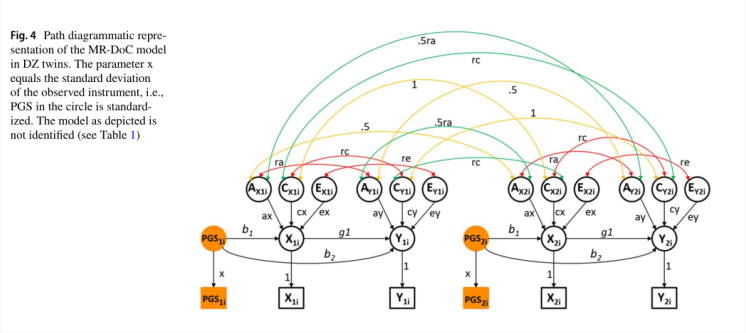


Fig. 4 Path diagrammatic representation of the MR-DoC model in DZ twins. The parameter x equals the standard deviation of the observed instrument, i.e., PGS in the circle is standardized. The model as depicted is not identified (see Table 1)

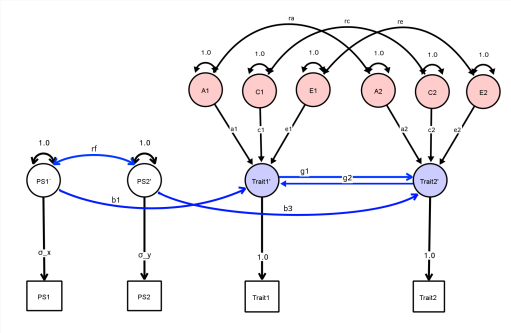
Figure 8: MR-DoC extension. Some confounding, not bidirectional. Not identified as depicted.

[22]Ibid.

[23]Ibid.

Bi-directional MR-DoC, MR-DoC2

Model specification



Modified MR-DOC

- Path diagram of the MR-DoC2 model for an individual.[a]
- 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).

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

- Which parameters drive power?

Revisiting limitations

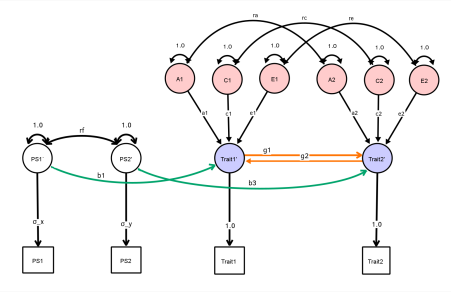
- Do we need phenotypes with distinct inheritance patterns
- What about measurement error at the phenotypic level?
- How robust it is regarding pleiotropy

WHICH PARAMETERS DRIVE POWER?[25]

Table 7: 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



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

[25]Van 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*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 $\sqrt{1-ay^2-cy^2}$.

- 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

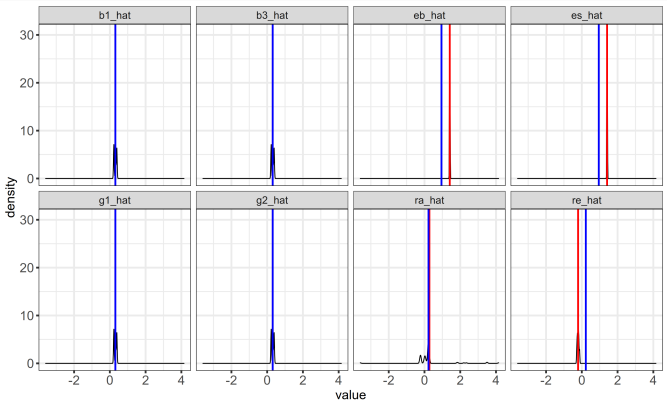
1. choosing a set of parameter values for the model shown in Figure 2;
2. exact data simulation, with arbitrary N=1,000 MZ pairs and N=1,000 DZ twin pairs;
3. fitting the true model using ML estimation in OpenMx;
4. fitting the false model by fixing one or more parameters to zero and refitting the model; 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.**

[26] Ibid.

[27] Ibid.

Revisiting limitations: Error at the phenotypic level



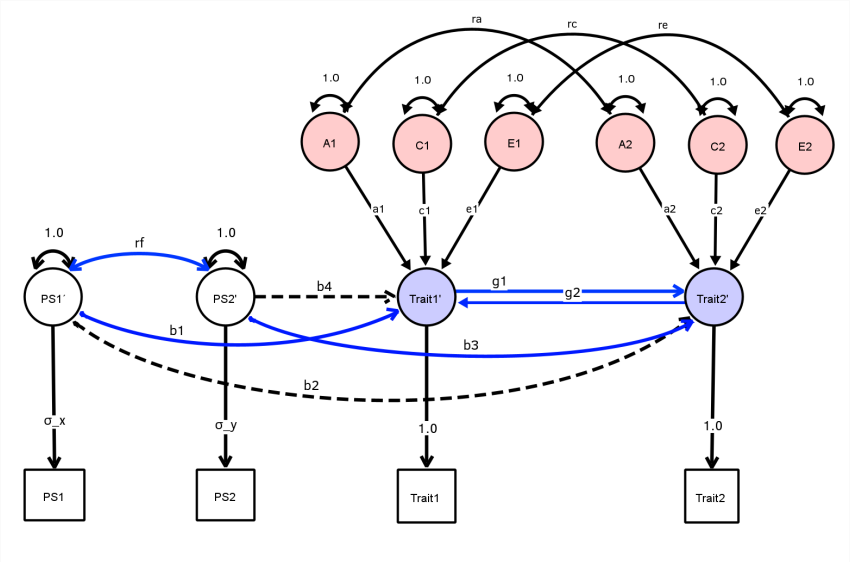
θ = {b1 = c(sqrt(.05), sqrt(.1), sqrt(.15)), b3 = c(sqrt(.05), sqrt(.1), sqrt(.15)), g1 = c(sqrt(.05), sqrt(.1), sqrt(.15)), g2 = c(sqrt(.05), sqrt(.1), sqrt(.15)), abs= .05, ass = 0.05, cbs=0.05, css=0.05, ra=.224, rc=.224, re=.224, rf=.224, reliability =c(.0, .1, .2, .3, .4)

Reliability

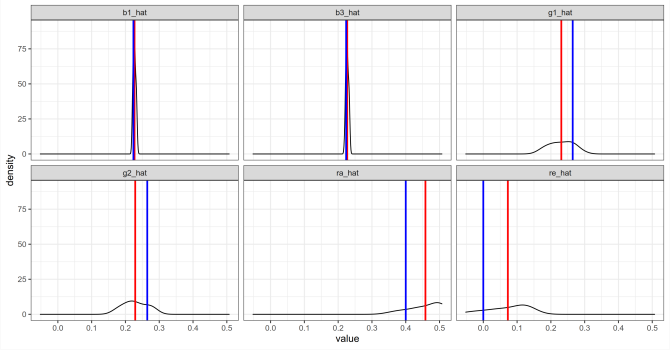
```
relB = var(B) / {var(B) + var(errorB)}
relS = var(S) / {var(S) + var(errorS)}
```

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

Other types of pleiotropy not included in the model



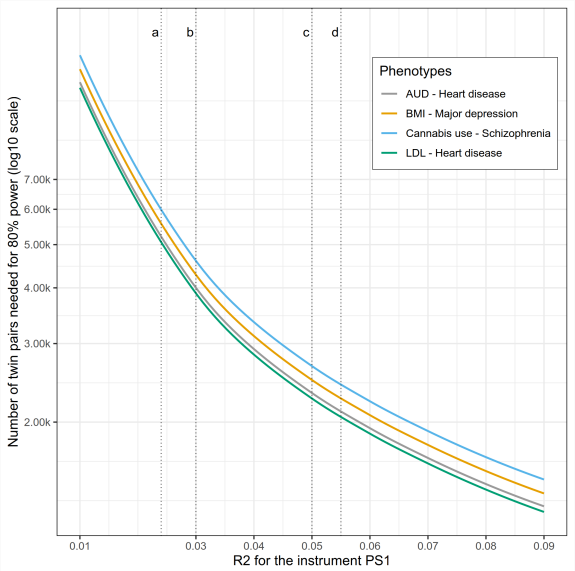
Not robust to pleiotropy (b2 and b4 !=0)



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, $\sqrt{.001}$, $\sqrt{.002}$, $\sqrt{.003}$, $\sqrt{.004}$).

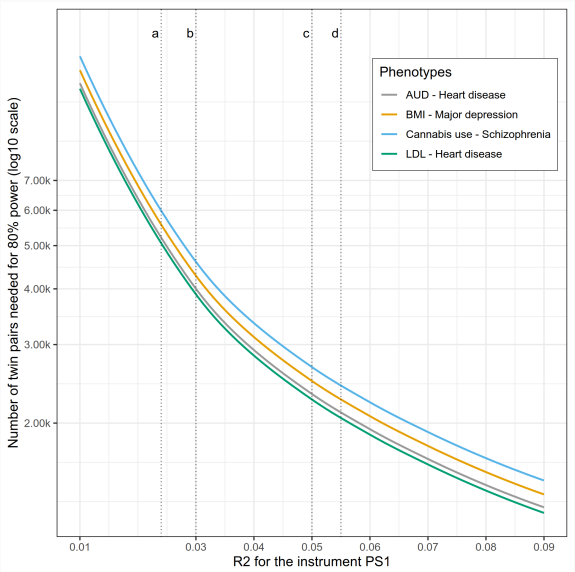
Reasonable sample sizes in relevant scenarios



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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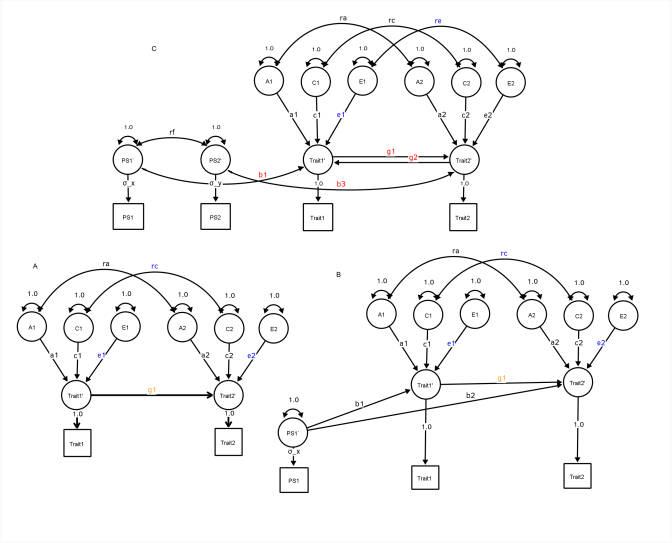
4. dyslipidemia (LDL) (a^2 60%, c^2 28%) (Zhang et al., 2010) and heart disease (a2 22%, c^2 0%) (Wu et al., 2014).

- 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).

Temporal precedence in causal inference, CLPM

Specification



MR-DoC (A), DoC (B), and MR-DoC2 (C) model specifications for a single twin member. They include the effects of additive genetic (A), common environment (C) and specific environment (E) factors for both Trait 1 and Trait 2, and their effects may correlate (parameters ra, rc, and re). Path labels in red are important to the model's overall power, those susceptible to measurement error in blue, and in orange are those that are both susceptible to measurement error and are important to the model's overall power.

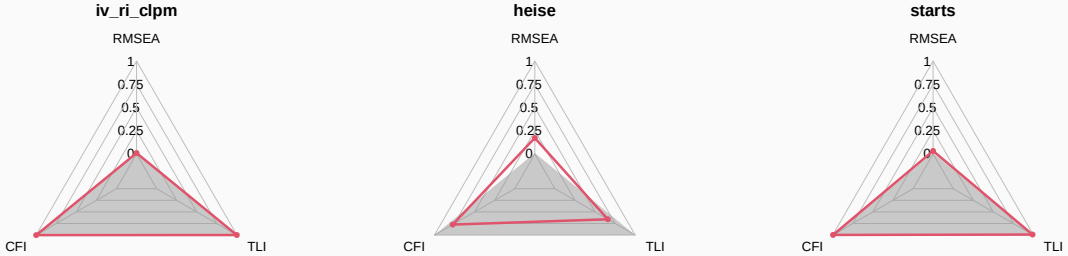


Figure 9: Gray silhouette marks the position of the reference model (IV RI CLPM), which had roughly same fit as the STARTS1995mod.

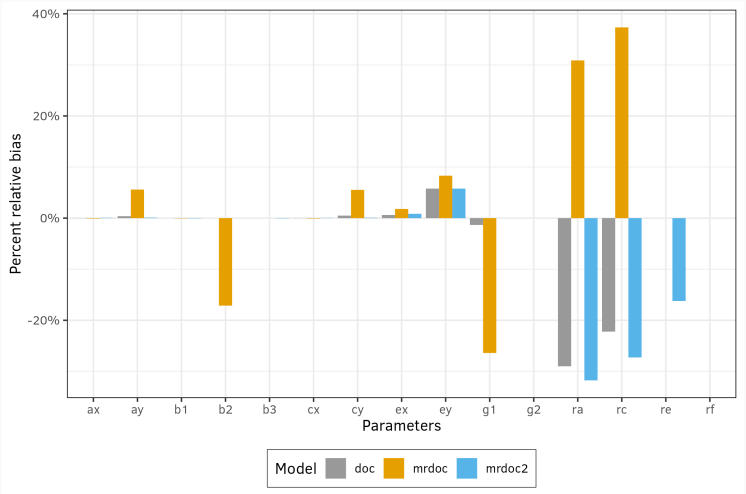
Table of Model Comparisons

Model	EP	Δ Fit	Δ df	p	AIC	Δ AIC	Compare with Model	Fit units
STARTS1995mod	22				107233	0		-2lnL
Heise1969	17	3457.219	5	< 0.001	110680	3447.219	STARTS1995mod	-2lnL
IV_RI_CLPM	30	25496.692	8969	< 0.001	132746	25512.692	STARTS1995mod	-2lnL

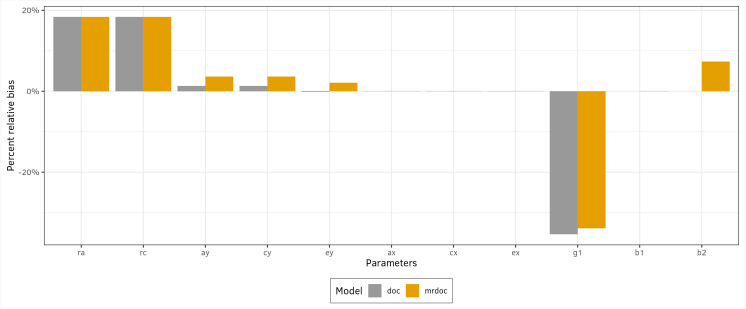
Table 9: Parameter levels on the three factorial designs, with respective total number of cells for each design simulation. The model specification can be seen in Figure 1.

theta	Design 1 (DoC)	Design 2 (MR-DoC)	Design 3 (MR-DoC2)
b1		sqrt(0.025, 0.05,0.75)	sqrt(0.025, 0.05,0.75)
b2		sqrt(0.025, 0.05,0.75)	
b3			sqrt(0.025, 0.05,0.75)
g1	sqrt(0.20, 0.40, 0.60)	sqrt(0.20, 0.40, 0.60)	sqrt(0.20, 0.40, 0.60)
g2			sqrt(0.20, 0.40, 0.60)
ra	.0,.25,.50	.0,.25,.50	.0,.25,.50
rc	.0,.25,.50	.0,.25,.50	.0,.25,.50
re			.0,.25,.50
rf			.0,.25,.50
ax	.0,.10,.25	.0,.10,.25	.0,.10,.25
ay	.0,.10,.25	.0,.10,.25	.0,.10,.25
cx	.0,.10,.25	.0,.10,.25	.0,.10,.25
cy	.0,.10,.25	.0,.10,.25	.0,.10,.25
Total cells	3^7=2187	3^9= 19683	3^12=531441

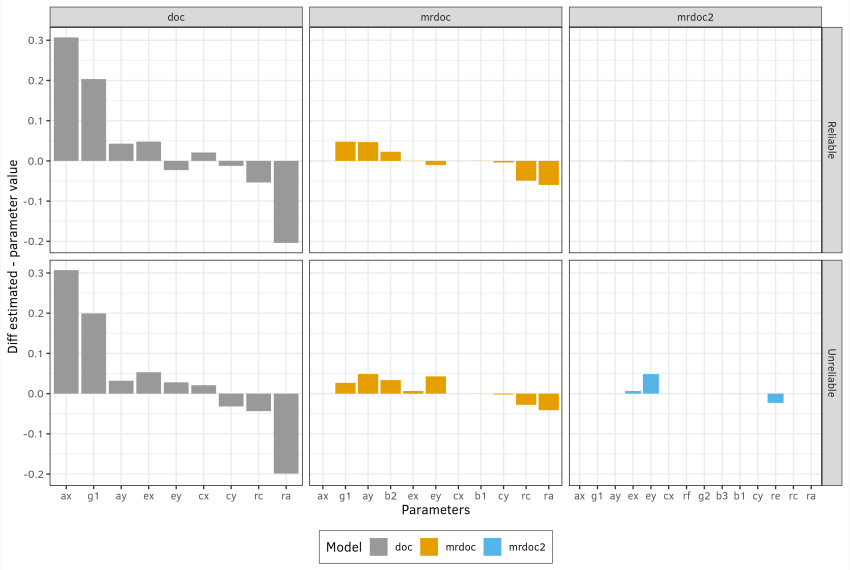
Percent bias - unreliability factor



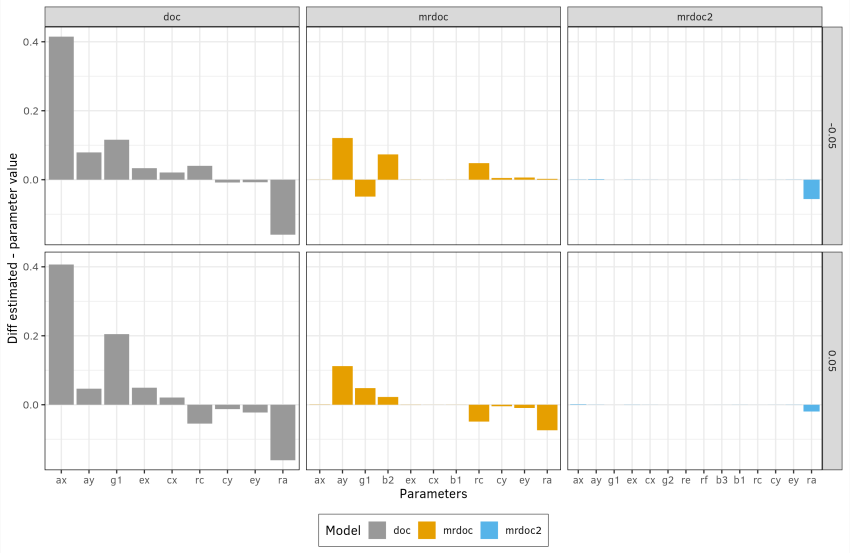
Percent bias - RE unmodelled



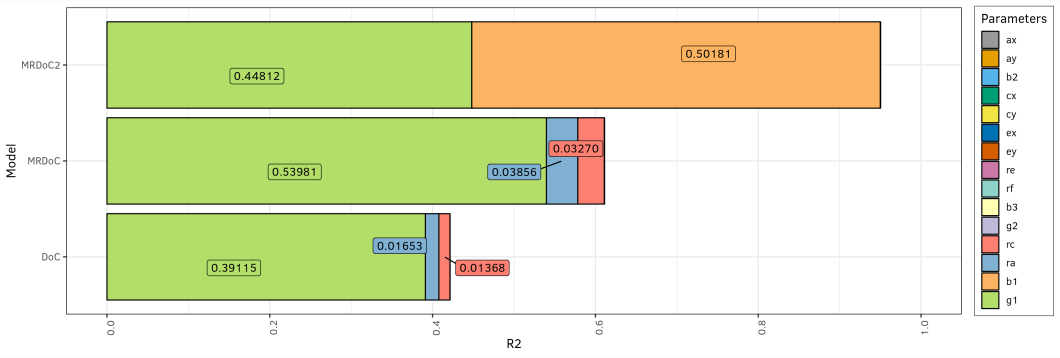
UNRELIABILITY FACTOR



RE IN DATA, BUT NOT IN THE FIT



VARIANCE EXPLAINED IN STATISTICAL POWER - V1



LONGITUDINAL MODEL

The model is identified as depicted (3 waves). It comprises 5 main elements: (A) the observed variables in green; (B) the between-person variances in orange; (C) the polygenic scores in blue; (D) the means in yellow; and (E) the random intercepts in red. Free paths are in black, and named. Fixed paths are marked with 1. The specific variances for the observed variables are equal across study waves, marked in green.

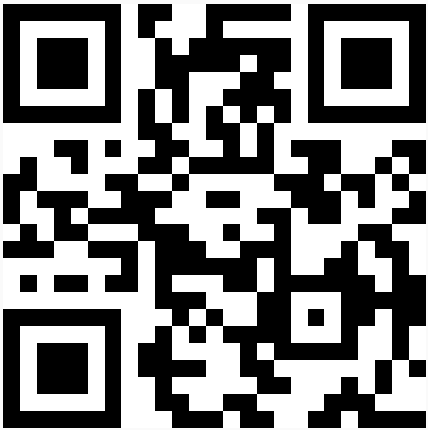
Acknowledgements

Team

- Madhur Singh.
- Daniel Zhou.
- Philip Vinh.
- Brad Verhulst.

- Conor V Dolan.
- Michael C Neale.
- NIH grant no R01 DA049867 and 5T32MH-020030

Contact



- **Thank you**