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Time-varying Mendelian Randomization

A methodological review

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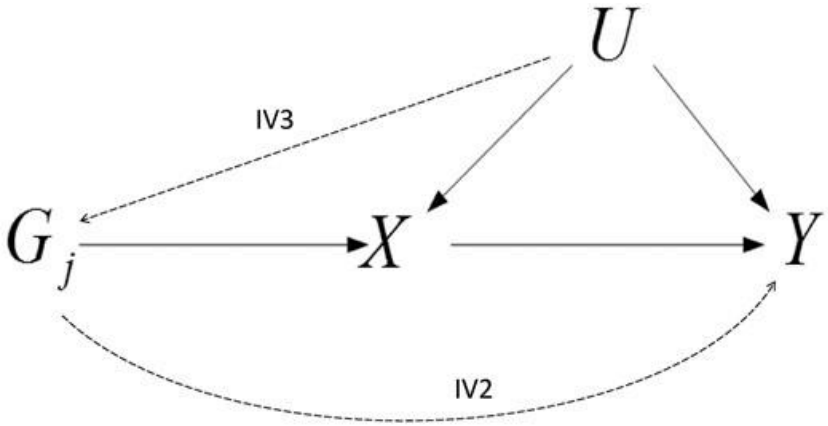
Outline

- Introduction: Controversies of MR results
- Time-varying MR methods
  - Multivariable MR (MVMR): UK – Cambridge, Bristol
    - MVMR: concept and application
    - MVMR for time-varying exposures
    - Controversies
  - G-estimation of structural nested mean model: US – Harvard
    - Definitions and identifiable assumptions
    - Estimation: Robins' g-methods
- Summary

Mendelian randomization

- IV1: associated with the exposure X (the ‘relevance’ assumption);
- IV2: independent of the outcome Y given the exposure X (the ‘exclusion restriction’);
- IV3: independent of all (observed or unobserved) confounders of X and Y, as represented by U (the ‘exchangeability’ assumption)



Model

$$Y = \beta_0 + \beta X + U + \nu_y$$

$$X = \pi_0 + \pi G + U + \nu_x$$

Summary data

$$\hat{\Gamma}_j = \beta \hat{\pi}_j$$

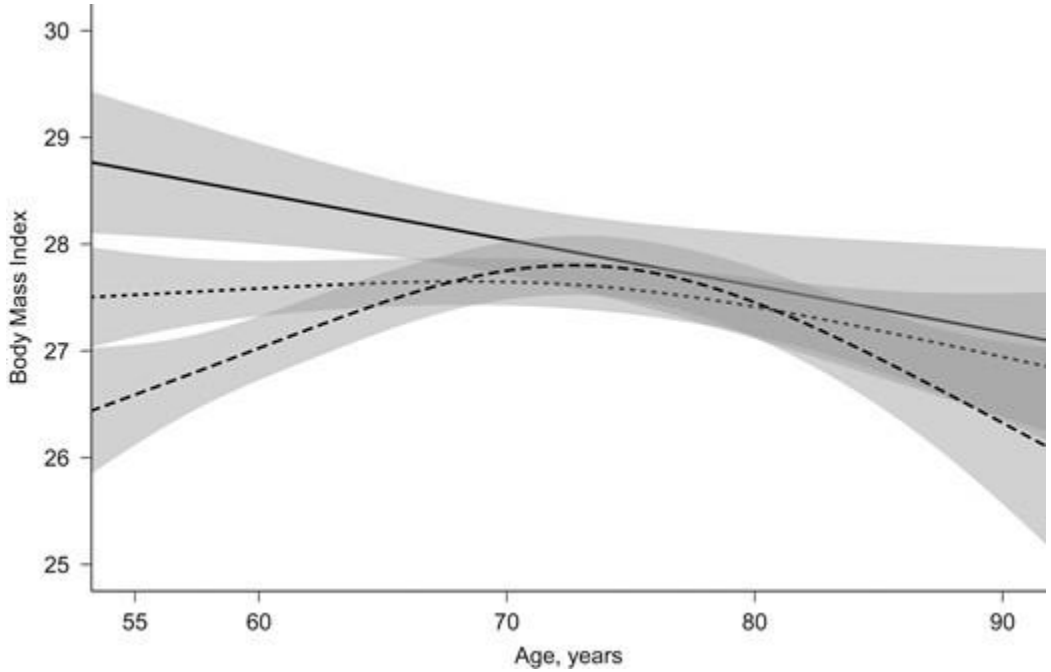
Individual-level data

$$Y = \Gamma_0 + \Gamma_j G_j + \epsilon_{y,j}$$

$$X = \pi_0 + \pi_j G_j + \epsilon_{x,j}$$

Controversy for time-varying exposures

- A usual interpretation of MR results for time-varying exposures: “lifetime effect” – but lacks clarify
- The G-X relationship varies with age: *FTO* (fat mass and obesity-associated gene)-BMI



- Solid: AA
- Short-dashed: AT
- Long-dashed: TT

Lifetime effect

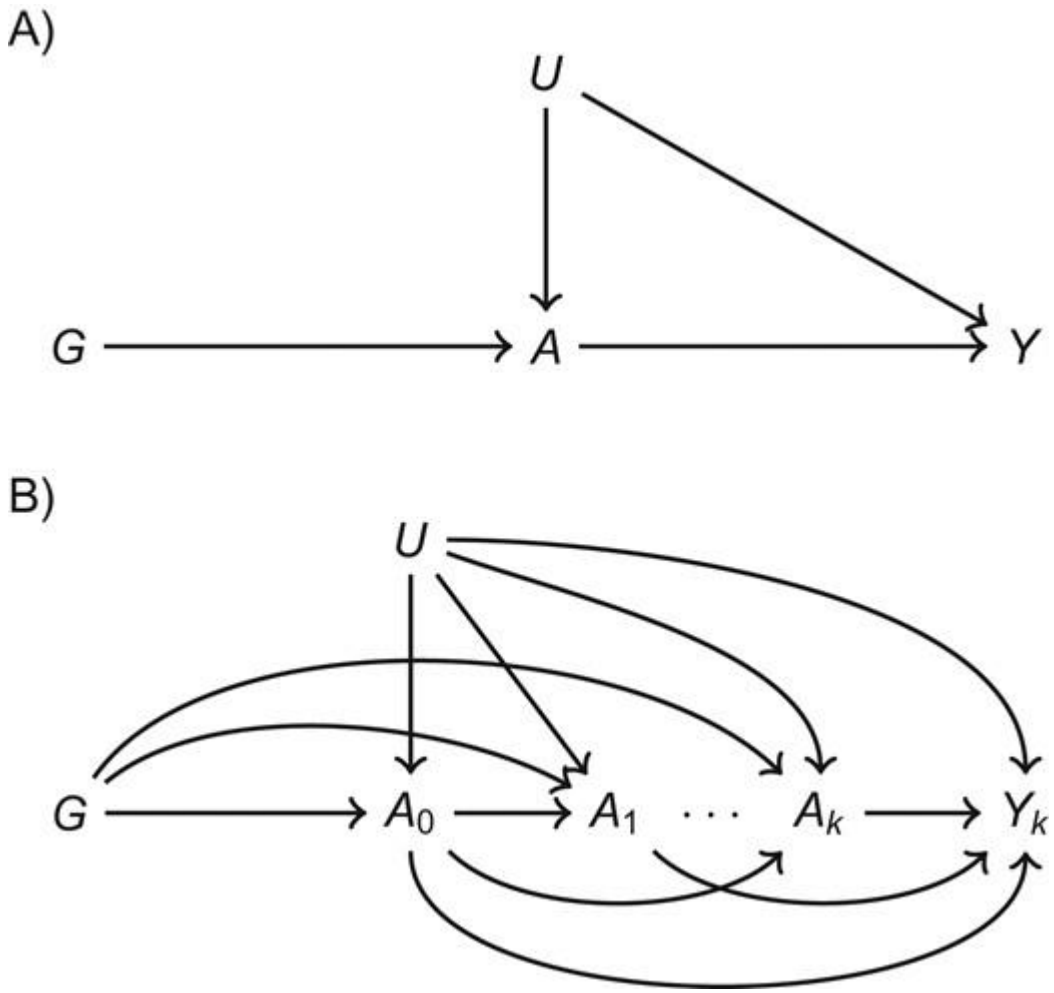
- Time-fixed exposure

$$E\left[Y_k^{a+1}\right] - E\left[Y_k^{a}\right]$$

- Time-varying exposure

$$E\left[Y_k^{\bar{a}+\bar{1}}\right] - E\left[Y_k^{\bar{a}}\right]$$

The effect of shifting the entire exposure trajectory ($\bar{A}$) by 1 unit on Y at time k.



Example

$$\beta_{AY} = \frac{\beta_{GY}}{\beta_{GA}}$$

Time-point IV estimate

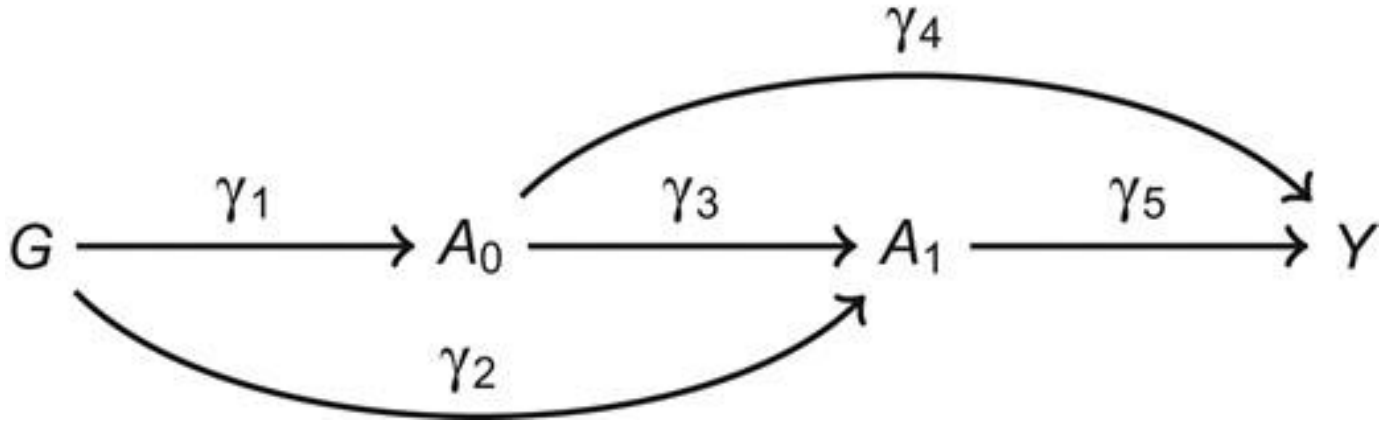
$$\mathrm{MR}_0 = \frac{\gamma_1 \times \gamma_4 + \gamma_1 \times \gamma_3 \times \gamma_5 + \gamma_2 \times \gamma_5}{\gamma_1}$$
$$= \gamma_4 + \gamma_5\left(\gamma_3 + \frac{\gamma_2}{\gamma_1}\right).$$
$$\mathrm{MR}_1 = \frac{\gamma_1 \times \gamma_4 + \gamma_1 \times \gamma_3 \times \gamma_5 + \gamma_2 \times \gamma_5}{\gamma_1 \times \gamma_3 + \gamma_2}$$
$$= \gamma_4\left(\frac{\gamma_1}{\gamma_1 \times \gamma_3 + \gamma_2}\right) + \gamma_5.$$

if the genetic effect is constant over time

$$\gamma_1 = \gamma_1 \times \gamma_3 + \gamma_2$$

$$\mathrm{MR}_0 = \gamma_4 + \gamma_5\left(1 - \frac{\gamma_2}{\gamma_1} + \frac{\gamma_2}{\gamma_1}\right) \qquad \mathrm{MR}_1 = \left(\frac{\gamma_1}{\gamma_1}\right) \times \gamma_4 + \gamma_5$$
$$= \gamma_4 + \gamma_5. \qquad = \gamma_4 + \gamma_5.$$

The IV estimate using either time point could potentially be a valid estimate of the lifetime effect of A on Y when the relationship between G and A is constant through time.



Simulations

- Solid line: G-A association

$$E[A_t^g] = \beta_0 + \beta_G * g + \beta_T * t + \beta_{GT} * g * t$$

$$E[A_K^{g=1}|T=k] - E[A_K^{g=0}|T=k] = \beta_0 + \beta_G + \beta_T * k + \beta_{GT} * k - (\beta_0 + \beta_T * k)$$
$$= \beta_G + \beta_{GT} * k$$

- Dotted line: A-Y association

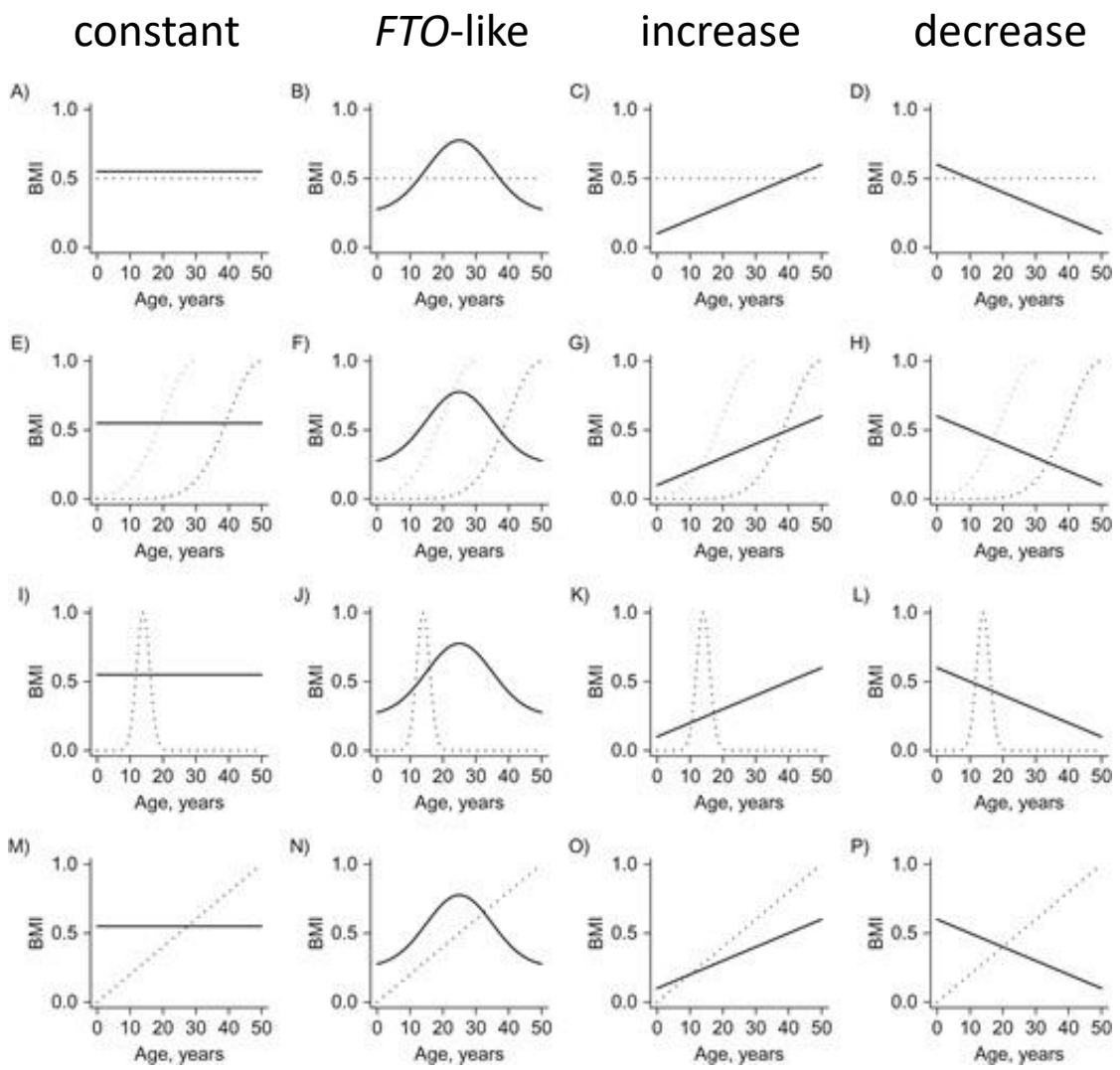
$$E[Y_k^{\bar{a}}] = \gamma_0 + \int_0^k \gamma_A(t) a_t \mathrm{d}t$$

$$E[Y_k^{g=1} - Y_k^{g=0}] = \int_0^K \gamma_A(t)(\beta_0 + \beta_G + \beta_T * t + \beta_{GT} * t)\mathrm{d}t - \int_0^K \gamma_A(t)(\beta_0 + \beta_T * t)\mathrm{d}t$$
$$= \int_0^k \gamma_A(t)(\beta_G + \beta_{GT} * t)\mathrm{d}t$$

- Estimation time: at 30 and 50

$$\frac{E[Y_k^{g=1} - Y_k^{g=0}]}{E[A_k^{g=1} - A_k^{g=0}]} = \frac{\int_0^k \gamma_A(t)(\beta_G + \beta_{GT} * t)\mathrm{d}t}{\beta_G + \beta_{GT} * k}$$

Genetic scenario G-A



Results

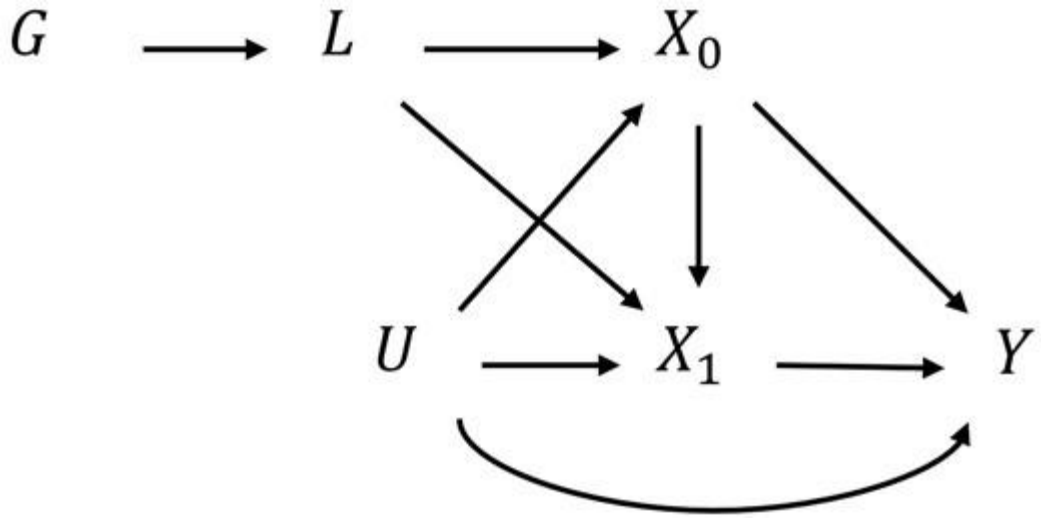
- The unbiased estimates when there is a constant genetic scenario (G-X)

Table 1. Results From the 16 Hypothetical Scenarios Described in Figure 4, Comparing the True Lifetime Effect of Exposure on the Outcome With a Mendelian Randomization Estimate When the Instrument Strength Varies Over Time

Exposure Window[a]	Age at Which Exposure Is Measured							
	Age 30 Years				Age 50 Years			
	True Effect	MR Estimate	Absolute Bias	Relative Bias, %	True Effect	MR Estimate	Absolute Bias	Relative Bias, %
Constant genetic scenario								
Uniform[b]	1.2	1.2	0.0	0	2.0	2.0	0.0	0
Recent[c]	2.0	2.0	0.0	0	2.0	2.0	0.0	0
Critical[d]	2.0	2.0	0.0	0	2.0	2.0	0.0	0
Increasing[e]	0.7	0.7	0.0	0	2.0	2.0	0.0	0
Increasing genetic scenario								
Uniform	1.2	1.0	−0.2	−18	2.0	1.5	−0.5	−25
Recent	2.0	1.8	−0.2	−10	2.0	1.8	−0.2	−8
Critical	2.0	1.6	−0.4	−20	2.0	1.3	−0.7	−36
Increasing	0.7	0.6	−0.1	−12	2.0	1.7	−0.3	−16
Decreasing genetic scenario								
Uniform	1.2	1.5	0.3	22	2.0	3.0	1.0	50
Recent	2.0	2.2	0.2	11	2.0	2.3	0.3	16
Critical	2.0	2.5	0.5	23	2.0	3.4	1.4	72
Increasing	0.7	0.8	0.1	14	2.0	2.7	0.7	34
FTO genetic scenario								
Uniform	1.2	0.9	−0.3	−22	2.0	3.7	1.7	85
Recent	2.0	2.0	0.0	−2	2.0	2.9	0.9	46
Critical	2.0	1.5	−0.5	−24	2.0	3.9	1.9	95
Increasing	0.7	0.7	−0.1	−8	2.0	3.7	1.7	85

Another interpretation: liability effect

- We are not estimating the causal effect of an exposure as it manifests at a given time point, but the effect of the underlying exposure liability. That is, we assume that there is some unobserved (latent) variable L, which is caused by the genotype G, and in turn causes the exposure at every instance across the lifecourse.



Example

The *total effect* of a one-unit change in X_0 on Y (β_{T_0}) is given by:

$$\beta_{T_0} = \gamma_4 + \gamma_5\gamma_6$$

The *total effect* of a one-unit change in X_1 on Y is given by:

$$\beta_{T_1} = \gamma_6$$

The liability effect is the causal effect of a one-unit increase in liability, which is given by:

$$\beta_L = \gamma_2\gamma_4 + \gamma_2\gamma_5\gamma_6 + \gamma_3\gamma_6$$

Turning to the liability effect at time 0, β_{L_0} (the effect of increasing the liability such that X_0 increases in expectation by one unit), a one-unit increase in $E(X_0)$ occurs because there is an increase in L from l_{10} to $L = l_{10} + \frac{1}{(\gamma_2)}$.

If $L = l_{10}$, then:

$$E(Y|do(l_{10})) = y_{00} = l_{10}(\gamma_2\gamma_4 + \gamma_2\gamma_5\gamma_6 + \gamma_3\gamma_6)$$

If $L = l_{10} + \frac{1}{(\gamma_2)}$, then:

$$E\left(\left(Y|do\left(l_{10} + \frac{1}{(\gamma_2)}\right)\right)\right) = y_{10}$$
$$= \left(l_{10} + \frac{1}{\gamma_2}\right)(\gamma_2\gamma_4 + \gamma_2\gamma_5\gamma_6 + \gamma_3\gamma_6)$$

The effect on Y of changing the liability L such that it raises X_0 by one unit is therefore given by:

$$\beta_{L_0} = y_{10} - y_{00} = \frac{(\gamma_2\gamma_4 + \gamma_2\gamma_5\gamma_6 + \gamma_3\gamma_6)}{\gamma_2} \quad (1)$$

A one-unit increase in expectation in X_1 would occur because there is an increase in L from l_{11} to $l_{11} + \frac{1}{(\gamma_2\gamma_5 + \gamma_3)}$

If $L = l_{11}$ then

$$E(Y|do(l_{11})) = y_{01} = l_{11}(\gamma_2\gamma_4 + \gamma_2\gamma_5\gamma_6 + \gamma_3\gamma_6)$$

If $L = l_{11} + \frac{1}{(\gamma_2\gamma_5 + \gamma_3)}$ then

$$E\left(\left(Y|do\left(l_{11} + \frac{1}{(\gamma_2\gamma_5 + \gamma_3)}\right)\right)\right) = y_{11}$$
$$= \left(l_{11} + \frac{1}{(\gamma_2\gamma_5 + \gamma_3)}\right)(\gamma_2\gamma_4 + \gamma_2\gamma_5\gamma_6 + \gamma_3\gamma_6)$$

The effect on Y of changing L such that X_1 is increased by one unit in expectation is given by:

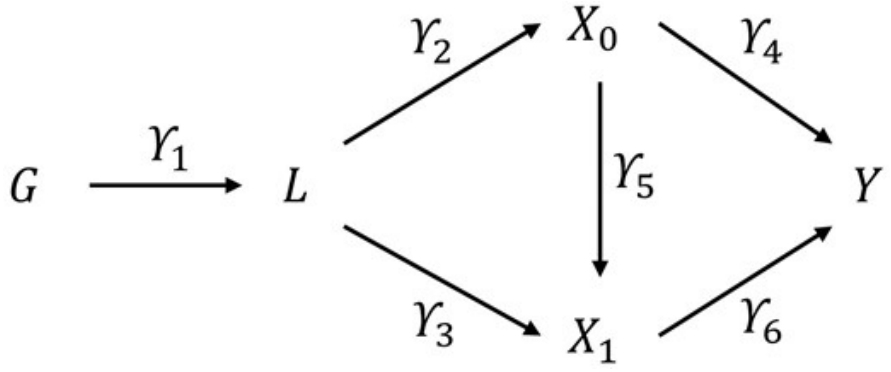
$$\beta_{L_1} = y_{11} - y_{01} = \frac{(\gamma_2\gamma_4 + \gamma_2\gamma_5\gamma_6 + \gamma_3\gamma_6)}{\gamma_2\gamma_5 + \gamma_3} \quad (2)$$

$$L = \gamma_1 G + \alpha_L U + \varepsilon_L$$

$$X_0 = \gamma_2 L + \alpha_0 U + \varepsilon_0$$

$$X_1 = \gamma_3 L + \gamma_5 X_0 + \alpha_1 U + \varepsilon_1$$

$$Y = \gamma_6 X_1 + \gamma_4 X_0 + \alpha_Y U + \varepsilon_Y$$



Example

- MR estimates the causal effect of a change in liability L that results in an expected one-unit change in exposure X_t

The effect of G on Y is:

$$\beta_{GY} = \gamma_1(\gamma_2\gamma_4 + \gamma_2\gamma_5\gamma_6 + \gamma_3\gamma_6) \quad (3)$$

The effect of G on X_0 is:

$$\beta_{GX_0} = \gamma_1\gamma_2 \quad (4)$$

The effect of G on X_1 is:

$$\beta_{GX_1} = \gamma_1(\gamma_2\gamma_4 + \gamma_2\gamma_5 + \gamma_1\gamma_3) \quad (5)$$

The Wald Ratio MR estimand with X_0 as a single exposure is given by Equation (3)/Equation (4):

$$\beta_{MR_0} = \frac{\gamma_1(\gamma_2\gamma_4 + \gamma_2\gamma_5\gamma_6 + \gamma_3\gamma_6)}{\gamma_1(\gamma_2)} = \frac{(\gamma_2\gamma_4 + \gamma_2\gamma_5\gamma_6 + \gamma_3\gamma_6)}{(\gamma_2)} \quad (6)$$

The Wald Ratio MR estimand with X_1 as a single exposure is given by Equation (3)/Equation (5):

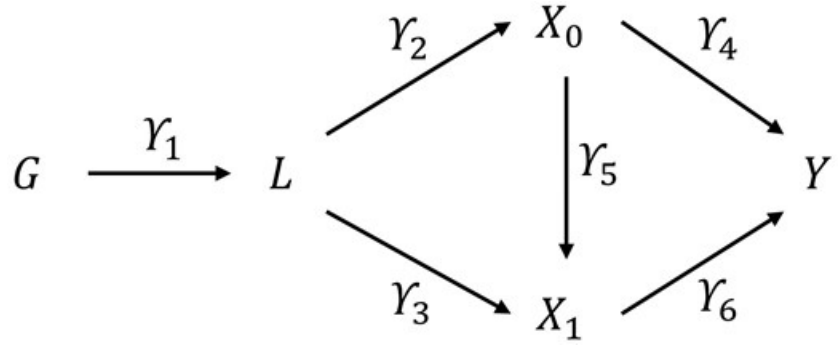
$$\beta_{MR_1} = \frac{\gamma_1(\gamma_2\gamma_4 + \gamma_2\gamma_5\gamma_6 + \gamma_3\gamma_6)}{\gamma_1(\gamma_2\gamma_5 + \gamma_3)} = \frac{(\gamma_2\gamma_4 + \gamma_2\gamma_5\gamma_6 + \gamma_3\gamma_6)}{(\gamma_2\gamma_5 + \gamma_3)} \quad (7)$$

$$L = \gamma_1 G + \alpha_L U + \varepsilon_L$$

$$X_0 = \gamma_2 L + \alpha_0 U + \varepsilon_0$$

$$X_1 = \gamma_3 L + \gamma_5 X_0 + \alpha_1 U + \varepsilon_1$$

$$Y = \gamma_6 X_1 + \gamma_4 X_0 + \alpha_Y U + \varepsilon_Y$$



Methods for time-varying MR

- Multivariable MR (MVMR)
- G-estimation of structural nested mean model (SNMM)

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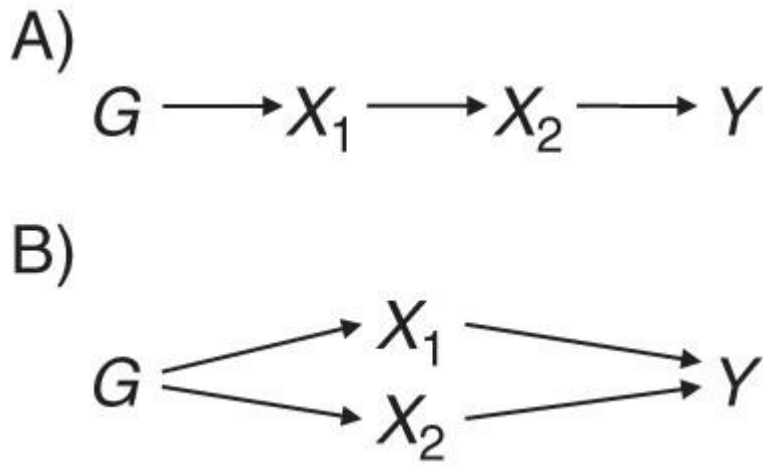
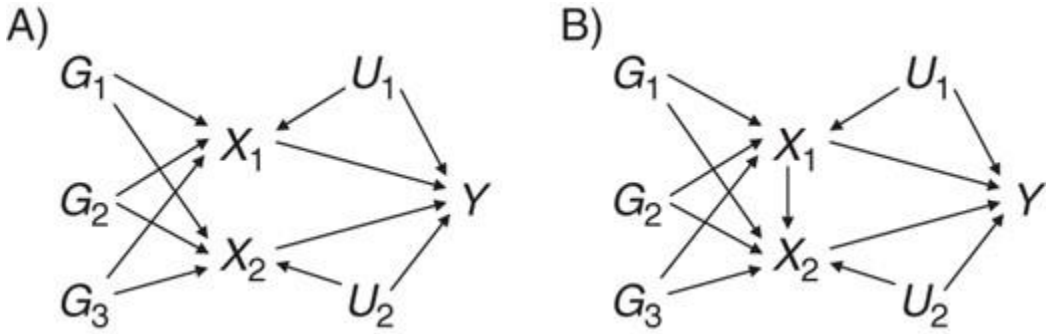
MVMR

- MVMR is proposed to cope with the horizontal pleiotropy.
- Assumptions:
  - the variant is associated with 1 or more of the risk factors,
  - the variant is not associated with a confounder of any of the risk factor–outcome associations,
  - the variant is conditionally independent of the outcome given all of the risk factors and confounders.





MVMR

- Individual-level

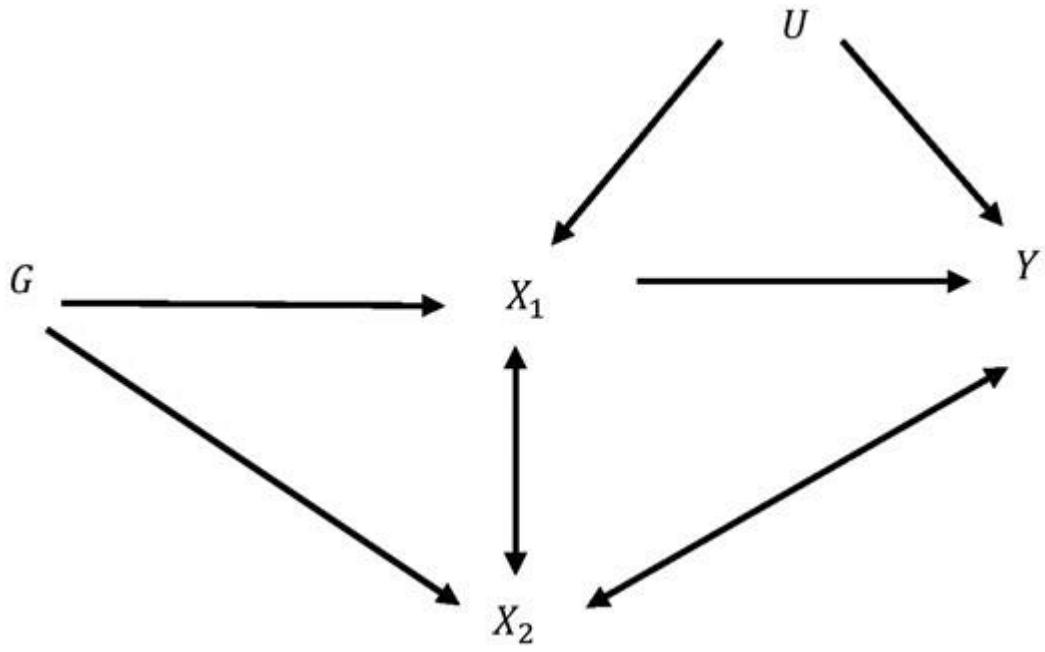
$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + U + \nu_y$$

$$X_1 = \pi_{01} + \pi_1 G + U + \nu_{x_1}$$

$$X_2 = \pi_{02} + \pi_2 G + U + \nu_{x_2}$$

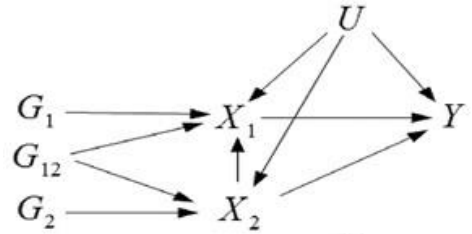
- Summary

$$\hat{\Gamma}_j = \beta_1 \hat{\pi}_{1,j} + \beta_2 \hat{\pi}_{2,j} + \epsilon_j$$



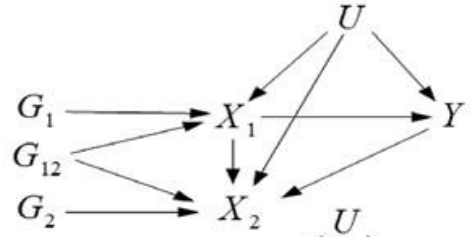
it is necessary to have at least as many genetic instruments as there are exposures to be instrumented in the model

Simulations



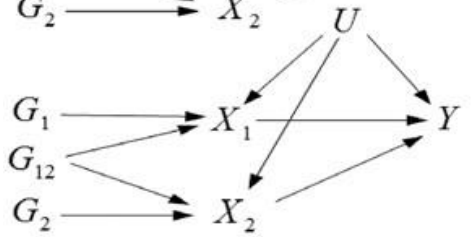
Scenario 1: Confounder

Models (4) (6) (8)



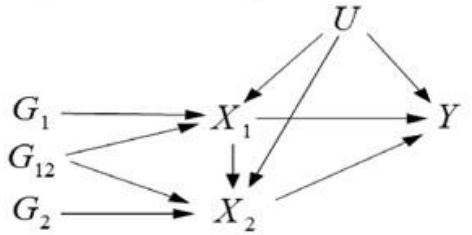
Scenario 2: Collider

Models (4) (5) (9)



Scenario 3: Pleiotropy

Models (4) (5) (6)



Scenario 4: Mediation

Models (4) (5) (10)

Simulated data generation mechanism

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + U + \upsilon_y. \quad (4)$$

$$X_1 = \pi_{01} + \pi_1 G + U + \upsilon_{x_1} \quad (5)$$

$$X_2 = \pi_{02} + \pi_2 G + U + \upsilon_{x_2}. \quad (6)$$

$$X_1 = \pi_1 G + \alpha_2 X_2 + U + \upsilon_{x_1}. \quad (8)$$

$$X_2 = \pi_2 G + \alpha_1 X_1 + \gamma_y Y + U + \upsilon_{x_2}. \quad (9)$$

$$X_2 = \pi_2 G + \alpha_1 X_1 + U + \upsilon_{x_2}. \quad (10)$$

Simulations

- With single-sample individual-level data, implemented:
  - OLS, both for X1 and X2 individually (i.e. univariable regressions) and together (i.e. a multivariable regression);
  - MR for X1 and X2 individually, each time using all the available SNPs as instruments;
  - MVMR including both X1 and X2 in the same analysis;
  - MR for X1 and X2 individually using only the SNPs that are valid instruments for that exposure (G1 and G2, respectively).
- With two-sample summary-level data, implemented:
  - MR for X1 and X2 individually using all of the instruments available;
  - MVMR including both X1 and X2;
  - MR for X1 and X2 individually using only the SNPs that are valid instruments for the exposure.

Results

- In general, MR estimates the total effect of the exposure on the outcome, whereas MVMR estimates the direct effect of each exposure on the outcome.

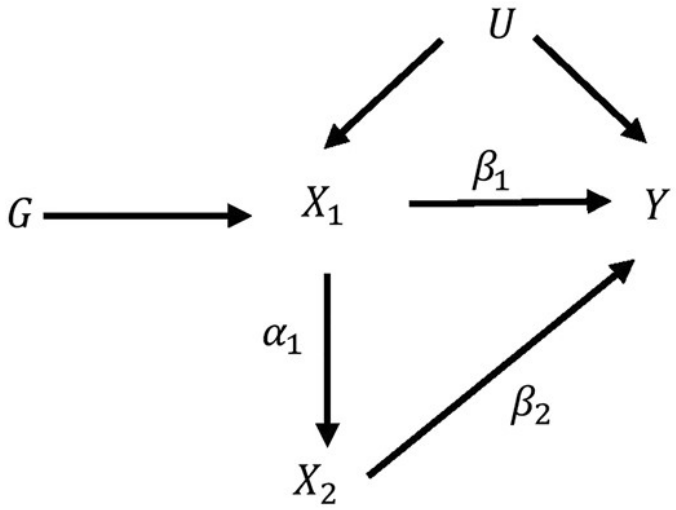


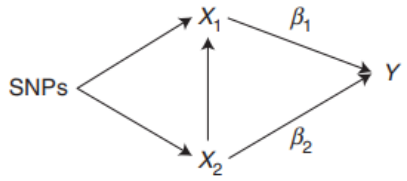
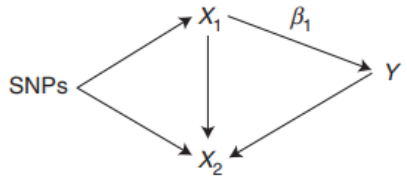
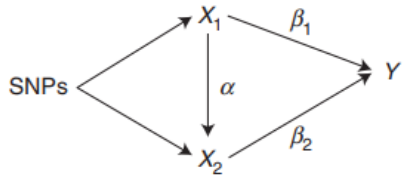
Table 1. Summary of estimated effects for β_1

	Scenario/which estimand is targeted?			
Method	1	2	3	4
Individual-level data				
OLS	x	x	x	x
Univariate MR	x	Direct/total	x	x
MVMR	Direct/total	Direct/total	Direct/total	Direct
Univariate MR—subset of SNPS	Direct/total	Direct/total	Direct/total	Total
Two-sample summary data analysis				
Univariate MR	x	Direct/total	x	x
MVMR	Direct/total	Direct/total	Direct/total	Direct
Univariate MR—subset of SNPS	Direct/total	Direct/total	Direct/total	Total

When each method of estimation estimates the direct and total effects for β_1 in each of the scenarios considered. An 'x' represents a biased method of estimation.

Summary for MR vs.. MVMR

Table 1. Results for the effect of exposure X_1 on outcome Y[a]

Relationship between X_2 and X_1	MR—including all SNPs	MR—including SNPs that only affect X_1	MVMR
Confounder 	Biased—assumption IV2 is violated	Direct effect = total effect = β_1	Direct effect = total effect = β_1
Collider 	Direct/total effect = β_1	Direct effect = total effect = β_1	Direct effect = total effect = β_1
Mediator 	Biased—assumption IV2 is violated	Total effect = $\beta_1 + \alpha\beta_2$	Direct effect = β_1

[a]Obtained from Mendelian randomization (MR) and multivariable MR (MVMR) under different relationships between exposures in a two-exposure model.

Test for assumptions

- Individual-level data
  - Instrument strength: Sanderson–Windmeijer conditional F-statistic
  - Instrument validity: Sargan test

- X_2 is regressed on the full set of genetic instruments (and any control variables included in the estimation) and the predicted value of X_2, $\hat{X}_2$, is calculated;
- X_1 is then regressed on $\hat{X}_2$ (and any control variables) to yield the TSLS estimate $\hat{\delta}$ and the residual error terms $X_1 - \hat{\delta}X_2$ are saved;
- the errors are then regressed on the full set of instruments (and any control variables); the conditional F-statistic is obtained as the F-statistic for the effect of the instruments in this regression;
- the conditional F-statistic must be adjusted for a degrees-of-freedom correction, and can be compared with the conventional weak-instrument critical values.[34]

- regress the outcome Y on the exposures using TSLS to yield causal estimates $\hat{\beta}_1$ and $\hat{\beta}_2$;
- calculate the residual error term $Y - (\hat{\beta}_1 X_1 + \hat{\beta}_2 X_2)$ and then regress the residuals on the full set of instruments; the Sargan test is then the sample size times the R^2 of this regression;
- evaluating with the Sargan statistic with respect to a χ^2 distribution with degrees of freedom equal to the number of instruments minus the number of predicted exposure variables (i.e. the null hypothesis that all of the instruments are valid).[4]

Test for assumptions

- Summary data
  - instrument strength: heterogeneity is ‘good’
    - the model will be at least exactly identified when there will be at least as many independent genetic instruments as there are exposure variables to be instrumented. we can test for under-identification in our estimation model by testing for over-identification using the Sargan test as described above.

$$Q_{x_1} = \sum_{j=1}^{L} \left(\frac{1}{\sigma^2_{x1j}}\right)\left(\hat{\pi}_{1j} - \hat{\delta}\hat{\pi}_{2j}\right)^2.$$

  - instrument validity: heterogeneity is ‘bad’
    - if all instruments are valid IVs, and the modelling assumptions necessary for two-sample MR are satisfied, then each genetic instrument should give the same estimate of the effect of the exposure on the outcome. Excessive heterogeneity in the causal-effect estimates obtained by each SNP individually now becomes an indicator of invalid instruments.

$$Q_A = \sum_{j=1}^{L} \left(\frac{1}{\sigma^2_{Aj}}\right)\left(\hat{\Gamma}_j - \left(\hat{\beta}_1\hat{\pi}_{1j} + \hat{\beta}_2\hat{\pi}_{2j}\right)\right)^2.$$

Application: mediation analysis

- Mediation analysis
  - Difference method
  - Product of coefficients method

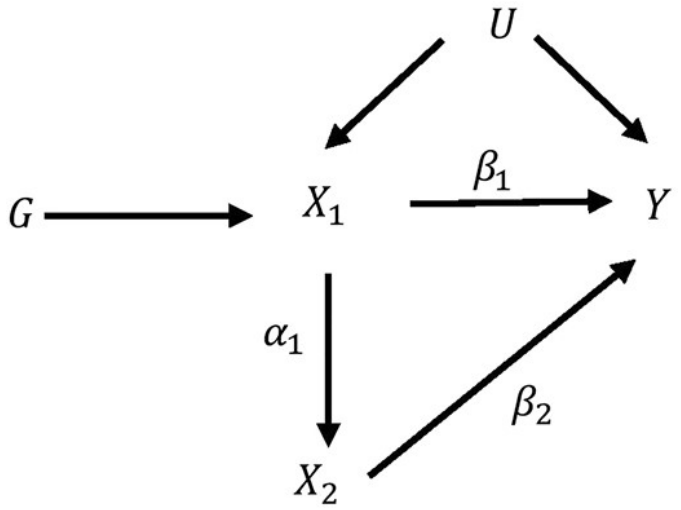


Table 2. Estimation of total, direct, and indirect effects and proportion mediated using Mendelian randomization (MR) and multivariable MR (MVMR)

Effect	Estimation—difference method		Estimation—product of coefficients method (network/two-step MR)	
Total effect	Univariable MR of exposure on outcome using single-nucleotide polymorphisms (SNPs) associated with exposure only (Fig. 3A)	β_1^*	Univariable MR of exposure on outcome using SNPs associated with exposure only (Fig. 3A)	β_1^*
Direct effect	Effect of exposure on outcome from MVMR including exposure and mediator as exposures (Fig. 3B)	β_1	Total effect—indirect effect	$\beta_1^* - \alpha\beta_2$
Indirect effect	Total effect—direct effect	$\beta_1^* - \beta_1$	Effect of exposure on mediator from univariable MR (Fig. 3C) multiplied by effect of mediator on the outcome from univariable MR (Fig. 3D) or MVMR (Fig. 3B)	$\alpha\beta_2$

MVMR for mediation analysis

- Advantages:
  - If M is not a mediator of X and Y but is in fact a confounder (or even collider) of X and Y, the estimated direct effect will be equal to the estimated total effect and so the lack of mediation will be clear from the results obtained.
  - Tolerant for pleiotropy and confounders of M and Y

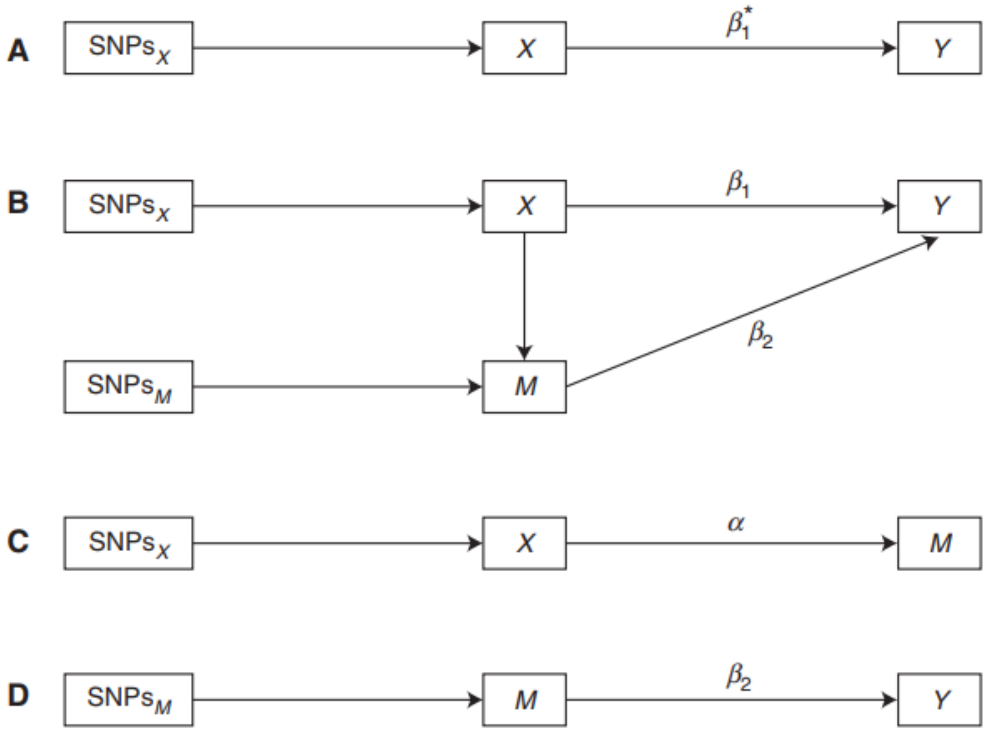
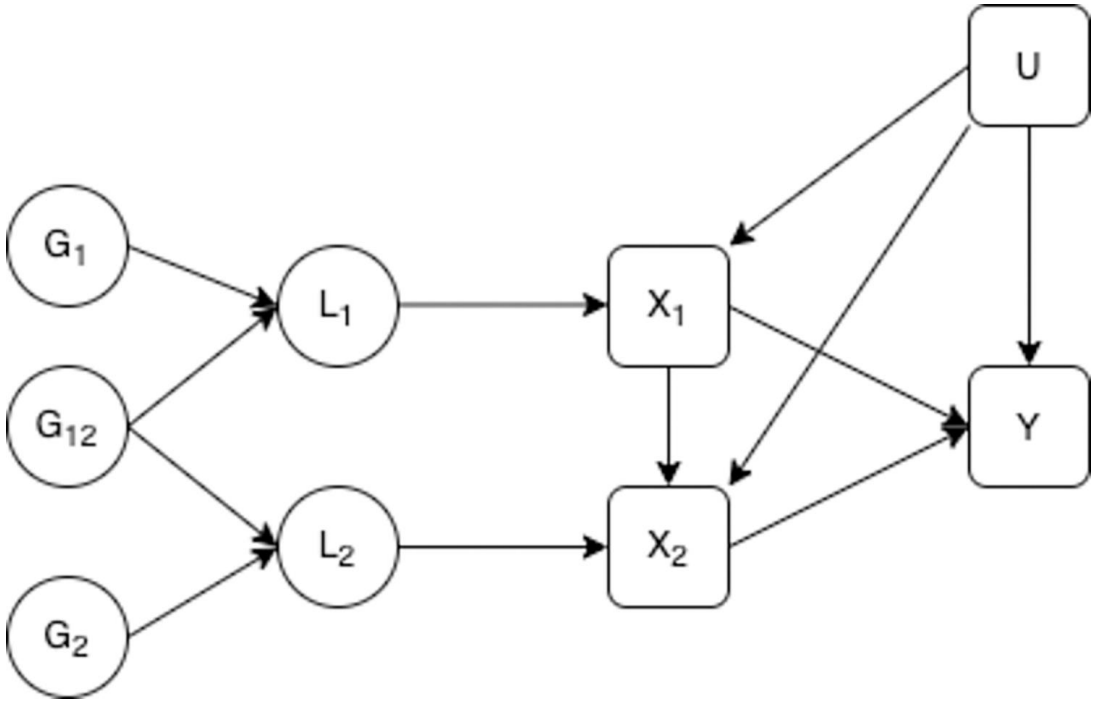


Figure 3. Illustration of the parameters estimated to obtain total, direct, and indirect effects and proportion mediated using Mendelian randomization (MR) and multivariable MR (MVMR). (X) exposure, (M) mediator, (Y) outcome, (SNPs$_X$) set of single-nucleotide polymorphisms associated with the exposure, (SNPs$_M$) set of SNPs associated with the mediator.

MVMR for time-varying exposures

- MVMR with multiple measures of a time-varying exposure estimates the direct effect of the liability to exposure at a particular period, i.e. the effect of the liability to the exposure at a time point that is not mediated by other time points included in the estimation.
- Genetic liability: the collective effect of all genetic variants associated with the exposure



$$\hat{\Gamma}_j = \beta_1 \hat{\pi}_{1,j} + \beta_2 \hat{\pi}_{2,j} + u \qquad \text{weighted by: } \frac{1}{\hat{\sigma}^2_{\Gamma,j}}$$

Assumptions

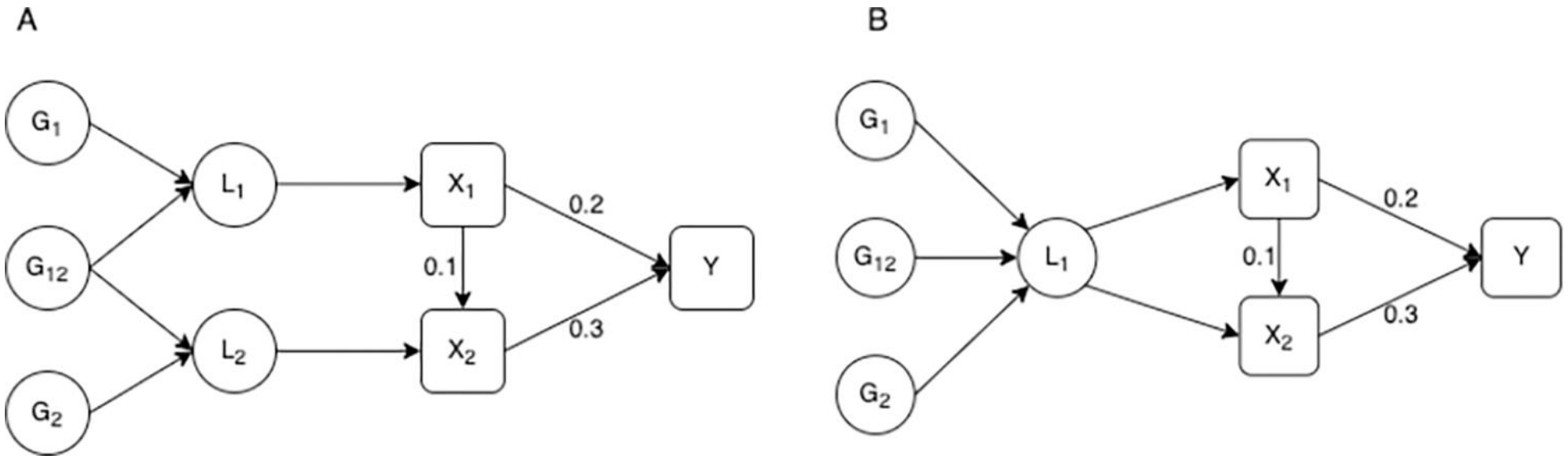
a) liability to each exposure is robustly predicted by the genetic variants conditional on the other exposures included in the estimation,

b) there is no confounding of the genetic variants and the outcome,

c) the genetic variants are not associated with the outcome other than via liabilities to exposures included in the estimation, i.e. there are no horizontal pleiotropic effects of the genetic variants on the outcome via other phenotypes.

Simulations

- In (a) X_1 and X_2 are associated with different liabilities.
- In (b) X_1 and X_2 are associated with the same liability.



Results

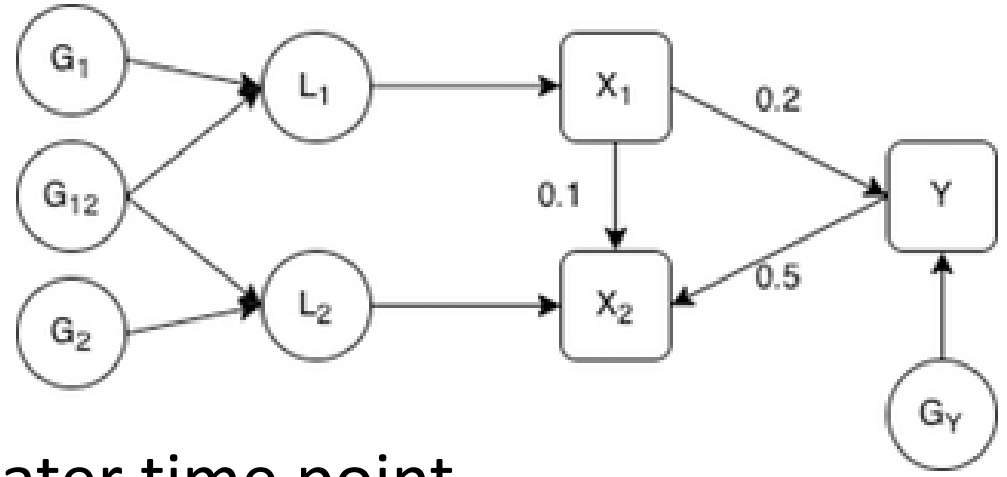
Table 1. Simulation results under different relationships between the genetic variants and the exposure at each time point.

		MR	MVMR
Exposures associated with different liability periods			
β_1	***Liability effect***	**0.344**	**0.200**
	Effect estimate	0.340	0.1958
	Est. Std. Error	0.029	0.0107
	Simulation Std. Error	0.011	0.0106
	Absolute bias	0.010	0.0092
	Coverage	100%	93%
	F-statistic	96.31	
	Conditional F-statistic		55.76
	No. SNPs	72	114
β_2	***Liability effect***	**0.376**	**0.300**
	Effect estimate	0.371	0.297
	Est. Std. Error	0.015	0.009
	Simulation Std. Error	0.008	0.009
	Absolute bias	0.008	0.008
	Coverage	99%	94%
	F-statistic	129.31	
	Conditional F-statistic		78.01
	No. SNPs	83	114
Exposures associated with the same liability period			
β_1	***Liability effect***	**0.530**	**0.200**
	Effect estimate	0.519	0.207
	Est. Std. Error	0.011	0.080
	Simulation Std. Error	0.011	0.080
	Absolute bias	0.013	0.063
	Coverage	82%	94%
	F-statistic	96.31	
	Conditional F-statistic		1.06
	No. SNPs	72	86
β_2	***Liability effect***	**0.480**	**0.300**
	Effect estimate	0.474	0.288
	Est. Std. Error	0.009	0.073
	Simulation Std. Error	0.009	0.072
	Absolute bias	0.009	0.058
	Coverage	89%	94%
	F-statistic	115.76	
	Conditional F-statistic		1.06
	No. SNPs	83	86

Results

- The univariable estimates give an estimate of the total effect of a liability that is associated with having a unit higher level of the exposure at the time point associated with the measured exposure.
- When the measured exposures are associated with different liabilities, MVMR consistently estimates the genetically predicted causal effect of being on a trajectory associated with a unit higher level of that exposure, given the liability to the exposure at the other time period.
- When the measured exposures are associated with the same liability there is no difference in the genetic effects on the measured exposures and therefore weak instrument bias is introduced into the MVMR estimation.

Scenario $Y \rightarrow X_2$



- A causal effect from the outcome to the later time point
- Simulation results without Steiger filtering show that although the genetic variants strongly predict the exposure at each time period conditional on the other, MVMR estimation gives biased estimates of the direct causal effect of the exposure at both time periods on Y. → collider bias
- Steiger filtering: to remove any SNPs that explain more variation in the outcome than the later exposure.

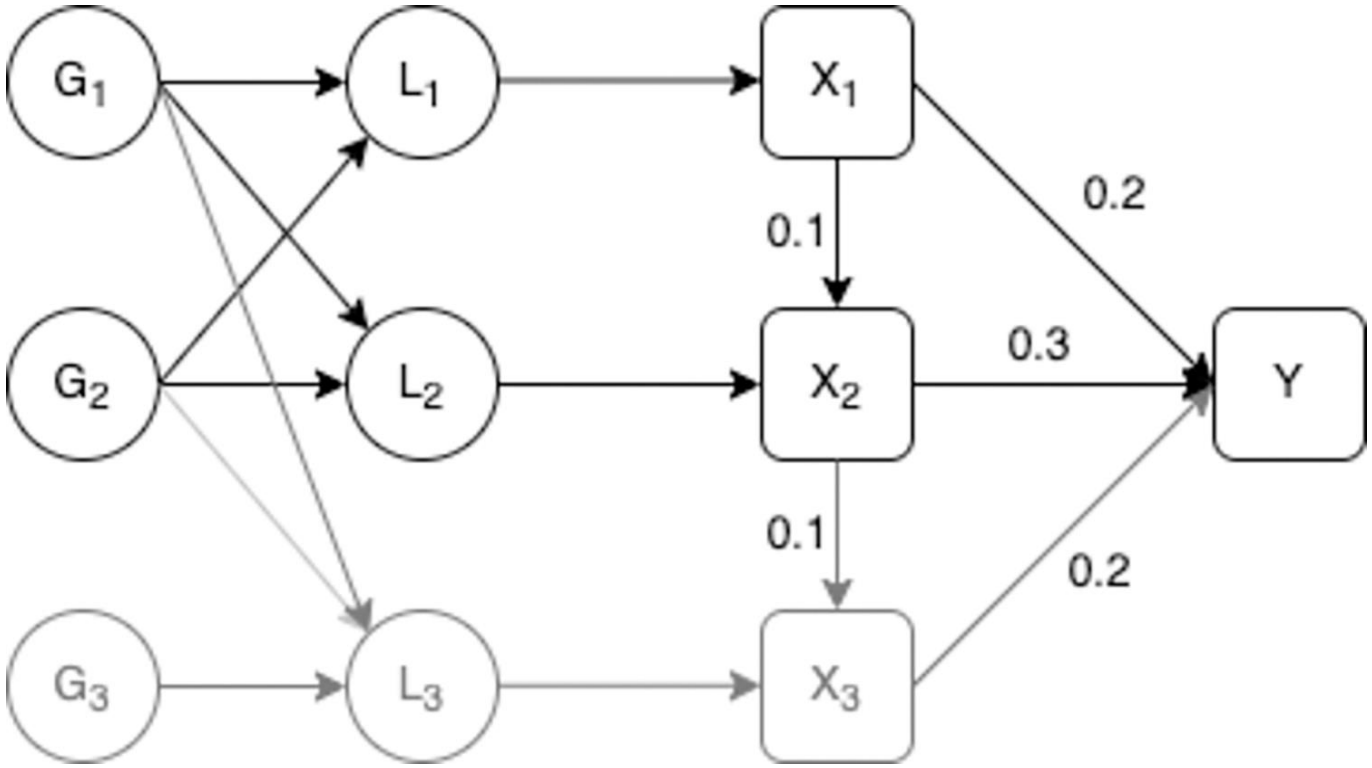
Results

Table 2. Simulation results for multiple time points with a causal effect from the outcome to the later time point.

		MR	MVMR
No Steiger filtering			
β_1	***Liability effect***	**0.200**	**0.200**
	Effect estimate	0.196	0.078
	Est. Std. Error	0.016	0.070
	Simulation Std. Error	0.016	0.022
	Absolute bias	0.013	0.122
	Coverage	93%	75%
	F-statistic	96.34	
	Conditional F-statistic		59.85
	No. SNPs	72	117
β_2	***Liability effect***	**0.076**	**0.000**
	Effect Estimate	0.223	0.189
	Est. Std. Error	0.056	0.055
	Simulation Std. Error	0.018	0.021
	Absolute bias	0.147	0.189
	Coverage	2%	0%
	F-statistic	101.72	
	Conditional F-statistic		70.82
	No. SNPs	82	117
With Steiger filtering			0.200
β_1	***Liability effect***	**0.200**	**0.200**
	Effect estimate	0.195	0.195
	Est. Std. Error	0.016	0.018
	Simulation Std. Error	0.016	0.018
	Absolute bias	0.013	0.015
	Coverage	92%	94%
	F-statistic	96.35	
	Conditional F-statistic		63.68
	No. SNPs	72	107
β_2	***Liability effect***	**0.076**	**0.000**
	Effect Estimate	0.083	0.001
	Est. Std. Error	0.017	0.015
	Simulation Std. Error	0.013	0.015
	Absolute bias	0.012	0.012
	Coverage	97%	94%
	F-statistic	106.80	
	Conditional F-statistic		69.98
	No. SNPs	72	107

Three liability time periods

- Correlated genetic effects
- Independent genetic effects
- When the association between the genetic variants and the excluded liability are correlated with those for the included periods the effect estimated will include some of the effect that acts via the omitted liability.



Results

Table 3. Simulation results with a relevant liability period excluded.

		MR	MVMR
Correlated genetic effects			
β_1	***Liability effect***	**0.363**	**0.191**
	Effect estimate	0.326	0.186
	Est. Std. Error	0.031	0.020
	Simulation Std. Error	0.015	0.013
	Absolute bias	0.037	0.011
	Coverage	95%	100%
	F-statistic	88.50	
	Conditional F-statistic		54.82
	No. SNPs	59	93
β_2	***Liability effect***	**0.428**	**0.353**
	Effect estimate	0.418	0.351
	Est. Std. Error	0.024	0.020
	Simulation Std. Error	0.012	0.013
	Absolute bias	0.013	0.010
	Coverage	100%	100%
	F-statistic	102.40	
	Conditional F-statistic		63.66
	No. SNPs	60	93
Independent genetic effects			
β_1	***Liability effect***	**0.378**	**0.220**
	Effect Estimate	0.321	0.211
	Est. Std. Error	0.037	0.024
	Simulation Std. Error	0.015	0.014
	Absolute bias	0.057	0.013
	Coverage	80%	100%
	F-statistic	80.20	
	Conditional F-statistic		48.00
	No. SNPs	53	92
β_2	***Liability effect***	**0.395**	**0.328**
	Effect estimate	0.386	0.322
	Est. Std. Error	0.027	0.022
	Simulation Std. Error	0.013	0.013
	Absolute bias	0.013	0.011
	Coverage	100%	100%
	F-statistic	98.63	
	Conditional F-statistic		66.32
	No. SNPs	62	92

Controversies

- Simulation studies:
  - Exposure $X(t) = \sum_{j=1}^{30} \alpha_j(t)\, G_j + \cos(t)\, U + \sin(t)\, \epsilon_X \qquad \alpha_j(t) = A_{1,j} + A_{2,j} \cos(A_{3,j}\, t - A_{4,j})$
  - Outcome
    - Scenario 1: outcome is a function of exposure at two fixed time-points: t=10 and 50
      - 1A: the exposure is measured at time 10 and 50
      - 1B: the exposure is measured at time 10, 40 and 50
      - 1C: the exposure is measured at time 15 and 30
      - 1D: the exposure is measured at time 15 and 50
    - Scenario 2: outcome is a continuous function of exposure varying over time [exposure measured at 10 and 50]
      - 2A: null in early life (up to 40) and positive in later life
      - 2B: positive in early life (up to 20) and null later life
      - 2C: constant and positive across the life course

$$Y = 0.4\, X(10) - 0.8\, X(50) + U + \epsilon_Y$$

$$Y = \int_0^{50} \beta(t)\, X(t)\, dt + U + \epsilon_Y$$

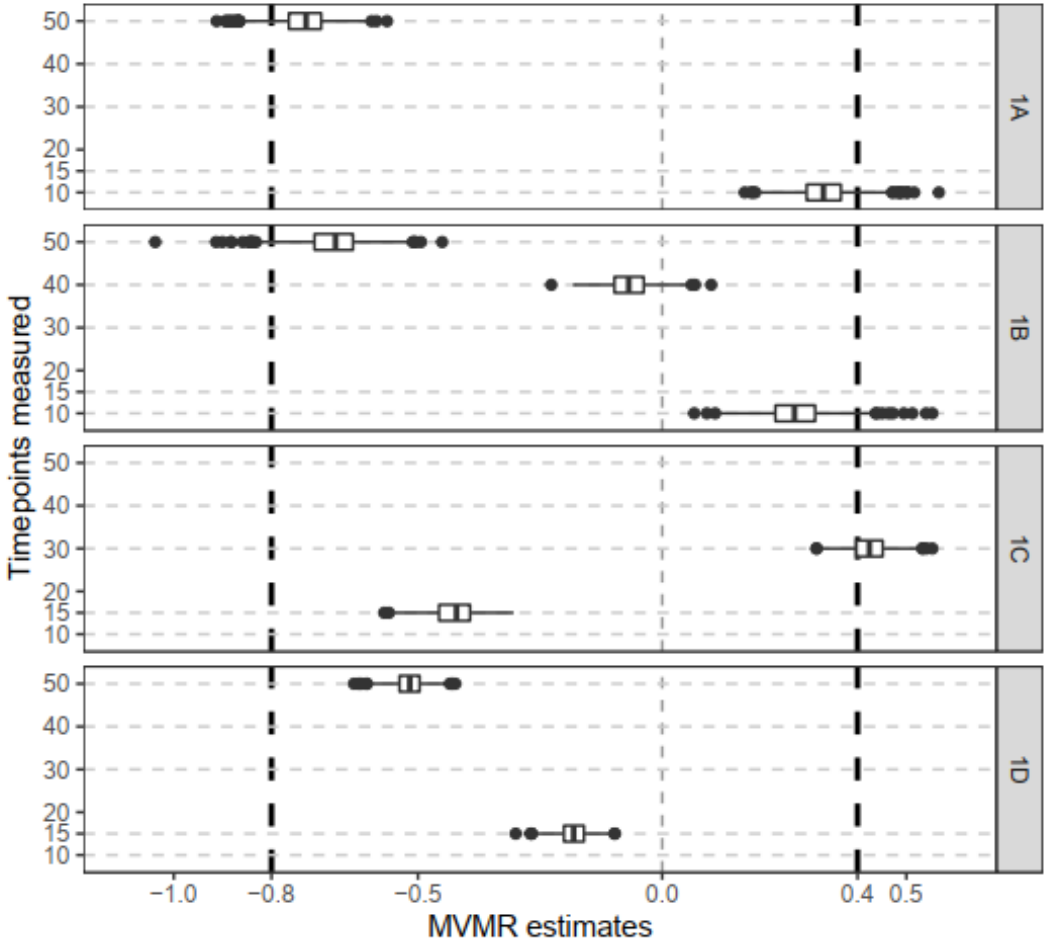
$$\beta(t) = \begin{cases} 0 & \text{for } t \in [0, 40] \\ 1 & \text{for } t \in [40, 50] \text{ (Scenario 2A)} \end{cases}$$

$$\beta(t) = \begin{cases} 0.5 & \text{for } t \in [0, 20] \\ 0 & \text{for } t \in [20, 50] \text{ (Scenario 2B)} \end{cases}$$

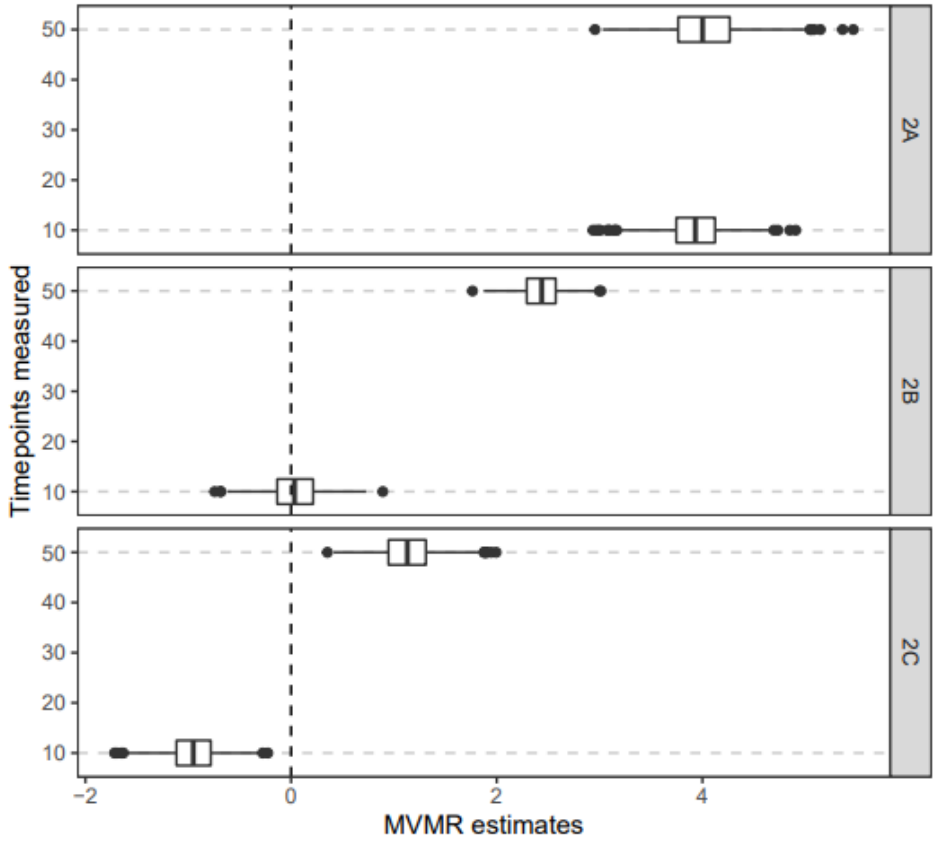
$$\beta(t) = 0.1 \quad \text{for } t \in [0, 50] \text{ (Scenario 2C).}$$

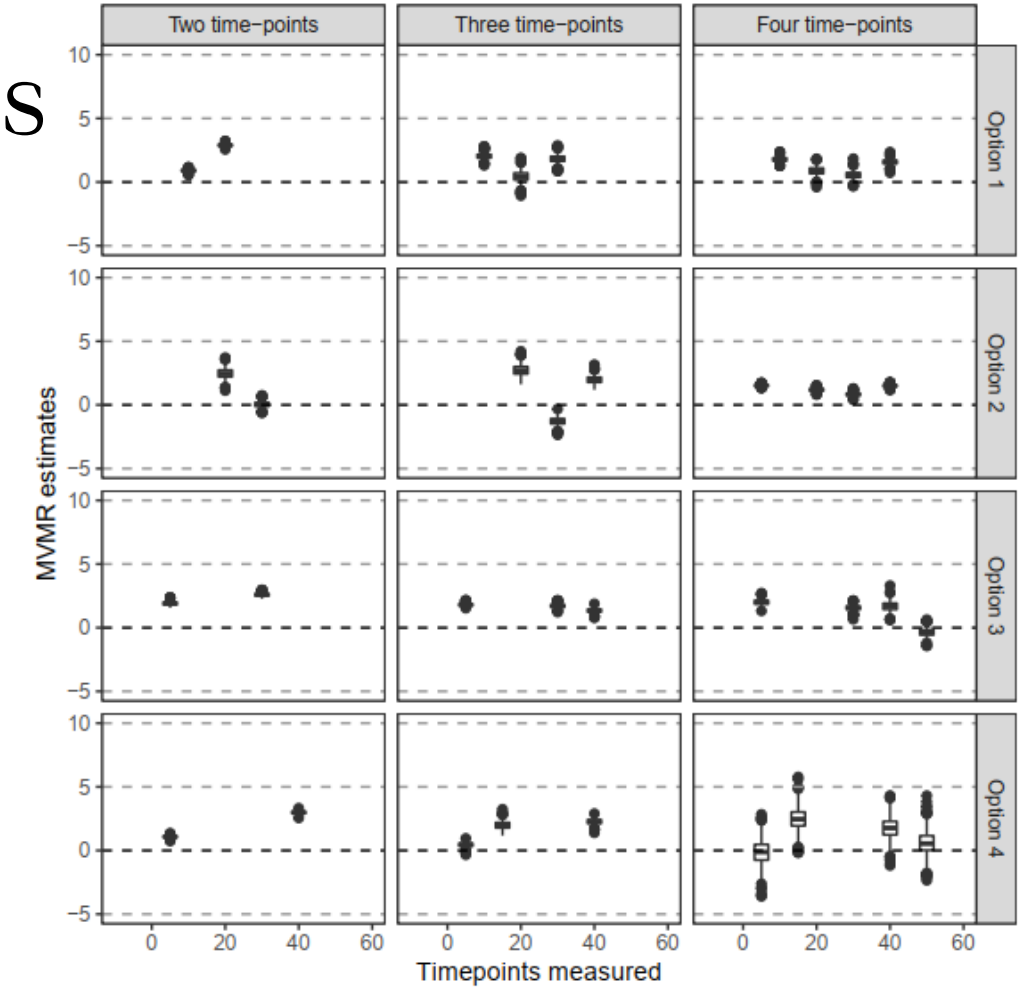
Results: discrete effects

- in Scenario 1C and in Scenario 1D, median estimates are substantially different to the true values.
- Bias in 1A and 1B due to weak instruments



Results: continuous effects





- Scenario 2C: a range of different choices of timepoints that exposures are measured.

Conclusion

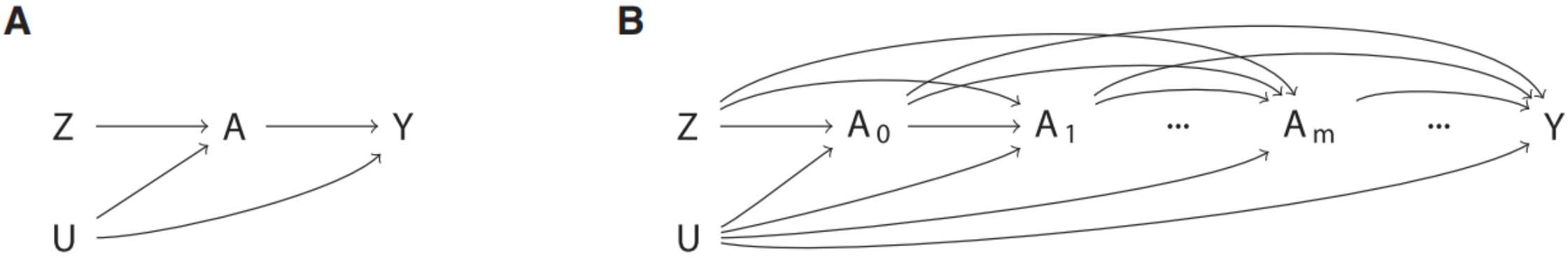
- When the exposure affects the outcome at a limited number of discrete timepoints and the risk factors in the multivariable Mendelian randomization analysis are the values of the exposure at these timepoints, causal effects at these timepoints can be unbiasedly estimated.

Methods for time-varying MR

- Multivariable MR (MVMR)
- G-estimation of structural nested mean model (SNMM)

Introduction

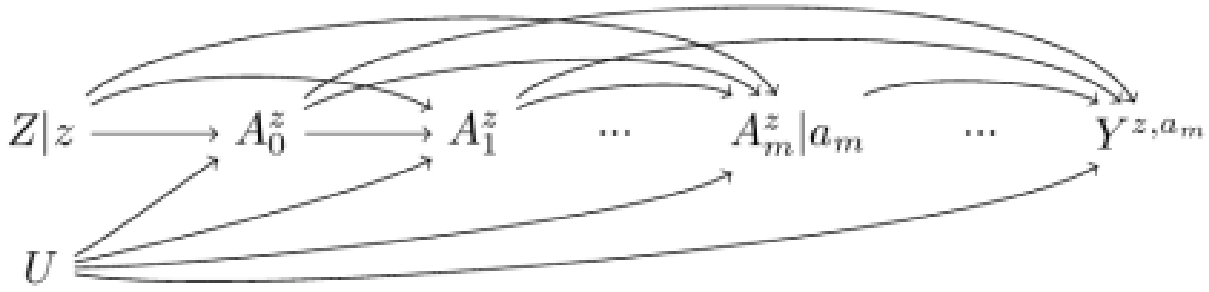
- instrumental condition (2) is violated with respect to the effect of Am on Y because Z has direct effects on the outcome Y through the exposure at time points other than m.



Definitions

- Three types of causal effects
  - the effect of exposure at a single time point on the outcome (point effect),
  - the effect of exposure during a period on the outcome (period effect),
  - the effect of exposure throughout the lifetime on the outcome (lifetime effect).

Point Exposure



- each component of the time-varying exposure other than Am is unaffected by the instrument (i.e., no arrow from Z into A_t when $t \neq m$) or does not affect the outcome through A_m (i.e., no arrow from A_t when $t \neq m$ to Y) $\quad E[Y^{a_m}] - E[Y^{a'_m}]$

A.1.2.1 Point effect

Suppose that we are interested in the causal effect of a time-varying exposure at age m on an outcome Y measured once at age $k > m$. That is, we are interested in identifying the following causal effect:

$$\mathrm{E}[Y^{a_m}] - \mathrm{E}[Y^{a'_m}]$$

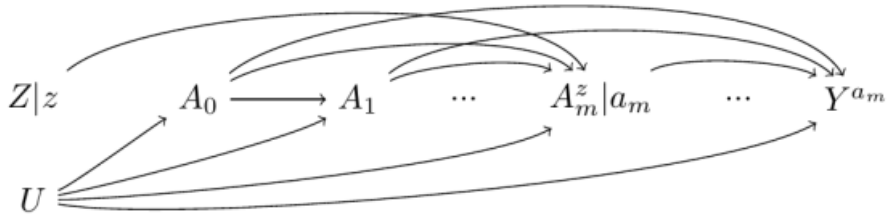
The instrumental conditions are:

1. $Z \perp\!\!\!\perp A_m$ does not hold; that is, there is a non-null association between Z and A_m
2. $Y_i^{z,a_m} = Y_i^{z',a_m} = Y_i^{a_m}$ for all z, z', all a_m, and all individuals i; that is, there is no direct effect of Z on Y
3. $Y^{z,a_m} \perp\!\!\!\perp Z$ for all z, a_m; that is, there are no common causes (or other sources of non-exchangeability) between the instrument and the outcome

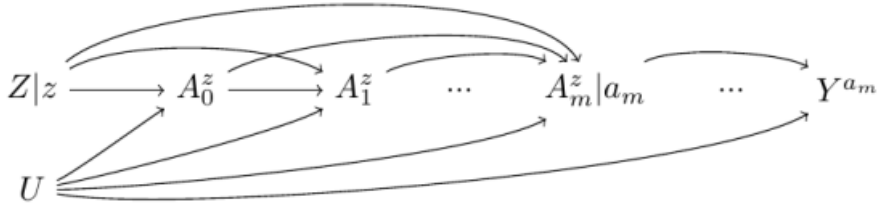
Point estimation assumption

However, by assuming no effect of Z on A_t or no direct effect of A_t on Y (i.e. not through A_m), where $t \neq m$, the second instrumental condition holds. For example:

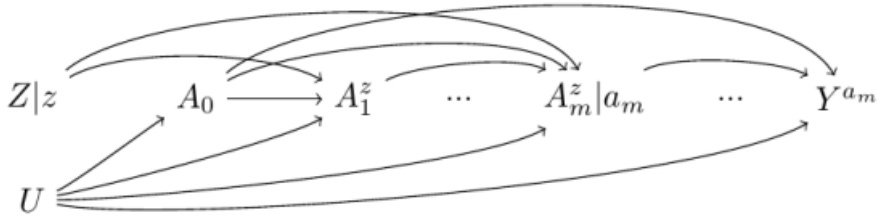
- We have removed the arrows from $\boldsymbol{Z}$ to $\boldsymbol{A_0}$ and from $\boldsymbol{Z}$ to $\boldsymbol{A_1}$ (thereby assuming no effect of the instrument on exposure at time 0 and time 1) in the following SWIG:



- We have removed the arrows from $\boldsymbol{A_0}$ to $\boldsymbol{Y^{a_m}}$ and from $\boldsymbol{A_1}$ to $\boldsymbol{Y^{a_m}}$ (thereby assuming no effect of the exposure at time 0 and time 1 on the outcome) in the following SWIG:



- We have removed the arrows from $\boldsymbol{Z}$ to $\boldsymbol{A_0}$ and from $\boldsymbol{A_1}$ to $\boldsymbol{Y^{a_m}}$ in the following SWIG:



For each point?

Now suppose that, for each individual in the study population, the time-varying exposure were measured at $p+1$ times: $m-p, \ \ldots \ , \ m-1, \ m$. If we conducted $p+1$ separate MR analyses, each using one of these exposure measurements, can we interpret the resulting MR estimates as an estimate of the point effect at each age? The answer is no, because we have, at best, a single instrument Z for all $p+1$ MR analyses. The answer would be yes if we had $p+1$ instruments, each satisfying the instrumental conditions for a distinct exposure time point a_h for $m-p \leq h \leq m$.

Period and Lifetime Exposure

- Generalized form $E[Y^{a_{m-p},\ldots,a_{m-1},a_m}] - E\left[Y^{a'_{m-p},\ldots,a'_{m-1},a'_m}\right]$
- To satisfy the second instrumental condition, each component of the time-varying exposure outside of the period $[m-p,\ldots,m-1,m]$ must be either unaffected by the instrument or affect the outcome only through affecting subsequent exposure at time points $m-p \to m$.
- First, suppose we have measured all relevant exposure time points during the period $[m-p,\ldots,m-1,m]$. Then, under the additional assumption of no interaction between the exposure at different time points, we can identify the controlled direct effects of each exposure time point during this period, $E[Y^{a_{m-p},\ldots,a_h,\ldots,a_m}] - E\left[Y^{a_{m-p},\ldots,a'_h,\ldots,a_m}\right]$

Period and Lifetime Exposure

- Generalized form

$$E\left[Y^{a_{m-p},\ldots,a_{m-1},a_m}\right] - E\left[Y^{a'_{m-p},\ldots,a'_{m-1},a'_m}\right]$$

A.2.1 Estimating average causal effects of time-varying exposures with multiple instruments under the assumption of no effect modification by the instrument or by prior treatment

Theorem. Under an IV model where $Z = (Z_1, Z_2)$, the average treatment effect $\mathrm{E}\left[Y^{a_0,a_1} - Y^{a'_0,a'_1}\right]$ is identifiable if the following assumptions hold:

Assumption 1. There is no additive effect modification for the effect of treatment A_0, A_1 on outcome Y by Z_1, by Z_2 or jointly by Z_1 and Z_2, conditional on exposure history; that is,

$$\begin{aligned}&\mathrm{E}\left[Y^{a_0,a_1} - Y^{a'_0,a'_1} | Z_1, Z_2, A_0, A_1\right]\\ =\ &\mathrm{E}\left[Y^{a_0,a_1} - Y^{a'_0,a'_1} | Z_1, A_0, A_1\right]\\ =\ &\mathrm{E}\left[Y^{a_0,a_1} - Y^{a'_0,a'_1} | Z_2, A_0, A_1\right]\\ =\ &\mathrm{E}\left[Y^{a_0,a_1} - Y^{a'_0,a'_1} | A_0, A_1\right]\end{aligned}$$

Assumption 2. There is no interaction between treatment time points, conditional on instrument and exposure history; that is,

$$\begin{aligned}&\mathrm{E}[Y^{a_0,a_1=1} - Y^{a_0,a_1=0} | Z_1, Z_2, A_0, A_1]\\ =\ &\mathrm{E}\left[Y^{a'_0,a_1=1} - Y^{a'_0,a_1=0} | Z_1, Z_2, A_0, A_1\right]\end{aligned}$$

Assumption 3. The relative change in the association between the instrument and exposure is not constant between instruments; that is,

$$\frac{\mathrm{E}[A_1|Z_1=1] - \mathrm{E}[A_1|Z_1=0]}{\mathrm{E}[A_0|Z_1=1] - \mathrm{E}[A_0|Z_1=0]} \neq \frac{\mathrm{E}[A_1|Z_2=1] - \mathrm{E}[A_1|Z_2=0]}{\mathrm{E}[A_0|Z_2=1] - \mathrm{E}[A_0|Z_2=0]}$$

Note: an extension of this assumption to more than 2 time points is available in A.2.2

Period and Lifetime Exposure

- Shifting trajectories $E[Y^{a_{m-p}+1,\ldots,a_{m-1}+1,a_m+1}] - E[Y^{a_{m-p},\ldots,a_{m-1},a_m}]$
  - one measurement of the exposure:
    - the Z— A_t association must be constant on the additive scale for $m-p \leq t \leq m$, or, for a dichotomous instrument Z, $E[A_t|Z=1] - E[A_t|Z=0]$ must be the same for all t in this period.

A.2.4 Estimating the effect of a shift in the exposure trajectory using a single instrument

Theorem. The average treatment effect $\mathrm{E}[Y^{a_0+1,a_1+1} - Y^{a_0,a_1}]$ is identifiable with a single instrument Z under an IV model where the three instrumental conditions are met, assumptions (1) and (2) hold, and *either* assumption (4) or assumption (5) hold:

Assumption 4. The association between Z and A_t is constant for $t = 0,1$; that is,

$$\mathrm{E}[A_0|Z=1] - \mathrm{E}[A_0|Z=0] = \mathrm{E}[A_1|Z=1] - \mathrm{E}[A_1|Z=0]$$

Association 5. The effect of A_t on outcome Y is constant for $t = 1,2$; that is,

$$\mathrm{E}[Y^{a_0,a_1} - Y^{0,a_1}] = \mathrm{E}[Y^{a_0,a_1} - Y^{a_0,0}]$$

Period and Lifetime Exposure

- Shifting trajectories $E[Y^{a_{m-p}+1,\ldots,a_{m-1}+1,a_m+1}] - E[Y^{a_{m-p},\ldots,a_{m-1},a_m}]$
  - multiple (not all) measurements of the exposure:
    - we can identify the effect of shifting the exposure trajectory across multiple time points within the period of interest if the exposure at some of those time points are unmeasured and the instrument–exposure association remains constant over those time points.
    - In general, given the period $[m-p,\ldots,m-1,m]$ with $p+1$ relevant exposure time points, of which $j < p+1$ are measured and $p+1-j$ are unmeasured, we can identify some period effects if the magnitude of the instrument–exposure association at each $p-j$ unmeasured exposure time point is equal to the magnitude of the instrument–exposure association for at least one of the j measured exposure time points.

Summary

TABLE 1. - Possible Causal Estimands in Mendelian Randomization Studies of time-varying Exposures and Their Identifiability Assumptions

	Estimand (on the Additive Scale)	Assumptions Required for Identification	
		With a Single Exposure Measurement	With Multiple Exposure Measurements
Point effect	Difference in mean counterfactual outcomes had everyone received exposure a at time m versus had everyone received exposure a' at time m: $\mathrm{E}\left[Y^{a_m}\right] - \mathrm{E}\left[Y^{a'_m}\right]$	Instrumental conditions hold for the proposed instrument for exposure at time m. For instrumental condition 2 to hold, each component of the time-varying exposure other than at time m must be unaffected by the instrument or have no effect on the outcome[a]	N/A
Period effect[b]		Instrumental conditions hold for the exposure, as a whole, between times $m-p$ and m (i.e., each component of the time-varying exposure outside of this time period is unaffected by the instrument or has no effect on the outcome)	
Generalized form	Difference in mean counterfactual outcomes had everyone received the exposure trajectory $(a_{m-p}, \ldots, a_{m-1}, a_m)$ between times $m-p$ and m versus had everyone received the exposure trajectory $(a'_{m-p}, \ldots, a'_{m-1}, a'_m)$ between times $m-p$ and m: $\mathrm{E}\left[Y^{a_{m-p}\ldots,a_{m-1},a_m}\right] - \mathrm{E}\left[Y^{a'_{m-p}\ldots,a'_{m-1},a'_m}\right]$	No realistic assumptions for identification in MR studies	All relevant exposure time points have been measured and at least as many instruments as the number of exposure time points are available. The association between instrument–exposure must vary between time points for at least one instrument No realistic assumptions for identification in MR studies if not all relevant exposure time points have been measured
Shift in exposure trajectories	Difference in mean counterfactual outcomes had everyone received the exposure trajectory $(a_{m-p}, \ldots, a_{m-1}, a_m)$ between times $m-p$ and m versus had everyone received the same exposure trajectory after shifting the exposure by one unit across the entire period $\mathrm{E}\left[Y^{a_{m-p}+1,\ldots,\ a_{m-1}+1,\ a_m+1}\right] - \mathrm{E}\left[Y^{a_{m-p}\ldots,\ a_{m-1},a_m}\right]$	1. The association between the instrument and the exposure is constant on the additive scale between times $m-p$ and m[c] 2. Instrumental conditions hold for the exposure trajectory between times $m-p$ and m. For instrumental condition 2 to hold, each component of the time-varying exposure outside of this time period must be unaffected by the instrument or have no effect on the outcome[c]	If all relevant exposure time points have been measured and there are a sufficient number of instruments, no additional assumptions are needed. If only a subset of relevant exposure time points have been measured, the instrument–exposure association during unmeasured time points must be the same as the instrument–exposure association for at least one of the measured time points

Structural mean models

- SMM for the point effect at time m
  $E[Y^{a_m} - Y^0 | A_m = a_m, Z] = \gamma(Z, a_m; \psi_m) = \psi_{m,1} a_m + \psi_{m,2} a_m Z$
- The parameters of this saturated model cannot be identified with IV estimation.

$$\gamma(Z, a_m; \psi_m) = \gamma(a_m; \psi_m)$$
$$E[Y^{a_m} - Y^0 | A_m = a_m, Z] = \psi_{m,1} a_m$$

Structural mean models

- SMM for the period effect between $m-p$ and m

$$E\left[Y^{a_{m-p},\ldots,a_{m-1},a_m} - Y^{\bar{0}} \mid A_{m-p} = a_{m-p}, \ldots, A_{m-1} = a_{m-1}, A_m = a_m, Z \right]$$
$$= \gamma(a_{m-p}, \ldots, a_{m-1}, a_m; \psi)$$
$$\bar{0} = (a_{m-p} = 0, \ldots, a_{m-1} = 0, a_m = 0)$$

- Structural nested mean model: it represents a series of nested equations, where each equation corresponds to an exposure time point.

Structural mean models

- With one measurement of the exposure at time h where $m - p \leq h \leq m$ and under the assumption that the instrument–exposure association is constant over this period, the period effect of shifting the exposure trajectory shift can be represented by ψ in the SMM.

$$E\left[Y^{a_{m-p}=a,\ldots,a_{m-1}=a,a_m=a} - Y^{\bar{0}} \mid A_{m-p} = a_{m-p}, \ldots, A_{m-1} = a_{m-1}, A_m = a_m, Z \right] = \psi a$$

- With up to $p + 1$ exposure measurements during the period $[m - p, \ldots, m - 1, m]$, the model expands to include up to $p + 1$ ψ parameters. Each ψ parameter corresponds to the controlled direct effect of its corresponding exposure time point.

$$E\left[Y^{a_{m-p},\ldots,a_{m-1},a_m} - Y^{\bar{0}} \mid A_{m-p} = a_{m-p}, \ldots, A_{m-1} = a_{m-1}, A_m = a_m, Z \right] = \psi_{m-p} a_{m-p} + \cdots + \psi_{m-1} a_{m-1} + \psi_m a_m$$

g-Estimation

- Point effect

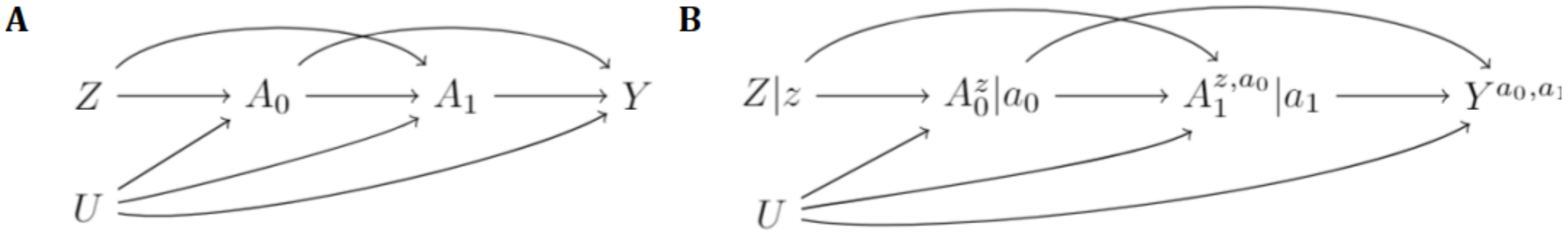
$$\hat{\psi}_{m,1} = \frac{\sum_{i=1}^{n} Y_i(Z_i - E(Z))}{\sum_{i=1}^{n} A_{m,i}(Z_i - E(Z))}$$

- Period or lifetime effect

$$\widehat{\boldsymbol{\psi}} = \boldsymbol{Y}'\big(\boldsymbol{Z} - E(\boldsymbol{Z})\big)\big(\boldsymbol{Z} - E(\boldsymbol{Z})\big)'\boldsymbol{A}_{m-p,\ldots,m}\left[\boldsymbol{A}'_{m-p,\ldots,m}\big(\boldsymbol{Z} - E(\boldsymbol{Z})\big)'\boldsymbol{A}_{m-p,\ldots,m}\right]^{-1}$$

g-estimation of SMM

- Exposure with two time points



Condition 1. $Z \perp\!\!\!\perp A_0, A_1$ does not hold; that is, there is a non-null association between the instrument and the exposure at both time points.

Condition 2. $Y_i^{z,a_0,a_1} = Y_i^{z',a_0,a_1} = Y_i^{a_0,a_1}$ for all z, z', a_0, a_1, and all individuals i; that is, there is no direct effect of the instrument on the outcome.

Condition 3. $Y^{z,a_0,a_1} \perp\!\!\!\perp Z$ for all z, a_0, a_1; that is, there are no common causes (or other sources of non-exchangeability) between the instrument and the outcome

g-estimation of SMM

- Saturated structural nested mean models (SNMMs)

$$\text{For time } t=0: \quad \mathrm{E}[Y^{a_0,a_1=0} - Y^{a_0=0,a_1=0} | Z=z, A_0^z = a_0,] = a_0(\beta_{01} + \beta_{02} z)$$
$$\text{For time } t=1: \quad \mathrm{E}\left[Y^{a_0,a_1} - Y^{a_0,a_1=0} \middle| Z=z, A_0^z = a_0, A_1^{z,a_0} = a_1\right] = a_1(\beta_{11} + \beta_{12} z + \beta_{13} a_0 + \beta_{14} a_0 z)$$

- rank-preserving structural nested model (SNM)
  - assumes the effects of treatment are the same for every individual
  - g-estimates of ψ from the rank-preserving model are consistent for the parameters β of the mean model (JM Robins, 1994)

$$Y_i^{a_0,0} - Y_i^{0,0} = \psi_{01} a_0 + \psi_{02} a_0 z$$
$$Y_i^{a_0,a_1} - Y_i^{a_0,0} = \psi_{11} a_1 + \psi_{12} a_1 z + \psi_{13} a_1 a_0 + \psi_{14} a_1 a_0 z$$

g-estimation of SMM

- Consistency: link the rank-preserving models to the observed data

$$Y^{A_0,0} = Y - (\psi_{11}A + \psi_{12}A_1Z + \psi_{13}A_1A_0 + \psi_{14}A_1A_0Z)$$
$$Y^{0,0} = Y^{A_0,0} - (\psi_{01}A_0 + \psi_{02}A_0Z)$$

$$Y^{A_0,0} = Y^{a_0,0}, \text{ if } A_0 = a_0$$
$$Y = Y^{a_0,a_1}, \text{ if } A_0 = a_0, A_1 = a_1$$

- candidate counterfactuals:

$$H_1(\psi^\dagger) = Y - (\psi_{11}^\dagger A_1 + \psi_{12}^\dagger A_1 z + \psi_{13}^\dagger A_1 a_0 + \psi_{14}^\dagger A_1 A_0 Z)$$
$$H_0(\psi^\dagger) = H_1(\psi^\dagger) - (\psi_{01}A_0 + \psi_{02}A_0Z)$$

When $\psi^\dagger = \psi$, the candidate counterfactuals, $H_0(\psi^\dagger)$ and $H_1(\psi^\dagger)$ are equal to the true counterfactuals $Y_{a0=0,a1=0}$ and $Y_{A0,a1=0}$

- Nested model

$$H_0(\psi^\dagger) = Y - (\psi_{11}^\dagger A_1 + \psi_{12}^\dagger A_1 Z + \psi_{13}^\dagger A_1 A_0 + \psi_{14}^\dagger A_1 A_0 Z) - (\psi_{01}A_0 + \psi_{02}A_0Z)$$

g-estimation of SMM

- Exchangeability: the g-estimate of ψ (and therefore β) is the value $\psi^{\dagger}$ that results in the estimate of α_1 that is closest to 0

$$\operatorname{logit}\Pr\left[Z=1\middle|H_0\left(\psi^{\dagger}\right)\right]=\alpha_0+\alpha_1 H_0\left(\psi^{\dagger}\right)$$

$$\sum_{i=1}^{n} H_{0i}\left(\psi^{\dagger}\right)\left(Z_i-\mathrm{E}[Z]\right)=0$$

$$\sum_{i=1}^{n}\left[Y_i-\left(\psi_{11}^{\dagger}A_{1i}+\psi_{12}^{\dagger}A_{1i}Z_i+\psi_{13}^{\dagger}A_{1i}A_{0i}+\psi_{14}^{\dagger}A_{1i}A_{0i}Z_i\right)-\left(\psi_{01}^{\dagger}A_{0i}+\psi_{02}^{\dagger}A_{0i}Z_i\right)\right]\left(Z_i-\mathrm{E}[Z]\right)=0$$

Unidentifiable: we have a single equation with six unknown parameters.

g-estimation of SMM

- Identifiability:

Assumption 1. There is no additive effect modification for the effect of treatment A_0, A_1 on outcome Y by Z_1, by Z_2 or jointly by Z_1 and Z_2, conditional on exposure history; that is,

$$\begin{aligned}&\mathrm{E}\left[Y^{a_0,a_1} - Y^{a_0',a_1'} | Z_1, Z_2, A_0, A_1\right]\\ =\ &\mathrm{E}\left[Y^{a_0,a_1} - Y^{a_0',a_1'} | Z_1, A_0, A_1\right]\\ =\ &\mathrm{E}\left[Y^{a_0,a_1} - Y^{a_0',a_1'} | Z_2, A_0, A_1\right]\\ =\ &\mathrm{E}\left[Y^{a_0,a_1} - Y^{a_0',a_1'} | A_0, A_1\right]\end{aligned}$$

Assumption 2. There is no interaction between treatment time points, conditional on instrument and exposure history; that is,

$$\begin{aligned}&\mathrm{E}[Y^{a_0,a_1=1} - Y^{a_0,a_1=0} | Z_1, Z_2, A_0, A_1]\\ =\ &\mathrm{E}\left[Y^{a_0',a_1=1} - Y^{a_0',a_1=0} | Z_1, Z_2, A_0, A_1\right]\end{aligned}$$

Assumption 3. The relative change in the association between the instrument and exposure is not constant between instruments; that is,

$$\frac{\mathrm{E}[A_1|Z_1=1] - \mathrm{E}[A_1|Z_1=0]}{\mathrm{E}[A_0|Z_1=1] - \mathrm{E}[A_0|Z_1=0]} \neq \frac{\mathrm{E}[A_1|Z_2=1] - \mathrm{E}[A_1|Z_2=0]}{\mathrm{E}[A_0|Z_2=1] - \mathrm{E}[A_0|Z_2=0]}$$

g-estimation of SMM

- no interaction between A and Z and t: simplify SMM and corresponding rank-preserved model

$$\text{For time } t=0: \quad \mathrm{E}\left[Y^{a_0,0} - Y^{0,0} \middle| Z_1 = z_1, Z_2 = z_2, A_0^{z_1,z_2} = a_0, \right] = \beta_{01} a_0$$
$$\text{For time } t=1: \quad \mathrm{E}\left[Y^{a_0,a_1} - Y^{a_0,0} \middle| Z_1 = z_1, Z_2 = z_2, A_0^{z_1,z_2} = a_0, A_1^{z_1,z_2,a_0} = a_1\right] = \beta_{11} a_1$$

- Independence

$$Z_1 \perp\!\!\!\perp Y^{a_0,a_1} \text{ and } Z_2 \perp\!\!\!\perp Y^{a_0,a_1}$$

$$\operatorname{logit} \Pr\left[Z_1 = 1 \middle| H_0(\psi^\dagger)\right] = \alpha_{10} + \alpha_{11} H_0(\psi^\dagger)$$
$$\operatorname{logit} \Pr\left[Z_2 = 1 \middle| H_0(\psi^\dagger)\right] = \alpha_{20} + \alpha_{21} H_0(\psi^\dagger)$$

$$\sum_{i=1}^{n} \left(Y_i - \psi_{01}^\dagger A_{0_i} - \psi_{11}^\dagger A_{1i}\right)\left(Z_{1i} - \mathrm{E}[Z_1]\right) = 0$$
$$\sum_{i=1}^{n} \left(Y_i - \psi_{01}^\dagger A_{0i} - \psi_{11}^\dagger A_{1i}\right)\left(Z_{2i} - \mathrm{E}[Z_2]\right) = 0$$

g-estimation of SMM

- When size of T equals to size of Z:

$$\sum_{i=1}^{n}\left(Y_i-\psi_{01}^{\dagger}A_{0_i}-\psi_{11}^{\dagger}A_{1i}\right)\left(Z_{1i}-\mathrm{E}[Z_1]\right)=0$$

$$\sum_{i=1}^{n}\left(Y_i-\psi_{01}^{\dagger}A_{0i}-\psi_{11}^{\dagger}A_{1i}\right)\left(Z_{2i}-\mathrm{E}[Z_2]\right)=0$$

$$0=\left(\boldsymbol{Y}-\boldsymbol{A}\widehat{\boldsymbol{\psi}}'\right)'\left(\boldsymbol{Z}-\widehat{\mathrm{E}}[\boldsymbol{Z}]\right)$$

$$0=\left(\boldsymbol{Y}-\boldsymbol{A}\widehat{\boldsymbol{\psi}}'\right)'\left(\boldsymbol{Z}-\widehat{\mathrm{E}}[\boldsymbol{Z}]\right)$$
$$0=\boldsymbol{Y}'\left(\boldsymbol{Z}-\widehat{\mathrm{E}}[\boldsymbol{Z}]\right)-\widehat{\boldsymbol{\psi}}\boldsymbol{A}'\left(\boldsymbol{Z}-\widehat{\mathrm{E}}[\boldsymbol{Z}]\right)$$
$$\widehat{\boldsymbol{\psi}}\boldsymbol{A}'\left(\boldsymbol{Z}-\widehat{\mathrm{E}}[\boldsymbol{Z}]\right)=\boldsymbol{Y}'\left(\boldsymbol{Z}-\widehat{\mathrm{E}}[\boldsymbol{Z}]\right)$$
$$\widehat{\boldsymbol{\psi}}\boldsymbol{A}'\left(\boldsymbol{Z}-\widehat{\mathrm{E}}[\boldsymbol{Z}]\right)\left(\boldsymbol{Z}-\widehat{\mathrm{E}}[\boldsymbol{Z}]\right)'\boldsymbol{A}=\boldsymbol{Y}'\left(\boldsymbol{Z}-\widehat{\mathrm{E}}[\boldsymbol{Z}]\right)\left(\boldsymbol{Z}-\widehat{\mathrm{E}}[\boldsymbol{Z}]\right)'\boldsymbol{A}$$
$$\widehat{\boldsymbol{\psi}}=\boldsymbol{Y}'\left(\boldsymbol{Z}-\widehat{\mathrm{E}}[\boldsymbol{Z}]\right)\left(\boldsymbol{Z}-\widehat{\mathrm{E}}[\boldsymbol{Z}]\right)'\boldsymbol{A}\left(\boldsymbol{A}'\left(\boldsymbol{Z}-\widehat{\mathrm{E}}[\boldsymbol{Z}]\right)\left(\boldsymbol{A}'\left(\boldsymbol{Z}-\widehat{\mathrm{E}}[\boldsymbol{Z}]\right)'\boldsymbol{A}\right)^{-1}\right.$$

- Over-identified: GMM - minimize $\left(\boldsymbol{Y}-\boldsymbol{A}\widehat{\boldsymbol{\psi}}'\right)'\left(\boldsymbol{Z}-\widehat{\mathrm{E}}[\boldsymbol{Z}]\right)$

$$\mathrm{E}\left[Y^{a_{m-p},\ldots,a_{m-1},a_m}-Y^{\bar{0}}\mid A_{m-p}=a_{m-p},\ldots,A_{m-1}=a_{m-1},A_m=a_m,Z\right]$$
$$=\psi_{m-p}a_{m-p}+\ldots+\psi_m a_m$$

shifting trajectory 1 unit: $\sum\boldsymbol{\psi}$

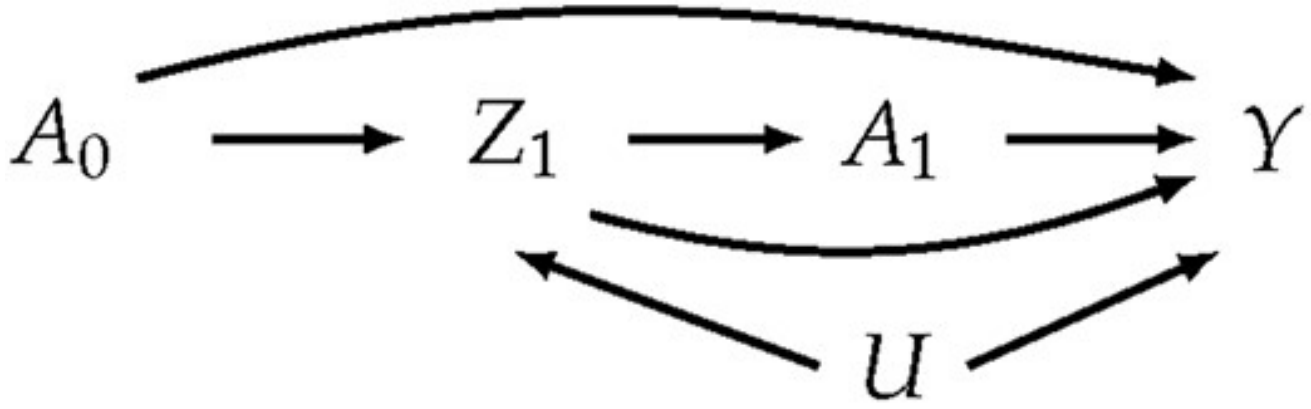
Bootstrapping confidence interval and SE

Supplementary: Robins' G-methods

- g-formula
- Marginal structural models: inverse probability weighting
- g-estimation of structure nested models

Example: sequential treatments

- Treatment on HIV is measured at baseline (A_0) and once during follow up (A_1)
- The sole covariate is elevated HIV viral load ($Z = 1$ for those with > 200 copies/ml, $Z = 0$ otherwise), which is constant by design at baseline ($Z_0 = 1$) and measured once during follow up just prior to the second treatment (Z_1).
- Outcome: CD4



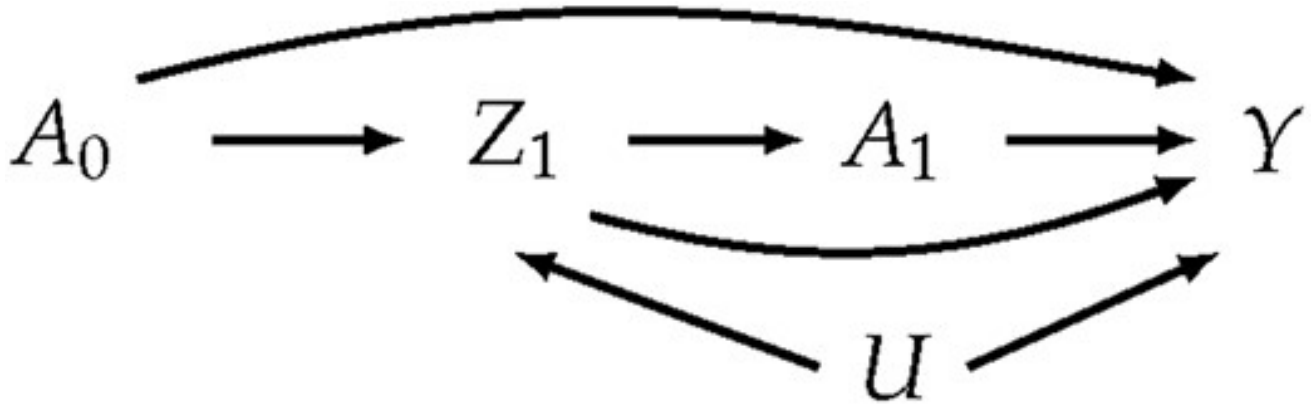
Conditions for identification

$$E[Y^{a_0,a_1}|A_0 = 1] = E[Y^{a_0,a_1}|A_0 = 0]$$

$$E[Y^{a_0,a_1}|A_0 = a_0, Z_1, A_1 = 1] = E[Y^{a_0,a_1}|A_0 = a_0, Z_1, A_1 = 0]$$

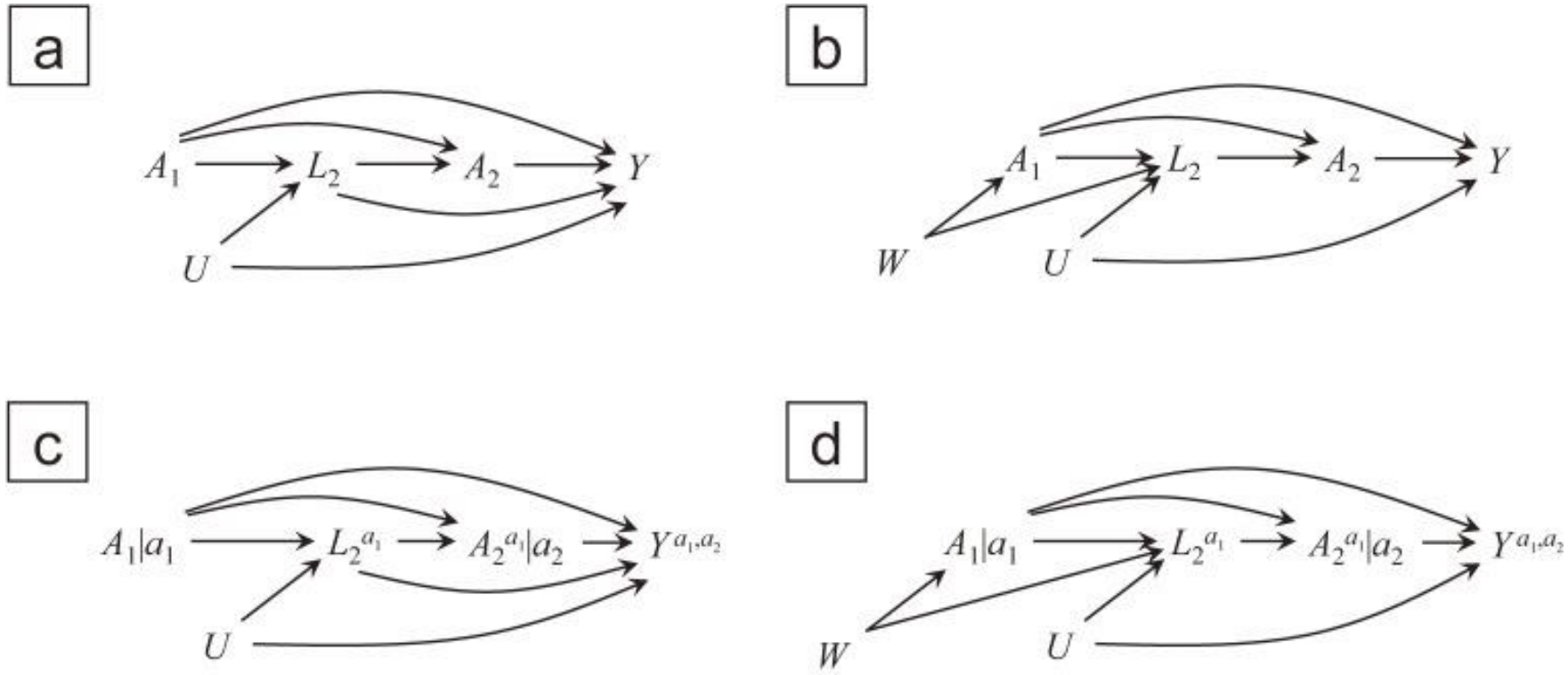
$$Y^{a_0,a_1} \perp A_0$$

$$Y^{a_0,a_1}|Z_1, A_0 \perp A_1$$



SWIGs

- Single World Intervention Graphs



Assumptions

- Counterfactual consistency

$$E(Y|A_0 = a_0, A_1 = a_1) = E(Y^{a_0,a_1}|A_0 = a_0, A_1 = a_1)$$

- Exchangeability

$$E[Y^{a_0,a_1}|A_0 = 1] = E[Y^{a_0,a_1}|A_0 = 0]$$

$$E[Y^{a_0,a_1}|A_0 = a_0, Z_1, A_1 = 1] = E[Y^{a_0,a_1}|A_0 = a_0, Z_1, A_1 = 0]$$

- Positivity

$$0 < P(A_1 = 1|Z_1 = z_1, A_0 = a_0) < 1$$

$$0 < P(A_0 = 1) < 1$$

g-formula

$$
\begin{aligned}
E(Y^{a_0,a_1}) &= E\{E(Y^{a_0,a_1} \mid A_0)\} \\
&= E\{E(Y^{a_0,a_1} \mid A_0 = a_0)\} \\
&= E[E\{E(Y^{a_0,a_1} \mid A_0 = a_0, Z_1, A_1) \mid A_0 = a_0\}] \\
&= E[E\{E(Y^{a_0,a_1} \mid A_0 = a_0, Z_1, A_1 = a_1) \mid A_0 = a_0\}] \\
&= E[E\{E(Y \mid A_0 = a_0, Z_1, A_1 = a_1) \mid A_0 = a_0\}] \\
&= \sum_{z_1} E(Y \mid A_0 = a_0, Z_1 = z_1, A_1 = a_1) P(Z_1 = z_1 \mid A_0 = a_0)
\end{aligned}
$$

Marginal structural models

- Saturated

$$E[Y^{a_0,a_1}] = \beta_0 + \psi_0 a_0 + \psi_1 a_1 + \psi_2 a_0 a_1$$

$$\beta_0 = E[Y^{0,0}]$$

$$\psi = E(Y^{1,1} - Y^{0,0}) = \psi_0 + \psi_1 + \psi_2$$

IPW of marginal structural models

$$E(Y^{a_0,a_1}) = E\left\{\frac{I(A_0 = a_0, A_1 = a_1)Y}{P(A_1 = a_1 \mid Z_1, A_0 = a_0)P(A_0 = a_0)}\right\},$$

$$\begin{aligned}
&E\left\{\frac{I(A_0 = a_0, A_1 = a_1)Y}{P(A_1 = a_1 \mid Z_1, A_0 = a_0)P(A_0 = a_0)}\right\} \\
&= E\left\{\frac{I(A_0 = a_0)I(A_1 = a_1)E(Y \mid A_0 = a_0, Z_1, A_1 = a_1)}{P(A_1 = a_1 \mid Z_1, A_0 = a_0)P(A_0 = a_0)}\right\} \\
&= E\left\{\frac{I(A_0 = a_0)P(A_1 = a_1 \mid Z_1, A_0 = a_0)E(Y \mid A_0 = a_0, Z_1, A_1 = a_1)}{P(A_1 = a_1 \mid Z_1, A_0 = a_0)P(A_0 = a_0)}\right\} \\
&= E\left\{\frac{I(A_0 = a_0)E(Y \mid A_0 = a_0, Z_1, A_1 = a_1)}{P(A_0 = a_0)}\right\} \\
&= E\left[\frac{I(A_0 = a_0)E\{E(Y \mid A_0 = a_0, Z_1, A_1 = a_1) \mid A_0 = a_0\}}{P(A_0 = a_0)}\right] \\
&= E\{E(Y \mid A_0 = a_0, Z_1, A_1 = a_1) \mid A_0 = a_0\}
\end{aligned}$$

equals the g-formula

Structural nested model

$$E(Y^{a_0,a_1} - Y^{a_0,0}|A_0 = a_0, Z_1 = z_1, A_1 = a_1)$$
$$= a_1(\psi_1 + \psi_2 a_0 + \psi_3 z_1 + \psi_4 a_0 z_1)$$
$$E(Y^{a_0,0} - Y^{0,0}|A_0 = a_0) = \psi_0 a_0$$

To simplify our exposition, we set $(\psi_3, \psi_4) = (0,0)$ in our data example,

$$0 = \mathrm{Cov}(Y^{a_0,0}, A_1|Z_1, A_0)$$
$$= \mathrm{Cov}(Y^{0,0}, A_0)$$

$$0 = \mathrm{Cov}\{Y - A_1(\psi_1 + \psi_2 A_0), A_1|Z_1, A_0\}$$
$$= \mathrm{Cov}\{Y - A_1(\psi_1 + \psi_2 A_0) - \psi_0 A_0, A_0\}.$$

$$\hat{\psi}_{1_{GE}} = \frac{\hat{E}[(1 - A_0)Y\{A_1 - \hat{E}(A_1|Z_1, A_0)\}]}{\hat{E}[(1 - A_0)A_1\{A_1 - \hat{E}(A_1|Z_1, A_0)\}]}$$

$$\hat{\psi}_{1_{GE}} + \hat{\psi}_{2_{GE}} = \frac{\hat{E}[A_0 Y\{A_1 - \hat{E}(A_1|Z_1, A_0)\}]}{\hat{E}[A_0 A_1\{A_1 - \hat{E}(A_1|Z_1, A_0)\}]}$$

$$\hat{\psi}_{0_{GE}} = \frac{\hat{E}[\tilde{Y}\{A_0 - \hat{E}(A_0)\}]}{\hat{E}[A_0\{A_0 - \hat{E}(A_0)\}]}.$$

Summary

- Identifiable assumptions
- Interpretations of estimates
- Practical utility?

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Thanks for listening!