

4. Results

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Results

Simulation Study

Data Simulation

Data were successfully simulated as intended. A selection of representative visualisations are presented in Figure 1. Full details of testing used to validate model outputs from parameter inputs are given in Appendix ???. The F -statistic calculated from simulated instruments was >10 , indicating that they were sufficiently strongly associated with exposure to meet the relevance assumption of **instrumental variable (IV)** analysis (Tables 1 and 2).

Analysis of Simulated Data

No Causal Effect

Across all cases where no causal effect was present (Table 1), the mean rate of reporting a causal effect (i.e. false positive rate) for MR-Hevo was 0.64% versus 2% for **weighted median estimator (WME)**. Of the 8 combinations of scenarios and parameters, MR-Hevo exhibited a favourable false positive rate versus **WME** in 8 (100%). For both MR-Hevo and **WME** methods, causal report rate generally increased with an increasing proportion of invalid instruments, and also as assumption violations progressively presented greater data variability and bias across scenarios 1 to 3.

The mean causal effect estimate (mean reported 95% **confidence interval (CI)**s) across all cases was 0.044 (-0.13 to 0.23) for MR-Hevo and 0.025 (-0.15 to 0.2) for **WME**. The mean (range) **standard error (SE)** of causal effect estimates across all cases was 0.0015 (0.001 to 0.002) for MR-Hevo and 0.088 (0.078 to 0.094). For both MR-Hevo and **WME** methods, causal effect estimates, width of **CI**s and **SE** all tended to increase slightly both with an increasing proportion of invalid instruments, and as assumption violations progressively presented greater data variability and bias across scenarios 1 to 3.

Positive Causal Effect

Across all cases where positive causal effect was present (Table 2), the mean rate of reporting a causal effect (i.e. sensitivity) for MR-Hevo was 19% versus 19% for **WME**. Of the 12 combinations of scenarios and parameters, MR-Hevo exhibited a favourable sensitivity versus **WME** in 5 (42%). For both MR-Hevo and **WME** methods, causal report rate generally increased with an increasing proportion of invalid instruments, and also as assumption violations progressively presented greater data variability and bias across scenarios 1 to 3.

The mean causal effect estimate (mean reported 95% **CI**s) across all cases was 0.14 (-0.04 to 0.34) for MR-Hevo and 0.11 (-0.063 to 0.29) for **WME**. The mean (range) **SE** of causal effect estimates across all cases was 0.0015 (0.001 to 0.002) for MR-Hevo and 0.09 (0.079 to 0.1). For both MR-Hevo and **WME** methods, causal effect estimates, width of **CI**s and **SE** all tended to increase slightly both with an increasing proportion of invalid instruments, and as assumption violations progressively presented greater data variability and bias across scenarios 1 to 3.

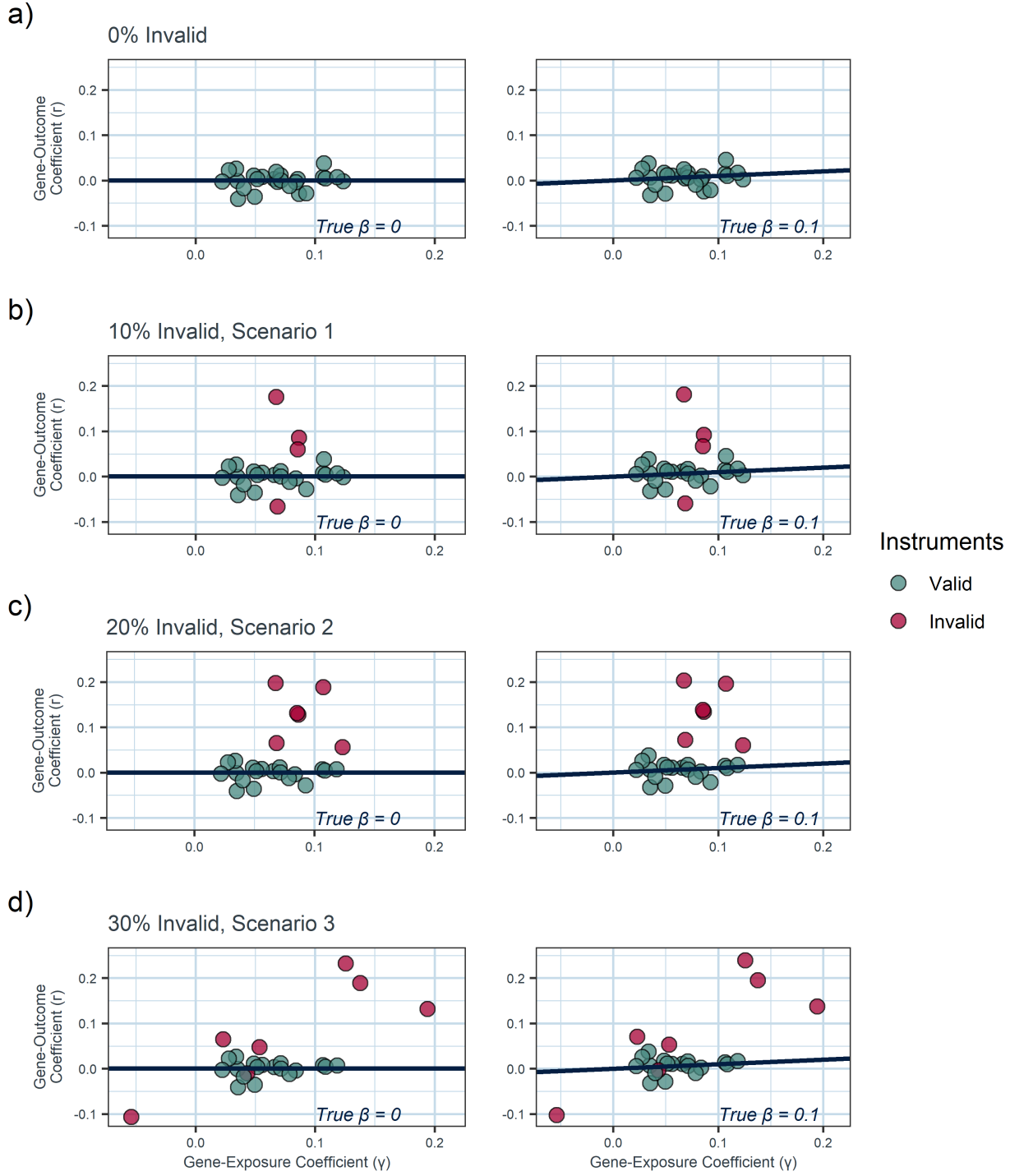


Figure 1: Plots of a representative group of simulated datasets; all simulate genetic instruments from the same index from the same random seed. Left and right columns demonstrate null and positive true causal effects, respectively. The scenario and the proportion of invalid (i.e. pleiotropic) genetic instruments changes with each row. a) 10% of instruments invalid, Scenario 1: balanced pleiotropy introduces noise around the causal effect. b) 20% of instruments invalid, Scenario 2: directional pleiotropy biases in the direction of the invalid instruments. c) 30% of instruments invalid, Scenario 3: directional pleiotropy and InSIDE assumption violation strongly biases towards a positive effect estimate.

Tables

Table 1: Summary of 1,000 simulated Mendelian randomisation studies per combination of scenario and parameters, all with null causal effect

N	Invalid IVs	F	R ²	Weighted			MR				
				Median			Hevo				
				Mean Estimate (Mean SE)	Mean 95% CI	Causal Report Rate	Mean Estimate (Mean SE)	Mean 95% CI	Causal Report Rate		
Scenario 1: Balanced pleiotropy, InSIDE assumption satisfied											
10,000	0%	11.7	2.8%	0.001 (0.078)	-0.15 to 0.15	0.2%	0.000	(0.001)	-0.12 to 0.12	0%	
10,000	10%	11.7	2.8%	0.026 (0.086)	-0.14 to 0.19	1.5%	0.032	(0.001)	-0.13 to 0.2	0%	
10,000	20%	11.7	2.8%	0.022 (0.092)	-0.16 to 0.2	2%	0.037	(0.002)	-0.17 to 0.25	0%	
10,000	30%	11.7	2.8%	0.014 (0.093)	-0.17 to 0.2	1.6%	0.022	(0.002)	-0.2 to 0.25	0%	
Scenario 2: Directional pleiotropy, InSIDE assumption satisfied											
10,000	0%	11.7	2.8%	0.001 (0.078)	-0.15 to 0.15	0.3%	0.000	(0.001)	-0.12 to 0.12	0%	
10,000	10%	11.7	2.8%	0.020 (0.087)	-0.15 to 0.19	0.8%	0.039	(0.001)	-0.13 to 0.22	0%	
10,000	20%	11.7	2.8%	0.050 (0.093)	-0.13 to 0.23	4.1%	0.098	(0.002)	-0.11 to 0.33	1.5%	
10,000	30%	11.7	2.8%	0.066 (0.094)	-0.12 to 0.25	5.8%	0.126	(0.002)	-0.09 to 0.38	3.6%	
Scenario 3: Directional pleiotropy, InSIDE assumption not satisfied											
10,000	0%	11.7	2.8%	0.001 (0.078)	-0.15 to 0.15	0.2%	0.000	(0.001)	-0.12 to 0.12	0%	
10,000	10%	13.7	3.3%	0.077 (0.087)	-0.09 to 0.25	8%	0.044	(0.001)	-0.12 to 0.21	0.1%	
10,000	20%	14.9	3.6%	0.144 (0.099)	-0.05 to 0.34	24.7%	0.107	(0.002)	-0.1 to 0.35	1.3%	
10,000	30%	12.8	3.1%	0.103 (0.097)	-0.09 to 0.29	11.9%	0.102	(0.002)	-0.11 to 0.36	0.6%	

CI: Confidence Interval, IV: Instrumental Variable, SE: Standard Error. Null Causal Effect ($\beta = 0$)

Table 2: Summary of 1,000 simulated Mendelian randomisation studies per combination of scenario and parameters, all with positive causal effect

N	Invalid IVs	F	R ²	Weighted Median			MR Hevo				
				Mean Estimate	Mean	Causal	Mean Estimate	Mean	Causal		
				(Mean SE)	95% CI	Report Rate	(Mean SE)	95% CI	Report Rate		
Scenario 1: Balanced pleiotropy, InSIDE assumption satisfied											
10,000	0%	11.7	2.8%	0.070 (0.079)	-0.08 to 0.22	4.9%	0.085	(0.001)	-0.04 to 0.21	6.2%	
10,000	10%	11.7	2.8%	0.094 (0.087)	-0.08 to 0.26	11%	0.118	(0.001)	-0.05 to 0.29	12.6%	
10,000	20%	11.7	2.8%	0.089 (0.093)	-0.09 to 0.27	10.3%	0.124	(0.002)	-0.08 to 0.34	5.6%	
10,000	30%	11.7	2.8%	0.081 (0.094)	-0.1 to 0.27	8.7%	0.108	(0.002)	-0.12 to 0.34	1.6%	
Scenario 2: Directional pleiotropy, InSIDE assumption satisfied											
10,000	0%	11.7	2.8%	0.070 (0.079)	-0.08 to 0.22	5.3%	0.085	(0.001)	-0.04 to 0.21	5.9%	
10,000	10%	11.7	2.8%	0.089 (0.088)	-0.08 to 0.26	9%	0.124	(0.001)	-0.05 to 0.31	11.9%	
10,000	20%	11.7	2.8%	0.119 (0.094)	-0.07 to 0.3	17.7%	0.187	(0.002)	-0.02 to 0.43	32.3%	
10,000	30%	11.7	2.8%	0.133 (0.095)	-0.05 to 0.32	23.3%	0.216	(0.002)	0 to 0.47	46.1%	
Scenario 3: Directional pleiotropy, InSIDE assumption not satisfied											
10,000	0%	11.7	2.8%	0.070 (0.079)	-0.08 to 0.22	5.2%	0.085	(0.001)	-0.04 to 0.21	5.7%	
10,000	10%	13.7	3.3%	0.150 (0.089)	-0.02 to 0.32	35%	0.137	(0.001)	-0.03 to 0.31	25.1%	
10,000	20%	14.9	3.6%	0.213 (0.1)	0.02 to 0.41	55.8%	0.202	(0.002)	-0.01 to 0.46	45.2%	
10,000	30%	12.8	3.1%	0.169 (0.099)	-0.03 to 0.36	37.1%	0.191	(0.002)	-0.03 to 0.46	29.1%	

CI: Confidence Interval, IV: Instrumental Variable, SE: Standard Error. Null Causal Effect ($\beta = 0$)

Citations Search

A total of *** abstracts and *** full texts were screened to identify the 10 studies listed in Table ??; the screening flow diagram is presented in Figure @ref(fig:screening_flow).

Table 3: Reanalysis of 10 highly-cited two-sample MR articles referencing Bowden et al[@bowden_consistent_2016], comparing results of both WME and MR-Hevo causal effect estimation methods

Author	Exposure	Outcome	SNPs	Weighted Median				MR Hevo			
				β	SE	OR	Causality Reported	β	SE	OR	Causality Reported
Choi et al	Self-Reported Physical Activity	Major Depressive Disorder	24	0.4 (0.4-0.41)	0.2400	1.5 (1.49-1.51)	Yes	0.28 (-0.12-0.66)	0.003000	1.32 (0.88-1.94)	No
Ligthart et al	Genetically Determined CRP	Schizophrenia	52	-0.49 (-1.73-0.76)	0.2500	0.62 (0.18-2.13)	No	0.47 (-0.47-1.88)	0.630000	1.61 (0.63-6.58)	No
Pearman et al	Likelihood to Schizophrenia	Cannabis Use	100	0.16 (0.16-0.16)	0.0200	1.16 (1.17-1.16)	Yes	0.17 (0.07-0.25)	0.00030	1.16 (1.06-1.26)	Yes
Carmona-Torres et al	Height	Pancreatic Cancer	550	0.11 (0.11-0.11)	0.0040	1 (0.15-0.36)	No	0.81 (-1.46-1.87)	0.90000	2.26 (0.22-6.5)	No
Carlier et al	Years of Education	Coronary Artery Disease	1,286	-0.46 (-0.46-0.46)	0.0400	0.63 (0.63-0.63)	Yes	-0.46 (-0.59-0.42)	0.00030	0.63 (0.56-0.66)	Yes
Milani et al	BBB	Multiple Sclerosis	70	40.22 (40.2-40.24)	1.3000	292403771868910144 (298523820100000044-298336600402072415)	Yes	0.75 (-1.17-0.71)	0.01000	2.12 (0.31-15.86)	No
Xu et al	Cardiac Disease	Cardiobacterium	100	0 (0-0)	0.0006	1 (1-1)	Yes	0 (0-0.01)	0.00031	1 (1-1.01)	No

β and OR presented as: estimate (95% CI).

β : causal effect estimate, CI: Confidence Interval, OR: Odds Ratio, SE: Standard Error.

CI confidence interval

CLT central limit theorem

IV instrumental variable

InSIDE Instrument Strength Independent of Direct Effect

MR Mendelian randomisation

RCT randomised-controlled trial

SD standard deviation

SE standard error

SNP single nucleotide polymorphism

UMREG Usher Masters Research Ethics Group

WME weighted median estimator