4. Results

Contents

Word count: 472

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 0.59% versus 5.1% for weighted median estimator (WME). Of the 12 combinations of scenarios and parameters, MR-Hevo exhibited a favourable false positive rate versus WME in 12 (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 0.051 (-0.13 to 0.24) for MR-Hevo and 0.044 (-0.13 to 0.22) 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 0.099). For both MR-Hevo and WME methods, causal effect estimates, width of CIs 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% CIs) 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 CIs 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.

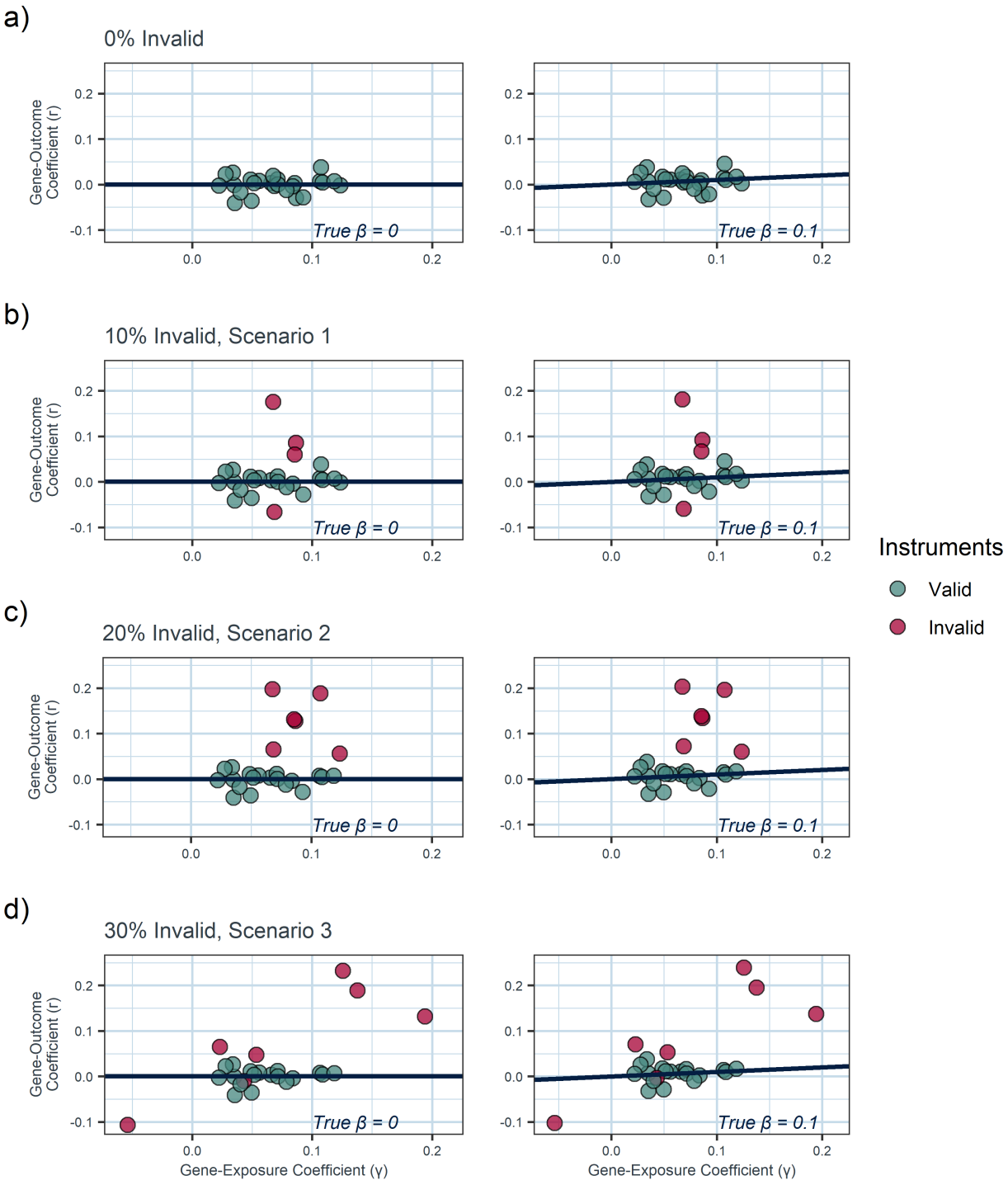

Figure 1: Plots of a representative group of simulated datasets; all simulate genetic instruments from the same index from the same random seed. Left and right columns demonstrate null and positive true causal effects, respectively. The scenario and the proportion of invalid (i.e. pleiotropic) genetic 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

				Weighted Median			MR Hevo		
N	Invalid IVs	*F*	R^2	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: Instumental Variable, SE: Standard Error. Null Causal Effect (β = 0)

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

				Weighted Median			MR Hevo		
N	Invalid IVs	*F*	R^2	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%	0.070 (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: Instumental Variable, SE: Standard Error. Null Causal Effect (β = 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	
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)	
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)	
Pasman et al	Liability to Schizophrenia	Cannabis Use	109	0.16 (0.16-0.16)	0.0500	1.18 (1.17-1.18)	Yes	0.17 (0.07-0.25)	0.000830	1.18 (1.08-1.29)	
Carreras-Torres et al	Height	Pancreatic Cancer	558	0 (-1.88-1.88)	0.0640	1 (0.15-6.56)	No	0.81 (-1.46-1.87)	0.960000	2.26 (0.23-6.5)	
Carter et al	Years of Education	Coronary Artery Disease	1,266	-0.46 (-0.46–0.46)	0.0430	0.63 (0.63-0.63)	Yes	-0.48 (-0.54–0.42)	0.000320	0.62 (0.58-0.66)	
Mokry et al	BMI	Multiple Sclerosis	70	40.22 (40.2-40.24)	1.3000	292403771890910144 (286528929130063648-298399069425972416)	Yes	0.75 (-1.17-2.71)	0.010000	2.12 (0.31-15.09)	
Budu-Aggrey et al	BMI	Psoriasis	97	0 (0-0)	0.1400	1 (1-1)	No	0.08 (-0.16-0.34)	0.002400	1.09 (0.85-1.4)	
Xu et al	Coeliac Disease	Gut Bifidobacterium	105	0 (0-0)	0.0034	1 (1-1)	Yes	0 (0-0.01)	0.000036	1 (1-1.01)	

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