4. Results

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Simulation Study 1

Results

Simulation Study

Data Simulation

Data were successfully simulated as intended. A selection of representative visualisations are presented in Figure 1.

Analysis of Simulated Data

Results of weighted median estimator (WME) and MR-Hevo analyses of simulated datasets are summarised in Tables 1 and 2.

Across all cases where no causal effect was present (Table 1), the mean rate of reporting a causal effect for MR-Hevo was -1.4% versus WME. Of the 8 combinations of scenarios and parameters, MR-Hevo exhibited a favourable false positive rate versus WME in 8. The mean estimate (95% confidence interval (CI)) across all cases was 0.04 (-0.13 to 0.23) for MR-Hevo and 0.03 (-0.15 to 0.2) for WME.

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%

IV: Instumental Variable, SE: Standard Error. Null Causal Effect ($\beta = 0$)

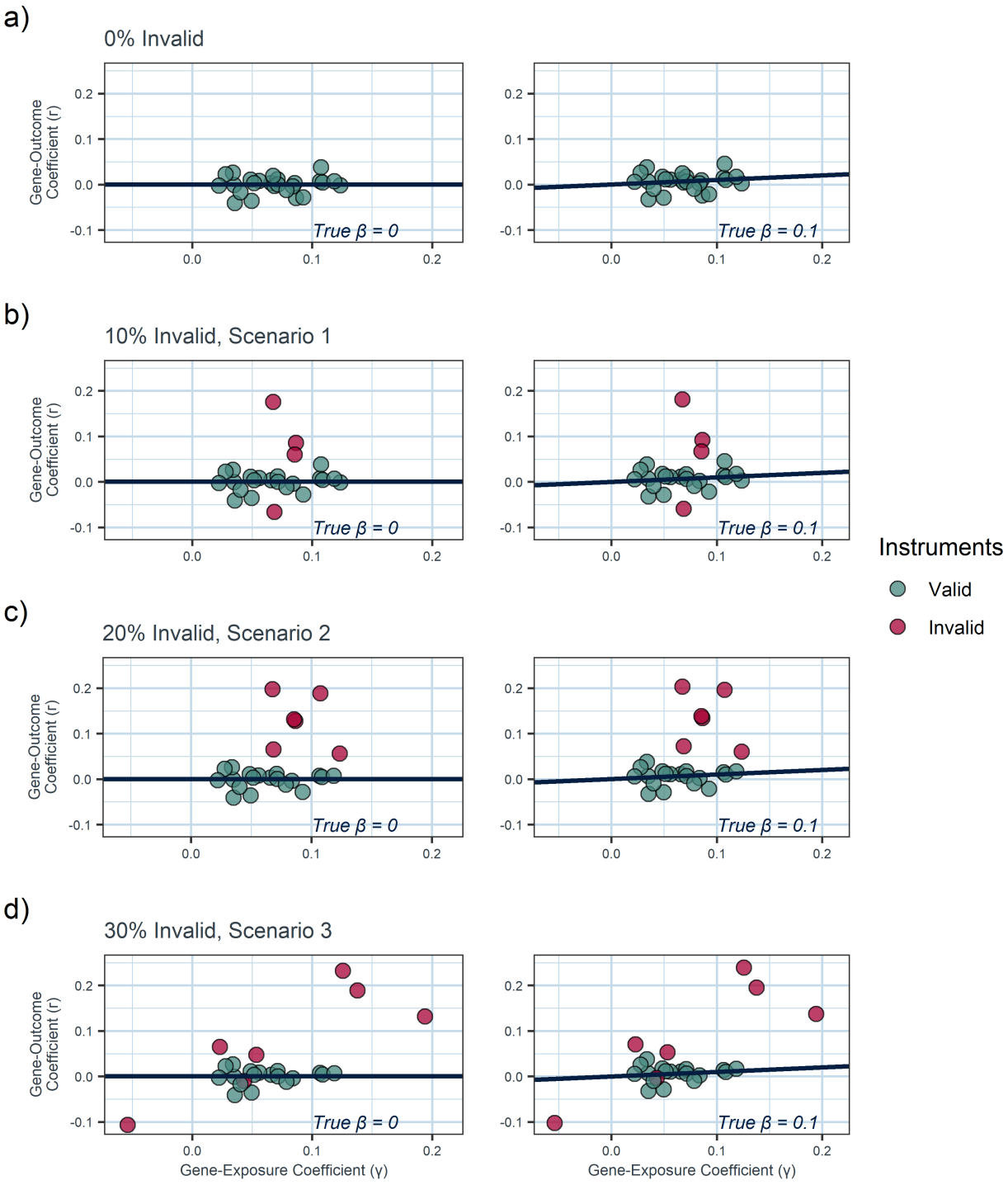

Figure 1: Plots of a representative group of simulated datasets; all simulate genetic instruments from the same index from the same random seed. Left and right columns demonstrate null and positive true causal effects, respectively. The scenario and the proportion of invalid (i.e. pleiotropic) genetic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

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

N	Proportion of Invalid IVs	*F*	R^2	Weighted Median		MR Hevo	
				Mean Estimate (Mean SE)	Positive Rate	Mean Estimate (Mean SE)	Positive Rate
Scenario 1: Balanced pleiotropy, InSIDE assumption satisfied							
10,000	0.0	11.7	2.8%	0.070 (0.079)	4.9	0.085 (0.001)	6.2
10,000	0.1	11.7	2.8%	0.094 (0.087)	11.0	0.118 (0.001)	12.6
10,000	0.2	11.7	2.8%	0.089 (0.093)	10.3	0.124 (0.002)	5.6
10,000	0.3	11.7	2.8%	0.081 (0.094)	8.7	0.108 (0.002)	1.6
Scenario 2: Directional pleiotropy, InSIDE assumption satisfied							
10,000	0.0	11.7	2.8%	0.070 (0.079)	5.3	0.085 (0.001)	5.9
10,000	0.1	11.7	2.8%	0.089 (0.088)	9.0	0.124 (0.001)	11.9
10,000	0.2	11.7	2.8%	0.119 (0.094)	17.7	0.187 (0.002)	32.3
10,000	0.3	11.7	2.8%	0.133 (0.095)	23.3	0.216 (0.002)	46.1
Scenario 3: Directional pleiotropy, InSIDE assumption not satisfied							
10,000	0.0	11.7	2.8%	0.070 (0.079)	5.2	0.085 (0.001)	5.7
10,000	0.1	13.7	3.3%	0.150 (0.089)	35.0	0.137 (0.001)	25.1
10,000	0.2	14.9	3.6%	0.213 (0.1)	55.8	0.202 (0.002)	45.2
10,000	0.3	12.8	3.1%	0.169 (0.099)	37.1	0.191 (0.002)	29.1

IV: Instumental Variable, SE: Standard Error
Data from 1000 Simulated Mendelian Randomisation Studies
Positive Causal Effect (β = 0.1)

Table reference[1]

Word count: 117

1. Bowden J, Smith GD, Haycock PC, Burgess S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. Genetic Epidemiology [Internet]. 2016 Apr [cited 2024 Oct 22];40(4):304. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4849733/