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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 0.41% versus 5.1% for weighted median estimator (WME). Of the 24 combinations of scenarios and parameters, MR-Hevo exhibited a favourable false-positive rate versus WME in 24 (100%).

For both MR-Hevo and WME methods, false-positive report rates generally increased with an increasing proportion of invalid instruments up to around 20% invalid IVs. As assumption violations progressively presented greater data variability and bias across scenarios 1 to 3, both MR-Hevo and WME methods tended to exhibit higher false-positive report rates, though this progression was noticably attenuated for MR-Hevo versus WME, particularly under the assumptions of Scenario 3. Both trends across invalid instrument proportions and scenarios were somewhat attenuated by increasing sample size from 10,000 to 20,000 participants for both methods.

The mean causal effect estimate (mean reported 95% confidence interval (CI)s) across all cases was 0.04 (-0.11 to 0.2) for MR-Hevo and 0.039 (-0.11 to 0.19) for WME. For standard error (SE), the mean (range) SE of causal effect estimates across all cases was 0.0012 (0 to 0.002) for MR-Hevo and 0.076 (0.056 to 0.099) for WME.

Causal effect estimates, width of CIs and SE all tended to increase slightly for each method, both with an increasing proportion of invalid instruments up to 20% invalid IVs, and as assumption violations progressively presented greater data variability and bias across scenarios 1 to 3. For both these trends, MR-Hevo estimates tended to be more affected than those from WME, in contrast to the false-positive report rates, though MR-Hevo causal effect estimates were once more relatively less affected by Scenario 3 assumptions. Again, both trends across differing scenarios and invalid instrument proportions were somewhat attenuated by increasing sample size from 10,000 to 20,000 participants for both methods.

Positive Causal Effect

Across all cases where no causal effect was present (Table 2), the mean rate of reporting a causal effect (i.e. sensitivity) for MR-Hevo was 31% versus 28% for WME. Of the 24 combinations of scenarios and parameters, MR-Hevo exhibited a favourable sensitivity versus WME in only 10 (42%).

For both MR-Hevo and WME methods, causal report rates increased with an increasing proportion of invalid instruments up to around 20% invalid IVs, though this was more consistent for WME versus MR-Hevo. As assumption violations progressively presented greater data variability and bias across scenarios 1 to 3, both MR-Hevo and WME methods tended to exhibit higher causal report rates. Both trends across differing scenarios and invalid instrument proportions were somewhat attenuated by increasing sample size from 10,000 to 20,000 participants for both methods, which also generally increased sensitivity for each method.

The mean causal effect estimate (mean reported 95% CIs) across all cases was 0.13 (-0.025 to 0.3) for MR-Hevo and 0.11 (-0.039 to 0.26) for WME. For SE, the mean (range) SE of causal effect estimates across all cases was 0.0013 (0.001 to 0.002) for MR-Hevo and 0.077 (0.056 to 0.1) for WME.

Causal effect estimates, width of CIs and SE all tended to increase slightly for each method with an increasing proportion of invalid instruments up to 20-30% invalid IVs; MR-Hevo estimates tended to be more affected by proportion of invalid instruments compared to WME estimates. As assumption violations progressively presented greater data variability and bias across scenarios 1 to 3, WME causal estimates tended to increase across all three; MR-Hevo estimates increased when switching from Scenario 1 to Scenario 2, but were relatively unaffected in Scenario 3 versus Scenario 2. Again, trends across invalid instrument proportions were somewhat attenuated by increasing sample from 10,000 to 20,000 participants for both methods, though the effects of sample size on trends across scenarios was less obvious.

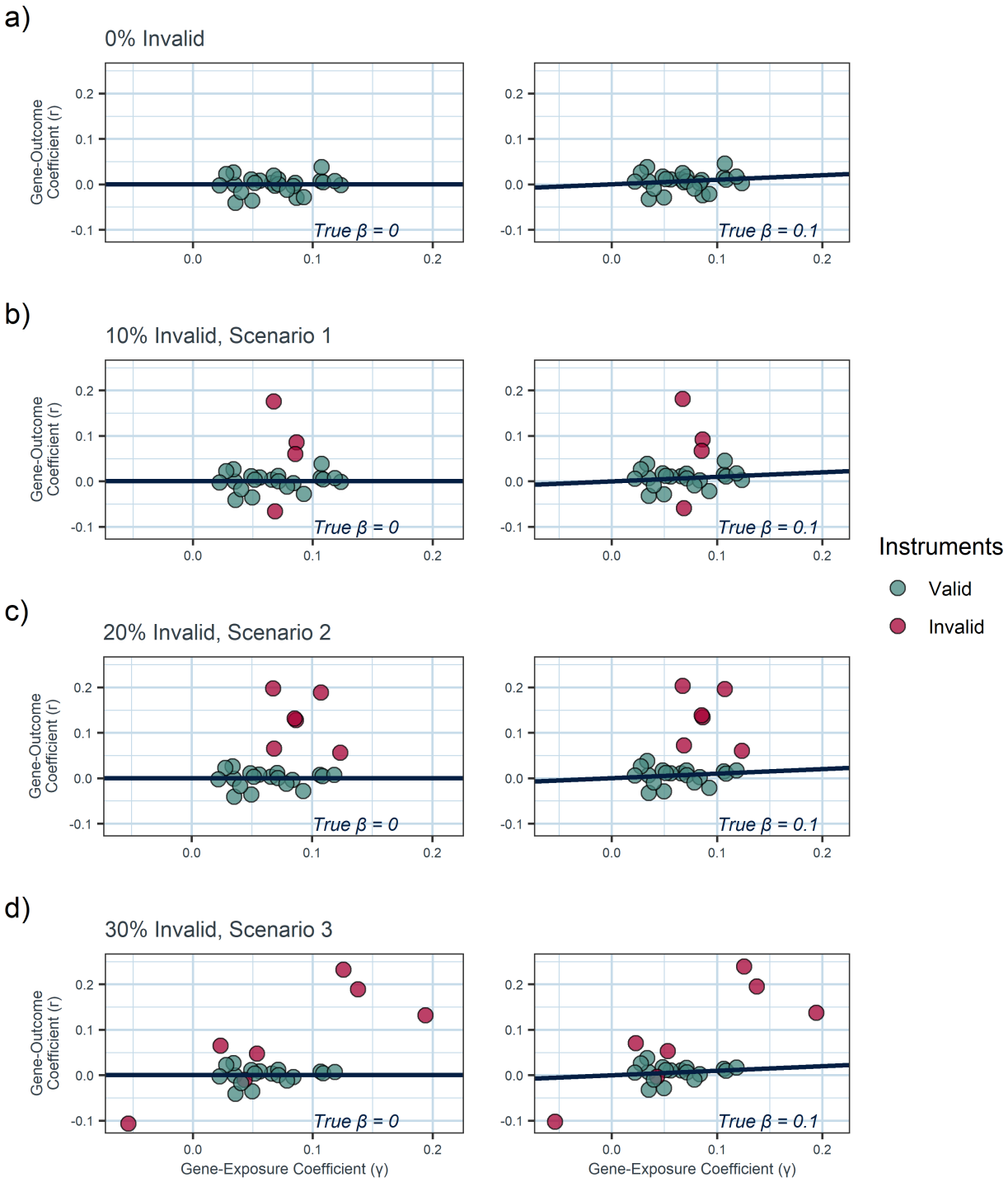

Figure 1: Plots of a representative group of simulated datasets; all simulate genetic instruments from the same index from the same random seed. Left and right columns demonstrate null and positive true causal effects, respectively; the true causal effect is represented by the gradient of the line shown. The scenario and the proportion of invalid (i.e. pleiotropic) genetic instruments changes with each row. a) 0% of instruments invalid, rendering scenario assumptions regarding invalid assumptions irrelevant. b) 10% of instruments invalid, Scenario 1: balanced pleiotropy introduces noise around the causal effect. c) 20% of instruments invalid, Scenario 2: directional pleiotropy biases in the direction of the invalid instruments. d) 30% of instruments invalid, Scenario 3: directional pleiotropy and InSIDE assumption violation strongly biases towards a positive effect estimate.

Simulation 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 Median			MR 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%
20,000	0%	26.2	3.2%	0.003 (0.056)	-0.11 to 0.11	0.3%	0.001 (0)	-0.09 to 0.09	0%
20,000	10%	24.5	3%	0.022 (0.062)	-0.1 to 0.14	0.5%	0.019 (0.001)	-0.1 to 0.14	0.1%
20,000	20%	24.5	3%	0.020 (0.067)	-0.11 to 0.15	1.3%	0.022 (0.001)	-0.13 to 0.18	0%
20,000	30%	24.5	3%	0.012 (0.067)	-0.12 to 0.14	0.8%	0.014 (0.001)	-0.15 to 0.18	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%
20,000	0%	24.5	3%	0.004 (0.056)	-0.11 to 0.11	0.2%	0.001 (0)	-0.08 to 0.09	0%
20,000	10%	24.5	3%	0.016 (0.062)	-0.11 to 0.14	0.7%	0.021 (0.001)	-0.1 to 0.15	0.1%
20,000	20%	24.5	3%	0.038 (0.067)	-0.09 to 0.17	2.2%	0.054 (0.001)	-0.1 to 0.22	0.5%
20,000	30%	24.5	3%	0.050 (0.068)	-0.08 to 0.18	4.9%	0.076 (0.002)	-0.08 to 0.25	1.2%
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%
20,000	0%	24.5	3%	0.004 (0.056)	-0.11 to 0.11	0.2%	0.001 (0)	-0.08 to 0.09	0%
20,000	10%	30.4	3.7%	0.061 (0.063)	-0.06 to 0.18	8.5%	0.030 (0.001)	-0.09 to 0.15	0.1%
20,000	20%	32.4	3.9%	0.111 (0.071)	-0.03 to 0.25	28.3%	0.060 (0.001)	-0.08 to 0.22	0.5%
20,000	30%	31.1	3.8%	0.079 (0.07)	-0.06 to 0.22	13.6%	0.058 (0.001)	-0.09 to 0.22	0.2%

CI: Confidence Interval, InSIDE: Instrument Strength Independent of Direct Effect, 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

N	Invalid IVs	*F*	R^2	Weighted Median			MR 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%	0.070 (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%
20,000	0%	24.5	3%	0.080 (0.056)	-0.03 to 0.19	21.3%	0.089 (0.001)	0 to 0.18	62.2%
20,000	10%	24.5	3%	0.098 (0.063)	-0.03 to 0.22	27.8%	0.108 (0.001)	-0.01 to 0.23	29.9%
20,000	20%	24.5	3%	0.095 (0.067)	-0.04 to 0.23	22.6%	0.113 (0.001)	-0.04 to 0.27	15%
20,000	30%	24.5	3%	0.088 (0.068)	-0.05 to 0.22	17.7%	0.104 (0.001)	-0.06 to 0.27	5.4%
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%
20,000	0%	24.5	3%	0.080 (0.057)	-0.03 to 0.19	21.1%	0.089 (0.001)	0 to 0.18	62.7%
20,000	10%	24.5	3%	0.093 (0.063)	-0.03 to 0.22	24%	0.109 (0.001)	-0.01 to 0.24	29.1%
20,000	20%	24.5	3%	0.116 (0.068)	-0.02 to 0.25	35.3%	0.146 (0.001)	-0.01 to 0.31	41.2%
20,000	30%	24.5	3%	0.127 (0.069)	-0.01 to 0.26	40.7%	0.168 (0.002)	0.01 to 0.35	56.2%
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%
20,000	0%	24.5	3%	0.080 (0.057)	-0.03 to 0.19	21.5%	0.089 (0.001)	0 to 0.18	62.8%
20,000	10%	30.4	3.7%	0.144 (0.064)	0.02 to 0.27	66%	0.125 (0.001)	0.01 to 0.25	63%
20,000	20%	32.4	3.9%	0.189 (0.073)	0.05 to 0.33	81.5%	0.154 (0.001)	0.01 to 0.32	58.6%
20,000	30%	31.1	3.8%	0.153 (0.071)	0.01 to 0.29	60.3%	0.146 (0.001)	-0.01 to 0.32	41%

CI: Confidence Interval, InSIDE: Instrument Strength Independent of Direct Effect, IV: Instumental Variable, SE: Standard Error.
Positive Causal Effect ($\beta = 0.1$)

Re-Analysis of Published Data

Citation Search Results

A total of 110 abstracts and 54 full texts were screened to identify the 10 studies included[1–10]; these are summarised in Table 3. The flow diagram of study screening and selection is presented in Figure 2.

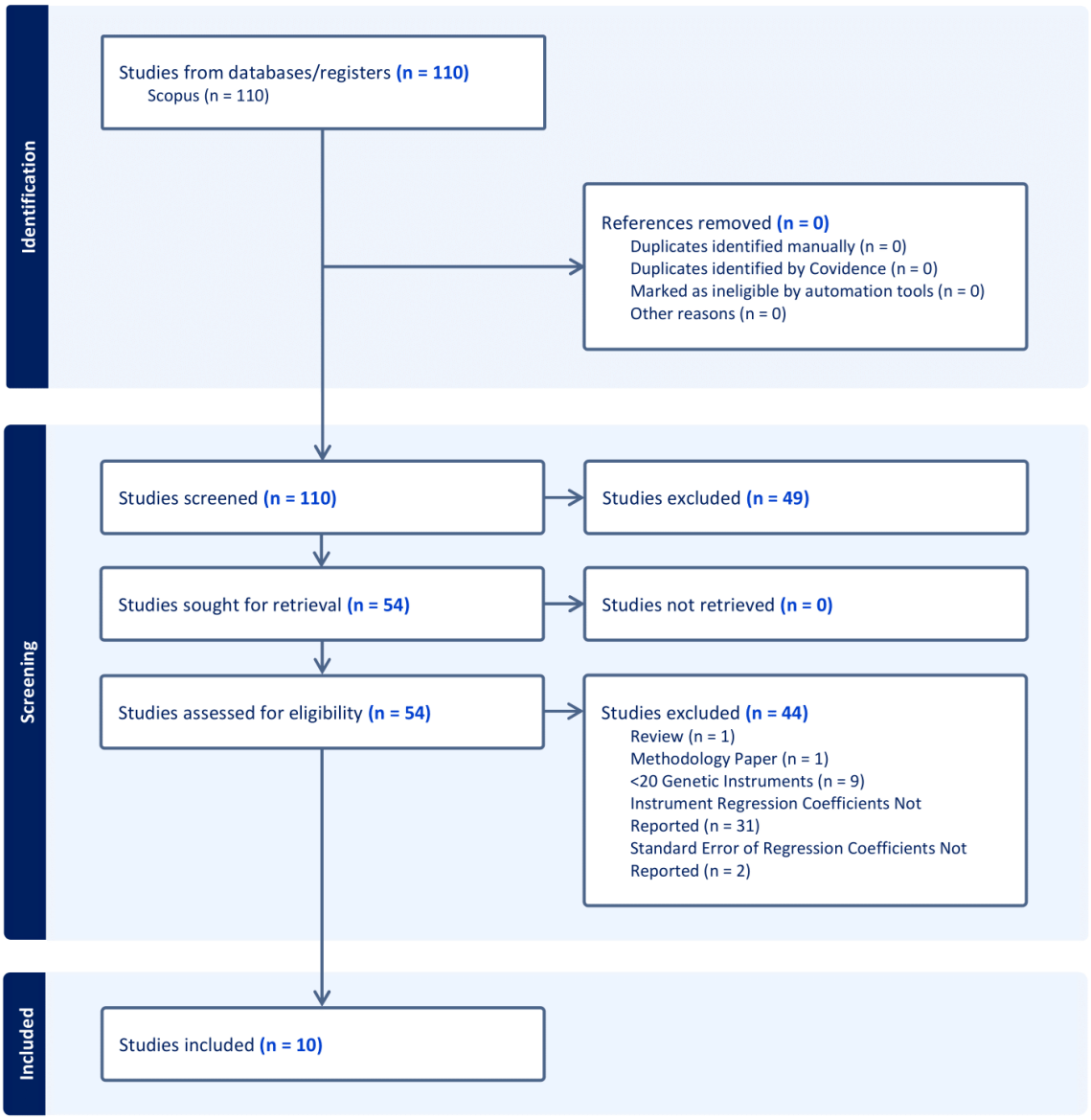

Figure 2: Flow diagram illustrating selection of sample of ten highly-cited two-sample Mendelian randomisation articles reporting a weighted median estimate of casual effect

Table 3: Summary of ten highly-cited two-sample Mendelian randomisation articles reporting a weighted median estimate of casual effect

Author	Citations	Association	*N* Instruments	Participants			Causal Effect		Causality Reported	*p*-value
				N		Maximum Estimated Overlap				
				Exposure	Outcome		Measure	Estimate		
Budu-Aggrey et al, 2019	182	BMI vs Psoriasis	97	339,224	12,559	NA%	OR	1.06 (1 to 1.12)	No	-
Carreras-Torres et al, 2017	200	Height vs Pancreatic Cancer	558	253,288	15,002	19%	OR	1.14 (1 to 1.29)	No	0.05
Carter et al, 2019	199	Education vs Coronary Disease	1,267	766,345	184,305	NA%	OR	0.62 (0.57 to 0.67)	Yes	<0.001
Choi et al, 2019	492	Activity vs Depression	24	377,234	143,265	NA%	OR	1.49 (0.94 to 2.36)	No	0.08
Clift et al, 2022	129	Smoking Initiation vs COVID-19 Infection	378	1,232,091	281,105	36%	OR	1.53 (1.02 to 2.28)	Yes	0.04
Ligthart et al, 2018	298	CRP vs Schizophrenia	52	204,402	82,315	NA%	OR	0.89 (0.81 to 0.96)	Yes	0.004
Mokry et al, 2016	199	BMI vs Multiple Sclerosis	70	322,105	38,589	2.5%	OR	1.26 (0.98 to 1.62)	No	0.08
Pasman et al, 2018	328	Schizophrenia vs Cannabis Use	102	150,064	184,765	NA%	β	0.163 (0.067 to 0.259)	Yes	0.001
Xie et al, 2023	138	T2DM vs NAFLD	449	441,016	218,792	NA%	OR	1.61 (1.09 to 2.38)	Yes	<0.001
Xu et al, 2022	183	Coeliac vs Gut Bifidobacterium	105	15,283	24,269	63%	OR	0.998 (0.99 to 1.005)	No	0.56

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

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

BMI: body mass index, CRP: C-reactive protein, NAFLD: non-alcoholic fatty liver disease, T2DM: type 2 diabetes mellitus

Re-Analysis Results

Data Validation and Re-analysis

There were missing gene-outcome coefficients for three instruments from Xie et al[9], and one instrument in Clift et al[10] was reported as having an implausibly large gene-outcome coefficient and standard error (-1243.03 and 19161.64, respectively); these were imputed as the respective mean value per study. Data were otherwise complete as expected per the descriptions in each study manuscript. A summary of the re-analysis results is presented in Table 4; estimates are presented both as β regression coefficients and odds ratio (OR)s to aid comparison across studies.

Re-Analysed vs Reported WME Causal Estimates

3 of the WME estimates generated through re-analysis matched the originally reported estimates poorly (Ligthart et al[3], Carreras-Torres et al[6], Mokry et al[5]), with a >0.1 difference in re-analysis estimates of OR versus the values originally reported. Re-analysed OR upper or lower CIs were >0.1 different to reported values for 4 studies (Ligthart et al[3], Carreras-Torres et al[6], Mokry et al[5], Budu-Aggrey et al[8]). Details of instruments used in re-analysis were re-checked against the relevant manuscripts to confirm accuracy of data used, with no discrepancies found.

Overall, estimates and CIs from re-analysis of the other 6 studies (Choi et al[1], Xie et al[9], Pasman et al[2], Carter et al[4], Clift et al[10], Xu et al[7]) appeared comparable to reported values, after accounting for rounding errors from published summary data, and random variation inherent in bootstrap generation of CIs.

Compared with reported values of ORs across the 9 studies using them, the mean difference for effect estimates (SE) from the re-analysis estimate was 0.03 (0.17). For 95% CIs, the mean differences between reported and re-analysed values were 0.07 for the lower bounds and -0.04 for upper bounds, i.e. reported CIs were narrower on average than re-analysed WME CIs.

Conclusions regarding presence of a causal effect were mostly consistent: reported WME and re-analysed WME estimates were discordant in detecting a causal exposure-outcome effect for 2 studies: 1 where a previously reported causal effect was not found (Ligthart et al[3]), and 1 where a causal effect was found that had not been reported previously (Mokry et al[5]).

Re-Analysed WME vs MR-Hevo Causal Estimates

Causal effect estimates generated by MR-Hevo were >0.1 different from re-analysed WME estimates for 2 studies (Choi et al[1], Carreras-Torres et al[6]). Compared with WME values of ORs across the 9 studies using them, the mean difference for effect estimates (SE) from the re-analysis estimate was -0.046 (-0.084). For 95% CIs, the mean differences between MR-Hevo and WME values were -0.044 for the lower bounds and -0.002 for upper bounds, i.e. MR-Hevo CIs were wider and slightly shifted in the negative direction on average than WME values. MR-Hevo OR upper or lower CIs were >0.1 different to WME values for 6 studies (Choi et al[1], Xie et al[9], Ligthart et al[3], Carreras-Torres et al[6], Clift et al[10], Mokry et al[5]).

Overall, estimates and CIs from MR-Hevo analysis of the other 4 studies (Pasman et al[2], Carter et al[4], Budu-Aggrey et al[8], Xu et al[7]) appeared comparable to re-analysed WME values.

Conclusions regarding presence of a causal effect were consistent: re-analysed WME estimates were discordant in detecting a causal exposure-outcome effect in 0 studies versus MR-Hevo, with both reporting a causal effect in the same 5 studies (Xie et al[9], Pasman et al[2], Carter et al[4], Clift et al[10], Mokry et al[5]).

Table 4: Re-analysis of ten highly-cited two-sample Mendelian randomisation articles reporting a weighted median estimate of casual effect, 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
Budu-Aggrey et al	BMI	Psoriasis	97	0 (-0.29-0.29)	0.148	1 (0.75-1.34)	No	0.08 (-0.17-0.33)	0.002	1.08 (0.84-1.39)	No
Carreras-Torres et al	Height	Pancreatic Cancer	558	0 (-0.13-0.13)	0.066	1 (0.88-1.14)	No	-0.28 (-1.34-0.5)	0.513	0.76 (0.26-1.64)	No
Carter et al	Years of Education	Coronary Artery Disease	1,266	-0.46 (-0.55–0.38)	0.044	0.63 (0.58-0.69)	Yes	-0.48 (-0.54–0.42)	0.000	0.62 (0.58-0.66)	Yes
Choi et al	Self-Reported Physical Activity	Major Depressive Disorder	25	0.39 (-0.06-0.83)	0.227	1.47 (0.94-2.29)	No	0.22 (-0.23-0.65)	0.004	1.25 (0.8-1.91)	No
Clift et al	Genetically Determined Smoking Initiation	COVID-19 Infection	378	0.43 (0.02-0.84)	0.209	1.53 (1.02-2.31)	Yes	0.37 (0.1-0.64)	0.001	1.45 (1.1-1.9)	Yes
Ligthart et al	Genetically Determined CRP	Schizophrenia	29	-0.41 (-0.88-0.08)	0.245	0.67 (0.41-1.08)	No	-0.38 (-1.24-0.54)	0.008	0.68 (0.29-1.72)	No
Mokry et al	BMI	Multiple Sclerosis	70	0.34 (0.09-0.59)	0.129	1.41 (1.09-1.81)	Yes	0.34 (0.16-0.52)	0.001	1.41 (1.17-1.67)	Yes
Pasman et al	Liability to Schizophrenia	Cannabis Use	109	0.16 (0.06-0.26)	0.050	1.18 (1.07-1.3)	Yes	0.17 (0.08-0.26)	0.001	1.18 (1.08-1.29)	Yes
Xie et al	T2DM	NAFLD	526	0.48 (0.09-0.87)	0.198	1.61 (1.09-2.38)	Yes	0.51 (0.28-0.75)	0.002	1.67 (1.32-2.13)	Yes
Xu et al	Coeliac Disease	Gut Bifidobacterium	105	0 (-0.01-0)	0.004	1 (0.99-1)	No	0 (-0.01-0)	0.000	1 (0.99-1)	No

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

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

BMI: body mass index, CRP: C-reactive protein, NAFLD: non-alcoholic fatty liver disease, T2DM: type 2 diabetes mellitus

BMI body mass index
CI confidence interval
CLT central limit theorem
CRP C-reactive protein
IV instrumental variable
InSIDE Instrument Strength Independent of Direct Effect
MR Mendelian randomisation
NAFLD non-alcoholic fatty liver disease
OR odds ratio
RCT randomised-controlled trial
SD standard deviation
SE standard error
SNP single nucleotide polymorphism
T2DM type 2 diabetes mellitus
UMREG Usher Masters Research Ethics Group
WME weighted median estimator

1. Choi KW, Chen CY, Stein MB, Klimentidis YC, Wang MJ, Koenen KC, et al. Assessment of Bidirectional Relationships Between Physical Activity and Depression Among Adults: A 2-Sample Mendelian Randomization Study. JAMA Psychiatry [Internet]. 2019 Apr [cited 2025 Apr 27];76(4):399–408. Available from: https://doi.org/10.1001/jamapsychiatry.2018.4175

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