Simulation results of eight Pleiotropy-robust MR Methods in scenario 4 (Directional pleiotropy, InSIDE violated)

Figs A-F (30% invalid variants, 50 variants), Figs G-L (30% invalid variants, 100 variants), Figs M-R (70% invalid variants, 50 variants) and Figs S-X (70% invalid variants, 100 variants) show the tendency of estimations, SEs, type I error rates and statistic power under different selection mechanisms and simulation situations when varying across selection effects of $X$, $Y$ or $G$ on selection ($S$) in scenario 4 (Directional pleiotropy, InSIDE violated). The results are similarly with scenario 3 (Directional pleiotropy).

**Fig A.** Simulation results for causal estimations of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Null causal effect in scenario 4 (30% invalid variants, 50 variants).
Fig B. Simulation results for SEs of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Null causal effect in scenario 4 (30% invalid variants, 50 genetic variants).
Fig C. Simulation results for type I error rates of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Null causal effect in scenario 4 (30% invalid variants, 50 genetic variants).
Fig D. Simulation results for causal estimations of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Positive causal effect in scenario 4 (30% invalid variants, 50 genetic variants).
Fig E. Simulation results for standard error of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Positive causal effect in scenario 4 (30% invalid variants, 50 genetic variants).
Fig F. Simulation results for statistic power of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Positive causal effect in scenario 4 (30% invalid variants, 50 genetic variants).
Fig G. Simulation results for causal estimations of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Null causal effect in scenario 4 (30% invalid variants, 100 variants).
Fig H. Simulation results for SEs of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Null causal effect in scenario 4 (30% invalid variants, 100 genetic variants).
**Fig I.** Simulation results for type I error rates of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Null causal effect in scenario 4 (30% invalid variants, 100 genetic variants).
Simulation results for causal estimations of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Positive causal effect in scenario 4 (30% invalid variants, 100 genetic variants).
Fig K. Simulation results for SEs of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Positive causal effect in scenario 4 (30% invalid variants, 100 genetic variants).
Fig L. Simulation results for statistic power of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Positive causal effect in scenario 4 (30% invalid variants, 100 genetic variants).
Fig M. Simulation results for causal estimations of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Null causal effect in scenario 4 (70% invalid variants, 50 variants).
Fig N. Simulation results for SEs of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Null causal effect in scenario 4 (70% invalid variants, 50 genetic variants).
**Fig O.** Simulation results for type I error rates of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Null causal effect in scenario 4 (70% invalid variants, 50 genetic variants).
**Fig P.** Simulation results for causal estimations of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Positive causal effect in scenario 4 (70% invalid variants, 50 genetic variants).
**Fig Q.** Simulation results for SEs of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Positive causal effect in scenario 4 (70% invalid variants, 50 genetic variants).
Fig R. Simulation results for statistic power of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Positive causal effect in scenario 4 (70% invalid variants, 50 genetic variants).
Fig S. Simulation results for causal estimations of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Null causal effect in scenario 4 (70% invalid variants, 100 variants).
Fig T. Simulation results for SEs of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Null causal effect in scenario 4 (70% invalid variants, 100 genetic variants).
Fig U. Simulation results for type I error rates of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Null causal effect in scenario 4 (70% invalid variants, 100 genetic variants).
**Fig V.** Simulation results for causal estimations of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Positive causal effect in scenario 4 (70% invalid variants, 100 genetic variants).
Fig W. Simulation results for SEs of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Positive causal effect in scenario 4 (70% invalid variants, 100 genetic variants).
Fig X. Simulation results for statistic power of eight Pleiotropy-robust MR Methods varying across selection effect from -2 to 2 under different selection mechanisms with Positive causal effect in scenario 4 (70% invalid variants, 100 genetic variants).