Appendix to "Pleiotropy-robust Mendelian Randomization"

1. Simulation study setup

As in Bowden et al. (2015), the data for the simulation were generated according to the following model:

$$U = G\varphi + \varepsilon^U \quad \text{(A1)}$$

$$X = G\gamma + U + \varepsilon^X \quad \text{(A2)}$$

$$Y = X\beta + G\alpha + U + \varepsilon^Y \quad \text{(A3)}$$

This is a more general model than model 1 and 2 in the main text, because it additionally allows the genetics variants that are being used as instrumental variables to have an influence on an unobserved confounding variable U. If $\varphi_j = 0$ for all genetic variants, this model reduces to model 1 and 2. If $\varphi_j \neq 0$ for a genetic variant, this introduces a violation of the independence assumption.

In each simulation run, one sample of 1,000 individuals is generated. Matrix G contains 25 independently generated SNPs with a minor allele frequency of 0.30. The error terms in the three equations come from three independent normal distributions with mean 0 and variance 2. The effect γ_j of the genetic variant on exposure X is drawn from a uniform distribution on the interval 0.5-4.0.

We consider four different scenarios (InSIDE refers to the "Instrument Strength Independent of Direct Effect" assumption):

1. No pleiotropy, InSIDE satisfied: $\alpha_j = 0$, $\varphi_j = 0$.
2. Balanced pleiotropy, InSIDE satisfied: $\alpha_j \sim$ Uniform(-0.2,0.2), $\varphi_j = 0$.

3. Directional pleiotropy, InSIDE satisfied: $\alpha_j \sim$ Uniform(0,0.2), $\varphi_j = 0$;
4. Directional pleiotropy, InSIDE not satisfied: $\alpha_j \sim$ Uniform(0,0.2), $\varphi_j \sim$ Uniform(0,0.5).

Each scenario is simulated with a null effect ($\beta = 0$) and a positive effect ($\beta = 0.05$). For PRMR, we assume α_j and φ_j are known in the simulations reported in Table 1 of the main text. The simulation results are based on 10,000 runs.

For the simulations reported in Table 2 in the main text, we simulate a second sample using 250, 500 and 1,000 individuals with (i) $\gamma_j = 0$ (zero first stage) and (ii) $\alpha_j = \alpha_j \times \xi$ (non homogenous pleiotropic effects), with $0.5 \leq \xi \leq 1.5$. Only for PRMR we use this subsample to obtain estimates of α_j, while for the other methods, this subsample is not used in the analysis. If we include this additional subsample in the analyses for 2SLS, IVW, and MR-Egger, this only increases the bias of these methods since we add a group of individuals without a first stage, decreasing the first stage *F*-statistic (results available upon request).

2. STATA code simulation study

See *PRMR_simulation_study_final.do* below.

3. STATA code empirical examples

See *script_PRMR_UKB_final.do* below.

4. References

Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol* 2015**;44:**512–525.