**Supplementary Methods**

**MR-Egger method**

In addition to test and estimate causal effects (similar to IVW), MR-Egger can also test for directional pleiotropy [1]. Compared to IVW that sets the intercept term to be 0, MR-Egger adds a parameter 𝜃0. If the intercept term 𝜃0 is exactly equal to 0, then the MR-Egger estimate will be equal to the IVW estimate. Otherwise, there are pleiotropic effects independently distributed from the effect of IVs on outcomes through exposures. This means that Assumption 3 in Figure 1 will not be met. Hence, the test for whether the intercept term 𝜃0 is exactly equal to 0 can be referred to as the pleiotropy test [1].

**Weighted median method**

Weighted median is another MR method to calculate the causal estimate by combining data of multiple genetic IVs. The main advantage of the Weighted median is that the causal estimator is consistent even when up to 50% of the information comes from invalid IVs. The weighted median method has better finite-sample Type 1 error rates than the IVW, and is complementary to MR-Egger [2].

**Mendelian Randomization Pleiotropy Residual Sum and Outlier**

MR-PRESSO can find the outlier IVs that cause pleiotropy. MR-PRESSO can obtain an outlier corrected causal estimator [3]. Usually, no more than 50% of the genetic pleiotropy can be excluded by removing the IV outliers.

**Multivariable MR**

Multivariable MR is an extension to the univariable MR that uses the same IVs strongly associated with one or more of several measured exposures to simultaneously estimate the causal effects of each exposure on the outcome [4]. Multivariable MR is useful to detect the causal effect when the same IV affects the outcome through more than one exposure. In addition, this type of pleiotropy can be corrected in the Multivariable MR estimate [4].

**Statistical power analysis**

We used the *F*-statistic to evaluate the strength of the IVs. The *F*-statistic can estimate the minimum detectable magnitude of the causal association in MR. In the univariable MR, the *F*-statistic and statistical power were calculated using an online tool, mRnd [5]. mRnd uses the non-centrality parameter to calculate power estimates. In addition, the fixed sample size, the heritability of exposure, and the true causal association between the exposure and the outcome were used as parameters. In the implementation, we used a 2-sided type I error rate of 0.05. In addition to the total number of individuals and proportion of cases, we provided the proportion of R2 variance based on SNP-Heritability listed in Table 1. We also provided the minimum detectable OR based on the IVW results. The value of 10 or higher is commonly used as the threshold of the *F*-statistic [6].

In the multivariable MR, we calculated a conditional *F-statistic* by regressing the IVs upon their corresponding exposure, conditioning on the remaining included exposures. The conditional *F-statistic* was independent of outcome because method did not use any information about the outcome.

**Heterogeneity test**

We tested the heterogeneity in the Wald-type estimators from IVs using Cochran’s Q test [7]. A *P-value* ≤ 0.10 was used as threshold to determine if there was heterogeneity.

**Reference**

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