Supporting Information

for “A Novel Penalized Inverse-Variance Weighted Estimator for Mendelian Randomization with Applications to COVID-19 Outcomes”

by Siqi Xu, Peng Wang, Wing Kam Fung, and Zhonghua Liu

Contents

Web Appendix A: Comparison of the Denominators for the IVW Estimator and the dIVW Estimator

Assume that the variances $\sigma^2_{\hat{\Gamma}_j}$ and $\sigma^2_{\hat{\gamma}_j}$ of $\hat{\Gamma}_j$ and $\hat{\gamma}_j$ are known, respectively, and $\hat{\gamma}_j$s are independently distributed as $\hat{\gamma}_j \sim N\left(\gamma_j, \sigma^2_{\hat{\gamma}_j}\right)$ for $j = 1, \ldots, p$. Then, the expectation and variance of the denominator in the IVW estimator are respectively

$$E\left(\sum\nolimits_{j=1}^{p} \sigma^{-2}_{\hat{\Gamma}_j} \hat{\gamma}_j^2\right) = \mu_2 + \sigma^{-2}_{\hat{\Gamma}_j} \sigma^2_{\hat{\gamma}_j},$$

$$\mathrm{Var}\left(\sum\nolimits_{j=1}^{p} \sigma^{-2}_{\hat{\Gamma}_j} \hat{\gamma}_j^2\right) = \sum\nolimits_{j=1}^{p} \sigma^{-4}_{\hat{\Gamma}_j}\left(4\sigma^2_{\hat{\gamma}_j}\gamma_j^2 + 2\sigma^4_{\hat{\gamma}_j}\right).$$

The expectation and variance of the denominator in the dIVW estimator are respectively

$$E\left(\sum\nolimits_{j=1}^{p} \sigma^{-2}_{\hat{\Gamma}_j}\left(\hat{\gamma}_j^2 - \sigma^2_{\hat{\gamma}_j}\right)\right) = \mu_2,$$

$$\mathrm{Var}\left(\sum\nolimits_{j=1}^{p} \sigma^{-2}_{\hat{\Gamma}_j}\left(\hat{\gamma}_j^2 - \sigma^2_{\hat{\gamma}_j}\right)\right) = \sum\nolimits_{j=1}^{p} \sigma^{-4}_{\hat{\Gamma}_j}\left(4\sigma^2_{\hat{\gamma}_j}\gamma_j^2 + 2\sigma^4_{\hat{\gamma}_j}\right).$$

Web Appendix B: Derivation of the pIVW Estimator

The penalized log-likelihood function of μ_1 and μ_2 is

$$l_p(\mu_1, \mu_2) = -\frac{1}{2}\left(1 - \frac{v_{12}^2}{v_1 v_2}\right)^{-1}\left\{\frac{(\hat{\mu}_1 - \mu_1)^2}{v_1} - \frac{2v_{12}(\hat{\mu}_1 - \mu_1)(\hat{\mu}_2 - \mu_2)}{v_1 v_2} + \frac{(\hat{\mu}_2 - \mu_2)^2}{v_2}\right\} + \lambda \log|\mu_2| + C,$$

where C is a constant unrelated to μ_1 and μ_2.

To maximize $l_p(\mu_1, \mu_2)$, we take its first derivative with respect to μ_1 as follows,

$$\frac{\partial l_p(\mu_1, \mu_2)}{\partial \mu_1} = -\left(1 - \frac{v_{12}^2}{v_1 v_2}\right)^{-1}\left\{-\frac{\hat{\mu}_1 - \mu_1}{v_1} + \frac{v_{12}(\hat{\mu}_2 - \mu_2)}{v_1 v_2}\right\}.$$

From $\partial l_p(\mu_1, \mu_2)/\partial \mu_1$, we can see that $l_p(\mu_1, \mu_2)$ attains its maximum when

$$\mu_1 = \hat{\mu}_1 + \frac{v_{12}(\mu_2 - \hat{\mu}_2)}{v_2}.$$

By profiling out μ_1, we get the following profile penalized log-likelihood function of μ_2

$$l_p(\mu_2) = -\frac{(\hat{\mu}_2 - \mu_2)^2}{2v_2} + \lambda \log|\mu_2| + C.$$

The first derivative of $l_p(\mu_2)$ with respect to μ_2 is

$$\frac{\partial l_p(\mu_2)}{\partial \mu_2} = \frac{\hat{\mu}_2 - \mu_2}{v_2} + \frac{\lambda}{\mu_2} = -\frac{(\mu_2 - \tilde{\mu}_{2,l})(\mu_2 - \tilde{\mu}_{2,r})}{\mu_2 v_2},$$

where

$$\tilde{\mu}_{2,l} = \frac{\hat{\mu}_2 - \sqrt{\hat{\mu}_2^2 + 4\lambda v_2}}{2} \text{ and } \tilde{\mu}_{2,r} = \frac{\hat{\mu}_2 + \sqrt{\hat{\mu}_2^2 + 4\lambda v_2}}{2}.$$

Since $\tilde{\mu}_{2,l} < 0 < \tilde{\mu}_{2,r}$, $l_p(\mu_2)$ increases when $\mu_2 \in (-\infty, \tilde{\mu}_{2,l}) \cup (0, \tilde{\mu}_{2,r})$ and decreases when $\mu_2 \in (\tilde{\mu}_{2,l}, 0) \cup (\tilde{\mu}_{2,r}, +\infty)$. Therefore, $l_p(\mu_2)$ can only attain its maximum at $\tilde{\mu}_{2,l}$ or $\tilde{\mu}_{2,r}$. Further, we have

$$l_p(\tilde{\mu}_{2,l}) = -\frac{\tilde{\mu}_{2,r}^2}{2v_2} + \lambda \log|\tilde{\mu}_{2,l}| + C,$$

$$l_p(\tilde{\mu}_{2,r}) = -\frac{\tilde{\mu}_{2,l}^2}{2v_2} + \lambda \log|\tilde{\mu}_{2,r}| + C.$$

When $\hat{\mu}_2 > 0$, we have $|\tilde{\mu}_{2,l}| < |\tilde{\mu}_{2,r}|$ and thus $l_p(\tilde{\mu}_{2,l}) < l_p(\tilde{\mu}_{2,r})$. When $\hat{\mu}_2 < 0$, we have $l_p(\tilde{\mu}_{2,l}) > l_p(\tilde{\mu}_{2,r})$. Hence, by maximizing $l_p(\mu_1, \mu_2)$, we obtain the following estimators of μ_1 and μ_2

$$\tilde{\mu}_1 = \hat{\mu}_1 + \frac{v_{12}(\tilde{\mu}_2 - \hat{\mu}_2)}{v_2},$$

$$\tilde{\mu}_2 = \frac{\hat{\mu}_2 + \text{sign}(\hat{\mu}_2)\sqrt{\hat{\mu}_2^2 + 4\lambda v_2}}{2} = \left(\frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\lambda v_2}{\hat{\mu}_2^2}}\right)\hat{\mu}_2.$$

Note that since the true values of v_2 and v_{12} are unknown in practice, we replace them with their unbiased estimators $\hat{v}_2$ and $\hat{v}_{12}$ to obtain $\tilde{\mu}_1$ and $\tilde{\mu}_2$.

Web Appendix C: Proof of Theorem 1

In the following proof, we write $a_n = O(b_n)$ if there exists a constant c such that $|a_n| \leq cb_n$ for all n, $a_n = o(b_n)$ if $a_n/b_n \to 0$ as $n \to \infty$, and $a_n = \Theta(b_n)$ if there exists a constant c such that $c^{-1}b_n \leq |a_n| \leq cb_n$ for all n. Let $\xrightarrow{p}$ denotes convergence in probability, and $\xrightarrow{d}$ denotes convergence in distribution. We write $X = O_p(Y)$ if X/Y is bounded in probability, and $X = o_p(Y)$ if $X/Y \xrightarrow{p} 0$. The following proof of Theorem 1 takes into account the balanced horizontal pleiotropy ($\tau \neq 0$). The situation without horizontal pleiotropy can be considered as a special case with $\tau = 0$.

1 Proof of Theorem 1 (a)

1.1 Bias of dIVW Estimator

The dIVW estimator is

$$\hat{\beta}_{\text{dIVW}} = \frac{\hat{\mu}_1}{\hat{\mu}_2} = \frac{\sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-2} \hat{\gamma}_j \hat{\Gamma}_j}{\sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-2} \left(\hat{\gamma}_j^2 - \sigma_{\hat{\gamma}_j}^2\right)}.$$

Let $\mu_1 = E(\hat{\mu}_1) = \beta \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-2} \gamma_j^2 = \Theta(\kappa p)$ and $\mu_2 = E(\hat{\mu}_2) = \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-2} \gamma_j^2 = \Theta(\kappa p)$ under Assumption 2. By Taylor series expansion, we have

$$\hat{\beta}_{\text{dIVW}} = \beta\ (\hat{x}_1 + 1)(\hat{x}_2 + 1)^{-1} = \beta + \beta\ (\hat{x}_1 - \hat{x}_2 + \hat{x}_2^2 - \hat{x}_1 \hat{x}_2) + o_p(\xi),$$

where $\hat{x}_1 = \hat{\mu}_1/\mu_1 - 1$, $\hat{x}_2 = \hat{\mu}_2/\mu_2 - 1$, and $\xi = 1/\kappa p + 1/\kappa^2 p \to 0$ as the effective sample size $\eta = \kappa\sqrt{p} \to \infty$. Then, the bias of the dIVW estimator is

$$E\big(\hat{\beta}_{\text{dIVW}} - \beta\big) = \beta \left(\frac{v_2}{\mu_2^2} - \frac{v_{12}}{\mu_1 \mu_2}\right) + o(\xi) = O(\xi),$$

where $v_2 = \text{Var}(\hat{\mu}_2) = \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4} \left(4\sigma_{\hat{\gamma}_j}^2 \gamma_j^2 + 2\sigma_{\hat{\gamma}_j}^4\right) = \Theta(\kappa p + p)$ and $v_{12} = \text{Cov}(\hat{\mu}_1, \hat{\mu}_2) = 2\beta \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4} \sigma_{\hat{\gamma}_j}^2 \gamma_j^2 = \Theta(\kappa p)$ by Assumption 2.

1.2 Bias of pIVW Estimator

The pIVW estimator is

$$\hat{\beta}_{\text{pIVW}} = \frac{\hat{\mu}_1}{\tilde{\mu}_2} + \frac{\hat{v}_{12}}{\hat{v}_2}\left(1 - \frac{\hat{\mu}_2}{\tilde{\mu}_2}\right),$$

where $\tilde{\mu}_2 = \hat{\mu}_2 \left(1 + \sqrt{1 + 4\lambda \hat{v}_2/\hat{\mu}_2^2}\right)/2$. The bias of the pIVW estimator is

$$E\big(\hat{\beta}_{\text{pIVW}} - \beta\big) = E\left(\frac{\hat{\mu}_1}{\tilde{\mu}_2} - \frac{\mu_1}{\mu_2}\right) + E\left(\frac{\hat{v}_{12}}{\hat{v}_2}\right)\left(1 - \frac{\hat{\mu}_2}{\tilde{\mu}_2}\right).$$

To evaluate $E\left(\frac{\hat{\mu}_1}{\tilde{\mu}_2} - \frac{\mu_1}{\mu_2}\right)$, we let $\tilde{x}_2 = \tilde{\mu}_2/m_2 - 1$ where $m_2 = E(\tilde{\mu}_2)$. By Taylor series expansion, we have

$$\frac{\hat{\mu}_1}{\tilde{\mu}_2} = \frac{\mu_1}{m_2}\ (\hat{x}_1 + 1)(\tilde{x}_2 + 1)^{-1} = \frac{\mu_1}{m_2} + \frac{\mu_1}{m_2}\ (\hat{x}_1 - \tilde{x}_2 + \tilde{x}_2^2 - \hat{x}_1 \tilde{x}_2) + o_p(\xi).$$

Then,

$$E\left(\frac{\hat{\mu}_1}{\tilde{\mu}_2} - \frac{\mu_1}{\mu_2}\right) = \frac{\mu_1}{m_2} - \frac{\mu_1}{\mu_2} + \frac{\mu_1}{m_2}\{E(\tilde{x}_2^2) - E(\hat{x}_1 \tilde{x}_2)\} + o(\xi). \qquad \text{(A1)}$$

To obtain Equation (A1), we let $\mu_2^* = \mu_2 \left(1 + \sqrt{1 + 4\lambda v_2/\mu_2^2}\right)/2$. By Taylor series expansion,

$$\frac{\tilde{\mu}_2}{\mu_2} = \frac{\mu_2^*}{\mu_2} + w\hat{x}_2 + \frac{\lambda v_2}{(2\mu_2^* - \mu_2)\mu_2}\hat{y}_2 + O_p(\xi^2) \qquad \text{(A2)}$$

where $w = \mu_2^*/(2\mu_2^* - \mu_2) = 1 + O(\xi)$ and $\hat{y}_2 = \hat{v}_2/v_2 - 1$. Then, the expectation of $\tilde{\mu}_2/\mu_2$ is

$$\frac{m_2}{\mu_2} = \frac{\mu_2^*}{\mu_2} + o(\xi).$$

Since $\mu_2^* = \mu_2 + \lambda v_2/\mu_2^*$, we have

$$\frac{m_2 - \mu_2}{m_2} = \frac{\lambda v_2}{\mu_2^2} + o(\xi) = O(\xi).$$

Therefore,

$$\frac{\mu_1}{m_2} - \frac{\mu_1}{\mu_2} = \frac{\beta(\mu_2 - m_2)}{m_2} = -\frac{\beta\lambda v_2}{\mu_2^2} + o(\xi).$$

From Equation (A2), we have

$$E(\tilde{x}_2^2) = \frac{w^2 v_2}{m_2^2} + \frac{2\lambda \mathrm{Cov}(\hat{\mu}_2, \hat{v}_2)}{\mu_2^3} + o(\xi^2) = \frac{v_2}{\mu_2^2} + o(\xi),$$

$$E(\hat{x}_1\tilde{x}_2) = \frac{w v_{12}}{\mu_1 m_2} + \frac{\lambda \mathrm{Cov}(\hat{\mu}_1, \hat{v}_2)}{\beta\mu_2^3} + o(\xi^2) = \frac{v_{12}}{\mu_1\mu_2} + o(\xi),$$

where $\mathrm{Cov}(\hat{\mu}_2, \hat{v}_2) = 8\sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-6}\sigma_{\hat{\gamma}_j}^{4}\left(2\gamma_j^2 + \sigma_{\hat{\gamma}_j}^2\right) = \Theta(\kappa p + p)$ and $\mathrm{Cov}(\hat{\mu}_1, \hat{v}_2) = 8\beta\sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-6}\sigma_{\hat{\gamma}_j}^{4}\gamma_j^2 = \Theta(\kappa p)$. Then, Equation (A1) becomes

$$E\left(\frac{\hat{\mu}_1}{\tilde{\mu}_2} - \frac{\mu_1}{\mu_2}\right) = -\frac{\beta\lambda v_2}{\mu_2^2} + \beta\left(\frac{v_2}{\mu_2^2} - \frac{v_{12}}{\mu_1\mu_2}\right) + o(\xi). \qquad \text{(A3)}$$

To evaluate $E\left(\frac{\hat{v}_{12}}{\hat{v}_2}\right)\left(1 - \frac{\hat{\mu}_2}{\tilde{\mu}_2}\right)$, we let $\hat{y}_{12} = \hat{v}_{12}/v_{12} - 1$. By Taylor series expansion,

$$\frac{\hat{v}_{12}}{\hat{v}_2} = \frac{v_{12}}{v_2}(\hat{y}_{12} + 1)(\hat{y}_2 + 1)^{-1} = \frac{v_{12}}{v_2}(1 + \hat{y}_{12} - \hat{y}_2 + \hat{y}_2^2 - \hat{y}_{12}\hat{y}_2) + o_p(\xi),$$

$$1 - \frac{\hat{\mu}_2}{\tilde{\mu}_2} = \frac{\lambda\hat{v}_2}{\tilde{\mu}_2^2} = \frac{\lambda v_2}{m_2^2}(\hat{y}_2 + 1)(\tilde{x}_2 + 1)^{-2} = \frac{\lambda v_2}{m_2^2}(1 + \hat{y}_2 - 2\tilde{x}_2) + O_p(\xi^2).$$

Then, we have

$$\frac{\hat{v}_{12}}{\hat{v}_2}\left(1 - \frac{\hat{\mu}_2}{\tilde{\mu}_2}\right) = \frac{\lambda v_{12}}{m_2^2}(\hat{y}_2 + 1 - 2\tilde{x}_2) + O_p(\xi^2),$$

and the expectation

$$E\left(\frac{\hat{v}_{12}}{\hat{v}_2}\right)\left(1 - \frac{\hat{\mu}_2}{\tilde{\mu}_2}\right) = \frac{\lambda v_{12}}{\mu_2^2} + o(\xi). \qquad \text{(A4)}$$

Combining Equations (A3) and (A4), the bias of our proposed pIVW estimator is

$$\begin{aligned} E(\hat{\beta}_{\mathrm{pIVW}} - \beta) &= E\left(\frac{\hat{\mu}_1}{\tilde{\mu}_2} - \frac{\mu_1}{\mu_2}\right) + E\left(\frac{\hat{v}_{12}}{\hat{v}_2}\right)\left(1 - \frac{\hat{\mu}_2}{\tilde{\mu}_2}\right) \\ &= -\frac{\beta\lambda v_2}{\mu_2^2} + \beta\left(\frac{v_2}{\mu_2^2} - \frac{v_{12}}{\mu_1\mu_2}\right) + \frac{\lambda v_{12}}{\mu_2^2} + o(\xi) \\ &= (1-\lambda)\beta\left(\frac{v_2}{\mu_2^2} - \frac{v_{12}}{\mu_1\mu_2}\right) + o(\xi). \end{aligned}$$

2 Proof of Theorem 1 (b)

By Taylor series expansion, we have

$$\begin{aligned} (\hat{\beta}_{\mathrm{dIVW}} - \beta)^2 = \beta^2(&\hat{x}_1^2 + \hat{x}_2^2 - 2\hat{x}_1\hat{x}_2 - 2\hat{x}_1^2\hat{x}_2 + 4\hat{x}_1\hat{x}_2^2 - 2\hat{x}_2^3 + 3\hat{x}_1^2\hat{x}_2^2 - 6\hat{x}_1\hat{x}_2^3 + 3\hat{x}_2^4) \\ &+ o_p(\xi^2). \end{aligned}$$

Therefore,

$$E\left(\hat{\beta}_{\text{dIVW}}-\beta\right)^2=\beta^2\left\{\frac{v_1}{\mu_1^2}+\frac{v_2}{\mu_2^2}-\frac{2v_{12}}{\mu_1\mu_2}-2E(\hat{x}_1^2\hat{x}_2)+4E(\hat{x}_1\hat{x}_2^2)-2E(\hat{x}_2^3)+3E(\hat{x}_1^2\hat{x}_2^2)\right.$$
$$\left.-6E(\hat{x}_1\hat{x}_2^3)+3E(\hat{x}_2^4)\right\}+o(\xi^2)=O(\xi), \qquad \text{(A5)}$$

where $v_1=\text{Var}(\hat{\mu}_1)=\sum_{j=1}^p\sigma_{\hat{\Gamma}_j}^{-4}\left\{\left(\sigma_{\hat{\gamma}_j}^2\beta^2+\sigma_{\hat{\Gamma}_j}^2+\tau^2\right)\gamma_j^2+\left(\sigma_{\hat{\Gamma}_j}^2+\tau^2\right)\sigma_{\hat{\gamma}_j}^2\right\}=\Theta(\kappa p+p)$ by Assumption 2, and after some algebra, the expectations $E(\hat{x}_1^2\hat{x}_2)$, $E(\hat{x}_1\hat{x}_2^2)$, $E(\hat{x}_2^3)$, $E(\hat{x}_1^2\hat{x}_2^2)$, $E(\hat{x}_1\hat{x}_2^3)$ and $E(\hat{x}_2^4)$ are all of order $O(\xi^2)$. Since $E\left(\hat{\beta}_{\text{dIVW}}-\beta\right)=O(\xi)$, the variance of the dIVW estimator is

$$\text{Var}\left(\hat{\beta}_{\text{dIVW}}\right)=E\left(\hat{\beta}_{\text{dIVW}}-\beta\right)^2-E^2\left(\hat{\beta}_{\text{dIVW}}-\beta\right)=O(\xi).$$

The difference of variance between $\hat{\beta}_{\text{dIVW}}$ and $\hat{\beta}_{\text{pIVW}}$ is

$$\text{Var}\left(\hat{\beta}_{\text{dIVW}}\right)-\text{Var}\left(\hat{\beta}_{\text{pIVW}}\right)$$
$$=E\left(\hat{\beta}_{\text{dIVW}}-\beta\right)^2-E\left(\hat{\beta}_{\text{pIVW}}-\frac{\mu_1}{m_2}\right)^2+E^2\left(\hat{\beta}_{\text{pIVW}}-\frac{\mu_1}{m_2}\right)-E^2\left(\hat{\beta}_{\text{dIVW}}-\beta\right).$$

First, we calculate $E^2\left(\hat{\beta}_{\text{pIVW}}-\frac{\mu_1}{m_2}\right)-E^2\left(\hat{\beta}_{\text{dIVW}}-\beta\right)$. Since

$$\beta-\frac{\mu_1}{m_2}=\beta\left(\frac{m_2-\mu_2}{m_2}\right)=\frac{\lambda\beta v_2}{\mu_2^2}+o(\xi),$$

we have

$$E^2\left(\hat{\beta}_{\text{pIVW}}-\frac{\mu_1}{m_2}\right)=\left\{E\left(\hat{\beta}_{\text{pIVW}}-\beta\right)+\left(\beta-\frac{\mu_1}{m_2}\right)\right\}^2$$
$$=\beta^2\left\{(1-\lambda)\left(\frac{v_2}{\mu_2^2}-\frac{v_{12}}{\mu_1\mu_2}\right)+\frac{\lambda v_2}{\mu_2^2}\right\}^2+o(\xi^2).$$

Therefore,

$$E^2\left(\hat{\beta}_{\text{pIVW}}-\frac{\mu_1}{m_2}\right)-E^2\left(\hat{\beta}_{\text{dIVW}}-\beta\right)=\frac{2\lambda\beta v_2v_{12}}{\mu_2^4}+\frac{v_{12}^2}{\mu_2^4}(\lambda^2-2\lambda)+o(\xi^2). \qquad \text{(A6)}$$

Next, we calculate $E\left(\hat{\beta}_{\text{dIVW}}-\beta\right)^2-E\left(\hat{\beta}_{\text{pIVW}}-\frac{\mu_1}{m_2}\right)^2$. By Taylor series expansion, we have

$$\hat{\beta}_{\text{pIVW}}-\frac{\mu_1}{m_2}=\frac{\hat{\mu}_1}{\tilde{\mu}_2}-\frac{\mu_1}{m_2}+\frac{\hat{v}_{12}}{\hat{v}_2}\left(1-\frac{\hat{\mu}_2}{\tilde{\mu}_2}\right)$$
$$=\frac{\mu_1}{m_2}(\hat{x}_1-\tilde{x}_2-\hat{x}_1\tilde{x}_2+\tilde{x}_2^2+\hat{x}_1\tilde{x}_2^2-\tilde{x}_2^3)+\frac{\lambda v_{12}}{m_2^2}(\hat{y}_2+1-2\tilde{x}_2)+O_p(\xi^2).$$

Then,

$$\left(\hat{\beta}_{\text{pIVW}}-\frac{\mu_1}{m_2}\right)^2=\left(\frac{\mu_1}{m_2}\right)^2(\hat{x}_1^2+\tilde{x}_2^2-2\hat{x}_1\tilde{x}_2-2\hat{x}_1^2\tilde{x}_2+4\hat{x}_1\tilde{x}_2^2-2\tilde{x}_2^3+3\hat{x}_1^2\tilde{x}_2^2-6\hat{x}_1\tilde{x}_2^3$$
$$+3\tilde{x}_2^4)-\frac{2\lambda\mu_1v_{12}}{m_2^3}(\hat{x}_1\hat{y}_2-\tilde{x}_2\hat{y}_2+\hat{x}_1-\tilde{x}_2-3\hat{x}_1\tilde{x}_2+3\tilde{x}_2^2)+\frac{\lambda^2v_{12}^2}{m_2^4}$$
$$+o_p(\xi^2).$$

From Equation (A2), we have $E(\tilde{x}_1^2\tilde{x}_2) = E(\hat{x}_1^2\hat{x}_2) + o(\xi^2)$, $E(\hat{x}_1\tilde{x}_2^2) = E(\hat{x}_1\hat{x}_2^2) + o(\xi^2)$, $E(\tilde{x}_2^3) = E(\hat{x}_2^3) + o(\xi^2)$, $E(\hat{x}_1^2\tilde{x}_2^2) = E(\hat{x}_1^2\hat{x}_2^2) + o(\xi^2)$, $E(\hat{x}_1\tilde{x}_2^3) = E(\hat{x}_1\hat{x}_2^3) + o(\xi^2)$, $E(\tilde{x}_2^4) = E(\hat{x}_2^4) + o(\xi^2)$, and $E(\tilde{x}_2\hat{y}_2) = \mathrm{Cov}(\hat{\mu}_2, \hat{v}_2)/(\mu_2 v_2) + o(\xi)$. After some algebra, we have

$$\begin{aligned}
&E\left(\hat{\beta}_{\mathrm{pIVW}} - \frac{\mu_1}{m_2}\right)^2 \\
&\quad = \left(\frac{\mu_1}{m_2}\right)^2\left(\frac{v_1}{\mu_1^2} + \frac{w^2 v_2}{m_2^2} - \frac{2wv_{12}}{\mu_1 m_2}\right) \\
&\quad + \beta^2\{-2E(\hat{x}_1^2\hat{x}_2) + 4E(\hat{x}_1\hat{x}_2^2) - 2E(\hat{x}_2^3) + 3E(\hat{x}_1^2\hat{x}_2^2) - 6E(\hat{x}_1\hat{x}_2^3) \\
&\quad + 3E(\hat{x}_2^4)\} + \frac{\lambda^2 v_{12}^2}{\mu_2^4} + \frac{6\lambda\beta v_{12}}{\mu_2^2}\left(\frac{v_2}{\mu_2^2} - \frac{v_{12}}{\mu_1\mu_2}\right) \\
&\quad - 16\lambda\beta\left(\frac{v_{12}}{v_2} - \beta\right)\frac{\sum_{j=1}^{p}\sigma_{\hat{\Gamma}_j}^{-6}\sigma_{\hat{\gamma}_j}^{6}\left(\gamma_j^2\sigma_{\hat{\gamma}_j}^{-2} + 1\right)}{\mu_2^3} + o(\xi^2). \qquad \text{(A7)}
\end{aligned}$$

From Equations (A5) and (A7), we have

$$\begin{aligned}
&E\left(\hat{\beta}_{\mathrm{dIVW}} - \beta\right)^2 - E\left(\hat{\beta}_{\mathrm{pIVW}} - \frac{\mu_1}{m_2}\right)^2 \\
&= \beta^2\left(\frac{v_1}{\mu_1^2} + \frac{v_2}{\mu_2^2} - \frac{2v_{12}}{\mu_1\mu_2}\right) - \left(\frac{\mu_1}{m_2}\right)^2\left(\frac{v_1}{\mu_1^2} + \frac{w^2 v_2}{m_2^2} - \frac{2wv_{12}}{\mu_1 m_2}\right) - \frac{\lambda^2 v_{12}^2}{\mu_2^4} \\
&\quad - \frac{6\lambda\beta v_{12}}{\mu_2^2}\left(\frac{v_2}{\mu_2^2} - \frac{v_{12}}{\mu_1\mu_2}\right) + 16\lambda\beta\left(\frac{v_{12}}{v_2} - \beta\right)\frac{\sum_{j=1}^{p}\sigma_{\hat{\Gamma}_j}^{-6}\sigma_{\hat{\gamma}_j}^{6}\left(\gamma_j^2\sigma_{\hat{\gamma}_j}^{-2} + 1\right)}{\mu_2^3} + o(\xi^2) \\
&= \frac{2\lambda v_1 v_2}{\mu_2^4} + \frac{6\lambda\beta^2 v_2^2}{\mu_2^4} - \frac{14\lambda\beta v_2 v_{12}}{\mu_2^4} + \frac{(6\lambda - \lambda^2)v_{12}^2}{\mu_2^4} \\
&\quad + 16\lambda\beta\left(\frac{v_{12}}{v_2} - \beta\right)\frac{\sum_{j=1}^{p}\sigma_{\hat{\Gamma}_j}^{-6}\sigma_{\hat{\gamma}_j}^{6}\left(\gamma_j^2\sigma_{\hat{\gamma}_j}^{-2} + 1\right)}{\mu_2^3} + o(\xi^2), \qquad \text{(A8)}
\end{aligned}$$

where we obtain the second equality by using $(m_2 - \mu_2)/m_2 = \lambda v_2/\mu_2^2 + o(\xi)$ and $1 - w = \lambda v_2/\mu_2^2 + o(\xi)$. Combining Equations (A6) and (A8), the difference in the variance between the dIVW estimator and the pIVW estimator is

$$\begin{aligned}
\mathrm{Var}\left(\hat{\beta}_{\mathrm{dIVW}}\right) - \mathrm{Var}\left(\hat{\beta}_{\mathrm{pIVW}}\right) &= \frac{2\lambda v_1 v_2}{\mu_2^4} + \frac{6\lambda\beta^2 v_2^2}{\mu_2^4} - \frac{12\lambda\beta v_2 v_{12}}{\mu_2^4} + \frac{4\lambda v_{12}^2}{\mu_2^4} \\
&\quad + 16\lambda\beta\left(\frac{v_{12}}{v_2} - \beta\right)\frac{\sum_{j=1}^{p}\sigma_{\hat{\Gamma}_j}^{-6}\sigma_{\hat{\gamma}_j}^{6}\left(\gamma_j^2\sigma_{\hat{\gamma}_j}^{-2} + 1\right)}{\mu_2^3} + o(\xi^2) \\
&= \frac{2\lambda\beta^2}{\mu_2^4}\Delta + o(\xi^2),
\end{aligned}$$

where

$$\Delta = \frac{3(\mu_1 v_2 - \mu_2 v_{12})^2}{\mu_2^2\beta^2} + \frac{v_1 v_2 - v_{12}^2}{\beta^2} + 8\mu_2\left(\frac{v_{12}}{v_2\beta} - 1\right)\sum_{j=1}^{p}\sigma_{\hat{\Gamma}_j}^{-6}\sigma_{\hat{\gamma}_j}^{6}\left(\gamma_j^2\sigma_{\hat{\gamma}_j}^{-2} + 1\right).$$

3 Proof of Theorem 1 (c)

We first prove

$$V^{-\frac{1}{2}}(\hat{\beta}_{\text{pIVW}}-\beta)=\left(\frac{\mu_2}{\sqrt{v}}\right)\frac{\hat{\mu}_1-\beta\hat{\mu}_2}{\tilde{\mu}_2}+\left(\frac{\mu_2}{\sqrt{v}}\right)\left(\frac{\hat{\mu}_2}{\tilde{\mu}_2}-1\right)\left(\beta-\frac{\hat{v}_{12}}{\hat{v}_2}\right)\xrightarrow{d}N(0,1),$$

where $V=\mu_2^{-2}\sum_{j=1}^{p}\left\{\sigma_{\hat{\Gamma}_j}^{-2}\left(\gamma_j^2+\sigma_{\hat{\gamma}_j}^2\right)\left(1+\tau^2\sigma_{\hat{\Gamma}_j}^{-2}\right)+\beta^2\sigma_{\hat{\gamma}_j}^2\sigma_{\hat{\Gamma}_j}^{-4}\left(\gamma_j^2+2\sigma_{\hat{\gamma}_j}^2\right)\right\}$ and $v=\mu_2^2V$. For this, we prove $\left(\frac{\mu_2}{\sqrt{v}}\right)\frac{\hat{\mu}_1-\beta\hat{\mu}_2}{\tilde{\mu}_2}\xrightarrow{d}N(0,1)$ and $\left(\frac{\mu_2}{\sqrt{v}}\right)\left(\frac{\hat{\mu}_2}{\tilde{\mu}_2}-1\right)\left(\beta-\frac{\hat{v}_{12}}{\hat{v}_2}\right)\xrightarrow{p}0$ in the following.

First, we prove $\tilde{\mu}_2/\mu_2\xrightarrow{p}1$. For this, we let $\tilde{\mu}_2=\hat{\mu}_2r_\lambda$ with $r_\lambda=\left(1+\sqrt{1+4\lambda\hat{v}_2/\hat{\mu}_2^2}\right)/2$. We have $\hat{\mu}_2/\mu_2\xrightarrow{p}1$ as $\eta\to\infty$, since $E(\hat{\mu}_2/\mu_2)=1$ and $\text{Var}(\hat{\mu}_2/\mu_2)=O(\xi)$. Similarly, $\hat{v}_2/v_2\xrightarrow{p}1$ as $\eta\to\infty$, since $E(\hat{v}_2/v_2)=1$ and $\text{Var}(\hat{v}_2/v_2)=O(\xi)$. Since $v_2/\mu_2^2=O(\xi)$, we have $r_\lambda\xrightarrow{p}1$ and thus $\tilde{\mu}_2/\mu_2\xrightarrow{p}1$ as $\eta\to\infty$.

Next, we prove $\frac{\hat{\mu}_1-\beta\hat{\mu}_2}{\sqrt{v}}\xrightarrow{d}N(0,1)$ as $p\to\infty$ by the Lindeberg Central Limit Theorem. Let

$$\frac{\hat{\mu}_1-\beta\hat{\mu}_2}{\sqrt{v}}=\frac{\sum_{j=1}^{p}\hat{x}_j}{\sqrt{\sum_{j=1}^{p}v_j}},$$

where $\hat{x}_j=\sigma_{\hat{\Gamma}_j}^{-2}\left\{\hat{\gamma}_j\hat{\Gamma}_j-\beta\left(\hat{\gamma}_j^2-\sigma_{\hat{\gamma}_j}^2\right)\right\}$ and $v_j=\sigma_{\hat{\Gamma}_j}^{-2}\left(\gamma_j^2+\sigma_{\hat{\gamma}_j}^2\right)\left(1+\tau^2\sigma_{\hat{\Gamma}_j}^{-2}\right)+\beta^2\sigma_{\hat{\gamma}_j}^2\sigma_{\hat{\Gamma}_j}^{-4}\left(\gamma_j^2+2\sigma_{\hat{\gamma}_j}^2\right)$. Let $\hat{z}_j=\hat{x}_j/\sqrt{v_j}$. Then, the Lindeberg's condition is

$$\frac{1}{v}\sum_{j=1}^{p}E\left(\hat{x}_j^2I\{|\hat{x}_j|>\epsilon\sqrt{v}\}\right)=\frac{1}{v}\sum_{j=1}^{p}E\left(v_j\hat{z}_j^2\,I\{\sqrt{v_j}|\hat{z}_j|>\epsilon\sqrt{v}\}\right)$$
$$\le\max_j E\left(\hat{z}_j^2\,I\{\sqrt{v_j}|\hat{z}_j|>\epsilon\sqrt{v}\}\right),$$

where $I\{\cdot\}$ denotes the indicative function. By Assumption 2, we have $v=\Theta(\kappa p+p)$. Therefore, $\max_j v_j/v\to0$ as $\max_j\gamma_j^2\sigma_{\hat{\gamma}_j}^{-2}/(\kappa p+p)\to0$. Together with $E\left(\hat{z}_j^2\right)=1$, we verify the Lindeberg's condition $\frac{1}{v}\sum_{j=1}^{p}E\left(\hat{x}_j^2I\{|\hat{x}_j|>\epsilon\sqrt{v}\}\right)\to0$ for any $\epsilon>0$. Then, $\left(\frac{\mu_2}{\sqrt{v}}\right)\frac{\hat{\mu}_1-\beta\hat{\mu}_2}{\tilde{\mu}_2}\xrightarrow{d}N(0,1)$ follows from Slutsky's theorem.

Lastly, we prove $\left(\frac{\mu_2}{\sqrt{v}}\right)\left(\frac{\hat{\mu}_2}{\tilde{\mu}_2}-1\right)\left(\beta-\frac{\hat{v}_{12}}{\hat{v}_2}\right)\xrightarrow{p}0$. For this, we rewrite $\hat{\mu}_2/\tilde{\mu}_2-1$ as

$$\frac{\hat{\mu}_2}{\tilde{\mu}_2}-1=\frac{1-r_\lambda}{r_\lambda}=-\frac{\lambda\hat{v}_2}{\hat{\mu}_2^2}\frac{1}{r_\lambda^2},$$

where the last equality follows from $(r_\lambda-1)r_\lambda=\lambda\hat{v}_2/\hat{\mu}_2^2$. As such,

$$\left(\frac{\mu_2}{\sqrt{v}}\right)\left(\frac{\hat{\mu}_2}{\tilde{\mu}_2}-1\right)=-\left(\frac{\lambda v_2}{\sqrt{v}\mu_2}\right)\frac{\mu_2^2}{\hat{\mu}_2^2}\frac{\hat{v}_2}{v_2}\frac{1}{r_\lambda^2}=O_p(\xi^{1/2}).$$

Together with $\beta-\frac{\hat{v}_{12}}{\hat{v}_2}=O_p(1)$, we have $\left(\frac{\mu_2}{\sqrt{v}}\right)\left(\frac{\hat{\mu}_2}{\tilde{\mu}_2}-1\right)\left(\beta-\frac{\hat{v}_{12}}{\hat{v}_2}\right)\xrightarrow{p}0$ as $\eta\to\infty$. Since $\left(\frac{\mu_2}{\sqrt{v}}\right)\frac{\hat{\mu}_1-\beta\hat{\mu}_2}{\tilde{\mu}_2}\xrightarrow{d}N(0,1)$ and $\left(\frac{\mu_2}{\sqrt{v}}\right)\left(\frac{\hat{\mu}_2}{\tilde{\mu}_2}-1\right)\left(\beta-\frac{\hat{v}_{12}}{\hat{v}_2}\right)\xrightarrow{p}0$, we get $V^{-\frac{1}{2}}(\hat{\beta}_{\text{pIVW}}-\beta)\xrightarrow{d}N(0,1)$

by Slutsky's theorem. Further, to prove that $\hat{V}^{-1/2}(\hat{\beta}_{\mathrm{pIVW}}-\beta) \xrightarrow{d} N(0,1)$ holds with the estimator $\hat{V}$ of V, it suffices to prove $\tilde{\mu}_2/\mu_2 \xrightarrow{p} 1$ and $\hat{v}/v \xrightarrow{p} 1$. We have shown $\tilde{\mu}_2/\mu_2 \xrightarrow{p} 1$ above. Following Ye et al., 2021, it can be shown that $\hat{v}/v \xrightarrow{p} 1$ after replacing $\hat{\beta}_{\mathrm{dIVW}}$ by $\hat{\beta}_{\mathrm{pIVW}}$. Thus, we omit the details here.

REFERENCE

YE, T., SHAO, J. and KANG, H. (2021). Debiased inverse-variance weighted estimator in two sample summary-data Mendelian randomization. *Annals of Statistics* 49, 2079-2100.

Web Appendix D: Proof of $\Delta > 0$

The following proof holds for both the situations with balanced horizontal pleiotropy ($\tau \neq 0$) and without horizontal pleiotropy ($\tau = 0$).

Let $\kappa_j = \gamma_j^2 \sigma_{\hat{\gamma}_j}^{-2}$. After some simple algebra, we have

$$\Delta = \frac{v_1 v_2}{\beta^2} + 3v_2^2 - \frac{6v_2 v_{12}}{\beta} + \frac{2v_{12}^2}{\beta^2} + 8\mu_2\left(\frac{v_{12}}{v_2\beta} - 1\right)\sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-6}\sigma_{\hat{\gamma}_j}^{6}(\kappa_j + 1)$$

$$> v_2 \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4}\sigma_{\hat{\gamma}_j}^{4}\kappa_j + 6v_2 \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4}\sigma_{\hat{\gamma}_j}^{4} + 8\left(\sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4}\sigma_{\hat{\gamma}_j}^{4}\kappa_j\right)^2 - 8\sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-2}\sigma_{\hat{\gamma}_j}^{2}\kappa_j \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-6}\sigma_{\hat{\gamma}_j}^{6}(\kappa_j + 1)$$

$$= 2\sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4}\sigma_{\hat{\gamma}_j}^{4}(2\kappa_j + 3)\sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4}\sigma_{\hat{\gamma}_j}^{4}(3\kappa_j + 2) - 8\sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-2}\sigma_{\hat{\gamma}_j}^{2}\kappa_j \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-6}\sigma_{\hat{\gamma}_j}^{6}(\kappa_j + 1),$$

where we obtain the second inequality by using $v_1 > \beta^2 \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4}\sigma_{\hat{\gamma}_j}^{4}\kappa_j$ and omitting the term $8\mu_2 v_{12}/(v_2\beta)\ \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-6}\sigma_{\hat{\gamma}_j}^{6}(\kappa_j + 1)$. Therefore, a sufficient condition of $\Delta > 0$ is

$$\sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4}\sigma_{\hat{\gamma}_j}^{4}(2\kappa_j + 3)\sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4}\sigma_{\hat{\gamma}_j}^{4}(3\kappa_j + 2) > 4\sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-2}\sigma_{\hat{\gamma}_j}^{2}\kappa_j \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-6}\sigma_{\hat{\gamma}_j}^{6}(\kappa_j + 1). \quad \text{(A9)}$$

Since $\hat{\gamma}_j$ and $\hat{\Gamma}_j$ in GWAS are estimated from the marginal linear models, we can further express the ratio of their variances as $\sigma_{\hat{\Gamma}_j}^{-2}\sigma_{\hat{\gamma}_j}^{2} = n_Y \mathrm{Var}(X)(1 - h_{X,j})/\{n_x \mathrm{Var}(Y)(1 - h_{Y,j})\}$, where $h_{X,j}$ and $h_{Y,j}$ denote the variances of X and Y explained by G_j, respectively. Let $c_j^2 = (1 - h_{X,j})/(1 - h_{Y,j})$. Then, the inequality (A9) can be simplified as

$$\sum_{j=1}^{p} c_j^4(2\kappa_j + 3)\sum_{j=1}^{p} c_j^4(3\kappa_j + 2) > 4\sum_{j=1}^{p} c_j^2\kappa_j \sum_{j=1}^{p} c_j^6(\kappa_j + 1).$$

Let

$$\Delta_{1j} = c_j^2 - c_j^4 = \left(\frac{1 - h_{X,j}}{1 - h_{Y,j}}\right)\left(\frac{h_{X,j} - h_{Y,j}}{1 - h_{Y,j}}\right),$$

$$\Delta_{2j} = c_j^6 - c_j^4 = -\left(\frac{1-h_{X,j}}{1-h_{Y,j}}\right)^2 \left(\frac{h_{X,j}-h_{Y,j}}{1-h_{Y,j}}\right).$$

Then, we have

$$\sum_{j=1}^{p} c_j^2\kappa_j \sum_{j=1}^{p} c_j^6(\kappa_j+1) = \sum_{j=1}^{p}(c_j^4+\Delta_{1j})\kappa_j \sum_{j=1}^{p}(c_j^4+\Delta_{2j})\kappa_j + \sum_{j=1}^{p}(c_j^4+\Delta_{1j})\kappa_j \sum_{j=1}^{p}(c_j^4+\Delta_{2j}).$$

Further, we have

$$\sum_{j=1}^{p} c_j^4(2\kappa_j+3) \sum_{j=1}^{p} c_j^4(3\kappa_j+2) > 6\sum_{j=1}^{p} c_j^4\kappa_j \sum_{j=1}^{p} c_j^4\kappa_j + 13\sum_{j=1}^{p} c_j^4\kappa_j \sum_{j=1}^{p} c_j^4$$

Therefore, the inequality (A9) holds when

$$6\sum_{j=1}^{p} c_j^4\kappa_j \sum_{j=1}^{p} c_j^4\kappa_j + 13\sum_{j=1}^{p} c_j^4\kappa_j \sum_{j=1}^{p} c_j^4$$
$$> 4\sum_{j=1}^{p}(c_j^4+\Delta_{1j})\kappa_j \sum_{j=1}^{p}(c_j^4+\Delta_{2j})\kappa_j + 4\sum_{j=1}^{p}(c_j^4+\Delta_{1j})\kappa_j \sum_{j=1}^{p}(c_j^4+\Delta_{2j}). \qquad \text{(A10)}$$

The inequality (A10) holds when $6c_j^4 > 4(c_j^4+\Delta_{1j})$ and $6c_j^4 > 4(c_j^4+\Delta_{2j})$, that is,

$$c_j^4 > 2\max(\Delta_{1j}, \Delta_{2j}),$$

which holds as long as $\max(h_{X,j}, h_{Y,j}) < 1/3$. Therefore, $\mathrm{Var}(\hat{\beta}_{\mathrm{pIVW}})$ is asymptotically smaller than $\mathrm{Var}(\hat{\beta}_{\mathrm{dIVW}})$ as long as both the proportions of variances of X and Y explained by each IV are less than $1/3$, which is generally true in the genetic context especially when X and Y are some complex traits.

Web Appendix E: Bootstrapping Fieller's Confidence Interval

Adopting Fieller's method to derive a confidence interval for a ratio, we let $\hat{z}(\beta) = (\tilde{\mu}_1 - \beta\tilde{\mu}_2)^2/(\tilde{v}_1 - 2\beta\tilde{v}_{12} + \beta^2\tilde{v}_2)$, where $\tilde{v}_1 = \hat{\gamma}_j^2\hat{\Gamma}_j^2 - \left(\hat{\Gamma}_j^2 - \sigma_{\hat{\Gamma}_j}^2 - \hat{\tau}^2\right)\left(\hat{\gamma}_j^2 - \sigma_{\hat{\gamma}_j}^2\right)$ and $\tilde{v}_2 = \tilde{\mu}_2^2/(2\tilde{\mu}_2 - \hat{\mu}_2)^2 \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4}\left(4\sigma_{\hat{\gamma}_j}^2\hat{\gamma}_j^2 - 2\sigma_{\hat{\gamma}_j}^4\right)$ are the estimated variances of $\tilde{\mu}_1$ and $\tilde{\mu}_2$, respectively, and $\tilde{v}_{12} = 2\tilde{\mu}_2/(2\tilde{\mu}_2 - \hat{\mu}_2)\sum_{j=1}^{p}\sigma_{\hat{\Gamma}_j}^{-4}\sigma_{\hat{\gamma}_j}^2\hat{\gamma}_j\hat{\Gamma}_j$ is the estimated covariance between $\tilde{\mu}_1$ and $\tilde{\mu}_2$. We obtain the $(1-\alpha)$th quantile $q_{1-\alpha}$ of the distribution of $\hat{z}(\beta)$ via the bootstrap method, where we calculate the bth bootstrap statistic $\hat{z}^{(b)}(\hat{\beta}_{\mathrm{pIVW}})$ based on the bootstrap sample $\hat{\gamma}_j^{(b)} \sim N\left(\hat{\gamma}_j, \sigma_{\hat{\gamma}_j}^2\right)$ and $\hat{\Gamma}_j^{(b)} \sim N\left(\hat{\gamma}_j\hat{\beta}_{\mathrm{pIVW}}, \sigma_{\hat{\Gamma}_j}^2 + \hat{\tau}^2\right)$. Then, we solve $\hat{z}(\beta) < q_{1-\alpha}$ for the $100(1-\alpha)\%$ confidence interval of β. When the IV selection is performed, we construct boostrapping Fieller's confidence interval in a similar way, where only the selected IVs are used to generate the bootstrap samples.

Web Appendix F: Proof of Theorem 2

The following proof of Theorem 2 takes into account balanced horizontal pleiotropy ($\tau \neq 0$). The situation without horizontal pleiotropy can be considered as a special case with $\tau = 0$.

1 Proof of Theorem 2 (a)

1.1 Bias of dIVW Estimator

When an independent selection dataset $\left\{\gamma_j^*, \sigma_{\hat{\gamma}_j}^*\right\}_{j=1,\ldots p}$ is available, the IVs are included into the analysis when $\left|\gamma_j^*\right| > \delta\sigma_{\hat{\gamma}_j}^*$ with a threshold δ. Then, the dIVW estimator can be written as

$$\hat{\beta}_{\delta,\text{dIVW}} = \frac{\hat{\mu}_{1,\delta}}{\hat{\mu}_{2,\delta}} = \frac{\sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-2} \hat{\gamma}_j \hat{\Gamma}_j s_j}{\sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-2} \left(\hat{\gamma}_j^2 - \sigma_{\hat{\gamma}_j}^2\right) s_j},$$

where $s_j = I\left\{\left|\gamma_j^*\right| > \delta\sigma_{\hat{\gamma}_j}^*\right\}$ with the indicative function $I\{\cdot\}$.

Similar to the proof in Section 1.1 of Web Appendix C, the bias of the dIVW estimator is

$$E\left(\hat{\beta}_{\delta,\text{dIVW}} - \beta\right) = \beta\left(\frac{v_{2,\delta}}{\mu_{2,\delta}^2} - \frac{v_{12,\delta}}{\mu_{1,\delta}\mu_{2,\delta}}\right) + o(\xi_\delta) = O(\xi_\delta),$$

where $\mu_{1,\delta} = E\left(\hat{\mu}_{1,\delta}\right) = \beta \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-2} \gamma_j^2 q_{\delta,j} = \Theta(\kappa_\delta p_\delta)$, $\mu_{2,\delta} = E\left(\hat{\mu}_{2,\delta}\right) = \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-2} \gamma_j^2 q_{\delta,j} = \Theta(\kappa_\delta p_\delta)$, $v_{2,\delta} = \text{Var}\left(\hat{\mu}_{2,\delta}\right) = \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4} \left(4\sigma_{\hat{\gamma}_j}^2 \gamma_j^2 + 2\sigma_{\hat{\gamma}_j}^4\right) q_{\delta,j} + \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4} \gamma_j^4 q_{\delta,j}\left(1 - q_{\delta,j}\right) = \Theta(\kappa_\delta p_\delta + p_\delta) + \Theta(\varphi^2 p_\delta)$ and $v_{12,\delta} = \text{Cov}\left(\hat{\mu}_{1,\delta}, \hat{\mu}_{2,\delta}\right) = 2\beta \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4} \sigma_{\hat{\gamma}_j}^2 \gamma_j^2 q_{\delta,j} + \beta \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4} \gamma_j^4 q_{\delta,j}\left(1 - q_{\delta,j}\right) = \Theta(\kappa_\delta p_\delta) + \Theta(\varphi^2 p_\delta)$ under Assumptions 2 and 3. As the effective sample size $\eta_\delta = \kappa_\delta\sqrt{p_\delta}/\max(1,\varphi) \to \infty$, $\xi_\delta = 1/\kappa_\delta p_\delta + \max(1,\varphi^2)/\kappa_\delta^2 p_\delta$ converges to zero.

1.2 Bias of pIVW Estimator

The proposed pIVW estimator $\hat{\beta}_{\delta,\text{pIVW}}$ can be written as

$$\hat{\beta}_{\delta,\text{pIVW}} = \frac{\hat{\mu}_{1,\delta}}{\tilde{\mu}_{2,\delta}} + \frac{\hat{v}_{12,\delta}}{\hat{v}_{2,\delta}}\left(1 - \frac{\hat{\mu}_{2,\delta}}{\tilde{\mu}_{2,\delta}}\right),$$

where $\hat{v}_{2,\delta} = \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4} \left\{4\left(\hat{\gamma}_j^2 - \sigma_{\hat{\gamma}_j}^2\right)\sigma_{\hat{\gamma}_j}^2 + 2\sigma_{\hat{\gamma}_j}^4\right\} s_j$, $\hat{v}_{12,\delta} = 2\sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4} \sigma_{\hat{\gamma}_j}^2 \hat{\Gamma}_j \hat{\gamma}_j s_j$ and $\tilde{\mu}_{2,\delta} = \hat{\mu}_{2,\delta}\left(1 + \sqrt{1 + 4\lambda\hat{v}_{2,\delta}/\hat{\mu}_{2,\delta}^2}\right)/2$. As in Section 1.2 of Web Appendix C, we have

$$E\left(\frac{\hat{\mu}_{1,\delta}}{\tilde{\mu}_{2,\delta}} - \frac{\mu_{1,\delta}}{\mu_{2,\delta}}\right) = -\frac{\beta\lambda v_{2,\delta}^*}{\mu_{2,\delta}^2} + \beta\left(\frac{v_{2,\delta}}{\mu_{2,\delta}^2} - \frac{v_{12,\delta}}{\mu_{1,\delta}\mu_{2,\delta}}\right) + o(\xi_\delta),$$

$$E\left(\frac{\hat{v}_{12,\delta}}{\hat{v}_{2,\delta}}\right)\left(1 - \frac{\hat{\mu}_{2,\delta}}{\tilde{\mu}_{2,\delta}}\right) = \frac{\lambda v_{12,\delta}^*}{\mu_{2,\delta}^2} + o(\xi_\delta),$$

where $v_{2,\delta}^{*} = E(\hat{v}_{2,\delta}) = \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4} \left(4\sigma_{\hat{\gamma}_j}^{2}\gamma_j^2 + 2\sigma_{\hat{\gamma}_j}^{4}\right) q_{\delta,j} = \Theta(\kappa_\delta p_\delta + p_\delta)$ and $v_{12,\delta}^{*} = E(\hat{v}_{12,\delta}) = 2\beta \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4}\sigma_{\hat{\gamma}_j}^{2}\gamma_j^2 q_{\delta,j} = \Theta(\kappa_\delta p_\delta)$. Then, the bias of the pIVW estimator is

$$E(\hat{\beta}_{\delta,\mathrm{pIVW}} - \beta) = E\left(\frac{\hat{\mu}_{1,\delta}}{\tilde{\mu}_{2,\delta}} - \frac{\mu_{1,\delta}}{\mu_{2,\delta}}\right) + E\left(\frac{\hat{v}_{12,\delta}}{\hat{v}_{2,\delta}}\right)\left(1 - \frac{\hat{\mu}_{2,\delta}}{\tilde{\mu}_{2,\delta}}\right)$$
$$= (1-\lambda)\beta\left(\frac{v_{2,\delta}}{\mu_{2,\delta}^{2}} - \frac{v_{12,\delta}}{\mu_{1,\delta}\mu_{2,\delta}}\right) + o(\xi_\delta).$$

2 Proof of Theorem 2 (b)

Similar to the proof in Section 2 of Web Appendix C, we have

$$E(\hat{\beta}_{\delta,\mathrm{dIVW}} - \beta)^2$$
$$= \beta^2\left\{\frac{v_{1,\delta}}{\mu_{1,\delta}^2} + \frac{v_{2,\delta}}{\mu_{2,\delta}^2} - \frac{2v_{12,\delta}}{\mu_{1,\delta}\mu_{2,\delta}} - 2E(\hat{x}_{1,\delta}^2\hat{x}_{2,\delta}) + 4E(\hat{x}_{1,\delta}\hat{x}_{2,\delta}^2) - 2E(\hat{x}_{2,\delta}^3)\right.$$
$$\left. + 3E(\hat{x}_{1,\delta}^2\hat{x}_{2,\delta}^2) - 6E(\hat{x}_{1,\delta}\hat{x}_{2,\delta}^3) + 3E(\hat{x}_{2,\delta}^4)\right\} + o(\xi_\delta^2)$$
$$= O(\xi_\delta). \tag{A11}$$

where $v_{1,\delta} = \mathrm{Var}(\hat{\mu}_{1,\delta}) = \sum_{j=1}^{p} \sigma_{\hat{\Gamma}_j}^{-4}\left\{\left(\sigma_{\hat{\gamma}_j}^2\beta^2 + \sigma_{\hat{\Gamma}_j}^2 + \tau^2\right)\gamma_j^2 + \left(\sigma_{\hat{\Gamma}_j}^2 + \tau^2\right)\sigma_{\hat{\gamma}_j}^2\right\} q_{\delta,j} + \beta^2\sum_{j=1}^{p}\sigma_{\hat{\Gamma}_j}^{-4}\gamma_j^4 q_{\delta,j}(1 - q_{\delta,j}) = \Theta(\kappa_\delta p_\delta + p_\delta) + \Theta(\varphi^2 p_\delta)$. Therefore, the variance of the dIVW estimator is

$$\mathrm{Var}(\hat{\beta}_{\delta,\mathrm{dIVW}}) = E(\hat{\beta}_{\delta,\mathrm{dIVW}} - \beta)^2 - E^2(\hat{\beta}_{\delta,\mathrm{dIVW}} - \beta) = O(\xi_\delta).$$

The difference in variance between the dIVW estimator and the pIVW estimator is

$$\mathrm{Var}(\hat{\beta}_{\delta,\mathrm{dIVW}}) - \mathrm{Var}(\hat{\beta}_{\delta,\mathrm{pIVW}})$$
$$= E(\hat{\beta}_{\delta,\mathrm{dIVW}} - \beta)^2 - E\left(\hat{\beta}_{\delta,\mathrm{pIVW}} - \frac{\mu_{1,\delta}}{m_{2,\delta}}\right)^2 + E^2\left(\hat{\beta}_{\delta,\mathrm{pIVW}} - \frac{\mu_{1,\delta}}{m_{2,\delta}}\right) - E^2(\hat{\beta}_{\delta,\mathrm{dIVW}} - \beta),$$

where $m_{2,\delta} = E(\tilde{\mu}_{2,\delta})$. As in Section 2 of Web Appendix C, we have

$$E^2\left(\hat{\beta}_{\delta,\mathrm{pIVW}} - \frac{\mu_{1,\delta}}{m_{2,\delta}}\right) = \left\{E(\hat{\beta}_{\delta,\mathrm{pIVW}} - \beta) + \left(\beta - \frac{\mu_{1,\delta}}{m_{2,\delta}}\right)\right\}^2$$
$$= \beta^2\left\{(1-\lambda)\left(\frac{v_{2,\delta}^{*}}{\mu_{2,\delta}^2} - \frac{v_{12,\delta}^{*}}{\mu_{1,\delta}\mu_{2,\delta}}\right) + \frac{\lambda v_{2,\delta}^{*}}{\mu_{2,\delta}^2}\right\}^2 + o(\xi_\delta^2),$$

and therefore

$$E^2\left(\hat{\beta}_{\delta,\mathrm{pIVW}} - \frac{\mu_{1,\delta}}{m_{2,\delta}}\right) - E^2(\hat{\beta}_{\delta,\mathrm{dIVW}} - \beta) = \frac{2\lambda\beta v_{2,\delta}^{*} v_{12,\delta}^{*}}{\mu_{2,\delta}^4} + \frac{v_{12,\delta}^{*2}}{\mu_{2,\delta}^4}(\lambda^2 - 2\lambda) + o(\xi_\delta^2) \tag{A12}$$

Next, we calculate $E(\hat{\beta}_{\delta,\mathrm{dIVW}} - \beta)^2 - E\left(\hat{\beta}_{\delta,\mathrm{pIVW}} - \frac{\mu_{1,\delta}}{m_{2,\delta}}\right)^2$. By Taylor series expansion,

$$
\begin{aligned}
&E\left(\hat{\beta}_{\delta,\mathrm{pIVW}}-\frac{\mu_{1,\delta}}{m_{2,\delta}}\right)^2\\
&\qquad=\left(\frac{\mu_{1,\delta}}{m_{2,\delta}}\right)^2\left(\frac{v_{1,\delta}}{\mu_{1,\delta}^2}+\frac{w_\delta^2 v_{2,\delta}}{m_{2,\delta}^2}-\frac{2w_\delta v_{12,\delta}}{\mu_{1,\delta}m_{2,\delta}}\right)\\
&\qquad+\beta^2\{-2E(\hat{x}_{1,\delta}^2\hat{x}_{2,\delta})+4E(\hat{x}_{1,\delta}\hat{x}_{2,\delta}^2)-2E(\hat{x}_{2,\delta}^3)+3E(\hat{x}_{1,\delta}^2\hat{x}_{2,\delta}^2)\\
&\qquad-6E(\hat{x}_{1,\delta}\hat{x}_{2,\delta}^3)+3E(\hat{x}_{2,\delta}^4)\}+\frac{\lambda^2 v_{12,\delta}^{*2}}{\mu_{2,\delta}^4}+\frac{6\lambda\beta v_{12,\delta}^*}{\mu_{2,\delta}^2}\left(\frac{v_{2,\delta}^*}{\mu_{2,\delta}^2}-\frac{v_{12,\delta}^*}{\mu_{1,\delta}\mu_{2,\delta}}\right)\\
&\qquad-16\lambda\beta\left(\frac{v_{12,\delta}^*}{v_{2,\delta}^*}-\beta\right)\frac{\sum_{j=1}^p\sigma_{\hat{\Gamma}_j}^{-6}\sigma_{\hat{\gamma}_j}^6\left(\gamma_j^2\sigma_{\hat{\gamma}_j}^{-2}+1\right)q_j}{\mu_{2,\delta}^3}+o(\xi_\delta^2),
\end{aligned}
\tag{A13}
$$

where $w_\delta=\mu_{2,\delta}^*/(2\mu_{2,\delta}^*-\mu_{2,\delta})$ with $\mu_{2,\delta}^*=\mu_{2,\delta}\left(1+\sqrt{1+4\lambda v_{2,\delta}^*/\mu_{2,\delta}^2}\right)/2$. From Equations (A11) and (A13), we have

$$
\begin{aligned}
&E(\hat{\beta}_{\delta,\mathrm{dIVW}}-\beta)^2-E\left(\hat{\beta}_{\delta,\mathrm{pIVW}}-\frac{\mu_{1,\delta}}{m_{2,\delta}}\right)^2\\
&\qquad=\frac{2\lambda v_{1,\delta}^* v_{2,\delta}^*}{\mu_{2,\delta}^4}+\frac{6\lambda\beta^2 v_{2,\delta}^{*2}}{\mu_{2,\delta}^4}-\frac{14\lambda\beta v_{2,\delta}^* v_{12,\delta}^*}{\mu_{2,\delta}^4}+\frac{(6\lambda-\lambda^2)v_{12,\delta}^{*2}}{\mu_{2,\delta}^4}\\
&\qquad+16\lambda\beta\left(\frac{v_{12,\delta}^*}{v_{2,\delta}^*}-\beta\right)\frac{\sum_{j=1}^p\sigma_{\hat{\Gamma}_j}^{-6}\sigma_{\hat{\gamma}_j}^6\left(\gamma_j^2\sigma_{\hat{\gamma}_j}^{-2}+1\right)q_j}{\mu_{2,\delta}^3}+o(\xi_\delta^2),
\end{aligned}
\tag{A14}
$$

where $v_{1,\delta}^*=\sum_{j=1}^p\sigma_{\hat{\Gamma}_j}^{-4}\left\{\left(\sigma_{\hat{\gamma}_j}^2\beta^2+\sigma_{\hat{\Gamma}_j}^2+\tau^2\right)\gamma_j^2+\left(\sigma_{\hat{\Gamma}_j}^2+\tau^2\right)\sigma_{\hat{\gamma}_j}^2\right\}q_{\delta,j}=\Theta(\kappa_\delta p_\delta+p_\delta)$. Combining Equations (A12) and (A14), the difference in the variance between the dIVW estimator and the pIVW estimator is

$$
\begin{aligned}
&\mathrm{Var}(\hat{\beta}_{\delta,\mathrm{dIVW}})-\mathrm{Var}(\hat{\beta}_{\delta,\mathrm{pIVW}})\\
&\qquad=\frac{2\lambda v_{1,\delta}^* v_{2,\delta}^*}{\mu_{2,\delta}^4}+\frac{6\lambda\beta^2 v_{2,\delta}^{*2}}{\mu_{2,\delta}^4}-\frac{12\lambda\beta v_{2,\delta}^* v_{12,\delta}^*}{\mu_{2,\delta}^4}+\frac{4\lambda v_{12,\delta}^{*2}}{\mu_{2,\delta}^4}\\
&\qquad+16\lambda\beta\left(\frac{v_{12,\delta}^*}{v_{2,\delta}^*}-\beta\right)\frac{\sum_{j=1}^p\sigma_{\hat{\Gamma}_j}^{-6}\sigma_{\hat{\gamma}_j}^6\left(\gamma_j^2\sigma_{\hat{\gamma}_j}^{-2}+1\right)q_j}{\mu_{2,\delta}^3}+o(\xi_\delta^2)\\
&\qquad=\frac{2\lambda\beta^2}{\mu_{2,\delta}^4}\Delta_\delta+o(\xi_\delta^2),
\end{aligned}
$$

where

$$
\begin{aligned}
\Delta_\delta=&\frac{3\left(\mu_{1,\delta}v_{2,\delta}^*-\mu_{2,\delta}v_{12,\delta}^*\right)^2}{\mu_{2,\delta}^2\beta^2}+\frac{v_{1,\delta}^*v_{2,\delta}^*-v_{12,\delta}^{*2}}{\beta^2}\\
&+8\mu_{2,\delta}\left(\frac{v_{12,\delta}^*}{v_{2,\delta}^*\beta}-1\right)\sum_{j=1}^p\sigma_{\hat{\Gamma}_j}^{-6}\sigma_{\hat{\gamma}_j}^6\left(\gamma_j^2\sigma_{\hat{\gamma}_j}^{-2}+1\right)q_j.
\end{aligned}
$$

As in Web Appendix D, it can be shown that $\Delta_\delta>0$ when both the proportions of variances of X and Y explained by each IV are less than $1/3$.

3 Proof of Theorem 2 (c)

To prove

$$V_\delta^{-\frac{1}{2}}(\hat\beta_{\delta,\mathrm{pIVW}}-\beta)=\left(\frac{\mu_{2,\delta}}{\sqrt{v_\delta}}\right)\frac{\hat\mu_{1,\delta}-\beta\hat\mu_{2,\delta}}{\tilde\mu_{2,\delta}}+\left(\frac{\mu_{2,\delta}}{\sqrt{v_\delta}}\right)\left(\frac{\hat\mu_{2,\delta}}{\tilde\mu_{2,\delta}}-1\right)\left(\beta-\frac{\hat v_{12,\delta}}{\hat v_{2,\delta}}\right)\xrightarrow{d}N(0,1),$$

where $V_\delta=\mu_{2,\delta}^{-2}\sum_{j=1}^{p}\left\{\sigma_{\hat\Gamma_j}^{-2}\left(\gamma_j^2+\sigma_{\hat\gamma_j}^2\right)\left(1+\tau^2\sigma_{\hat\Gamma_j}^{-2}\right)+\beta^2\sigma_{\hat\gamma_j}^2\sigma_{\hat\Gamma_j}^{-4}\left(\gamma_j^2+2\sigma_{\hat\gamma_j}^2\right)\right\}q_{\delta,j}$ and $v_\delta=\mu_{2,\delta}^2V_\delta=\Theta(\kappa_\delta p_\delta+p_\delta)$, it suffices to prove $\left(\frac{\mu_{2,\delta}}{\sqrt{v_\delta}}\right)\frac{\hat\mu_{1,\delta}-\beta\hat\mu_{2,\delta}}{\tilde\mu_{2,\delta}}\xrightarrow{d}N(0,1)$ and $\left(\frac{\mu_{2,\delta}}{\sqrt{v_\delta}}\right)\left(\frac{\hat\mu_{2,\delta}}{\tilde\mu_{2,\delta}}-1\right)\left(\beta-\frac{\hat v_{12,\delta}}{\hat v_{2,\delta}}\right)\xrightarrow{p}0$. As the proof in Section 3 of Web Appendix C, we first prove $\tilde\mu_{2,\delta}/\mu_{2,\delta}\xrightarrow{p}1$ as $\eta_\delta\to\infty$. Then, we prove $\frac{\hat\mu_{1,\delta}-\beta\hat\mu_{2,\delta}}{\sqrt{v_\delta}}\xrightarrow{d}N(0,1)$ as $p\to\infty$ by the Lindeberg Central Limit Theorem provided that $\max_j\gamma_j^2\sigma_{\hat\gamma_j}^{-2}q_{\delta,j}/(\kappa_\delta p_\delta+p_\delta)\to 0$. Lastly, we prove $\left(\frac{\mu_{2,\delta}}{\sqrt{v_\delta}}\right)\left(\frac{\hat\mu_{2,\delta}}{\tilde\mu_{2,\delta}}-1\right)\left(\beta-\frac{\hat v_{12,\delta}}{\hat v_{2,\delta}}\right)\xrightarrow{p}0$ by showing $\left(\frac{\mu_{2,\delta}}{\sqrt{v_\delta}}\right)\left(\frac{\hat\mu_{2,\delta}}{\tilde\mu_{2,\delta}}-1\right)=\left(\frac{\lambda v_{2,\delta}^*}{\sqrt{v_\delta}\mu_{2,\delta}}\right)\frac{\mu_{2,\delta}^2}{\hat\mu_{2,\delta}^2}\frac{\hat v_{2,\delta}}{v_{2,\delta}^*}\frac{1}{r_{\lambda,\delta}^2}\xrightarrow{p}0$ and $\beta-\frac{\hat v_{12,\delta}}{\hat v_{2,\delta}}=O_p(1)$ as $\eta_\delta\to\infty$. Further, the normality of $\hat V_\delta^{-\frac{1}{2}}(\hat\beta_{\delta,\mathrm{pIVW}}-\beta)$ with the plug-in estimator $\hat V_\delta$ of V_δ follows from $\tilde\mu_{2,\delta}/\mu_{2,\delta}\xrightarrow{p}1$ and $\hat v_\delta/v_\delta\xrightarrow{p}1$ as $\eta_\delta\to\infty$. We omit the details here.

Web Appendix G: Simulation with Individual-Level Data

First, we randomly generate the individual-level data for the genetic variants from $G_j\sim Bin(2,\mathrm{MAF}_j)$ where the minor allele frequencies $\mathrm{MAF}_j\sim U(0.1,0.5)$. Then, we simulate the individual-level data for the exposure X and the outcome Y based on the linear structural models (1) and (6), where we consider similar settings of model parameters as in Section 4.1. Specifically, we set $\beta=0.5$, and U,ϵ_X and ϵ_Y are generated from $N(0,2)$ independently. The IV effects γ_j and the balanced horizontal pleiotropy α_j are generated in the same ways as in Section 4.1. We set the sample sizes of the exposure dataset $n_X=100{,}000$ and the outcome dataset $n_Y=2n_X$. To consider the IV selection, we generate an independent dataset based on model (1) with the sample size $n_X^*=2n_X$. Lastly, we obtain the summary-level data $\left\{\hat\gamma_j^*,\sigma_{\hat\gamma_j}^*\right\}_{j=1}^{1000}$, $\left\{\hat\gamma_j,\sigma_{\hat\gamma_j}\right\}_{j=1}^{1000}$ and $\left\{\hat\Gamma_j,\sigma_{\hat\Gamma_j}\right\}_{j=1}^{1000}$ by estimating the marginal effects and their standard errors in the corresponding linear regressions, which are based on three independent datasets for the selection, the exposure, and the outcome data respectively. The simulation results are provided in Web Tables 6-9.

Web Appendix H: Estimation of the Effective Sample Size

When no IV selection is performed, we estimate the effective sample size η by

$$\hat{\eta} = \hat{\kappa}\sqrt{p},$$

where the estimated IV strength $\hat{\kappa} = p^{-1}\sum_{j=1}^{p}\left(\hat{\gamma}_j^2 - \sigma_{\hat{\gamma}_j}^{-2}\right)\sigma_{\hat{\gamma}_j}^2$.

When IV selection is performed, we estimate the effective sample size η_δ by

$$\hat{\eta}_\delta = \frac{\hat{\kappa}_\delta\sqrt{\hat{p}_\delta}}{\max(1, \hat{\varphi})},$$

where $\hat{p}_\delta$ is the number of selected IVs within the set S_δ, the estimated IV strength $\hat{\kappa}_\delta = \hat{p}_\delta^{-1}\sum_{j\in S_\delta}\left(\hat{\gamma}_j^2 - \sigma_{\hat{\gamma}_j}^{-2}\right)\sigma_{\hat{\gamma}_j}^2$, and $\hat{\varphi} = \sqrt{\hat{p}_\delta^{-1}\sum_{j=1}^{p}\left(\hat{\gamma}_j^4\sigma_{\hat{\gamma}_j}^{-4} - 6\hat{\gamma}_j^2\sigma_{\hat{\gamma}_j}^{-2} + 3\right)\hat{q}_{\delta,j}\left(1 - \hat{q}_{\delta,j}\right)}$ is the estimate of φ, where $\hat{q}_{\delta,j} = \Phi\left(\hat{\gamma}_j^*/\sigma_{\hat{\gamma}_j}^* - \delta\right) + \Phi\left(-\hat{\gamma}_j^*/\sigma_{\hat{\gamma}_j}^* - \delta\right)$ and $\Phi(\cdot)$ is the cumulative distribution function for standard normal distribution.

Web Tables

Web Table 1

The pIVW estimator with various penalty parameter λ. The true causal effect $\beta = 0.5$ and no horizontal pleiotropy exists ($\tau = 0$). The IV selection threshold $\delta = \sqrt{2\log p}$. The simulation is based on 10,000 replicates. Bias (%): bias divided by β; SE: empirical standard error; CP (%): coverage probability of the 95% confidence interval.

η_δ	λ	Bias	SE	CP
6.76	0	3.2	0.144	95.7
	0.5	1.5	0.140	95.5
	1	-0.1	0.136	95.3
	1.5	-1.4	0.133	95.2
	2	-2.6	0.131	95.2
	2.5	-3.7	0.129	95.0
10.26	0	1.4	0.090	95.1
	0.5	0.7	0.089	95.1
	1	0.1	0.088	95.1
	1.5	-0.6	0.088	95.0
	2	-1.2	0.087	95.1
	2.5	-1.8	0.086	95.1
17.84	0	0.7	0.056	94.7
	0.5	0.4	0.055	94.7
	1	0.1	0.055	94.7
	1.5	-0.1	0.055	94.7
	2	-0.4	0.055	94.7
	2.5	-0.6	0.055	94.7

Web Table 2

The pIVW estimator with various penalty parameter λ. The true causal effect $\beta = 0.5$ and balanced horizontal pleiotropy exists $\tau = 0.01$. No IV selection is conducted. The simulation is based on 10,000 replicates. Bias (%): bias divided by β; SE: empirical standard error; CP (%): coverage probability of the 95% confidence interval.

η	λ	Bias	SE	CP
4.33	0	28.0	2.441	94.9
	0.5	5.1	0.444	94.7
	1	-2.2	0.389	94.4
	1.5	-7.5	0.357	94.2
	2	-11.6	0.335	93.9
	2.5	-14.9	0.318	93.3
9.52	0	2.9	0.194	95.0
	0.5	1.2	0.189	94.8
	1	-0.3	0.185	94.8
	1.5	-1.7	0.181	94.6
	2	-3.0	0.178	94.4
	2.5	-4.3	0.175	94.3
21.85	0	0.5	0.091	94.7
	0.5	0.1	0.091	94.7
	1	-0.1	0.090	94.7
	1.5	-0.6	0.090	94.6
	2	-0.9	0.090	94.6
	2.5	-1.2	0.089	94.5

Web Table 3

The pIVW estimator with various penalty parameter λ. The true causal effect $\beta = 0.5$ and balanced horizontal pleiotropy exists ($\tau = 0.01$). The IV selection threshold $\delta = \sqrt{2 \log p}$. The simulation is based on 10,000 replicates. Bias (%): bias divided by β; SE: empirical standard error; CP (%): coverage probability of the 95% confidence interval.

η_δ	λ	Bias	SE	CP
6.76	0	3.9	0.198	95.1
	0.5	2.2	0.193	95.0
	1	0.7	0.189	94.9
	1.5	-0.7	0.186	94.9
	2	-1.9	0.183	94.9
	2.5	-3.0	0.180	94.9
10.26	0	1.2	0.125	94.9
	0.5	0.5	0.124	94.8
	1	-0.2	0.123	94.8
	1.5	-0.8	0.122	94.7
	2	-1.4	0.121	94.7
	2.5	-2.0	0.120	94.6
17.84	0	0.4	0.078	94.9
	0.5	0.1	0.078	94.9
	1	-0.2	0.078	94.9
	1.5	-0.4	0.078	94.8
	2	-0.7	0.077	94.8
	2.5	-0.9	0.077	94.8

Web Table 4

Comparison of the pIVW estimator (λ_{opt} = 1) with other competing MR methods. The true causal effect $\beta = 0.5$ and balanced horizontal pleiotropy exists ($\tau = 0.01$). No IV selection is conducted. The simulation is based on 10,000 replicates. Bias (%): bias divided by β; SE: empirical standard error; CP (%): coverage probability of the 95% confidence interval.

η	Method	Bias	SE	CP
4.33	IVW	-88.0	0.040	0.0
	MR-Egger	-80.1	0.065	0.0
	MR-Median	-81.7	0.057	0.0
	MR-RAPS	33.1	2.471	96.3
	dIVW	28.0	2.441	96.4
	pIVW	-2.2	0.389	94.4
9.52	IVW	-76.9	0.038	0.0
	MR-Egger	-63.5	0.059	0.0
	MR-Median	-66.0	0.056	0.0
	MR-RAPS	2.9	0.195	95.7
	dIVW	2.9	0.194	95.9
	pIVW	-0.3	0.185	94.8
21.85	IVW	-59.2	0.034	0.0
	MR-Egger	-42.0	0.051	1.6
	MR-Median	-46.8	0.050	0.2
	MR-RAPS	0.5	0.093	94.9
	dIVW	0.5	0.091	94.9
	pIVW	-0.2	0.090	94.7

Web Table 5

Comparison of the pIVW estimator (λ_{opt} = 1) with other competing MR methods. The true causal effect $\beta = 0.5$ and balanced horizontal pleiotropy exists ($\tau = 0.01$). The IV selection threshold $\delta = \sqrt{2\log p}$. The simulation is based on 10,000 replicates. Bias (%): bias divided by β; SE: empirical standard error; CP (%): coverage probability of the 95% confidence interval.

η_δ	Method	Bias	SE	CP
6.76	IVW	-6.6	0.172	90.6
	MR-Egger	-42.7	0.534	88.1
	MR-Median	-11.3	0.199	88.3
	MR-RAPS	2.8	0.193	92.8
	dIVW	3.9	0.198	95.8
	pIVW	0.7	0.189	94.9
10.26	IVW	-8.1	0.111	91.0
	MR-Egger	-44.2	0.289	83.7
	MR-Median	-12.6	0.137	86.3
	MR-RAPS	0.9	0.124	93.1
	dIVW	1.2	0.125	95.1
	pIVW	-0.2	0.123	94.8
17.84	IVW	-8.1	0.070	89.4
	MR-Egger	-48.8	0.183	70.8
	MR-Median	-12.8	0.089	82.3
	MR-RAPS	0.4	0.078	93.7
	dIVW	0.4	0.078	95.0
	pIVW	-0.2	0.078	94.9

Web Table 6

The simulation with individual-level data. Comparison of the pIVW estimator (λ_{opt} = 1) with other competing MR methods. The true causal effect $\beta = 0.5$. No horizontal pleiotropy exists ($\tau = 0$). No IV selection is conducted. The simulation is based on 10,000 replicates. Bias (%): bias divided by β; SE: empirical standard error; CP (%): coverage probability of the 95% confidence interval.

η	Method	Bias	SE	CP
4.33	IVW	-87.9	0.028	0.0
	MR-Egger	-80.0	0.045	0.0
	MR-Median	-83.0	0.041	0.0
	MR-RAPS	8.4	0.694	94.1
	dIVW	18.0	2.535	95.2
	pIVW	-1.9	0.298	94.2
9.52	IVW	-76.8	0.026	0.0
	MR-Egger	-63.3	0.041	0.0
	MR-Median	-67.5	0.040	0.0
	MR-RAPS	0.9	0.118	95.2
	dIVW	3.1	0.148	95.7
	pIVW	-0.1	0.139	95.0
21.85	IVW	-59.0	0.023	0.0
	MR-Egger	-41.8	0.035	0.0
	MR-Median	-46.6	0.035	0.0
	MR-RAPS	0.1	0.058	95.2
	dIVW	0.6	0.067	95.5
	pIVW	-0.1	0.066	95.3

Web Table 7

The simulation with individual-level data. Comparison of the pIVW estimator (λ_{opt} = 1) with other competing MR methods. The true causal effect $\beta = 0.5$. No horizontal pleiotropy exists ($\tau = 0$). The IV selection threshold $\delta = \sqrt{2\log p}$. The simulation is based on 10,000 replicates. Bias (%): bias divided by β; SE: empirical standard error; CP (%): coverage probability of the 95% confidence interval.

η_δ	Method	Bias	SE	CP
6.76	IVW	-7.4	0.120	93.7
	MR-Egger	-41.6	0.384	89.0
	MR-Median	-11.7	0.139	95.0
	MR-RAPS	1.4	0.135	95.9
	dIVW	3.1	0.142	96.1
	pIVW	-0.1	0.134	95.4
10.26	IVW	-8.2	0.078	91.3
	MR-Egger	-43.1	0.204	79.4
	MR-Median	-12.3	0.095	93.1
	MR-RAPS	0.2	0.087	95.4
	dIVW	0.9	0.090	95.4
	pIVW	-0.4	0.088	95.0
17.84	IVW	-7.9	0.049	86.9
	MR-Egger	-48.5	0.129	51.0
	MR-Median	-12.3	0.061	88.7
	MR-RAPS	0.5	0.054	95.4
	dIVW	0.7	0.055	95.4
	pIVW	0.2	0.055	94.9

Web Table 8

The simulation with individual-level data. Comparison of the pIVW estimator (λ_{opt} = 1) with other competing MR methods. The true causal effect $\beta = 0.5$ and balanced horizontal pleiotropy exists ($\tau = 0.01$). No IV selection is conducted. The simulation is based on 10,000 replicates. Bias (%): bias divided by β; SE: empirical standard error; CP (%): coverage probability of the 95% confidence interval.

η	Method	Bias	SE	CP
4.33	IVW	-87.8	0.040	0.0
	MR-Egger	-79.9	0.065	0.0
	MR-Median	-81.6	0.058	0.0
	MR-RAPS	32.7	17.548	96.6
	dIVW	-181.3	93.937	96.7
	pIVW	-1.7	0.392	94.4
9.52	IVW	-76.8	0.038	0.0
	MR-Egger	-63.2	0.059	0.1
	MR-Median	-65.5	0.056	0.0
	MR-RAPS	3.6	0.194	95.8
	dIVW	3.5	0.194	95.9
	pIVW	0.3	0.185	94.7
21.85	IVW	-59.2	0.034	0.0
	MR-Egger	-42.1	0.052	1.4
	MR-Median	-46.8	0.050	0.2
	MR-RAPS	0.1	0.092	95.2
	dIVW	0.2	0.090	95.3
	pIVW	-0.5	0.089	95.0

Web Table 9

The simulation with individual-level data. Comparison of the pIVW estimator (λ_{opt} = 1) with other competing MR methods. The true causal effect $\beta = 0.5$ and balanced horizontal pleiotropy exists ($\tau = 0.01$). The IV selection threshold $\delta = \sqrt{2\log p}$. The simulation is based on 10,000 replicates. Bias (%): bias divided by β; SE: empirical standard error; CP (%): coverage probability of the 95% confidence interval.

η_δ	Method	Bias	SE	CP
6.76	IVW	-6.8	0.172	90.7
	MR-Egger	-41.7	0.532	87.7
	MR-Median	-11.0	0.199	88.4
	MR-RAPS	2.6	0.192	92.7
	dIVW	3.7	0.198	95.5
	pIVW	0.5	0.189	95.1
10.26	IVW	-8.2	0.111	90.8
	MR-Egger	-43.7	0.289	83.8
	MR-Median	-12.6	0.136	87.2
	MR-RAPS	0.7	0.123	93.4
	dIVW	1.0	0.124	95.5
	pIVW	-0.4	0.122	95.1
17.84	IVW	-8.2	0.070	89.9
	MR-Egger	-48.7	0.181	71.0
	MR-Median	-12.7	0.088	82.1
	MR-RAPS	0.3	0.078	94.1
	dIVW	0.4	0.078	95.2
	pIVW	-0.1	0.077	95.0

Web Table 10

Description of the GWAS datasets used in this paper:

<table>
<tr><th>Trait</th><th>Dataset</th><th>Source</th><th>Population</th><th>Sample size (case/control)</th><th>Trait Description</th></tr>
<tr><td rowspan="2">Type 2 diabetes</td><td>Selection</td><td>GERA</td><td>European</td><td>7,624/54,223</td><td>ICD-9: 250</td></tr>
<tr><td>Exposure</td><td>UK BioBank</td><td>European</td><td>6,024/106,314</td><td>Self-reported: diabetes, type 2 diabetes
ICD-10: E11</td></tr>
<tr><td rowspan="2">Dyslipidemia</td><td>Selection</td><td>GERA</td><td>European</td><td>33,024/28,823</td><td>ICD-9: 272</td></tr>
<tr><td>Exposure</td><td>UK BioBank</td><td>European</td><td>16,818/95,520</td><td>Self-reported: high cholesterol
ICD-10: E78</td></tr>
<tr><td rowspan="2">Hypertensive disease</td><td>Selection</td><td>GERA</td><td>European</td><td>31,000/30,847</td><td>ICD-9: 401, 402, 403, 404</td></tr>
<tr><td>Exposure</td><td>UK BioBank</td><td>European</td><td>32,689/79,649</td><td>Self-reported: essential hypertension, hypertension, gestational hypertension /preeclampsia
ICD-10: I10, I11, I12, I13</td></tr>
<tr><td rowspan="2">Peripheral Vascular Disease</td><td>Selection</td><td>GERA</td><td>European</td><td>4,708/57,139</td><td>ICD-9: 415, 440, 453</td></tr>
<tr><td>Exposure</td><td>UK BioBank</td><td>European</td><td>1,816/110,522</td><td>Self-reported: peripheral vascular disease, leg claudication/intermittent claudication, arterial embolism, pulmonary embolism +/- dvt
ICD-10: I26, I70, I82</td></tr>
<tr><td rowspan="2">BMI</td><td>Selection</td><td>Akiyama et al</td><td>Asian</td><td>173,430</td><td>Body mass index</td></tr>
<tr><td>Exposure</td><td>UK BioBank (GWAS round 2)</td><td>European</td><td>359,983</td><td>Body mass index</td></tr>
<tr><td>COVID-19 infection</td><td rowspan="3">Outcome</td><td rowspan="3">COVID19 Host Genetics Initiative (GWAS round 5)

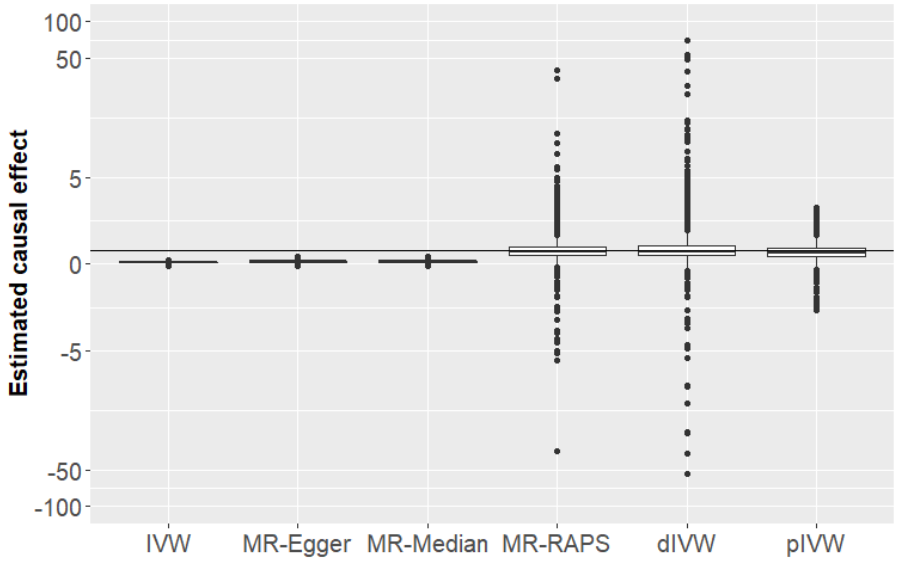
*The datasets excluding UK BioBank are used to avoid possible sample overlap</td><td rowspan="3">European, African, Admixed American, Middle Eastern, South Asian and East Asian</td><td>42,557/1,424,707</td><td>Reported SARS-CoV-2 infection</td></tr>
<tr><td>Hospitalized COVID-19</td><td>11,829/1,725,210</td><td>Moderate or severe COVID-19 (i.e., hospitalized due to symptoms associated with the infection)</td></tr>
<tr><td>Critically ill COVID-19</td><td>5,870/1,155,203</td><td>Very severe respiratory confirmed covid (i.e., required respiratory support in hospital or deceased due to COVID-19)</td></tr>
</table>

Web Table 11

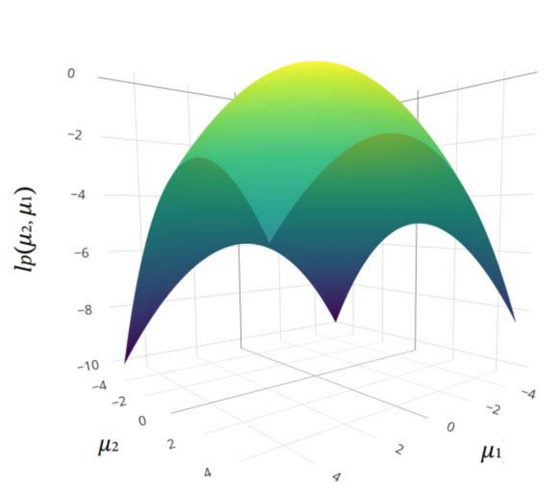
The numbers of IVs and the estimated effective sample sizes of five obesity-related exposures (i.e., peripheral vascular disease (PVD), dyslipidemia, hypertensive disease (HD), type 2 diabetes (T2D) and BMI).

Outcome	Exposure	No IV selection		IV selection threshold $\delta = \sqrt{2\log p}$	
		p	$\hat{\eta}$	$\hat{p}_\delta$	$\hat{\eta}_\delta$
COVID-19 infection	PVD	1799	2.19	60	5.63
	Dyslipidemia	2338	36.42	143	37.57
	HD	2311	26.61	165	11.28
	T2D	2331	15.25	148	14.72
	BMI	1902	217.33	375	37.08
Hospitalized COVID-19	PVD	1768	1.68	60	3.98
	Dyslipidemia	2068	37.67	147	39.52
	HD	2075	28.85	164	12.04
	T2D	2091	14.17	140	14.81
	BMI	1887	218.93	374	37.36
Critically ill COVID-19	PVD	1781	1.86	61	4.28
	Dyslipidemia	2082	40.57	153	39.30
	HD	2060	30.29	172	11.62
	T2D	2042	13.48	145	14.97
	BMI	1889	218.25	377	36.98

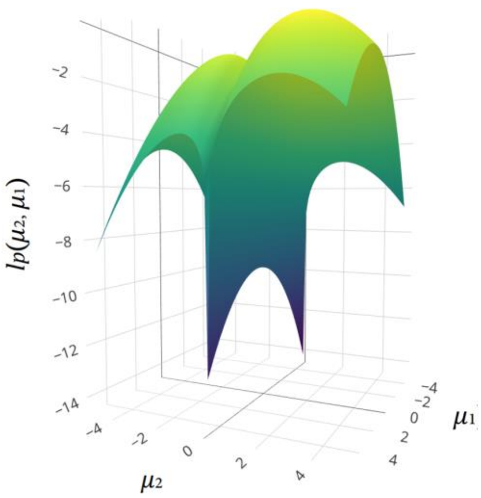
Web Figures



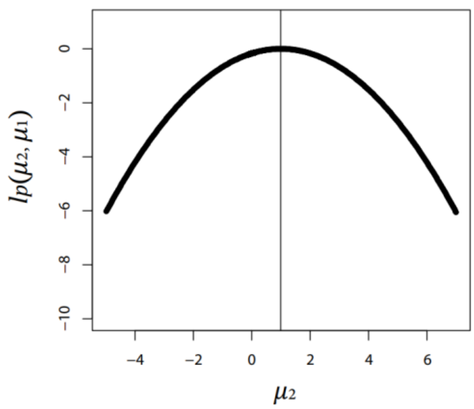
Web Figure 1. The box plot of the estimated causal effects of six methods. The true causal effect $\beta = 0.5$ (shown by the horizontal line). The effective sample size $\eta = 4.33$. No pleiotropy exists ($\tau = 0$). No IV selection is conducted. The simulation is based on 10,000 replicates. The pIVW estimator with the optimal $\lambda_{opt} = 1$.



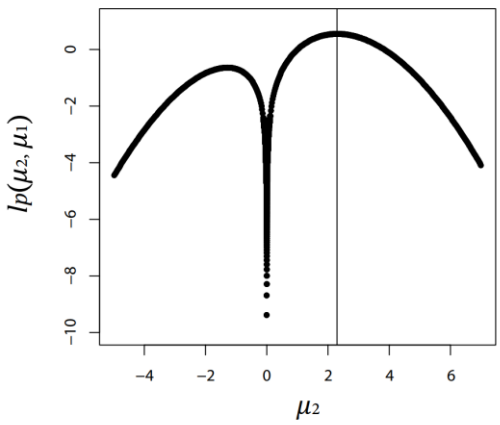
(a) $\lambda = 0$



(b) $\lambda = 1$

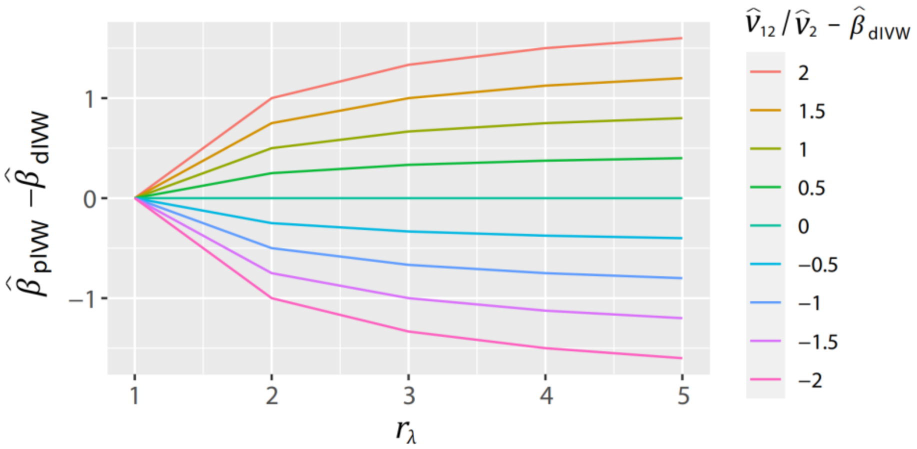


(c) $\lambda = 0$

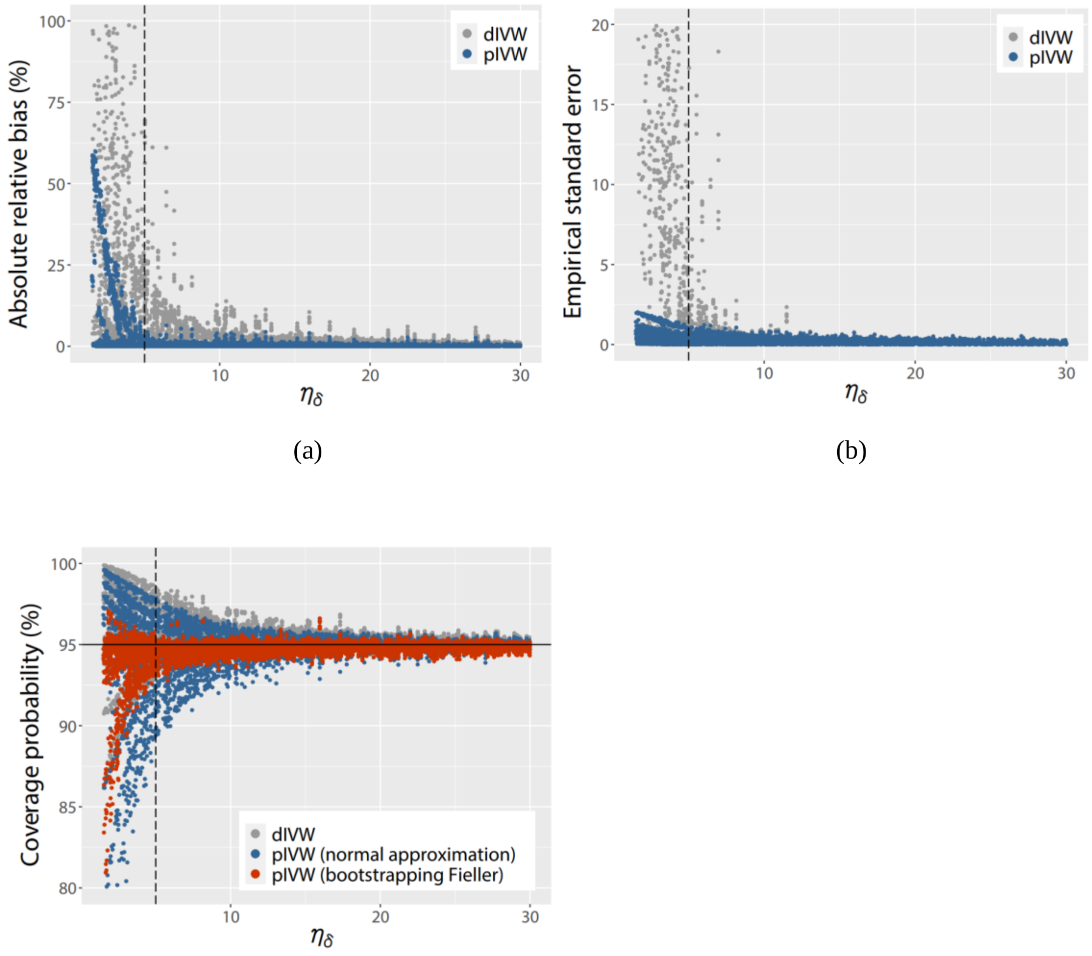


(d) $\lambda = 1$

Web Figure 2. The plots (a) and (b) show the penalized likelihood function $l_p(\mu_1, \mu_2)$ against μ_1 and μ_2 under $\lambda = 0$ and $\lambda = 1$, respectively, when $\hat{\mu}_1 = 0.5$, $\hat{\mu}_2 = 1$, $v_1 = 3$, $v_2 = 3$ and $v_{12} = 0.3$. The plots (c) and (d) shows $l_p(\mu_1, \mu_2)$ against μ_2 with μ_1 being fixed at the MLE estimates under $\lambda = 0$ and $\lambda = 1$, respectively. The vertical lines in (c) and (d) show the MLE estimates of μ_2 under $\lambda = 0$ and $\lambda = 1$, respectively.



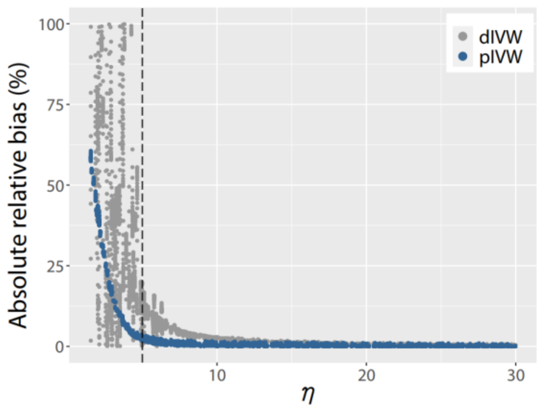
Web Figure 3. The plots of $\hat{\beta}_{\mathrm{pIVW}} - \hat{\beta}_{\mathrm{dIVW}}$ against r_λ under different value of $\hat{v}_{12}/\hat{v}_2 - \hat{\beta}_{\mathrm{dIVW}}$. When $r_\lambda = 1$, $\hat{\beta}_{\mathrm{pIVW}} = \hat{\beta}_{\mathrm{dIVW}}$. When r_λ increases, the difference between $\hat{\beta}_{\mathrm{pIVW}}$ and $\hat{\beta}_{\mathrm{dIVW}}$ increases.



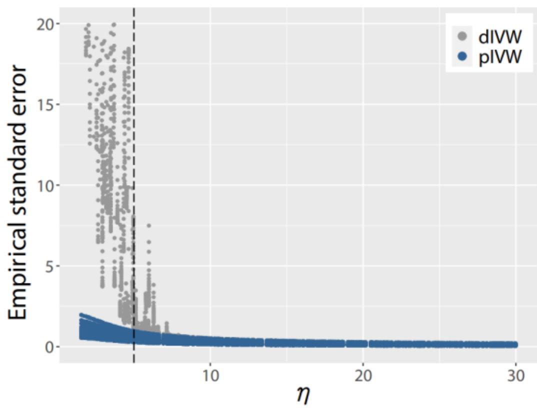
(a) (b)

(c)

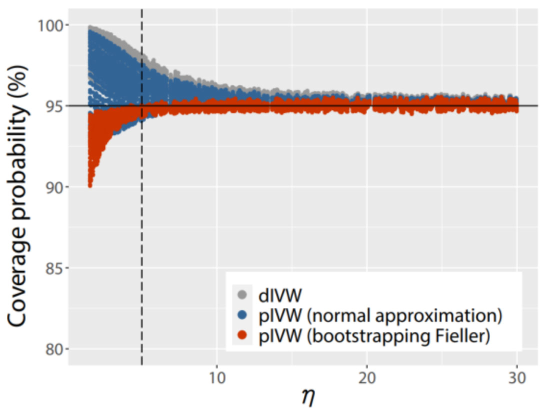
Web Figure 4. The plots of (a) absolute relative biases (%); (b) empirical standard errors; and (c) coverage probabilities (%) of the dIVW estimator and the pIVW estimator (λ_{opt} = 1) against the effective sample size η_δ. The dashed line shows $\eta_\delta = 5$. The dots represent the simulation results under different settings of parameters based on 10,000 replicates. There is no horizontal pleiotropy ($\tau = 0$). The IV selection threshold $\delta = \sqrt{2 \log p}$.



(a)

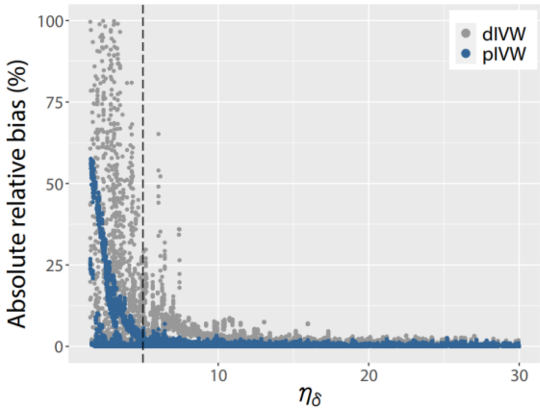


(b)

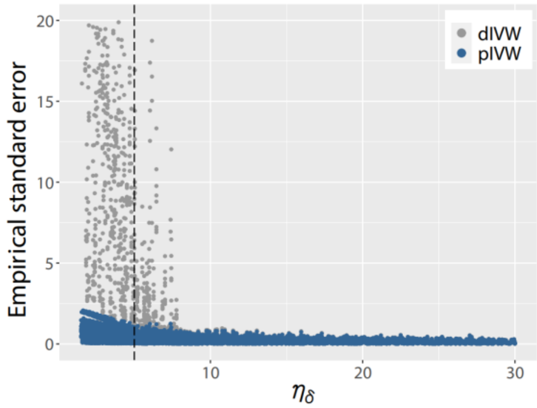


(c)

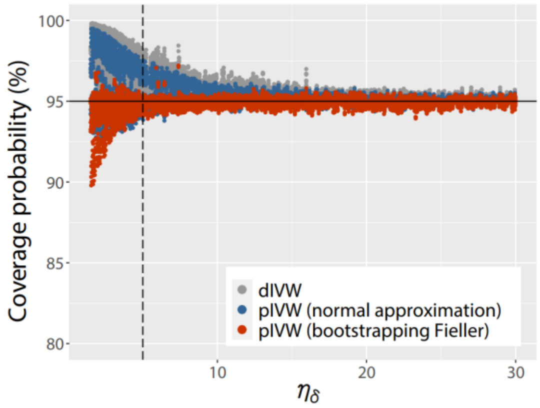
Web Figure 5. The plots of (a) absolute relative biases (%); (b) empirical standard errors; and (c) coverage probabilities (%) of the dIVW estimator and the pIVW estimator ($\lambda_{opt} = 1$) against the effective sample size η. The dashed line shows $\eta = 5$. The dots represent the simulation results under different settings of parameters based on 10,000 replicates. The balanced horizontal pleiotropy has $\tau = 0.01$. There is no IV selection conducted.



(a)



(b)



(c)

Web Figure 6. The plots of (a) absolute relative biases (%); (b) empirical standard errors; and (c) coverage probabilities (%) of the dIVW estimator and the pIVW estimator (λ_{opt} = 1) against the effective sample size η_δ. The dashed line shows $\eta_\delta = 5$. The dots represent the simulation results under different settings of parameters based on 10,000 replicates. The balanced horizontal pleiotropy has $\tau = 0.01$. The IV selection threshold $\delta = \sqrt{2 \log p}$.

(a) Outcome: COVID-19 infection

	IVW	MR-Egger	MR-Median	MR-RAPS	dIVW	pIVW
PVD	0.003 (0.007)	0.003 (0.01)	0.005 (0.011)	0.097 (0.223)	0.102 (0.27)	0.057 (0.14)
Dyslipidemia	0.007 (0.013)	0.010 (0.017)	-0.004 (0.025)	0.017 (0.033)	0.018 (0.032)	0.018 (0.032)
HD	0.025 (0.018)	0.032 (0.025)	0.019 (0.031)	0.083 (0.055)	0.074 (0.052)	0.074 (0.052)
T2D	-0.005 (0.01)	-0.006 (0.013)	-0.012 (0.018)	-0.023 (0.042)	-0.023 (0.042)	-0.022 (0.041)
BMI	0.095 (0.041) *	0.119 (0.055) *	0.038 (0.082)	0.116 (0.05) *	0.116 (0.05) *	0.115 (0.05) *

* P<0.05

Estimates: 0.08, 0.04, 0.00

(b) Outcome: hospitalized COVID-19

	IVW	MR-Egger	MR-Median	MR-RAPS	dIVW	pIVW
PVD	0.007 (0.013)	0.022 (0.019)	0.032 (0.02)	0.379 (0.55)	4.413 (95.942)	0.219 (0.429)
Dyslipidemia	-0.005 (0.025)	-0.008 (0.033)	-0.013 (0.046)	-0.013 (0.063)	-0.011 (0.059)	-0.011 (0.059)
HD	0.089 (0.033) *	0.068 (0.047)	0.109 (0.059)	0.241 (0.095) *	0.246 (0.093) *	0.244 (0.093) *
T2D	-5e-04 (0.019)	-0.031 (0.026)	-0.038 (0.041)	-0.003 (0.085)	-0.002 (0.085)	-0.002 (0.083)
BMI	0.382 (0.077) *	0.455 (0.105) *	0.549 (0.141) *	0.466 (0.097) *	0.468 (0.096) *	0.468 (0.096) *

* P<0.05

Estimates: 0.6, 0.4, 0.2, 0.0

(c) Outcome: critically ill COVID-19

	IVW	MR-Egger	MR-Median	MR-RAPS	dIVW	pIVW
PVD	0.009 (0.019)	0.014 (0.029)	0.030 (0.029)	0.320 (0.578)	0.464 (1.326)	0.202 (0.449)
Dyslipidemia	-0.008 (0.036)	0.014 (0.047)	-0.022 (0.066)	-0.020 (0.078)	-0.017 (0.077)	-0.017 (0.077)
HD	0.092 (0.049)	0.051 (0.07)	0.081 (0.089)	0.247 (0.133)	0.244 (0.132)	0.243 (0.131)
T2D	-0.033 (0.028)	-0.065 (0.041)	-0.042 (0.058)	-0.146 (0.124)	-0.139 (0.122)	-0.138 (0.12)
BMI	0.366 (0.115) *	0.431 (0.155) *	0.391 (0.206)	0.439 (0.141) *	0.441 (0.14) *	0.441 (0.14) *

* P<0.05

Estimates: 0.4, 0.2, 0.0

Web Figure 7. Estimated causal effects and standard errors (in parentheses) of five obesity-related exposures (i.e., peripheral vascular disease (PVD), dyslipidemia, hypertensive disease (HD), type 2 diabetes (T2D) and BMI) on (a) COVID-19 infection, (b) hospitalized COVID-19, and (c) critically ill COVID-19. No IV selection is conducted. The pIVW estimator with the optimal λ_{opt} = 1.

(a) Outcome: COVID-19 infection

	IVW	MR-Egger	MR-Median	MR-RAPS	dIVW	pIVW
PVD	0.121 (0.034) *	0.163 (0.043) *	0.076 (0.065)	0.278 (0.091) *	0.297 (0.116) *	0.272 (0.098) *
Dyslipidemia	0.027 (0.025)	0.023 (0.032)	-0.004 (0.03)	0.031 (0.027)	0.030 (0.027)	0.030 (0.027)
HD	0.013 (0.037)	0.022 (0.051)	0.039 (0.054)	0.017 (0.046)	0.016 (0.046)	0.016 (0.045)
T2D	-0.010 (0.022)	-0.066 (0.029) *	-0.048 (0.035)	-0.012 (0.028)	-0.012 (0.029)	-0.012 (0.028)
BMI	0.109 (0.056)	0.123 (0.08)	0.036 (0.095)	0.117 (0.061)	0.116 (0.06)	0.116 (0.06)

* P<0.05

Estimates: 0.2, 0.1, 0.0

(b) Outcome: hospitalized COVID-19

	IVW	MR-Egger	MR-Median	MR-RAPS	dIVW	pIVW
PVD	0.233 (0.055) *	0.292 (0.071) *	0.367 (0.098) *	0.419 (0.217) *	0.670 (0.317) *	0.594 (0.245) *
Dyslipidemia	-0.001 (0.038)	4e-04 (0.05)	-0.013 (0.057)	-0.002 (0.042)	-0.002 (0.042)	-0.002 (0.042)
HD	0.135 (0.065) *	0.199 (0.091) *	0.132 (0.099)	0.161 (0.08) *	0.163 (0.079) *	0.163 (0.078) *
T2D	-0.026 (0.041)	-0.098 (0.054)	-0.047 (0.066)	-0.032 (0.052)	-0.033 (0.053)	-0.033 (0.052)
BMI	0.371 (0.1) *	0.563 (0.14) *	0.361 (0.176) *	0.397 (0.106) *	0.397 (0.106) *	0.397 (0.106) *

* P<0.05

Estimates: 0.6, 0.4, 0.2, 0.0

(c) Outcome: critically ill COVID-19

	IVW	MR-Egger	MR-Median	MR-RAPS	dIVW	pIVW
PVD	0.228 (0.086) *	0.291 (0.111) *	0.381 (0.135) *	0.555 (0.265) *	0.613 (0.308) *	0.549 (0.25) *
Dyslipidemia	0.016 (0.056)	0.015 (0.073)	-0.026 (0.076)	0.016 (0.06)	0.017 (0.062)	0.017 (0.062)
HD	0.108 (0.098)	0.093 (0.136)	0.087 (0.158)	0.130 (0.122)	0.133 (0.111)	0.132 (0.111)
T2D	0.025 (0.066)	-0.072 (0.088)	-0.036 (0.089)	0.058 (0.092)	0.032 (0.089)	0.031 (0.088)
BMI	0.292 (0.149) *	0.450 (0.207) *	0.379 (0.251)	0.309 (0.158)	0.311 (0.159)	0.311 (0.159)

* P<0.05

Estimates: 0.6, 0.4, 0.2, 0.0

Web Figure 8. Estimated causal effects and standard errors (in parentheses) of five obesity-related exposures (i.e., peripheral vascular disease (PVD), dyslipidemia, hypertensive disease (HD), type 2 diabetes (T2D) and BMI) on (a) COVID-19 infection, (b) hospitalized COVID-19, and (c) critically ill COVID-19. The IV selection is conducted at threshold $\delta = \sqrt{2\log p}$. The pIVW estimator with the optimal $\lambda_{opt} = 1$.