Supplementary Materials for "Pseudo-p-Value-Based Clumping Enhanced Proteome-wide Mendelian Randomization for Identifying Coronary Heart Disease-Associated Plasma Proteins"

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1 Supplementary Notes

We organize the supplementary notes as follows: In subsection **??**, we provide the variance-covariance matrix for the MR-GMM estimator. In subsection **??**, we outline the steps of the Deterministic Annealing Expectation-Maximization (DAEM) algorithm, including its optimization process presented in Algorithm 1.

1.1 The variance-covariance matrix of the MR-GMM estimator

The derivation of the variance-covariance matrix of the MR-GMM estimator is omitted for brevity. We only provide the final expression here. One can verify the results using the R package *NumDeriv*. In practice, because we only need the variance of $\hat{\beta}$ for subsequential analyses, we reparameterize the original parameter θ as $\tilde{\theta} = [\beta, \tilde{\tau}, \tilde{\eta}, \tilde{\pi}_1, \tilde{\pi}_2, \tilde{\pi}_3]^T = \left[\beta, \log\tau, \log\eta, \log\frac{\pi_1}{1-\sum_{k=1}^3 \pi_k}, \log\frac{\pi_2}{1-\sum_{k=1}^3 \pi_k}, \log\frac{\pi_3}{1-\sum_{k=1}^3 \pi_k}\right]^T$ to avoid calculation problems arising from large values of τ and η. Let

$$
\begin{aligned}
\tilde{V}_1 =& \frac{1}{m}\mathrm{E}_{P_0}\frac{\partial^2 \log L_\lambda}{\partial\tilde{\theta}\partial\tilde{\theta}^T} \\
=& \frac{1}{m}\sum_{j=1}^{m}\mathrm{E}_{P_0}\begin{bmatrix}
\frac{\partial^2 l_j^\lambda}{\partial\beta^2} & \frac{\partial^2 l_j^\lambda}{\partial\beta\partial\tilde{\tau}} & \frac{\partial^2 l_j^\lambda}{\partial\beta\partial\tilde{\eta}} & \frac{\partial^2 l_j^\lambda}{\partial\beta\partial\tilde{\pi}_1} & \frac{\partial^2 l_j^\lambda}{\partial\beta\partial\tilde{\pi}_2} & \frac{\partial^2 l_j^\lambda}{\partial\beta\partial\tilde{\pi}_3} \\
\frac{\partial^2 l_j^\lambda}{\partial\tilde{\tau}\partial\beta} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\tau}^2} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\tau}\partial\tilde{\eta}} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\tau}\partial\tilde{\pi}_1} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\tau}\partial\tilde{\pi}_2} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\tau}\partial\tilde{\pi}_3} \\
\frac{\partial^2 l_j^\lambda}{\partial\tilde{\eta}\partial\beta} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\eta}\partial\tilde{\tau}} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\eta}^2} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\eta}\partial\tilde{\pi}_1} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\eta}\partial\tilde{\pi}_2} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\eta}\partial\tilde{\pi}_3} \\
\frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_1\partial\beta} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_1\partial\tilde{\tau}} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_1\partial\tilde{\eta}} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_1^2} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_1\partial\tilde{\pi}_2} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_1\partial\tilde{\pi}_3} \\
\frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_2\partial\beta} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_2\partial\tilde{\tau}} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_2\partial\tilde{\eta}} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_2\partial\tilde{\pi}_1} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_2^2} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_2\partial\tilde{\pi}_3} \\
\frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_3\partial\beta} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_3\partial\tilde{\tau}} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_3\partial\tilde{\eta}} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_3\partial\tilde{\pi}_1} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_3\partial\tilde{\pi}_2} & \frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_3^2}
\end{bmatrix}, \\
\tilde{V}_2 =& \frac{1}{m}\mathrm{Var}_{P_0}\left[\frac{\partial \log L_\lambda}{\partial\tilde{\theta}}\right] \\
=& \frac{1}{m}\sum_{j=1}^{m}\mathrm{E}_{P_0}\begin{bmatrix}
(\frac{\partial l_j^\lambda}{\partial\beta})^2 & \frac{\partial l_j^\lambda}{\partial\beta}\frac{\partial l_j^\lambda}{\partial\tilde{\tau}} & \frac{\partial l_j^\lambda}{\partial\beta}\frac{\partial l_j^\lambda}{\partial\tilde{\eta}} & \frac{\partial l_j^\lambda}{\partial\beta}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_1} & \frac{\partial l_j^\lambda}{\partial\beta}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_2} & \frac{\partial l_j^\lambda}{\partial\beta}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_3} \\
\frac{\partial l_j^\lambda}{\partial\tilde{\tau}}\frac{\partial l_j^\lambda}{\partial\beta} & (\frac{\partial l_j^\lambda}{\partial\tilde{\tau}})^2 & \frac{\partial l_j^\lambda}{\partial\tilde{\tau}}\frac{\partial l_j^\lambda}{\partial\tilde{\eta}} & \frac{\partial l_j^\lambda}{\partial\tilde{\tau}}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_1} & \frac{\partial l_j^\lambda}{\partial\tilde{\tau}}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_2} & \frac{\partial l_j^\lambda}{\partial\tilde{\tau}}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_3} \\
\frac{\partial l_j^\lambda}{\partial\tilde{\eta}}\frac{\partial l_j^\lambda}{\partial\beta} & \frac{\partial l_j^\lambda}{\partial\tilde{\eta}}\frac{\partial l_j^\lambda}{\partial\tilde{\tau}} & (\frac{\partial l_j^\lambda}{\partial\tilde{\eta}})^2 & \frac{\partial l_j^\lambda}{\partial\tilde{\eta}}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_1} & \frac{\partial l_j^\lambda}{\partial\tilde{\eta}}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_2} & \frac{\partial l_j^\lambda}{\partial\tilde{\eta}}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_3} \\
\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_1}\frac{\partial l_j^\lambda}{\partial\beta} & \frac{\partial l_j^\lambda}{\partial\tilde{\pi}_1}\frac{\partial l_j^\lambda}{\partial\tilde{\tau}} & \frac{\partial l_j^\lambda}{\partial\tilde{\pi}_1}\frac{\partial l_j^\lambda}{\partial\tilde{\eta}} & (\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_1})^2 & \frac{\partial l_j^\lambda}{\partial\tilde{\pi}_1}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_2} & \frac{\partial l_j^\lambda}{\partial\tilde{\pi}_1}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_3} \\
\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_2}\frac{\partial l_j^\lambda}{\partial\beta} & \frac{\partial l_j^\lambda}{\partial\tilde{\pi}_2}\frac{\partial l_j^\lambda}{\partial\tilde{\tau}} & \frac{\partial l_j^\lambda}{\partial\tilde{\pi}_2}\frac{\partial l_j^\lambda}{\partial\tilde{\eta}} & \frac{\partial l_j^\lambda}{\partial\tilde{\pi}_2}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_1} & (\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_2})^2 & \frac{\partial l_j^\lambda}{\partial\tilde{\pi}_2}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_3} \\
\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_3}\frac{\partial l_j^\lambda}{\partial\beta} & \frac{\partial l_j^\lambda}{\partial\tilde{\pi}_3}\frac{\partial l_j^\lambda}{\partial\tilde{\tau}} & \frac{\partial l_j^\lambda}{\partial\tilde{\pi}_3}\frac{\partial l_j^\lambda}{\partial\tilde{\eta}} & \frac{\partial l_j^\lambda}{\partial\tilde{\pi}_3}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_1} & \frac{\partial l_j^\lambda}{\partial\tilde{\pi}_3}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_2} & (\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_3})^2
\end{bmatrix}.
\end{aligned}
\tag{S1}
$$

Therefore, to obtain the variance of $\hat{\beta}$, it suffices to derive the first and second partial derivations of the individual penalized log-likelihood function l_j^λ with respect to each element in $\tilde{\theta}$. They can be calculated as follows:

$$
\frac{\partial l_j^\lambda}{\partial\beta} = \frac{1}{L_j}\left(\frac{\pi_1 f_1}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\frac{\partial \log f_1}{\partial\beta} + \frac{\pi_2 f_2}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\frac{\partial \log f_2}{\partial\beta}\right)
$$

$$\frac{\partial l_j^\lambda}{\partial\tilde{\tau}} = \frac{\tau}{L_j}\left(\frac{\pi_1 f_1}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\frac{\partial\log f_1}{\partial\tau} + \frac{\pi_3 f_3}{\Phi(-t)}\frac{\partial\log f_3}{\partial\tau}\right)$$

$$\frac{\partial l_j^\lambda}{\partial\tilde{\eta}} = \frac{\eta}{L_j}\left(\frac{\pi_1 f_1}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\left(\frac{\partial\log f_1}{\partial\eta} - \frac{\partial\log\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}{\partial\eta}\right) + \right.$$

$$\left.\frac{\pi_2 f_2}{\Phi(-t)}\left(\frac{\partial\log f_2}{\partial\eta} - \frac{\partial\log\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}{\partial\eta}\right)\right)$$

$$\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_1} = \pi_1\left(\frac{f_1}{L_j\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)} - 1\right) + \frac{\lambda}{m}(1-4\pi_1)$$

$$\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_2} = \pi_2\left(\frac{f_2}{L_j\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)} - 1\right) + \frac{\lambda}{m}(1-4\pi_2)$$

$$\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_3} = \pi_3\left(\frac{f_3}{L_j\Phi(-t)} - 1\right) + \frac{\lambda}{m}(1-4\pi_3)$$

$$\frac{\partial^2 l_j^\lambda}{\partial\beta^2} = -\left(\frac{\partial l_j^\lambda}{\partial\beta}\right)^2 + \frac{1}{L_j}\left(\frac{\pi_1 f_1}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\left(\left(\frac{\partial\log f_1}{\partial\beta}\right)^2 + \frac{\partial^2\log f_1}{\partial\beta^2}\right) + \right.$$

$$\left.\frac{\pi_2 f_2}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\left(\left(\frac{\partial\log f_2}{\partial\beta}\right)^2 + \frac{\partial^2\log f_2}{\partial\beta^2}\right)\right)$$

$$\frac{\partial^2 l_j^\lambda}{\partial\beta\partial\tilde{\tau}} = -\frac{\partial l_j^\lambda}{\partial\beta}\frac{\partial l_j^\lambda}{\partial\tilde{\tau}} + \frac{\tau\pi_1 f_1}{L_j\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\left(\frac{\partial\log f_1}{\partial\beta}\frac{\partial\log f_1}{\partial\tau} + \frac{\partial^2\log f_1}{\partial\beta\partial\tau}\right)$$

$$\frac{\partial^2 l_j^\lambda}{\partial\beta\partial\tilde{\eta}} = -\frac{\partial l_j^\lambda}{\partial\beta}\frac{\partial l_j^\lambda}{\partial\tilde{\eta}} + \frac{\eta}{L_j}\left(\frac{\pi_1 f_1}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\left(\frac{\partial\log f_1}{\partial\beta}\left(\frac{\partial\log f_1}{\partial\eta} - \frac{\partial\log\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}{\partial\eta}\right) + \frac{\partial^2\log f_1}{\partial\beta\partial\eta}\right)\right.$$

$$\left.\frac{\pi_2 f_2}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\left(\frac{\partial\log f_2}{\partial\beta}\left(\frac{\partial\log f_2}{\partial\eta} - \frac{\partial\log\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}{\partial\eta}\right) + \frac{\partial^2\log f_2}{\partial\beta\partial\eta}\right)\right)$$

$$\frac{\partial^2 l_j^\lambda}{\partial\beta\partial\tilde{\pi}_1} = -\frac{\partial l_j^\lambda}{\partial\beta}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_1} + \frac{1}{L_j}\left(\frac{\pi_1(1-\pi_1)f_1}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\frac{\partial\log f_1}{\partial\beta} - \frac{\pi_1\pi_2 f_2}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\frac{\partial\log f_2}{\partial\beta}\right)$$

$$\frac{\partial^2 l_j^\lambda}{\partial\beta\partial\tilde{\pi}_2} = -\frac{\partial l_j^\lambda}{\partial\beta}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_2} + \frac{1}{L_j}\left(\frac{\pi_2(1-\pi_2)f_2}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\frac{\partial\log f_2}{\partial\beta} - \frac{\pi_1\pi_2 f_1}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\frac{\partial\log f_1}{\partial\beta}\right)$$

$$\frac{\partial^2 l_j^\lambda}{\partial\beta\partial\tilde{\pi}_3} = -\frac{\partial l_j^\lambda}{\partial\beta}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_3} + \frac{1}{L_j}\left(-\frac{\pi_1\pi_3 f_1}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\frac{\partial\log f_1}{\partial\beta} - \frac{\pi_2\pi_3 f_2}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\frac{\partial\log f_2}{\partial\beta}\right)$$

$$\frac{\partial^2 l_j^\lambda}{\partial\tilde{\tau}^2} = -\left(\frac{\partial l_j^\lambda}{\partial\tilde{\tau}}\right)^2 + \frac{\partial l_j^\lambda}{\partial\tilde{\tau}} + \frac{\tau^2}{L_j}\left(\frac{\pi_1 f_1}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\left(\left(\frac{\partial\log f_1}{\partial\tau}\right)^2 + \frac{\partial^2\log f_1}{\partial\tau^2}\right) + \right.$$

$$\left.\frac{\pi_3 f_3}{\Phi(-t)}\left(\left(\frac{\partial\log f_3}{\partial\tau}\right)^2 + \frac{\partial^2\log f_3}{\partial\tau^2}\right)\right)$$

$$\frac{\partial^2 l_j^\lambda}{\partial\tilde{\tau}\partial\tilde{\eta}} = -\frac{\partial l_j^\lambda}{\partial\tilde{\tau}}\frac{\partial l_j^\lambda}{\partial\tilde{\eta}} + \frac{\eta\tau\pi_1 f_1}{L_j\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\left(\frac{\partial\log f_1}{\partial\tau}\left(\frac{\partial\log f_1}{\partial\eta} - \frac{\partial\log\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}{\partial\eta}\right) + \frac{\partial^2\log f_1}{\partial\tau\partial\eta}\right)$$

$$\frac{\partial^2 l_j^\lambda}{\partial\tilde\tau\partial\tilde\pi_1} = -\frac{\partial l_j^\lambda}{\partial\tilde\tau}\frac{\partial l_j^\lambda}{\partial\tilde\pi_1} + \frac{\tau}{L_j}\left(\frac{\pi_1(1-\pi_1)f_1}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\frac{\partial\log f_1}{\partial\tau} - \frac{\pi_3\pi_1 f_3}{\Phi\left(-t\right)}\frac{\partial\log f_3}{\partial\tau}\right)$$

$$\frac{\partial^2 l_j^\lambda}{\partial\tilde\tau\partial\tilde\pi_2} = -\frac{\partial l_j^\lambda}{\partial\tilde\tau}\frac{\partial l_j^\lambda}{\partial\tilde\pi_2} + \frac{\tau}{L_j}\left(\frac{-\pi_1\pi_2 f_1}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\frac{\partial\log f_1}{\partial\tau} - \frac{\pi_3\pi_2 f_3}{\Phi\left(-t\right)}\frac{\partial\log f_3}{\partial\tau}\right)$$

$$\frac{\partial^2 l_j^\lambda}{\partial\tilde\tau\partial\tilde\pi_3} = -\frac{\partial l_j^\lambda}{\partial\tilde\tau}\frac{\partial l_j^\lambda}{\partial\tilde\pi_3} + \frac{\tau}{L_j}\left(\frac{-\pi_1\pi_3 f_1}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\frac{\partial\log f_1}{\partial\tau} + \frac{\pi_3(1-\pi_3) f_3}{\Phi\left(-t\right)}\frac{\partial\log f_3}{\partial\tau}\right)$$

$$\frac{\partial^2 l_j^\lambda}{\partial\tilde\eta^2} = -\left(\frac{\partial l_j^\lambda}{\partial\tilde\eta}\right)^2 + \frac{\partial l_j^\lambda}{\partial\tilde\eta} + \frac{\eta^2}{L_j}\left(\frac{\pi_1 f_1}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\left(\left(\frac{\partial\log f_1}{\partial\eta} - \frac{\partial\log\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}{\partial\eta}\right)^2 + \right.\right.$$

$$\left.\frac{\partial^2\log f_1}{\partial\eta^2} - \frac{\partial^2\log\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}{\partial\eta^2}\right) + \frac{\pi_2 f_2}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\left(\left(\frac{\partial\log f_2}{\partial\eta} - \frac{\partial\log\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}{\partial\eta}\right)^2 + \right.$$

$$\left.\left.\frac{\partial^2\log f_2}{\partial\eta^2} - \frac{\partial^2\log\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}{\partial\eta^2}\right)\right)$$

$$\frac{\partial^2 l_j^\lambda}{\partial\tilde\eta\partial\tilde\pi_1} = -\frac{\partial l_j^\lambda}{\partial\tilde\eta}\frac{\partial l_j^\lambda}{\partial\tilde\pi_1} + \frac{\eta}{L_j}\left(\frac{\pi_1(1-\pi_1)f_1}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\left(\frac{\partial\log f_1}{\partial\eta} - \frac{\partial\log\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}{\partial\eta}\right) - \right.$$

$$\left.\frac{\pi_2\pi_1 f_2}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}\left(\frac{\partial\log f_2}{\partial\eta} - \frac{\partial\log\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}{\partial\eta}\right)\right)$$

$$
\begin{aligned}
\frac{\partial^2 l_j^\lambda}{\partial\tilde{\eta}\partial\tilde{\pi}_2} =& - \frac{\partial l_j^\lambda}{\partial\tilde{\eta}}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_2} + \frac{\eta}{L_j}\left(\frac{-\pi_1\pi_2 f_1}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma^2_{X_j}}}\right)}\left(\frac{\partial \log f_1}{\partial \eta} - \frac{\partial \log \Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma^2_{X_j}}}\right)}{\partial\eta}\right)+\right.\\
&\left.\frac{\pi_2(1-\pi_2)f_2}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma^2_{X_j}}}\right)}\left(\frac{\partial \log f_2}{\partial \eta} - \frac{\partial \log \Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma^2_{X_j}}}\right)}{\partial\eta}\right)\right)\\
\frac{\partial^2 l_j^\lambda}{\partial\tilde{\eta}\partial\tilde{\pi}_3} =& - \frac{\partial l_j^\lambda}{\partial\tilde{\eta}}\frac{\partial l_j^\lambda}{\partial\tilde{\pi}_3} + \frac{\eta}{L_j}\left(\frac{-\pi_1\pi_3 f_1}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma^2_{X_j}}}\right)}\left(\frac{\partial \log f_1}{\partial \eta} - \frac{\partial \log \Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma^2_{X_j}}}\right)}{\partial\eta}\right)-\right.\\
&\left.\frac{\pi_2\pi_3 f_2}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma^2_{X_j}}}\right)}\left(\frac{\partial \log f_2}{\partial \eta} - \frac{\partial \log \Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma^2_{X_j}}}\right)}{\partial\eta}\right)\right)\\
\frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_1^2} =& -\left(\frac{\pi_1 f_1}{L_j\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma^2_{X_j}}}\right)} - \pi_1\right)\left(\frac{\pi_1 f_1}{L_j\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma^2_{X_j}}}\right)} + \pi_1\right) + \left(\frac{\pi_1 f_1}{L_j\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma^2_{X_j}}}\right)} - \pi_1\right)\\
&- \frac{4\lambda\pi_1(1-\pi_1)}{m}\\
\frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_1\partial\tilde{\pi}_2} =& -\pi_1\pi_2\left(\frac{f_1 f_2}{L_j^2\Phi^2\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma^2_{X_j}}}\right)} - 1 - \frac{4\lambda}{m}\right)\\
\frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_1\partial\tilde{\pi}_3} =& -\pi_1\pi_3\left(\frac{f_1 f_3}{L_j^2\Phi\left(-t\right)\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma^2_{X_j}}}\right)} - 1 - \frac{4\lambda}{m}\right)\\
\frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_2^2} =& -\left(\frac{\pi_2 f_2}{L_j\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma^2_{X_j}}}\right)} - \pi_2\right)\left(\frac{\pi_2 f_2}{L_j\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma^2_{X_j}}}\right)} + \pi_2\right) + \left(\frac{\pi_2 f_2}{L_j\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma^2_{X_j}}}\right)} - \pi_2\right)
\end{aligned}
$$

$$
-\frac{4\lambda\pi_2(1-\pi_2)}{m}
$$

$$
\begin{aligned}
\frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_2\partial\tilde{\pi}_3} &= -\pi_2\pi_3\left(\frac{f_2 f_3}{L_j^2\Phi\left(-t\right)\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}-1-\frac{4\lambda}{m}\right)\\
\frac{\partial^2 l_j^\lambda}{\partial\tilde{\pi}_3^2} &= -\left(\frac{\pi_3 f_3}{L_j\Phi\left(-t\right)}-\pi_3\right)\left(\frac{\pi_3 f_3}{L_j\Phi\left(-t\right)}+\pi_3\right)+\left(\frac{\pi_3 f_3}{L_j\Phi\left(-t\right)}-\pi_3\right)-\frac{4\lambda\pi_3(1-\pi_3)}{m}.
\end{aligned} \tag{S2}
$$

We omit the "2" preceding Φ because it can be factored out as $-\log 2$ in the log-likelihood function. Since this constant term does not influence the optimization or the final results, it is excluded for simplicity. The f_1, f_2, f_3, f_4 are the normal density functions of the four components, and L_j is the likelihood function of $\hat{d}_j$, i.e., $\frac{\pi_1 f_1}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}+\frac{\pi_2 f_2}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}+\frac{\pi_3 f_3}{\Phi(-t)}+\frac{\pi_4 f_4}{\Phi(-t)}$. Then the Sandwitch estimator of the variance of $\hat{\beta}$ is obtained by replacing the expectations with the sample averages.

1.2 Details of DAEM algorithm

The complete data penalized log-likelihood function of the GMM model is given by

$$
\begin{aligned}
& l_{c,j}^\lambda(\theta;\alpha_{j0},\gamma_{j0},L_j,\hat{\Gamma}_j,\hat{\gamma}_j,\sigma_{Y_j},\sigma_{X_j})\\
=& L_{j1}\left(\log\pi_1 N\left(\hat{d}_j;\begin{bmatrix}\alpha_{j0}+\beta\gamma_{j0}\\ \gamma_{j0}\end{bmatrix},\begin{bmatrix}\sigma_{Y_j}^2 & 0\\ 0 & \sigma_{X_j}^2\end{bmatrix}\right)N\left(\alpha_{j0};0,\tau^{-1}\right)N\left(\gamma_{j0};0,\eta^{-1}\right)-\log\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)\right)+\\
& L_{j2}\left(\log\pi_2 N\left(\hat{d}_j;\begin{bmatrix}\beta\gamma_{j0}\\ \gamma_{j0}\end{bmatrix},\begin{bmatrix}\sigma_{Y_j}^2 & 0\\ 0 & \sigma_{X_j}^2\end{bmatrix}\right)N\left(\alpha_{j0};0,\tau^{-1}\right)N\left(\gamma_{j0};0,\eta^{-1}\right)-\log\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)\right)+\\
& L_{j3}\left(\log\pi_3 N\left(\hat{d}_j;\begin{bmatrix}\alpha_{j0}\\ 0\end{bmatrix},\begin{bmatrix}\sigma_{Y_j}^2 & 0\\ 0 & \sigma_{X_j}^2\end{bmatrix}\right)N\left(\alpha_{j0};0,\tau^{-1}\right)N\left(\gamma_{j0};0,\eta^{-1}\right)-\log\Phi\left(-t\right)\right)+\\
& L_{j4}\left(\log\pi_4 N\left(\hat{d}_j;\begin{bmatrix}0\\ 0\end{bmatrix},\begin{bmatrix}\sigma_{Y_j}^2 & 0\\ 0 & \sigma_{X_j}^2\end{bmatrix}\right)N\left(\alpha_{j0};0,\tau^{-1}\right)N\left(\gamma_{j0};0,\eta^{-1}\right)-\log\Phi\left(-t\right)\right)-(\sum_{k=1}^{4}\pi_k-1)+\lambda\sum_{k=1}^{4}\log\pi_k,
\end{aligned} \tag{S3}
$$

For E-step, the posterior probabilities of the latent variables are derived based on Equation (S3). After factoring the joint posterior probabilities as

$$
\begin{aligned}
&p(\alpha_{j0},\gamma_{j0},L_j|\hat{\Gamma}_j,\hat{\gamma}_j,\sigma_{Y_j},\sigma_{X_j})\\
=&(p(\alpha_{j0},\gamma_{j0}|L_{j1}=1,\hat{\Gamma}_j,\hat{\gamma}_j,\sigma_{Y_j},\sigma_{X_j})p(L_{j1}=1|\hat{\Gamma}_j,\hat{\gamma}_j,\sigma_{Y_j},\sigma_{X_j}))^{L_{j1}}\\
&(p(\alpha_{j0},\gamma_{j0}|L_{j2}=1,\hat{\Gamma}_j,\hat{\gamma}_j,\sigma_{Y_j},\sigma_{X_j})p(L_{j2}=1|\hat{\Gamma}_j,\hat{\gamma}_j,\sigma_{Y_j},\sigma_{X_j}))^{L_{j2}}\\
&(p(\alpha_{j0},\gamma_{j0}|L_{j3}=1,\hat{\Gamma}_j,\hat{\gamma}_j,\sigma_{Y_j},\sigma_{X_j})p(L_{j3}=1|\hat{\Gamma}_j,\hat{\gamma}_j,\sigma_{Y_j},\sigma_{X_j}))^{L_{j3}}\\
&(p(\alpha_{j0},\gamma_{j0}|L_{j4}=1,\hat{\Gamma}_j,\hat{\gamma}_j,\sigma_{Y_j},\sigma_{X_j})p(L_{j4}=1|\hat{\Gamma}_j,\hat{\gamma}_j,\sigma_{Y_j},\sigma_{X_j}))^{L_{j4}},
\end{aligned}
\tag{S4}
$$

one can obtain the posterior probabilities of the latent variables as

$$
\begin{aligned}
p(\alpha_{j0},\gamma_{j0}|L_{jk}=1,\hat{\Gamma}_j,\hat{\gamma}_j,\sigma_{Y_j},\sigma_{X_j}) =&N(\mu_{jk},\Sigma_{jk}),\\
p(L_{jk}=1|\hat{\Gamma}_j,\hat{\gamma}_j,\sigma_{Y_j},\sigma_{X_j}) =&\rho_{jk},
\end{aligned}
\tag{S5}
$$

for $k=1,2,3,4$, where

$$
\begin{aligned}
\mu_{j1}=\Sigma_{j1}\begin{bmatrix}\hat{\Gamma}_j\sigma_{Y_j}^{-2}\\ \beta\hat{\Gamma}_j\sigma_{Y_j}^{-2}+\hat{\gamma}_j\sigma_{X_j}^{-2}\end{bmatrix}, \Sigma_{j1}=&\begin{bmatrix}\tau+\sigma_{Y_j}^{-2} & \beta\sigma_{Y_j}^{-2}\\ \beta\sigma_{Y_j}^{-2} & \eta+\beta^2\sigma_{Y_j}^{-2}+\sigma_{X_j}^{-2}\end{bmatrix}^{-1},\\
\mu_{j2}=\Sigma_{j2}\begin{bmatrix}0\\ \beta\hat{\Gamma}_j\sigma_{Y_j}^{-2}+\hat{\gamma}_j\sigma_{X_j}^{-2}\end{bmatrix}, \Sigma_{j2}=&\begin{bmatrix}\tau & 0\\ 0 & \eta+\beta^2\sigma_{Y_j}^{-2}+\sigma_{X_j}^{-2}\end{bmatrix}^{-1},\\
\mu_{j3}=\Sigma_{j3}\begin{bmatrix}\hat{\Gamma}_j\sigma_{Y_j}^{-2}\\ 0\end{bmatrix}, \Sigma_{j3}=&\begin{bmatrix}\tau+\sigma_{Y_j}^{-2} & 0\\ 0 & \eta\end{bmatrix}^{-1},\\
\mu_{j4}=\Sigma_{j4}\begin{bmatrix}0\\ 0\end{bmatrix}, \Sigma_{j4}=&\begin{bmatrix}\tau & 0\\ 0 & \eta\end{bmatrix}^{-1},
\end{aligned}
\tag{S6}
$$

and

$$
\begin{aligned}
\rho_{jk} =&\frac{\pi_k\exp\{\frac{1}{2}\log|\Sigma_{jk}|+\frac{1}{2}\mu_{jk}^T\Sigma_{jk}^{-1}\mu_{jk}\}/\Phi_k}{\sum_{k=1}^4\pi_k\exp\{\frac{1}{2}\log|\Sigma_{jk}|+\frac{1}{2}\mu_{jk}^T\Sigma_{jk}^{-1}\mu_{jk}\}/\Phi_k},\\
\Phi_k =&\begin{cases}\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right) & \text{for k=1, 2}\\ \Phi\left(-t\right) & \text{for k=3, 4}\end{cases}.
\end{aligned}
\tag{S7}
$$

For M-step, the parameters are updated by maximizing the expected complete data penalized log-likelihood function. The update of the parameters is given by

$$
\begin{aligned}
\hat{\beta} =& \frac{\sum_{j=1}^{m} \rho_{j1}\sigma_{Y_j}^{-2}\left(\mu_{j1,2}(\hat{\Gamma}_j - \mu_{j1,1}) - \Sigma_{j1,12}\right) + \rho_{j2}\sigma_{Y_j}^{-2}\mu_{j2,2}\hat{\Gamma}_j}{\sum_{j=1}^{m} \rho_{j1}\sigma_{Y_j}^{-2}\left(\mu_{j1,2}^2 + \Sigma_{j1,22}^2\right) + \rho_{j2}\sigma_{Y_j}^{-2}\left(\mu_{j2,2}^2 + \Sigma_{j2,22}^2\right)}, \\
\hat{\tau} =& m/\sum_{j=1}^{m}\sum_{k=1}^{4} \rho_{jk}\left(\mu_{jk,1}^2 + \Sigma_{jk,11}^2\right), \\
\hat{\pi}_k =& (\lambda + \sum_{j=1}^{m} \rho_{jk})/(4\lambda + m), \text{ for } k = 1, 2, 3, 4,
\end{aligned} \tag{S8}
$$

where $\mu_{jk,a}$ and $\Sigma_{jk,ab}$ represent the ath element and (a, b)th element of μ_{jk} and Σ_{jk}, respectively. However, $\hat{\eta}$ has no explicit form. It is the solution of the following equation:

$$
m/\eta + \sum_{j=1}^{m} \frac{\phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}(\rho_{j1} + \rho_{j2})t\sigma_{X_j}(\eta^{-1} + \sigma_{X_j}^2)^{-3/2}\eta^{-2} = \sum_{j=1}^{m}\sum_{k=1}^{4} \rho_{jk}\left(\mu_{jk,2}^2 + \Sigma_{jk,22}^2\right). \tag{S9}
$$

We use the following fixed point iteration to update $\hat{\eta}$:

$$
\eta^{t+1} = \left(\frac{m/\sqrt{\eta^t} + \sum_{j=1}^{m} \frac{\phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}{\Phi\left(-\frac{t\sigma_{X_j}}{\sqrt{\eta^{-1}+\sigma_{X_j}^2}}\right)}(\rho_{j1} + \rho_{j2})t\sigma_{X_j}(1 + \sigma_{X_j}^2\eta^t)^{-3/2}}{\sum_{j=1}^{m}\sum_{k=1}^{4} \rho_{jk}\left(\mu_{jk,2}^2 + \Sigma_{jk,22}^2\right)}\right)^2. \tag{S10}
$$

In summary, the DAEM algorithm is given as follows,

Algorithm 1: DAEM algorithm for the GMM model.

Data: $\hat{\Gamma}_j, \hat{\gamma}_j, \sigma_{Y_j}, \sigma_{X_j}$, for $j = 1, ..., m$
Init: $\theta^0 = (\beta^0, \tau^0, \eta^0, \pi_k^0)^T, 0 < \xi^0 < 1, ELBO^0$
Const: $\lambda \geq 1, r > 1, \varepsilon > 0$
for $t = 0, ..., \mathcal{T} - 1$ **do**
    Update $\mu_{jk}^t, \Sigma_{jk}^t, \rho_{jk}^t$ according to (S6) and (S7); `/* E-step */`
    $\rho_{jk}^t \leftarrow {\rho_{jk}^t}^{\xi^t} / \sum_{k=1}^4 {\rho_{jk}^t}^{\xi^t}$; `/* Annealing */`
    Update θ^{t+1} according to (7); `/* M-step */`
    $ELBO^{t+1} \leftarrow ELBO(\theta^t; \hat{\Gamma}, \hat{\gamma}, \sigma_Y, \sigma_X)$;
    $\xi^{t+1} \leftarrow \min(1, r\xi^t)$;
    if $|ELBO^{t+1} - ELBO^t| < \varepsilon$ **then**
        break;
    end
end

Computing the original penalized log-likelihood is time-consuming, so we use the evidence lower bound (ELBO) as the convergence criterion. The ELBO is defined as the expected complete data penalized log-likelihood function minus the entropy of the posterior distribution of the latent variables, which is given by

$$\begin{aligned} ELBO = &\sum_{j=1}^{m} \sum_{k=1}^{4} \rho_{jk} \left(\frac{1}{2} (\log |\Sigma_{jk}| + \mu_{jk}^T \Sigma_{jk}^{-1} \mu_{jk}) + \log \pi_k - \log \rho_{jk} - \log \Phi_k \right) + \\ &\frac{1}{2} (\log \tau + \log \eta) + \lambda \sum_{k=1}^{4} \pi_k + const. \end{aligned} \tag{S11}$$

2 Supplementary Figures

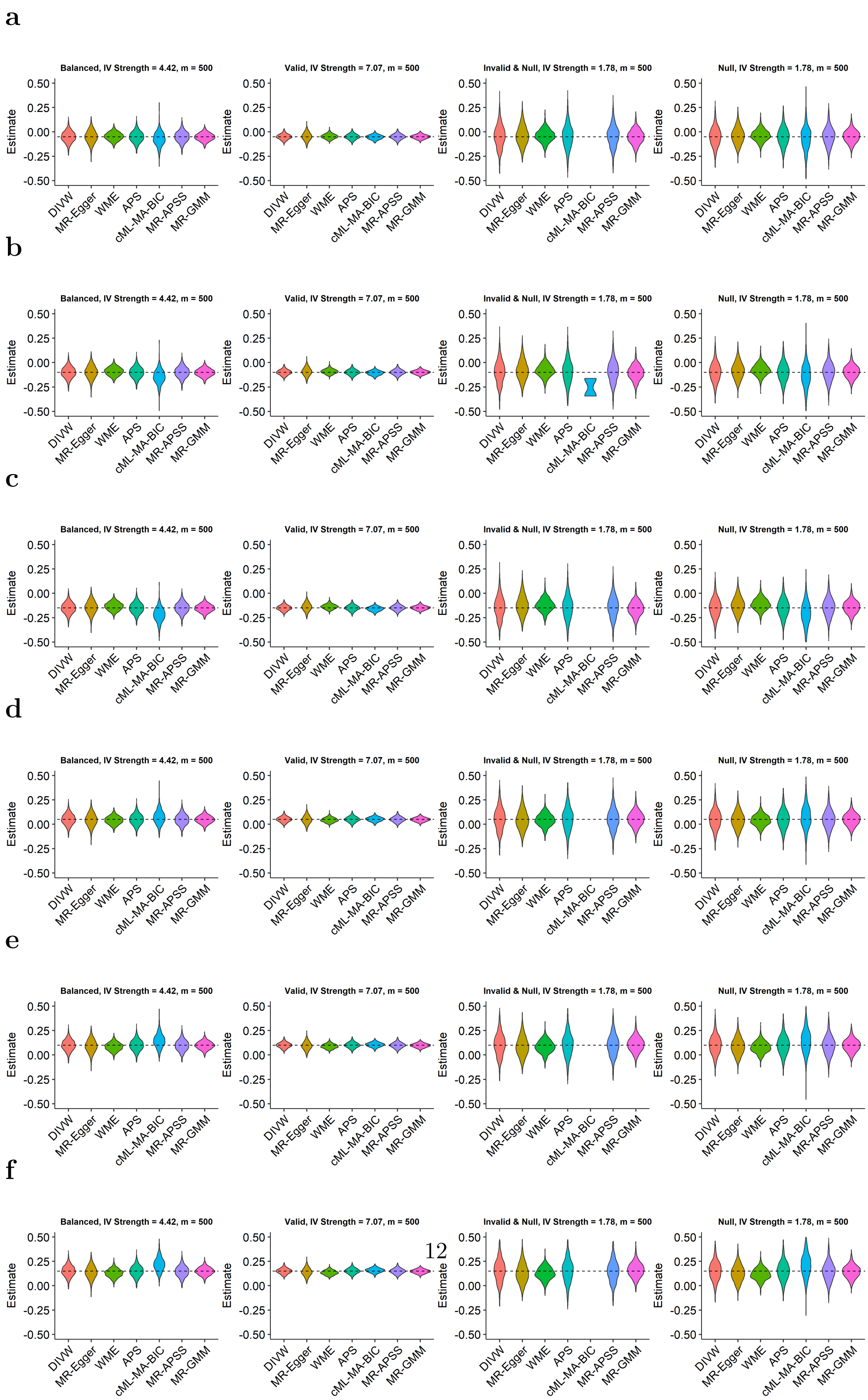

Fig. S1: **Comparison of point estimates under different β values.** Violin plots display the distribution of point estimates from 1000 simulations for varying true causal effects, β. The dashed line in each plot indicates the true value of β. **a.** $\beta = -0.05$. **b.** $\beta = -0.10$. **c.** $\beta = -0.15$. **d.** $\beta = 0.05$. **e.** $\beta = 0.10$. **f.** $\beta = 0.15$.

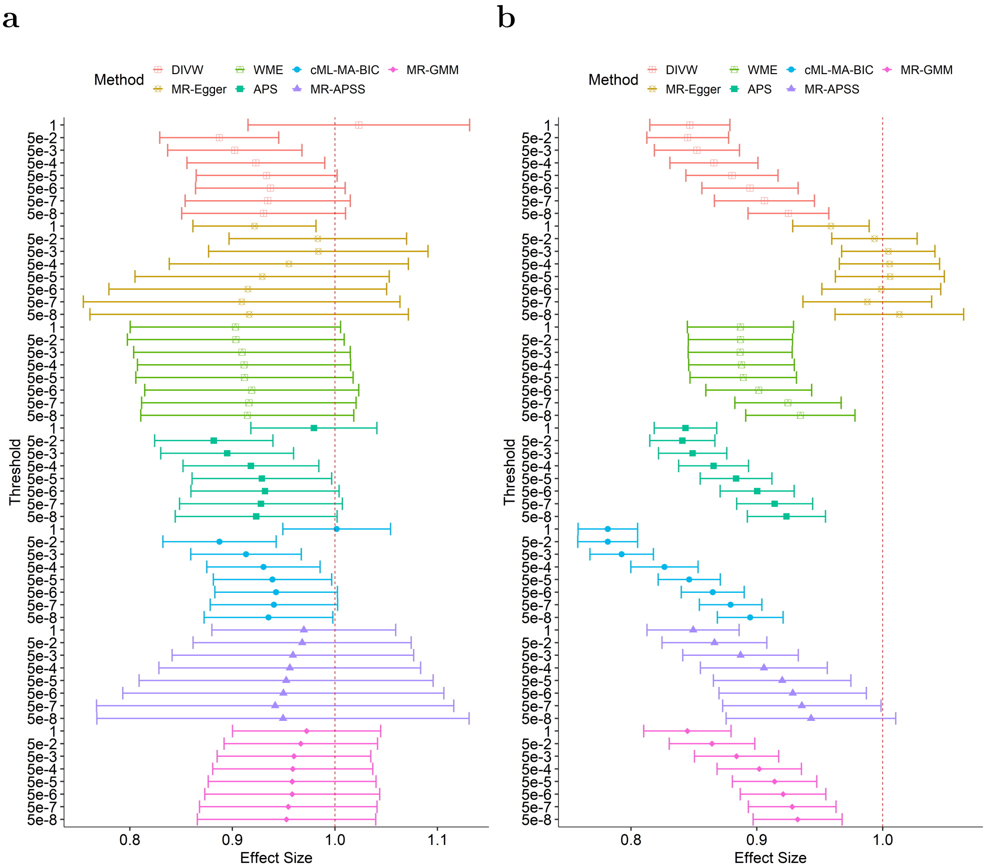

Fig. S2: **Benchmark HDL-HDL identity causal effect estimates obtained by using pseudo-p-value-based versus p-value-based LD clumping procedures under different IV selection thresholds. a.** The forest plot of all methods using pseudo-p-value-based LD clumping procedure, which is conducted by first clumping based on pseudo p-values and then thresholding based on observed p-values. The 95% confidence intervals of point estimates are represented by error bars. **b.** The forest plot of all methods using standard p-value-based LD clumping procedure. These plots allow for a visual comparison of how different clumping methods and IV selection thresholds affect the estimation of causal effects in MR studies.

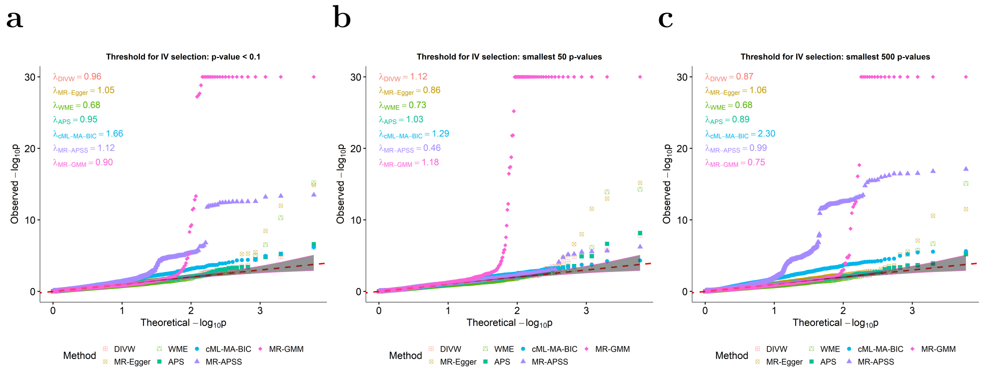

Fig. S3: **The Q-Q plot diagnosis of competing methods in the proteome-wide MR study under different p-value thresholds.** Q-Q plots of the negative log-transformed p-values for each method are presented, with the λ_{GC} values listed in the top-left corner of each plot for quantitative comparison. The grey regions on the plots represent the 95% confidence intervals for these p-values. After the pseudo-p-value-based LD clumping procedure, SNPs are selected based on different p-value thresholds: **a.** threshold of p-value < 0.1; **b.** smallest 50 p-values **c.** smallest 500 p-values.

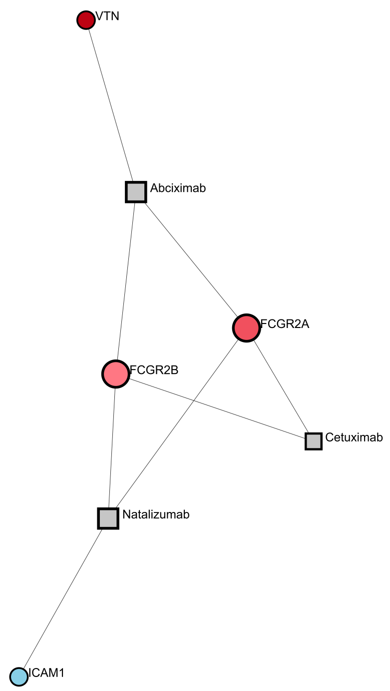

Fig. S4: The trimmed protein-drug interaction network of the 45 identified plasma proteins, with protein sizes proportional to their degrees. Proteins are color-coded according to their causal effects on CHD: red represents proteins that increase CHD risk, and blue indicates those that decrease it.

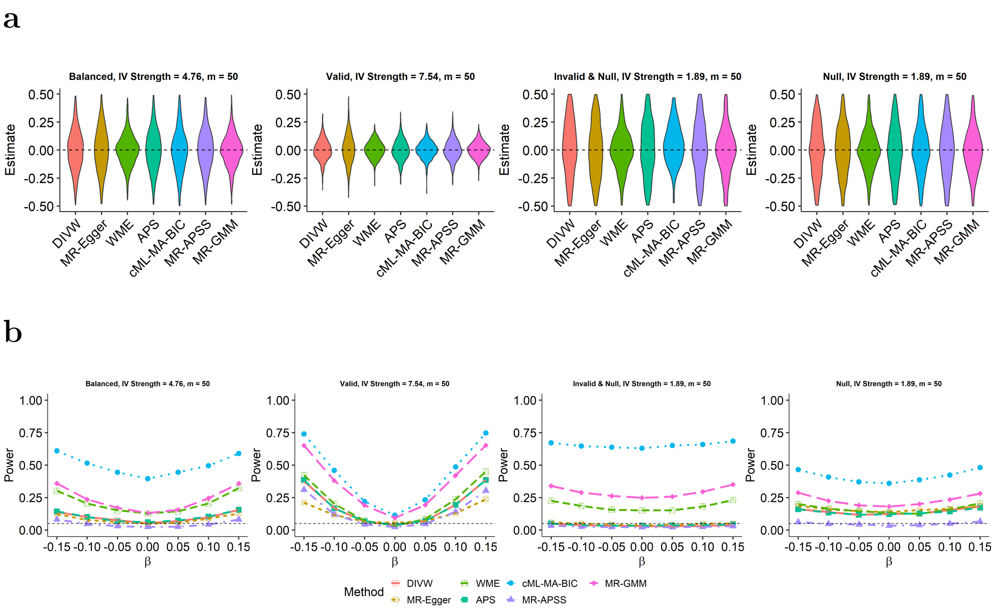

Fig. S5: **Benchmark all seven methods in various simulation scenarios when the number of IVs** $m = 50$**. a.** Violin plots depict the point estimates from 1000 replications when the true causal effect $\beta = 0$, indicated by the dashed line. **b.** The power of compared methods, calculated as the proportion of simulations in which the null hypothesis $H_0 : \beta = 0$ is rejected across 1000 replications.

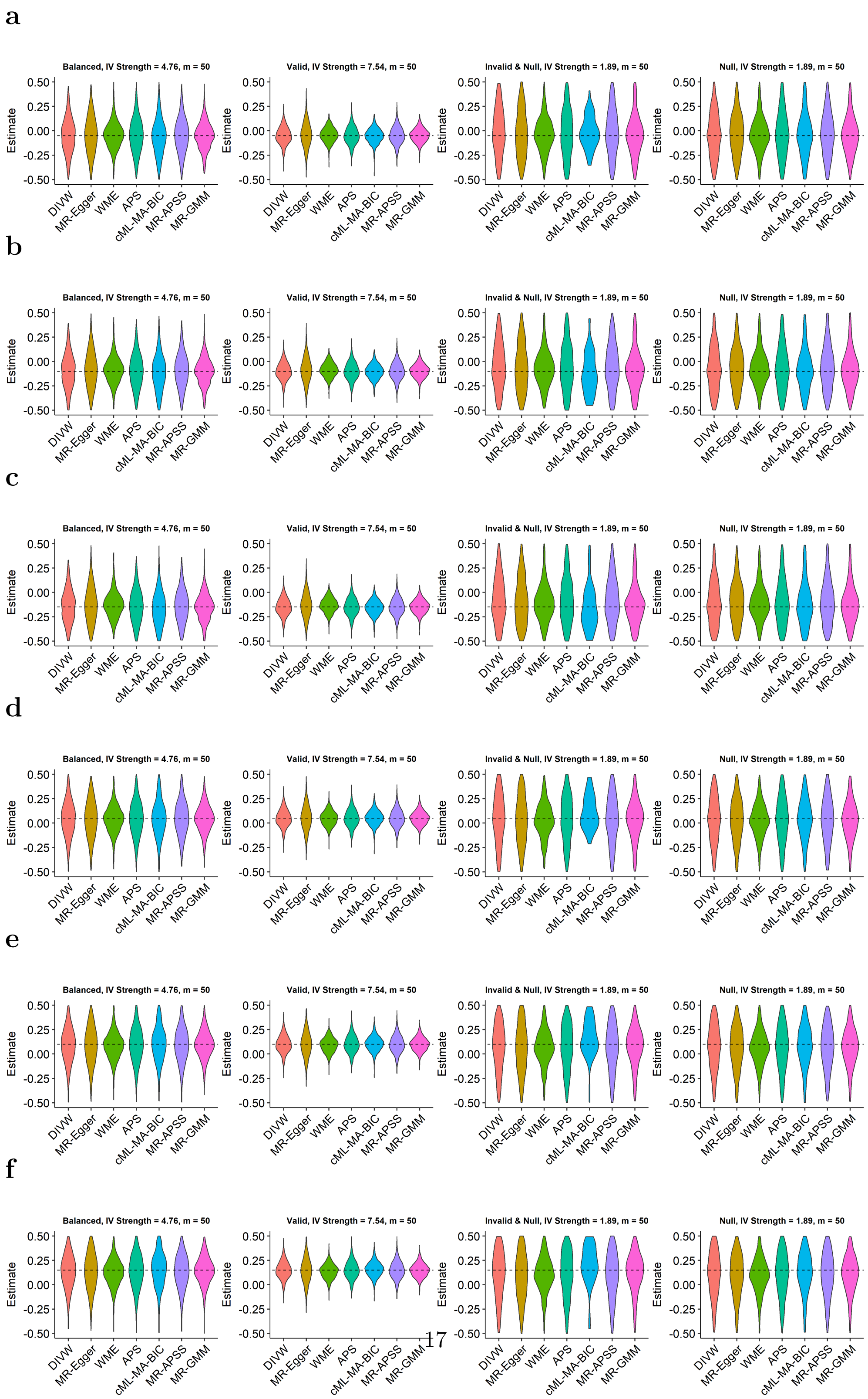

Fig. S6: **Comparison of point estimates under different β values when the number of IVs $m = 50$.** Violin plots display the distribution of point estimates from 1000 simulations for varying true causal effects, β. The dashed line in each plot indicates the true value of β. **a.** $\beta = -0.05$. **b.** $\beta = -0.10$. **c.** $\beta = -0.15$. **d.** $\beta = 0.05$. **e.** $\beta = 0.10$. **f.** $\beta = 0.15$.

3 Supplementary Tables

P	# of IVs	IV strength	Exposure ID	Outcome ID	DIVW	MR-Egger	WME	APS	cML-MA-BIC	MR-APSS	MR-GMM
5e-08	46	71.669	ukb-b-19953	ieu-a-2	0.963(0.031)	1.044(0.072)	1.003(0.048)	0.962(0.031)	0.961(0.031)	0.982(0.083)	0.987(0.032)
5e-07	60	61.143	ukb-b-19953	ieu-a-2	0.947(0.031)	1.064(0.070)	0.997(0.047)	0.945(0.031)	0.946(0.030)	0.970(0.075)	0.984(0.031)
5e-06	76	52.901	ukb-b-19953	ieu-a-2	**0.935(0.030)**	1.072(0.066)	0.994(0.045)	**0.934(0.030)**	**0.933(0.029)**	0.961(0.068)	0.977(0.030)
5e-05	107	42.632	ukb-b-19953	ieu-a-2	**0.929(0.029)**	1.063(0.063)	0.994(0.044)	**0.927(0.029)**	**0.927(0.028)**	0.970(0.061)	0.981(0.028)
5e-04	162	32.636	ukb-b-19953	ieu-a-2	**0.916(0.027)**	1.049(0.057)	0.980(0.041)	**0.913(0.027)**	**0.914(0.027)**	0.967(0.054)	0.983(0.027)
0.005	253	24.015	ukb-b-19953	ieu-a-2	**0.903(0.025)**	1.047(0.050)	0.925(0.040)	**0.899(0.025)**	**0.895(0.027)**	0.961(0.047)	0.976(0.027)
0.050	479	14.856	ukb-b-19953	ieu-a-2	**0.878(0.022)**	1.047(0.039)	**0.880(0.038)**	**0.875(0.022)**	**0.854(0.024)**	0.950(0.040)	0.962(0.026)
1.000	1773	4.048	ukb-b-19953	ieu-a-2	0.961(0.022)	**0.886(0.024)**	**0.879(0.037)**	**0.932(0.024)**	**0.902(0.024)**	**0.934(0.032)**	**0.946(0.026)**

Table S1: BMI-BMI causal effect estimates and SEs using the pseudo-p-value-based LD clumping procedure. Estimates with 95% confidence intervals that fail to include the true causal effect, $\beta = 1$, are highlighted in bold.

P	# of IVs	IV strength	Exposure ID	Outcome ID	DIVW	MR-Egger	WME	APS	cML-MA-BIC	MR-APSS	MR-GMM
5e-08	405	63.031	ukb-b-19953	ieu-a-2	**0.841(0.015)**	**1.096(0.034)**	**0.864(0.021)**	**0.830(0.015)**	**0.793(0.015)**	**0.859(0.029)**	**0.855(0.018)**
5e-07	510	55.505	ukb-b-19953	ieu-a-2	**0.827(0.013)**	**1.072(0.030)**	**0.853(0.020)**	**0.816(0.014)**	**0.771(0.016)**	**0.850(0.026)**	**0.844(0.017)**
5e-06	620	49.566	ukb-b-19953	ieu-a-2	**0.812(0.013)**	**1.066(0.029)**	**0.839(0.019)**	**0.801(0.013)**	**0.751(0.013)**	**0.836(0.024)**	**0.834(0.017)**
5e-05	774	43.193	ukb-b-19953	ieu-a-2	**0.802(0.012)**	1.045(0.026)	**0.824(0.019)**	**0.792(0.012)**	**0.741(0.012)**	**0.822(0.022)**	**0.821(0.016)**
5e-04	940	37.873	ukb-b-19953	ieu-a-2	**0.794(0.011)**	1.021(0.024)	**0.815(0.018)**	**0.785(0.011)**	**0.731(0.011)**	**0.813(0.020)**	**0.811(0.015)**
0.005	1156	32.433	ukb-b-19953	ieu-a-2	**0.783(0.011)**	1.009(0.022)	**0.807(0.018)**	**0.773(0.011)**	**0.719(0.011)**	**0.800(0.019)**	**0.800(0.015)**
0.050	1383	27.907	ukb-b-19953	ieu-a-2	**0.776(0.011)**	0.985(0.020)	**0.798(0.017)**	**0.767(0.011)**	**0.712(0.011)**	**0.782(0.017)**	**0.783(0.015)**
1.000	1820	21.326	ukb-b-19953	ieu-a-2	**0.780(0.011)**	**0.911(0.017)**	**0.797(0.017)**	**0.772(0.010)**	**0.709(0.011)**	**0.770(0.016)**	**0.768(0.015)**

Table S2: BMI-BMI causal effect estimates and SEs using the classic p-value-based LD clumping procedure. Estimates with 95% confidence intervals that fail to include the true causal effect, $\beta = 1$, are highlighted in bold.

P	# of IVs	IV strength	Exposure ID	Outcome ID	DIVW	MR-Egger	WME	APS	cML-MA-BIC	MR-APSS	MR-GMM
5e-08	40	105.400	ieu-b-109	ebi-a-GCST002223	0.930(0.041)	0.916(0.079)	0.915(0.053)	0.923(0.040)	**0.935(0.032)**	0.949(0.093)	0.953(0.044)
5e-07	44	98.277	ieu-b-109	ebi-a-GCST002223	0.934(0.041)	0.909(0.079)	0.916(0.053)	0.928(0.041)	0.940(0.032)	0.942(0.089)	0.954(0.044)
5e-06	59	78.905	ieu-b-109	ebi-a-GCST002223	0.937(0.037)	0.915(0.069)	0.919(0.053)	0.932(0.037)	0.943(0.030)	0.950(0.080)	0.958(0.043)
5e-05	78	63.886	ieu-b-109	ebi-a-GCST002223	0.933(0.035)	0.929(0.063)	0.912(0.054)	**0.929(0.035)**	**0.939(0.029)**	0.952(0.073)	0.958(0.042)
5e-04	113	48.175	ieu-b-109	ebi-a-GCST002223	**0.923(0.034)**	0.955(0.059)	0.911(0.053)	**0.918(0.034)**	**0.930(0.028)**	0.956(0.065)	0.959(0.040)
0.005	178	33.723	ieu-b-109	ebi-a-GCST002223	**0.902(0.033)**	0.984(0.055)	0.909(0.054)	**0.895(0.033)**	**0.913(0.028)**	0.959(0.060)	0.960(0.038)
0.050	389	17.863	ieu-b-109	ebi-a-GCST002223	**0.887(0.030)**	0.983(0.044)	0.903(0.054)	**0.882(0.029)**	**0.887(0.028)**	0.968(0.054)	0.967(0.038)
1.000	1775	3.850	ieu-b-109	ebi-a-GCST002223	1.023(0.055)	**0.921(0.031)**	0.903(0.052)	0.979(0.031)	1.002(0.027)	0.970(0.046)	0.972(0.037)

Table S3: HDL-HDL causal effect estimates and SEs using the pseudo-p-value-based LD clumping procedure. Estimates with 95% confidence intervals that fail to include the true causal effect, $\beta = 1$, are highlighted in bold.

P	# of IVs	IV strength	Exposure ID	Outcome ID	DIVW	MR-Egger	WME	APS	cML-MA-BIC	MR-APSS	MR-GMM
5e-08	313	127.690	ieu-b-109	ebi-a-GCST002223	**0.925(0.016)**	1.013(0.026)	**0.935(0.022)**	**0.924(0.016)**	**0.895(0.013)**	0.943(0.034)	**0.932(0.018)**
5e-07	369	112.260	ieu-b-109	ebi-a-GCST002223	**0.906(0.020)**	0.988(0.026)	**0.925(0.022)**	**0.914(0.015)**	**0.879(0.013)**	**0.936(0.032)**	**0.928(0.018)**
5e-06	461	94.237	ieu-b-109	ebi-a-GCST002223	**0.895(0.020)**	0.999(0.024)	**0.902(0.021)**	**0.900(0.015)**	**0.865(0.013)**	**0.928(0.030)**	**0.921(0.017)**
5e-05	592	77.234	ieu-b-109	ebi-a-GCST002223	**0.880(0.019)**	1.006(0.022)	**0.889(0.022)**	**0.884(0.015)**	**0.846(0.013)**	**0.920(0.028)**	**0.914(0.017)**
5e-04	775	62.090	ieu-b-109	ebi-a-GCST002223	**0.866(0.018)**	1.005(0.020)	**0.888(0.021)**	**0.866(0.014)**	**0.827(0.014)**	**0.906(0.026)**	**0.902(0.017)**
0.005	1021	49.242	ieu-b-109	ebi-a-GCST002223	**0.852(0.017)**	1.004(0.019)	**0.887(0.021)**	**0.849(0.014)**	**0.793(0.013)**	**0.887(0.023)**	**0.884(0.017)**
0.050	1310	39.408	ieu-b-109	ebi-a-GCST002223	**0.845(0.017)**	0.993(0.017)	**0.887(0.021)**	**0.841(0.013)**	**0.782(0.012)**	**0.866(0.021)**	**0.864(0.017)**
1.000	1809	28.678	ieu-b-109	ebi-a-GCST002223	**0.847(0.016)**	**0.959(0.015)**	**0.887(0.022)**	**0.843(0.013)**	**0.782(0.012)**	**0.849(0.019)**	**0.845(0.018)**

Table S4: HDL-HDL causal effect estimates and SEs using the classic p-value-based LD clumping procedure. Estimates with 95% confidence intervals that fail to include the true causal effect, $\beta = 1$, are highlighted in bold.

Exposure ID	Exposure	Outcome ID	Outcome	\# of IVs	IV strength	Estimate	SE	P-value
ieu-a-1024	Multiple sclerosis	ukb-d-1747_1	hair color	97	7.455	-0.001	0.005	0.826
ieu-a-789	Urate	ukb-d-1747_1	hair color	88	5.113	-0.001	0.011	0.941
ieu-a-1097	Microalbuminuria	ukb-d-1747_1	hair color	81	4.648	0.012	0.017	0.485
ieu-a-1049	Iron	ukb-d-1747_1	hair color	107	4.697	-0.017	0.034	0.627
ieu-a-961	Cigarettes smoked per day	ukb-d-1747_1	hair color	92	4.743	0.001	0.004	0.740
ieu-a-1085	Amyotrophic lateral sclerosis	ukb-d-1747_1	hair color	138	4.758	0.065	0.083	0.428
ieu-a-964	Age of smoking initiation	ukb-d-1747_1	hair color	94	4.850	0.157	0.132	0.235
ieu-a-801	Bipolar disorder	ukb-d-1747_1	hair color	136	4.821	0.003	0.016	0.876
ieu-a-1170	Knee and hip osteoarthritis	ukb-d-1747_1	hair color	95	4.765	-0.005	0.014	0.711
ieu-a-989	Squamous cell lung cancer	ukb-d-1747_1	hair color	161	5.497	-0.006	0.004	0.149
ieu-a-1052	Transferrin	ukb-d-1747_1	hair color	134	5.062	0.006	0.011	0.585
ieu-a-55	Hip circumference	ukb-d-1747_1	hair color	170	9.228	0.011	0.009	0.225
ieu-a-12	Crohn's disease	ukb-d-1747_1	hair color	203	17.974	0.003	0.002	0.155
ieu-a-91	Obesity class 2	ukb-d-1747_1	hair color	91	4.826	-0.002	0.009	0.804
ieu-a-27	Birth weight	ukb-d-1747_1	hair color	119	4.617	0.004	0.062	0.945
ieu-a-1044	Caudate volume	ukb-d-1747_1	hair color	112	4.372	0.000	0.000	0.967
ieu-a-835	Body mass index	ukb-d-1747_1	hair color	203	10.075	-0.006	0.009	0.516
ieu-a-970	Ulcerative colitis	ukb-d-1747_1	hair color	174	13.223	-0.001	0.002	0.822
ieu-a-85	Extreme body mass index	ukb-d-1747_1	hair color	120	4.596	-0.011	0.023	0.646
ieu-a-28	Infant head circumference	ukb-d-1747_1	hair color	97	5.071	-0.010	0.010	0.313
ieu-a-806	Autism	ukb-d-1747_1	hair color	123	4.892	0.011	0.009	0.216
ieu-a-1047	Putamen volume	ukb-d-1747_1	hair color	124	4.623	0.000	0.000	0.789
ieu-a-1041	Intracranial volume	ukb-d-1747_1	hair color	110	4.865	0.000	0.000	0.723
ieu-a-79	Waist-to-hip ratio	ukb-d-1747_1	hair color	140	7.476	0.008	0.010	0.429
ieu-a-803	PGC cross-disorder traits	ukb-d-1747_1	hair color	135	5.124	-0.004	0.011	0.721
ieu-a-1169	Hip osteoarthritis	ukb-d-1747_1	hair color	95	4.788	-0.009	0.014	0.527
ieu-a-1096	Childhood obesity	ukb-d-1747_1	hair color	99	4.663	-0.116	0.264	0.661
ieu-a-276	Celiac disease	ukb-d-1747_1	hair color	117	4.661	0.001	0.015	0.927
ieu-a-984	Lung adenocarcinoma	ukb-d-1747_1	hair color	136	5.054	-0.009	0.007	0.157
ieu-a-16	Childhood intelligence	ukb-d-1747_1	hair color	105	4.808	0.003	0.016	0.853
ieu-a-114	Neo-conscientiousness	ukb-d-1747_1	hair color	109	4.463	-0.051	0.061	0.399
ieu-a-86	Extreme height	ukb-d-1747_1	hair color	93	5.982	0.007	0.003	0.055
ieu-a-1050	Ferritin	ukb-d-1747_1	hair color	122	4.799	0.049	0.039	0.212
ieu-a-8	Coronary heart disease	ukb-d-1747_1	hair color	108	5.257	0.002	0.008	0.804
ieu-a-1008	Platelet count	ukb-d-1747_1	hair color	127	5.121	0.000	0.001	0.866
ieu-a-1000	Depressive symptoms	ukb-d-1747_1	hair color	136	5.725	0.023	0.026	0.373
ieu-a-962	Ever vs never smoked	ukb-d-1747_1	hair color	119	4.914	-0.004	0.018	0.803
ieu-a-1037	Difference in height between childhood and adulthood	ukb-d-1747_1	hair color	116	4.951	0.008	0.018	0.637
ieu-a-832	Rheumatoid arthritis	ukb-d-1747_1	hair color	153	7.137	-0.003	0.002	0.144
ieu-a-1054	Gout	ukb-d-1747_1	hair color	73	4.709	0.016	0.028	0.557
ieu-a-1101	Urinary albumin-to-creatinine ratio	ukb-d-1747_1	hair color	108	4.551	0.106	0.078	0.171
ieu-a-1183	ADHD	ukb-d-1747_1	hair color	159	5.182	0.013	0.007	0.089
ieu-a-67	Waist circumference	ukb-d-1747_1	hair color	168	7.804	0.015	0.014	0.256
ieu-a-92	Obesity class 3	ukb-d-1747_1	hair color	113	4.413	-0.029	0.020	0.150
ieu-a-996	Eczema	ukb-d-1747_1	hair color	147	4.826	0.003	0.012	0.823
ieu-a-298	Alzheimer's disease	ukb-d-1747_1	hair color	420	9.326	0.001	0.002	0.601
ieu-a-1171	Knee osteoarthritis	ukb-d-1747_1	hair color	102	4.482	-0.276	1.847	0.881
ieu-a-836	College completion	ukb-d-1747_1	hair color	126	5.758	-0.001	0.010	0.905
ieu-a-1045	Hippocampus volume	ukb-d-1747_1	hair color	94	4.481	0.000	0.000	0.535
ieu-a-1051	Transferrin Saturation	ukb-d-1747_1	hair color	107	5.061	-0.007	0.014	0.620
ieu-a-87	Extreme waist-to-hip ratio	ukb-d-1747_1	hair color	56	4.571	0.004	0.056	0.942
ieu-a-1009	Subjective well being	ukb-d-1747_1	hair color	129	5.786	0.032	0.020	0.117
ieu-a-89	Height	ukb-d-1747_1	hair color	350	10.433	-0.006	0.011	0.579
ieu-a-1003	Leptin	ukb-d-1747_1	hair color	114	4.432	0.257	0.141	0.068
ieu-a-963	Former vs current smoker	ukb-d-1747_1	hair color	96	4.863	-0.011	0.011	0.310
ieu-a-115	Neo-extraversion	ukb-d-1747_1	hair color	89	4.407	0.026	0.035	0.455
ieu-a-29	Birth length	ukb-d-1747_1	hair color	102	4.720	0.056	0.051	0.272
ieu-a-804	Major depressive disorder	ukb-d-1747_1	hair color	168	4.834	-0.009	0.008	0.245
ieu-a-1042	Nucleus accumbens volume	ukb-d-1747_1	hair color	88	4.787	0.000	0.000	0.928
ieu-a-117	Neo-openness to experience	ukb-d-1747_1	hair color	102	4.678	0.003	0.012	0.814
ieu-a-93	Overweight	ukb-d-1747_1	hair color	112	4.924	-0.011	0.016	0.482
ieu-a-26	Type 2 diabetes	ukb-d-1747_1	hair color	118	5.112	-0.008	0.006	0.154
ieu-a-1184	Autism Spectrum Disorder	ukb-d-1747_1	hair color	123	4.892	0.011	0.009	0.216
ieu-a-90	Obesity class 1	ukb-d-1747_1	hair color	94	5.395	-0.004	0.008	0.578
ieu-a-44	Asthma	ukb-d-1747_1	hair color	107	5.174	0.007	0.005	0.141
ieu-a-999	Body fat	ukb-d-1747_1	hair color	113	5.894	-0.021	0.009	0.020
ieu-a-837	Years of schooling	ukb-d-1747_1	hair color	130	5.422	0.021	0.028	0.455
ieu-a-1070	Sitting height ratio	ukb-d-1747_1	hair color	118	4.975	-0.017	0.015	0.247
ieu-a-987	Lung cancer	ukb-d-1747_1	hair color	168	5.583	-0.001	0.006	0.876
ieu-a-1006	Mean platelet volume	ukb-d-1747_1	hair color	108	7.643	-0.016	0.055	0.776
ieu-a-118	Neuroticism	ukb-d-1747_1	hair color	135	4.496	1.001	2.013	0.619
ieu-a-113	Neo-agreeableness	ukb-d-1747_1	hair color	89	4.582	0.040	0.055	0.469
ieu-a-1048	Thalamus volume	ukb-d-1747_1	hair color	100	4.940	-0.001	0.001	0.255
ieu-a-116	Neo-neuroticism	ukb-d-1747_1	hair color	71	5.104	0.002	0.001	0.160
ieu-a-1189	Obsessive Compulsive Disorder	ukb-d-1747_1	hair color	108	4.745	0.007	0.011	0.537
ieu-a-1012	Plasma cortisol	ukb-d-1747_1	hair color	105	4.533	0.045	0.054	0.406
ieu-a-1046	Pallidum volume	ukb-d-1747_1	hair color	95	4.489	0.000	0.000	0.933
ieu-a-45	Anorexia nervosa	ukb-d-1747_1	hair color	106	5.332	-0.006	0.003	0.053
ieu-a-988	Small cell lung carcinoma	ukb-d-1747_1	hair color	121	4.950	0.006	0.007	0.411
ieu-a-292	Inflammatory bowel disease	ukb-d-1747_1	hair color	422	16.914	0.000	0.001	0.970
ieu-a-1043	Amygdala volume	ukb-d-1747_1	hair color	112	4.678	0.000	0.000	0.349

Table S5: Detailed information on the 81 exposures and the outcome used in the negative control study. The causal effect estimates, SEs, and p-values obtained using MR-GMM under the threshold $p < 0.05$ are presented.

Exposure ID	Exposure	Outcome ID	Outcome	Uniprot	Symbol	# of IVs	IV strength	Estimate	SE	P-value
prot-a-10	Histo-blood group ABO system transferase	ieu-a-7	CHD	P16442	ABO	100	87.414	0.033	0.000	0.000
prot-a-1074	Low affinity immunoglobulin gamma Fc region receptor II-a	ieu-a-7	CHD	P12318	FCGR2A	98	102.962	0.004	0.000	0.000
prot-a-1075	Low affinity immunoglobulin gamma Fc region receptor II-b	ieu-a-7	CHD	P31994	FCGR2B	90	26.761	0.005	0.001	0.000
prot-a-1112	Four-jointed box protein 1	ieu-a-7	CHD	Q86VR8	FJX1	112	4.861	0.367	0.009	0.000
prot-a-1115	Inactive peptidyl-prolyl cis-trans isomerase FKBP6	ieu-a-7	CHD	O75344	FKBP6	112	38.743	0.024	0.000	0.000
prot-a-1196	Growth/differentiation factor 5	ieu-a-7	CHD	P43026	GDF5	111	16.688	0.036	0.002	0.000
prot-a-1199	GTP-binding protein GEM	ieu-a-7	CHD	P55040	GEM	109	20.534	0.034	0.000	0.000
prot-a-1277	Granulins	ieu-a-7	CHD	P28799	GRN	87	15.172	0.119	0.000	0.000
prot-a-1397	Intercellular adhesion molecule 1	ieu-a-7	CHD	P05362	ICAM1	122	68.277	-0.003	0.001	0.000
prot-a-1400	Intercellular adhesion molecule 4	ieu-a-7	CHD	Q14773	ICAM4	106	4.511	-0.463	0.142	0.001
prot-a-1502	Interleukin-1 receptor-like 1	ieu-a-7	CHD	Q01638	IL1RL1	115	20.308	0.017	0.001	0.000
prot-a-1540	Interleukin-6 receptor subunit alpha	ieu-a-7	CHD	P08887	IL6R	105	52.887	-0.044	0.000	0.000
prot-a-1741	Leukocyte immunoglobulin-like receptor subfamily A member 6	ieu-a-7	CHD	Q6PI73	LILRA6	90	4.428	-0.404	0.127	0.001
prot-a-18	Low molecular weight phosphotyrosine protein phosphatase	ieu-a-7	CHD	P24666	ACP1	89	59.839	-0.017	0.000	0.000
prot-a-180	Arf-GAP with SH3 domain, ANK repeat and PH domain-containing protein 2	ieu-a-7	CHD	O43150	ASAP2	100	10.746	0.052	0.003	0.000
prot-a-1863	Mannose-binding protein C	ieu-a-7	CHD	P11226	MBL2	114	19.979	-0.022	0.001	0.000
prot-a-1902	MICOS complex subunit MIC10	ieu-a-7	CHD	Q5TGZ0	MICOS10	97	73.117	0.021	0.000	0.000
prot-a-1949	Beta-microseminoprotein	ieu-a-7	CHD	P08118	MSMB	119	17.924	0.030	0.003	0.000
prot-a-2023	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 4	ieu-a-7	CHD	O95168	NDUFB4	106	11.173	0.044	0.005	0.000
prot-a-2025	NADH dehydrogenase [ubiquinone] iron-sulfur protein 4, mitochondrial	ieu-a-7	CHD	O43181	NDUFS4	94	12.264	-0.033	0.003	0.000
prot-a-2095	Neuregulin-1	ieu-a-7	CHD	Q02297	NRG1	95	4.686	-0.316	0.069	0.000
prot-a-2230	Platelet-derived growth factor receptor beta	ieu-a-7	CHD	P09619	PDGFRB	88	26.856	-0.004	0.000	0.000
prot-a-2247	Proenkephalin-A	ieu-a-7	CHD	P01210	PENK	105	8.102	-0.023	0.003	0.000
prot-a-2284	Group XIIB secretory phospholipase A2-like protein	ieu-a-7	CHD	Q9BX93	PLA2G12B	97	6.633	0.222	0.008	0.000
prot-a-2291	Secretory phospholipase A2 receptor	ieu-a-7	CHD	Q13018	PLA2R1	101	27.242	0.002	0.000	0.000
prot-a-2499	RNA binding protein fox-1 homolog 2	ieu-a-7	CHD	O43251	RBFOX2	80	4.433	0.624	0.176	0.000
prot-a-2575	rRNA methyltransferase 3, mitochondrial	ieu-a-7	CHD	Q9HC36	MRM3	98	11.949	0.046	0.000	0.000
prot-a-2731	Sialic acid-binding Ig-like lectin 9	ieu-a-7	CHD	Q9Y336	SIGLEC9	88	116.985	-0.009	0.000	0.000
prot-a-2732	Tyrosine-protein phosphatase non-receptor type substrate 1	ieu-a-7	CHD	P78324	SIRPA	94	70.662	-0.003	0.000	0.000
prot-a-276	ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase 2	ieu-a-7	CHD	Q10588	BST1	101	9.825	-0.029	0.002	0.000
prot-a-2829	Spondin-1	ieu-a-7	CHD	Q9HCB6	SPON1	108	6.638	0.032	0.009	0.001
prot-a-2940	Teratocarcinoma-derived growth factor 1	ieu-a-7	CHD	P13385	CRIPTO	106	14.723	0.015	0.000	0.000
prot-a-2941	Tyrosyl-DNA phosphodiesterase 1	ieu-a-7	CHD	Q9NUW8	TDP1	95	4.340	0.429	0.126	0.001
prot-a-303	Complement C1q tumor necrosis factor-related protein 1	ieu-a-7	CHD	Q9BXJ1	C1QTNF1	98	9.776	0.153	0.001	0.000
prot-a-3214	Vitronectin	ieu-a-7	CHD	P04004	VTN	101	39.214	0.025	0.000	0.000
prot-a-426	CD209 antigen	ieu-a-7	CHD	Q9NNX6	CD209	97	9.276	0.054	0.005	0.000
prot-a-540	Chitinase-3-like protein 1	ieu-a-7	CHD	P36222	CHI3L1	96	39.579	0.014	0.000	0.000
prot-a-570	C-type lectin domain family 12 member A	ieu-a-7	CHD	Q5QGZ9	CLEC12A	108	88.240	-0.001	0.000	0.000
prot-a-635	COP9 signalosome complex subunit 2	ieu-a-7	CHD	P61201	COPS2	108	11.106	0.050	0.005	0.000
prot-a-643	Carboxypeptidase A4	ieu-a-7	CHD	Q9UI42	CPA4	99	60.600	0.013	0.000	0.000
prot-a-854	Dedicator of cytokinesis protein 9	ieu-a-7	CHD	Q9BZ29	DOCK9	124	4.695	0.391	0.106	0.000
prot-a-91	Anaphase-promoting complex subunit 7	ieu-a-7	CHD	Q9UJX3	ANAPC7	89	13.040	-0.036	0.004	0.000
prot-a-96	Angiopoietin-related protein 1	ieu-a-7	CHD	O95841	ANGPTL1	103	7.317	-0.064	0.004	0.000
prot-a-971	Endoplasmic reticulum aminopeptidase 1	ieu-a-7	CHD	Q9NZ08	ERAP1	102	22.514	-0.023	0.003	0.000
prot-a-972	Endoplasmic reticulum aminopeptidase 2	ieu-a-7	CHD	Q6P179	ERAP2	104	42.251	0.023	0.000	0.000

Table S6: The identified 45 CHD-associated plasma proteins. The proteins are annotated with Uniprot accession and gene symbols. The causal effect estimates, SEs, and p-values obtained using MR-GMM under the threshold $p < 0.05$ are presented.