# Single-population MR using hierarchical Bayesian model (no prior for $\beta$ and $\alpha$, no CHP effect)

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## 1 Model settings

True causal relationship for the $k$th IV,

$$\Gamma_k = \theta_k + \beta\gamma_k \tag{1}$$

$$\begin{pmatrix} \hat{\gamma}_k \\ \hat{\Gamma}_k \end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix} \gamma_k \\ \Gamma_k \end{pmatrix}, \hat{\boldsymbol{S}}_k\right) = \mathcal{N}\left(\begin{pmatrix} \gamma_k \\ \theta_k + \beta\gamma_k \end{pmatrix}, \begin{pmatrix} \hat{s}_{\gamma k}^2 & \\ & \hat{s}_{\Gamma k}^2 \end{pmatrix}\right), \tag{2}$$

where $\hat{\boldsymbol{S}}_k$ is a diagonal variance-covariance matrix for observations. The diagonal elements can be estimated empirically from GWAS.

## 2 Bayesian hierarchical model

We set the following priors: $\gamma_k \sim N(0, \sigma_\gamma^2)$, $\theta_k \sim N(0, \sigma_\theta^2)$. Hyper priors for $\sigma_\gamma^2, \sigma_\theta^2$ are chosen to be conjugate with the corresponding likelihood.

## 3 Full likelihood

Full likelihood is:

$$L\left(\Theta|\hat{\boldsymbol{\Gamma}}, \hat{\boldsymbol{\gamma}}\right) = \prod_k \left[P(\hat{\Gamma}_k|\gamma_k, \theta_k, \beta) \cdot P(\hat{\gamma}_k|\gamma_k) \cdot P(\gamma_k|\sigma_\gamma^2) \cdot P(\theta_k|\sigma_\theta^2)\right] \cdot \pi\left(\sigma_\gamma^2, \sigma_\theta^2\right)$$

where

$$P(\hat{\Gamma}_k|\gamma_k, \theta_k, \beta) \propto \exp\left[-\frac{1}{2}\left(\hat{\Gamma}_k - \theta_k - \beta\gamma_k\right)^2 / \hat{s}_{\Gamma k}^2\right]$$

$$P(\hat{\gamma}_k|\gamma_k) \propto \exp\left[-\frac{1}{2}\left(\hat{\gamma}_k - \gamma_k\right)^2 / \hat{s}_{\gamma k}^2\right]$$

$$P(\gamma_k|\sigma_\gamma^2) \propto \left(\sigma_\gamma^2\right)^{-\frac{1}{2}} \exp\left(-\frac{1}{2}\gamma_k^2/\sigma_\gamma^2\right)$$

$$P(\theta_k|\sigma_\theta^2) \propto \left(\sigma_\theta^2\right)^{-\frac{1}{2}} \exp\left(-\frac{1}{2}\theta_k^2/\sigma_\theta^2\right)$$

# 4 Full conditional

## 4.1 IV-to-exposure effect $\gamma_k$

$$\begin{aligned} p\left(\gamma_k|rest\right) &\propto \exp\left[-\frac{1}{2}\left(\hat{\Gamma}_k - \theta_k - \beta\gamma_k\right)^2/\hat{s}_{\Gamma k}^2 - \frac{1}{2}\left(\hat{\gamma}_k - \gamma_k\right)^2/\hat{s}_{\gamma k}^2 - \frac{1}{2}\gamma_k^2/\sigma_\gamma^2\right] \\ &\propto \exp\left\{-\frac{1}{2}\left[\gamma_k^2\left(\frac{\beta^2}{\hat{s}_{\Gamma k}^2} + \frac{1}{\hat{s}_{\gamma k}^2} + \frac{1}{\sigma_\gamma^2}\right) - 2\gamma_k\left(\frac{\beta(\hat{\Gamma}_k - \theta_k)}{\hat{s}_{\Gamma k}^2} + \frac{\hat{\gamma}_k}{\hat{s}_{\gamma k}^2}\right)\right]\right\} \end{aligned}$$

So the posterior

$$\gamma_k|rest \sim \mathcal{N}\left(B_{\gamma k}/A_{\gamma k}, 1/A_{\gamma k}\right)$$

where

$$A_{\gamma k} = \frac{\beta^2}{\hat{s}_{\Gamma k}^2} + \frac{1}{\hat{s}_{\gamma k}^2} + \frac{1}{\sigma_\gamma^2},\ B_{\gamma k} = \frac{\beta(\hat{\Gamma}_k - \theta_k)}{\hat{s}_{\Gamma k}^2} + \frac{\hat{\gamma}_k}{\hat{s}_{\gamma k}^2}$$

## 4.2 UHP effect $\theta_k$

$$\begin{aligned} p\left(\theta_k|rest\right) &\propto \exp\left[-\frac{1}{2}\left(\hat{\Gamma}_k - \theta_k - \beta\gamma_k\right)^2/\hat{s}_{\Gamma k}^2 - \frac{1}{2}\theta_k^2/\sigma_\theta^2\right] \\ &\propto \exp\left\{-\frac{1}{2}\left[\theta_k^2\left(\frac{1}{\hat{s}_{\Gamma k}^2} + \frac{1}{\sigma_\theta^2}\right) - 2\theta_k\left(\hat{\Gamma}_k - \beta\gamma_k\right)/\hat{s}_{\Gamma k}^2\right]\right\} \end{aligned}$$

So the posterior

$$\theta_k|rest \sim \mathcal{N}\left(B_{\theta k}/A_{\theta k}, 1/A_{\theta k}\right)$$

where

$$A_{\theta k} = \frac{1}{\hat{s}_{\Gamma k}^2} + \frac{1}{\sigma_\theta^2},\ B_{\theta k} = \left(\hat{\Gamma}_k - \beta\gamma_k\right)/\hat{s}_{\Gamma k}^2$$

## 4.3 IV-to-exposure variance $\sigma_\gamma^2$

Assume a conjugate prior $IG(a_\gamma, b_\gamma)$. Then,

$$p(\sigma_\gamma^2|rest) \propto \exp\left(-\frac{1}{2}\sum_k \gamma_k^2/\sigma_\gamma^2\right)\cdot\left(\sigma_\gamma^2\right)^{-K/2}\cdot\pi\left(\sigma_\gamma^2\right) \propto \left(\sigma_\gamma^2\right)^{-\left(a_\gamma + \frac{K}{2}\right)-1}\cdot\exp\left[-\left(b_\gamma + \frac{1}{2}\sum_k \gamma_k^2\right)/\sigma_\gamma^2\right]$$

So the posterior

$$\sigma_\gamma^2|rest \sim IG\left(a_\gamma + \frac{K}{2}, b_\gamma + \frac{1}{2}\sum_k \gamma_k^2\right)$$

### 4.4 UHP variance $\sigma_\theta^2$

Assume a conjugate prior $IG(a_\theta, b_\theta)$. Then,

$$p(\sigma_\theta^2|rest) \propto \exp\left(-\frac{1}{2}\sum_k \theta_k^2/\sigma_\theta^2\right)\cdot\left(\sigma_\theta^2\right)^{-K/2}\cdot\pi\left(\sigma_\theta^2\right) \propto \left(\sigma_\theta^2\right)^{-\left(a_\theta+\frac{K}{2}\right)-1}\cdot\exp\left[-\left(b_\theta+\frac{1}{2}\sum_k\theta_k^2\right)/\sigma_\theta^2\right]$$

So the posterior

$$\sigma_\theta^2|rest \sim IG\left(a_\theta+\frac{K}{2}, b_\theta+\frac{1}{2}\sum_k\theta_k^2\right)$$

### 4.5 Causal effect $\beta$

$$\begin{aligned}
p(\beta|rest) &\propto \exp\left[-\frac{1}{2}\sum_k\left(\hat{\Gamma}_k-\theta_k-\beta\gamma_k\right)^2/\hat{s}_{\Gamma k}^2\right]\\
&\propto \exp\left[-\frac{1}{2}\left(\boldsymbol{U}_\beta-\beta\boldsymbol{W}_\beta\right)'\hat{\boldsymbol{\Omega}}_\Gamma\left(\boldsymbol{U}_\beta-\beta\boldsymbol{W}_\beta\right)\right]\\
&\propto \exp\left\{-\frac{1}{2}\left[\beta^2\left(\boldsymbol{W}_\beta'\hat{\boldsymbol{\Omega}}_\Gamma\boldsymbol{W}_\beta\right)-2\beta\left(\boldsymbol{W}_\beta'\hat{\boldsymbol{\Omega}}_\Gamma\boldsymbol{U}_\beta\right)\right]\right\}\\
&\propto \exp\left[-\frac{1}{2}A_\beta\cdot\left(\beta^2-2\mu_\beta\beta\right)\right]
\end{aligned}$$

So the posterior

$$\beta|rest \sim N\left(\mu_\beta, A_\beta^{-1}\right)$$

where

$$A_\beta = \boldsymbol{W}_\beta'\hat{\boldsymbol{\Omega}}_\Gamma\boldsymbol{W}_\beta,\ \mu_\beta = \boldsymbol{W}_\beta'\hat{\boldsymbol{\Omega}}_\Gamma\boldsymbol{U}_\beta/A_\beta$$

$$\hat{\boldsymbol{\Omega}}_\Gamma = \mathrm{diag}\left(1/\hat{s}_{\Gamma 1}^2,\cdots,1/\hat{s}_{\Gamma K}^2\right),\ \boldsymbol{U}_\beta' = \left(\hat{\Gamma}_1-\theta_1,\cdots,\hat{\Gamma}_K-\theta_K\right),\ \boldsymbol{W}_\beta' = \left(\gamma_1,\cdots,\gamma_K\right)$$

## 5 Model with no horizontal pleiotropy

True causal relationship for the $k$th IV is $\Gamma_k = \beta\gamma_k$. The joint model can be written as:

$$\begin{pmatrix}\hat{\gamma}_k\\ \hat{\Gamma}_k\end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix}\gamma_k\\ \Gamma_k\end{pmatrix}, \hat{\boldsymbol{S}}_k\right) = \mathcal{N}\left(\begin{pmatrix}\gamma_k\\ \beta\gamma_k\end{pmatrix}, \begin{pmatrix}\hat{s}_{\gamma k}^2 & \\ & \hat{s}_{\Gamma k}^2\end{pmatrix}\right), \tag{3}$$

where $\hat{\boldsymbol{S}}_k$ is a diagonal variance-covariance matrix for observations. The diagonal elements can be estimated empirically from GWAS. We set the prior $\gamma_k \sim N(0, \sigma_\gamma^2)$. Hyper priors for $\sigma_\gamma^2$ is chosen to be conjugate with the corresponding likelihood. The full likelihood is:

$$L\left(\Theta|\hat{\boldsymbol{\Gamma}}, \hat{\boldsymbol{\gamma}}\right) = \prod_k\left[P(\hat{\Gamma}_k|\gamma_k,\beta)\cdot P(\hat{\gamma}_k|\gamma_k)\cdot P(\gamma_k|\sigma_\gamma^2)\right]\cdot\pi\left(\sigma_\gamma^2\right)$$

where

$$P(\hat{\Gamma}_k|\gamma_k,\beta) \propto \exp\left[-\frac{1}{2}\left(\hat{\Gamma}_k-\beta\gamma_k\right)^2/\hat{s}^2_{\Gamma k}\right]$$

$$P(\hat{\gamma}_k|\gamma_k) \propto \exp\left[-\frac{1}{2}\left(\hat{\gamma}_k-\gamma_k\right)^2/\hat{s}^2_{\gamma k}\right],\ P(\gamma_k|\sigma^2_\gamma) \propto \left(\sigma^2_\gamma\right)^{-\frac{1}{2}}\exp\left(-\frac{1}{2}\gamma_k^2/\sigma^2_\gamma\right)$$

Full conditional:

IV-to-exposure effect $\gamma_k$:

$$\begin{aligned} p\left(\gamma_k|rest\right) &\propto \exp\left[-\frac{1}{2}\left(\hat{\Gamma}_k-\beta\gamma_k\right)^2/\hat{s}^2_{\Gamma k}-\frac{1}{2}\left(\hat{\gamma}_k-\gamma_k\right)^2/\hat{s}^2_{\gamma k}-\frac{1}{2}\gamma_k^2/\sigma^2_\gamma\right] \\ &\propto \exp\left\{-\frac{1}{2}\left[\gamma_k^2\left(\frac{\beta^2}{\hat{s}^2_{\Gamma k}}+\frac{1}{\hat{s}^2_{\gamma k}}+\frac{1}{\sigma^2_\gamma}\right)-2\gamma_k\left(\frac{\beta\hat{\Gamma}_k}{\hat{s}^2_{\Gamma k}}+\frac{\hat{\gamma}_k}{\hat{s}^2_{\gamma k}}\right)\right]\right\} \end{aligned}$$

So the posterior

$$\gamma_k|rest \sim \mathcal{N}\left(B_{\gamma k}/A_{\gamma k}, 1/A_{\gamma k}\right)$$

where

$$A_{\gamma k}=\frac{\beta^2}{\hat{s}^2_{\Gamma k}}+\frac{1}{\hat{s}^2_{\gamma k}}+\frac{1}{\sigma^2_\gamma},\ B_{\gamma k}=\frac{\beta\hat{\Gamma}_k}{\hat{s}^2_{\Gamma k}}+\frac{\hat{\gamma}_k}{\hat{s}^2_{\gamma k}}$$

IV-to-exposure variance $\sigma^2_\gamma$:

Assume a conjugate prior $IG(a_\gamma, b_\gamma)$. Then,

$$p(\sigma^2_\gamma|rest) \propto \exp\left(-\frac{1}{2}\sum_k\gamma_k^2/\sigma^2_\gamma\right)\cdot\left(\sigma^2_\gamma\right)^{-K/2}\cdot\pi\left(\sigma^2_\gamma\right) \propto \left(\sigma^2_\gamma\right)^{-\left(a_\gamma+\frac{K}{2}\right)-1}\cdot\exp\left[-\left(b_\gamma+\frac{1}{2}\sum_k\gamma_k^2\right)/\sigma^2_\gamma\right]$$

So the posterior

$$\sigma^2_\gamma|rest \sim IG\left(a_\gamma+\frac{K}{2}, b_\gamma+\frac{1}{2}\sum_k\gamma_k^2\right)$$

Causal effect $\beta$:

$$\begin{aligned} p(\beta|rest) &\propto \exp\left[-\frac{1}{2}\sum_k\left(\hat{\Gamma}_k-\beta\gamma_k\right)^2/\hat{s}^2_{\Gamma k}\right] \\ &\propto \exp\left[-\frac{1}{2}\left(\boldsymbol{U}_\beta-\beta\boldsymbol{W}_\beta\right)'\hat{\boldsymbol{\Omega}}_\Gamma\left(\boldsymbol{U}_\beta-\beta\boldsymbol{W}_\beta\right)\right] \\ &\propto \exp\left\{-\frac{1}{2}\left[\beta^2\left(\boldsymbol{W}_\beta'\hat{\boldsymbol{\Omega}}_\Gamma\boldsymbol{W}_\beta\right)-2\beta\left(\boldsymbol{W}_\beta'\hat{\boldsymbol{\Omega}}_\Gamma\boldsymbol{U}_\beta\right)\right]\right\} \\ &\propto \exp\left[-\frac{1}{2}A_\beta\cdot\left(\beta^2-2\mu_\beta\beta\right)\right] \end{aligned}$$

So the posterior

$$\beta|rest \sim N\left(\mu_\beta, A_\beta^{-1}\right)$$

where

$$A_\beta=\boldsymbol{W}_\beta'\hat{\boldsymbol{\Omega}}_\Gamma\boldsymbol{W}_\beta,\ \mu_\beta=\boldsymbol{W}_\beta'\hat{\boldsymbol{\Omega}}_\Gamma\boldsymbol{U}_\beta/A_\beta$$

$$\hat{\boldsymbol{\Omega}}_\Gamma=\mathrm{diag}\left(1/\hat{s}^2_{\Gamma 1},\cdots,1/\hat{s}^2_{\Gamma K}\right),\ \boldsymbol{U}_\beta'=\left(\hat{\Gamma}_1,\cdots,\hat{\Gamma}_K\right),\ \boldsymbol{W}_\beta'=\left(\gamma_1,\cdots,\gamma_K\right)$$