1 Supplementary Note S1: Derivation of Bayes factors for a set of risk factors

Building on the 2-sample MR approach [1] our work is based on summarised data, where genetic variants are used as instrumental variables. For each genetic variant $i = 1, ..., n$ we observe the association of variant i with the risk factor X measured by the beta-coefficient β_{X_i} from a univariable regression where the genetic variant i is regressed on the risk factor X, and the association of variant i with the outcome Y measured by the beta-coefficient β_{Y_i} where the genetic variant i is regressed on the outcome Y, respectively. In fact, the beta-coefficients are estimates of the genetic association, but we omit the "hat" notation and treat the beta-coefficient as observations.

Multivariable MR [2] can be cast as a weighted linear regression model

$$\begin{aligned} \beta_Y &= \theta_1\beta_{X_1} + ... + \theta_d\beta_{X_d} + \epsilon, \text{ weights} = se(\beta_Y)^{-2} \\ &= \beta_X\theta + \epsilon, \text{ weights} = se(\beta_Y)^{-2}, \end{aligned} \tag{1}$$

where the dependent variable is the association with the outcome β_Y measured on $i = 1, ..., n$ instrumental variables and the predictors are the $j = 1, ..., d$ genetic associations with the d risk factors $\beta_X = \{\beta_{X_1}, ..., \beta_{X_d}\}$, which is a matrix of dimension $n \times d$ where d is the number of risk factors and n is the number of genetic variants. Again each individual element $\beta_{X_{i,j}}$ of the predictor matrix is derived from a univariable regression where the genetic variant i is regressed on the risk factor X_j. In other words, the risk factors represent the variable space and the instrumental genetic variants are our observations. In practise, we standardise each observation of both, β_{Y_i} and β_{X_i} by dividing by $se(\beta_{Y_i})$ before the analysis and we assume in the following derivations that β_Y and β_X are standardised.

We use Bayes factors [3] in order to quantify the evidence for a particular model. With model we refer to either one or a set of risk factors to have a causal effect on the outcome of interest. In order to formalise which risk factors are part of a specific model M_γ we introduce a binary indicator γ of length d that indicates which risk factors are selected and which ones are not

$$\gamma_j = \begin{cases} 1, \text{ if the } j\text{th risk factor is selected,} \\ 0 \text{ otherwise.} \end{cases} \tag{2}$$

The indicator γ encodes a specific regression model M_γ that includes the risk factors as indicated in γ. Accordingly, we define β_{X_γ} as the design matrix of the risk factors included and θ_γ as the respective causal effects.

The computation of the Bayes factor for model M_γ against the Null model M_0 as presented in the Methods section of the main article requires two ingredients: First the the marginal probability of β_Y given β_{X_γ} of model M_γ and second, the marginal probability of β_Y given the Null model M_0, which we derive as follows:

1. $p_\gamma(\beta_Y \mid \beta_{X_\gamma})$: the marginal probability of β_Y given β_{X_γ}

   In order to model the correlation between risk factors we base our likelihood on a multivariante Gaussian distribution

$$\beta_Y \mid \beta_{X_\gamma}, \theta_\gamma, \tau \sim N(\beta_{X_\gamma}\theta_\gamma, \frac{1}{\tau}). \tag{3}$$

   Following Servin and Stephens' D_2 prior [4] we use the following conjugate prior assumptions for the causal effects θ, the residual ϵ and the precison τ

$$\begin{aligned} \theta_\gamma \mid \tau &\sim N(0, \nu/\tau), \\ \epsilon &\sim N(0, \frac{1}{\tau}), \\ \tau &\sim \Gamma(\kappa/2, \lambda/2). \end{aligned} \tag{4}$$

   Further we can derive analytically the joint posterior distribution for θ_γ and τ as

$$\begin{aligned} \tau \mid \beta_Y, \beta_{X_\gamma} &\sim \Gamma((n+\kappa)/2, 1/2(\beta_Y^t\beta_Y - \Theta^t\Omega^{-1}\Theta + \lambda)), \\ \theta_\gamma \mid \beta_Y, \beta_{X_\gamma}, \tau &\sim N(\Theta, \frac{1}{\tau}\Omega), \end{aligned}$$

   where

$$\underbrace{\Theta}_{d\times 1} = \underbrace{\Omega}_{d\times d}\underbrace{\beta_{X_\gamma}^t}_{d\times n}\underbrace{\beta_Y}_{n\times 1}, \tag{5}$$

$$\Omega = \underbrace{(\nu^{-1} + \beta_{X_\gamma}^t\beta_{X_\gamma})^{-1}}_{d\times d}. \tag{6}$$

   Next we integrate out the causal effects θ_γ. To begin with we sort the equation so that the integral contains only terms dependent on θ_γ

$$\begin{aligned} p_\gamma(\beta_Y \mid \beta_{X_\gamma}, \tau) &= \int_{-\inf}^{\inf} \frac{p_\gamma(\beta_Y \mid \beta_{X_\gamma}, \theta_\gamma, \tau)p_\gamma(\theta_\gamma \mid \tau)}{p_\gamma(\theta_\gamma \mid \beta_Y, \beta_{X_\gamma}, \tau)}\delta\theta_\gamma \\ &= \int_{-\inf}^{\inf} \frac{(2\pi)^{-\frac{n}{2}}\tau^{\frac{n}{2}}\exp\left(-\frac{\tau}{2}(\beta_Y - \beta_{X_\gamma}\theta_\gamma)^t(\beta_Y - \beta_{X_\gamma}\theta_\gamma)\right)}{(2\pi)^{-\frac{1}{2}}\frac{|\Omega|^{-1/2}}{|\tau|^{-1/2}}\exp\left(-\frac{\tau}{2}(\theta_\gamma - \Theta)^t\Omega^{-1}(\theta_\gamma - \Theta)\right)} \\ &\quad \times(2\pi)^{-\frac{1}{2}}\frac{|\nu|^{-1/2}}{|\tau|^{-1/2}}\exp\left(-\frac{\tau}{2\nu}\theta_\gamma^t\theta_\gamma\right)\delta\theta_\gamma \\ &= (2\pi)^{-\frac{n}{2}}\tau^{\frac{n}{2}}\frac{|\Omega|^{1/2}}{|\nu|^{1/2}}\exp\left(-\frac{1}{2}(\beta_Y^t\beta_Y - \Theta^t\Omega^{-1}\Theta)\tau\right) \\ &\quad \int_{-\inf}^{\inf}\exp\left(-\frac{1}{2}(2\theta_\gamma^t\beta_{X_\gamma}^t\beta_Y + \theta_\gamma^t\beta_{X_\gamma}^t\beta_{X_\gamma}\theta_\gamma - \frac{1}{\nu}\theta_\gamma^t\theta_\gamma - \theta_\gamma^t\Omega^{-1}\theta_\gamma + 2\theta_\gamma^t\Omega^{-1}\Theta)\tau\right)\delta\theta_\gamma. \end{aligned}$$

By completing the square and integrating out θ_γ this simplifies to

$$p_\gamma(\beta_Y \mid \beta_{X_\gamma}, \tau) = (2\pi)^{-\frac{n}{2}} \tau^{\frac{n}{2}} \frac{|\Omega|^{1/2}}{|\nu|^{1/2}} \exp\left(-\frac{1}{2}(\beta_Y^t \beta_Y - \Theta^t \Omega^{-1} \Theta)\tau\right) \quad (7)$$

Next we integrate out the precision τ

$$\begin{aligned} p_\gamma(\beta_Y \mid \beta_{X_\gamma}) &= \int_0^{\inf} p_\gamma(\beta_Y \mid \beta_{X_\gamma}, \tau) p(\tau) \delta\tau \quad (8) \\ &= (2\pi)^{-\frac{n}{2}} \frac{|\Omega|^{1/2}}{|\nu|^{1/2}} \times \\ &\quad \int_0^{\inf} \tau^{\frac{(n+\kappa)}{2}-1} \exp\left(-\frac{1}{2}(\beta_Y^t \beta_Y - \Theta^t \Omega^{-1} \Theta + \lambda)\tau\right) \delta\tau. \end{aligned}$$

The above integral is the normalisation constant of a Gamma distribution with shape $\alpha = \frac{(n+\kappa)}{2}$ and rate $\beta = \frac{1}{2}(\beta_Y^t \beta_Y - \Theta^t \Omega^{-1} \Theta + \lambda)$. Thus the above simplifies to

$$p_\gamma(\beta_Y \mid \beta_{X_\gamma}) = (2\pi)^{-\frac{n}{2}} \frac{|\Omega|^{1/2}}{|\nu|^{1/2}} (\frac{\lambda}{2})^{\frac{\kappa}{2}} \frac{\Gamma(\frac{n+\kappa}{2})}{\Gamma(\frac{\kappa}{2})} \left(\frac{1}{2}(\beta_Y^t \beta_Y - \Theta^t \Omega^{-1} \Theta + \lambda)\right)^{\frac{-(n+\kappa)}{2}}. \quad (9)$$

2. $p_0(\beta_Y)$: the marginal probability of β_Y given the Null model M_0

   Next, we derive the marginal probability of the Null model, i.e. where no risk factor and no intercept is included. Under the Null we assume

$$\beta_Y \mid \frac{1}{\tau} \sim N(0, \frac{1}{\tau}) \quad (10)$$

   with an expectation fixed at zero, which is a consequence of the missing intercept.

   First, we integrate out the precision τ

$$\begin{aligned} p_0(\beta_Y) &= \int_0^{\inf} p_0(\beta_Y \mid \tau) p(\tau) \delta\tau \\ &= (2\pi)^{-\frac{n}{2}} \int_0^{\inf} \tau^{\frac{(n+\kappa)}{2}-1} \exp\left(-\frac{1}{2}(\beta_Y^t \beta_Y + \lambda)\tau\right) \delta\tau. \quad (11) \end{aligned}$$

   Again the above integral is the normalisation constant of a Gamma distribution with shape $\alpha = \frac{(n+\kappa)}{2}$ and rate $\beta_0 = \frac{1}{2}(\beta_Y^t \beta_Y + \lambda)$. Thus the above simplifies to

$$p_0(\beta_Y) = (2\pi)^{-\frac{n}{2}} (\frac{\lambda}{2})^{\frac{\kappa}{2}} \frac{\Gamma(\frac{n+\kappa}{2})}{\Gamma(\frac{\kappa}{2})} \left(\frac{1}{2}(\beta_Y^t \beta_Y + \lambda)\right)^{-\frac{(n+\kappa)}{2}}. \quad (12)$$

The Bayes factor for model M_γ against M_0 is defined as the ratio of the marginal probability of β_Y given model M_γ (9) over the marginal probability of β_Y given the Null model (12)

$$\begin{aligned} BF(M_\gamma) &= \frac{p_\gamma(\beta_Y \mid \beta_{X_\gamma})}{p_0(\beta_Y)} \\ &= \frac{\frac{|\Omega|^{1/2}}{|\nu|^{1/2}} \left(\frac{1}{2}(\beta_Y^t \beta_Y - \Theta^t \Omega^{-1} \Theta + \lambda)\right)^{-(n+\kappa)/2}}{\left(\frac{1}{2}(\beta_Y^t \beta_Y + \lambda)\right)^{-(n+\kappa)/2}} \\ &= \frac{|\Omega|^{1/2}}{|\nu|^{1/2}} \left(\frac{\beta_Y^t \beta_Y - \Theta^t \Omega^{-1} \Theta + \lambda}{\beta_Y^t \beta_Y + \lambda}\right)^{-(n+\kappa)/2}. \end{aligned} \tag{13}$$

In limit κ and $\lambda \to 0$ the Bayes Factor simplifies to the following closed form expression

$$BF(M_\gamma) = \frac{|\Omega|^{1/2}}{|\nu|^{1/2}} \left(\frac{\beta_Y^t \beta_Y - \Theta^t \Omega^{-1} \Theta}{\beta_Y^t \beta_Y}\right)^{-n/2}. \tag{14}$$

References

[1] Pierce, B. L. and Burgess, S. (2013). Efficient design for mendelian randomization studies: Subsample and 2-sample instrumental variable estimators. American Journal of Epidemiology *178*, 1177–1184.

[2] Burgess, S. and Thompson, S. G. (2015). Multivariable mendelian randomization: the use of pleiotropic genetic variants to estimate causal effects. Am J Epidemiol *181*, 251–60.

[3] Kass, R. E. and Raftery, A. E. (1995). Bayes factors. Journal of the American Statistical Association *90*, 773–795.

[4] Servin, B. and Stephens, M. (2007). Imputation-based analysis of association studies: candidate regions and quantitative traits. PLoS Genet *3*, e114.