Bayesian estimation of the **MR-Egger** model using **informative priors** can **reduce bias** in the presence of **pleiotropy.**

Investigating a pseudo-horseshoe prior for the MR-Egger model

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Introduction

- The MR-Egger model can consistently estimate the causal effect in the presence of pleiotropy given the InSIDE assumption holds (**Bowden, Davey Smith, and Burgess (2015)**).
- **Schmidt and Dudbridge (2017)** used weakly informative priors for the MR-Egger model. Other authors have investigated alternative prior distributions in MR analyses (**Berzuini et al. (2018)**).

The objectives of this research work are to:

- implement Bayesian estimation of IVW and MR-Egger models for a range of prior distributions in an R package.
- investigate model performance for a range of simulated pleiotropic scenarios and a range of priors.

Methods

- We implemented Bayesian estimation of the IVW and MR-Egger models in an R package `mrbayes` which automates fitting these models in the JAGS software.
- We provide the user with a choice of priors or let them specify their own.
- The MR-Egger model is written as;

$$\frac{\Gamma_j}{\sigma^2_{y_j}} = \frac{\alpha}{\sigma^2_{y_j}} + \frac{\beta\gamma_j}{\sigma^2_{y_j}} + \varepsilon_j, \quad \varepsilon_j \sim N(0, \sigma^2)$$

- Uninformative Prior

$$p(\alpha) \sim N(0, 1000),\ p(\beta) \sim N(0, 1000),\ p(\sigma) \sim U(10, 10)$$

- Weakly Informative Prior

$$p(\alpha) \sim N(0, 1),\ p(\beta) \sim N(0, 1),\ p(\sigma) \sim U(10, 10)$$

- Pseudo-Horseshoe Prior

$$p(\alpha) \sim N(0, 1),\ p(\beta) \sim C(0, 1),\ p(\sigma) \sim IG(0.5, 0.5)$$

- Figure 1 shows the densities of the priors.

Results

Simulations

- We simulated two-sample summary-level data under directional pleiotropy with a true value of the causal effect of 0.05. The performance of the model was assessed using coverage and power. Results in table 1 and figure 2.

Example

- We fitted summary data models to a dataset investigating the effect of body mass index on insulin resistance **(Richmond et al. 2017)**.
- We compared Bayesian MR-Egger model estimates from models including horseshoe priors from the horseshoe package **(van der Pas et al. 2016)**.
- Results are presented in table 2 and figure 3.

Conclusion

- We present Bayesian estimation of the IVW and MR-Egger models in our `mrbayes` package.
- In future work we could implement Bayesian estimation of MVMR models and perform estimation using other programs such as Stan.

References

Berzuini, Carlo, Hui Guo, Stephen Burgess, and Luisa Bernardinelli. 2018. "A Bayesian Approach to Mendelian Randomization with Multiple Pleiotropic Variants." *Biostatistics*.

Bowden, Jack, George Davey Smith, and Stephen Burgess. 2015. "Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression." *International Journal of Epidemiology* 44 (2): 512–25. https://dx.doi.org/10.1093/ije/dyv080.

Richmond, Rebecca, Kaitlin Wade, Laura Corbin, Jack Bowden, Gibran Hemani, Nicholas Timpson, and George Davey Smith. 2017. "Investigating the role of insulin in increased adiposity: Bi-directional Mendelian randomization study." *bioRxiv*, 155739. https://doi.org/10.1101/155739.

Schmidt, A F, and F Dudbridge. 2017. "Mendelian randomization with Egger pleiotropy correction and weakly informative Bayesian priors." *International Journal of Epidemiology* 47 (4): 1217–28. https://dx.doi.org/10.1093/ije/dyx254.

van der Pas, Stephanie, James Scott, Antik Chakraborty, and Anirban Bhattacharya. 2016. *Horseshoe: Implementation of the Horseshoe Prior*. https://CRAN.R-project.org/package=horseshoe.

Figures and Tables

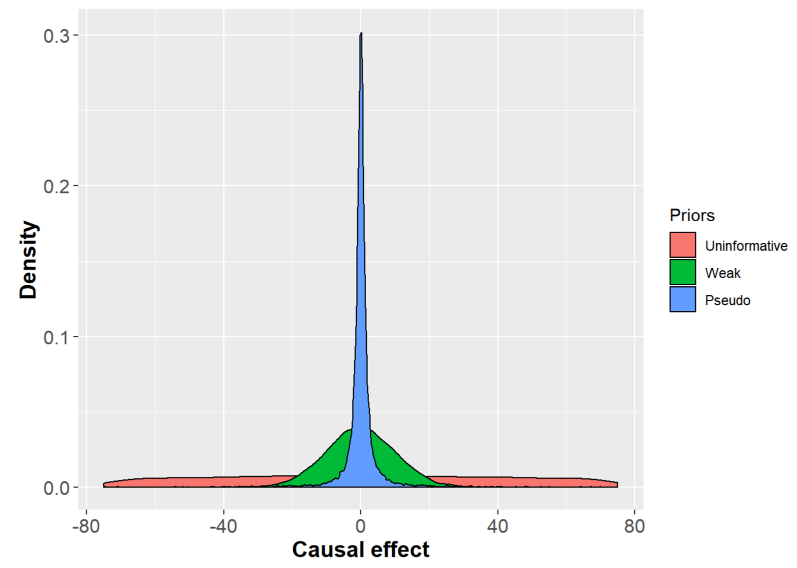

Figure 1: Density of alternative prior distributions implemented in our package.

Table 1: Model performance under directional pleiotropy.

	IVW	MR-Egger	MR-Egger with pseudo-HS prior	MR-Egger with horseshoe prior
Estimate	0.1607	0.0293	0.0302	0.0374
Power	1.0000	0.1044	0.0950	0.0994
Coverage	0.0036	0.8946	0.9046	0.9044

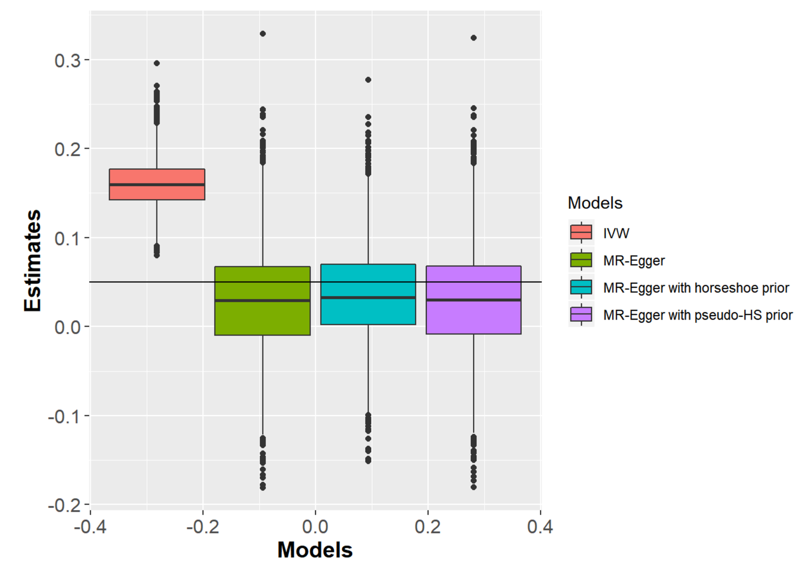

Figure 2: Distribution of causal effect estimates under directional pleiotropy.

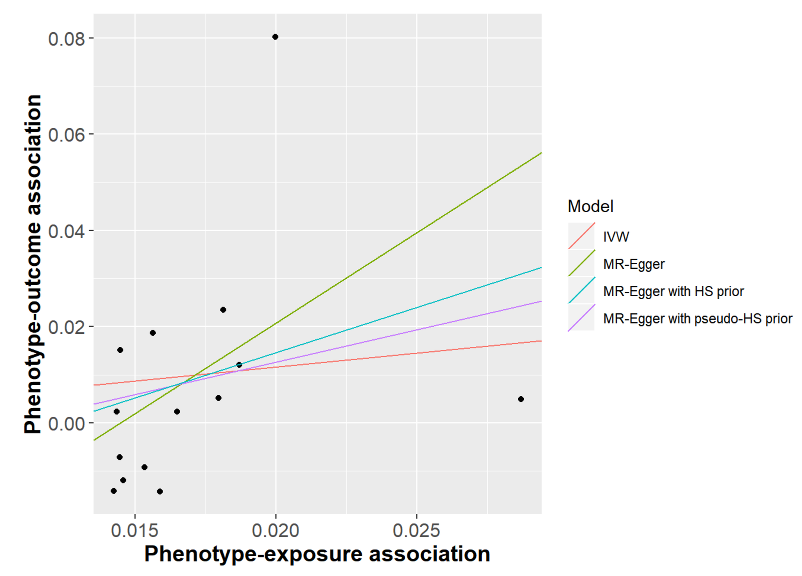

Figure 3: Scatter plot of genotype-disease versus genotype-phenotype estimates for the effect of BMI on insulin resistance.

Table 2: Estimates of the causal effect of BMI on insulin resistance.

Model	Coefficient	Estimate	95% Confidence/Credible Interval
IVW	Slope	0.5797	-0.1985, 1.3579
MR-Egger	Intercept	-0.0544	-0.1258, 04
MR-Egger	Slope	3.7586	-0.4793, 7.9966
MR-Egger with pseudo-HS prior	Intercept	-0.0143	-0.0862, 0.0327
MR-Egger with pseudo-HS prior	Slope	1.3488	-1.2967, 5.6133
MR-Egger with HS prior	Intercept	-0.023	-0.0997, 0.0248
MR-Egger with HS prior	Slope	1.8779	-0.9604, 64