Bayesian Mendelian Randomization

Carlo Berzuini\textsuperscript{1}, Hui Guo\textsuperscript{1}, Stephen Burgess\textsuperscript{2}, Luisa Bernardinelli\textsuperscript{3}

\textsuperscript{1}Centre for Biostatistics, The University of Manchester, Manchester, UK\textsuperscript{*}
\textsuperscript{2}Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom
\textsuperscript{3}Department of Brain and Behavioural Sciences, University of Pavia, Italy

Keywords: Pleiotropy; Horseshoe Prior; Shrinkage Estimators; Egger Regression; Median Estimator; Causal Inference; Instrumental Variable Analysis; Invalid Instruments; Instrument-Exposure Interaction; Metabolomics

Abstract

Our Bayesian approach to Mendelian Randomization uses multiple instruments to assess the putative causal effect of an exposure on an outcome. The approach is robust to violations of the (untestable) Exclusion Restriction condition, and hence it does not require instruments to be independent of the outcome conditional on the exposure and on the confounders of the exposure-outcome relationship. The Bayesian approach offers a rigorous handling of the uncertainty (e.g. about the estimated instrument-exposure associations), freedom from asymptotic approximations of the null distribution and the possibility to elaborate the model in any direction of scientific relevance. We illustrate the last feature with the aid of a study of the metabolic mediators of the disease-inducing effects of obesity, where we elaborate the model to investigate whether the causal effect of interest interacts with a covariate. The proposed model contains a vector of unidentifiable parameters, $\beta$, whose $j$th element represents the pleiotropic (i.e.,

\textsuperscript{*}carlo.berzuini@manchester.ac.uk
not mediated by the exposure) component of the association of instrument \( j \) with the outcome. We deal with the incomplete identifiability by assuming that the pleiotropic effect of some instruments is null, or nearly so, formally by imposing on \( \beta \) Carvalho’s horseshoe shrinkage prior, in such a way that different components of \( \beta \) are subjected to different degrees of shrinking, adaptively and in accord with the compatibility of each individual instrument with the hypothesis of no pleiotropy. This prior requires a minimal input from the user. We present the results of a simulation study into the performance of the proposed method under different types of pleiotropy and sample sizes. Comparisons with the performance of the weighted median estimator are made. Choice of the prior and inference via Markov chain Monte Carlo are discussed.

1 Introduction

Mendelian randomization (MR) is a method for testing and estimating the causal effect of an exposure, \( X \), on an outcome, \( Y \) in situations where the relationship between these two variables is confounded, based on information from the genotyping of variants associated with the exposure [3] [8] [9]. The method assumes that the genotypes are the result of a randomised experiment performed by Nature during meiosis, and therefore their effect on the outcome is likely to mimic the effect we would obtain through an intervention on the exposure. Standard MR theory requires the instruments to be (i) associated with the exposure, (ii) independent of the outcome conditional on the exposure and on the confounders of the exposure-outcome relationship, and (iii) independent of those confounders. Many authors, e.g. Jones, Didelez and colleagues [13] [14] [18] call (ii) the Exclusion Restriction condition.

Current, state-of-the-art, MR methods combine the strengths of multiple instrumental variants, \( Z = (Z_1, \ldots, Z_J) \), and are robust to violations of the Exclusion Restriction condition (ii). Examples include the Egger regression and the median estimator method [2] [4] [5], both of which work from the estimated coefficient, \( \beta_{YZ_j} \), of the regression of \( Y \) on each \( Z_j \), and the estimated coefficient, \( \beta_{XZ_j} \), of the regression of \( X \) on each \( Z_j \). The Egger regression method interprets a linear relationship between the \( \{\beta_{YZ_j}\} \) and the \( \{\beta_{XZ_j}\} \) as evidence that an exogenous change in \( X \) will cause a corresponding proportional change in \( Y \), and allows any proportion of the \( J \) instruments to violate the Exclusion Restriction condition [1], whereas the median estimator assumes that only a minority of the instruments
violates that condition.

One limitation of the median and Egger estimators is that they both treat the estimated coefficient of the regression of $X$ on each instrument as fixed, despite the considerable uncertainty that may surround it. This confronts the user with a problematic trade-off between using all the available data information and excluding the weakly associated variants.

This paper presents a Bayesian approach to MR that uses multiple instruments and relaxes the Exclusion Restriction condition. Not only does this approach overcome the above mentioned limitations; it also offers the typical advantages of Bayesian analysis, including a rigorous handling of the uncertainty, the freedom from asymptotic approximations of the null distribution and the possibility of a straightforward elaboration of the model in any direction of scientific relevance. We illustrate the last feature in Section 5 with the aid of a study of the metabolic mediators of the disease-inducing effects of obesity, where we elaborate the model to investigate whether the causal effect of obesity on certain mediators interacts with sex.

We start our journey in Section 2 by specifying the causal assumptions behind the method. An additional assumption is introduced in Section 3.1. The model proposed in Section 3 contains a vector of unidentifiable parameters, $\beta$, whose $j$th element represents the pleiotropic (i.e., not mediated by the exposure) component of the association of instrument $j$ with the outcome. In the same Section we show that the incomplete identifiability can be dealt with by assuming that the pleiotropic effect of some instruments is null, or nearly so. We do this by imposing on $\beta$ the horseshoe shrinkage prior proposed by Carvalho and colleagues [7], under which different components of $\beta$ will be subjected to different degrees of shrinkage, inferred from the data. The horseshoe prior requires a minimal input from the user. This and other prior specifications are discussed in Section 3.2.

In Section 4 we perform a simulation experiment to assess the performance of the method in the presence of different types of pleiotropy and with different sample sizes, and to compare it with that of the weighted median estimator. The inference is performed by sampling the model posterior distribution via the Hamiltonian dynamics Markov chain Monte Carlo techniques [22] [24] incorporated in the program Stan [25] [26]. Sensible initial values for the chains are obtained from estimates of the posterior means obtained via variational inference techniques [27].
This work restricts attention to the case where $X$ and $Y$ are continuous. The discrete case is under investigation.

Figure 1: Graphical representation of the assumptions at the basis of the proposed method.

Figure 2: The three instruments in example (a) satisfy Condition 2 whereas instrument $Z_3$ in example (b) violates it.
2 Causal Assumptions

Let the symbol $Z$, with $Z \equiv (Z_1, \ldots, Z_J)$, represent a set of instruments, and $U$ the set of (generally unknown) common causal influences of $X$ and $Y$. Let the notation $A \perp B \mid C$ hereafter stand for ”$A$ independent of $B$ given $C$” [10]. Within our method, $Z$ qualifies as a set of instruments for assessing the putative causal effect of $X$ on $Y$ if there exists a (possibly empty) set of observed variables $W$ such that, conditional on $W$, each instrument $Z_j$ satisfies the following conditions:

**Condition 1 (relevance)** the instrument is associated (not necessarily in a causal way) with the exposure: $Z_j \not\perp\!\!\!\perp X$.

**Condition 2 (confounder independence)** the instrument is independent of the confounders $U$: $Z_j \perp\!\!\!\perp U$.

We say that the variables in $Z$ unconditionally qualify as instruments within our method if the above conditions hold with $W$ empty. Conditioning on $W$ will hereafter be taken as implicit in the notation. Condition 2 is untestable, as it involves the unknown quantity $U$. Our method is robust to violations of the (untestable) Exclusion Restriction condition, $Y \perp\!\!\!\perp Z \mid (X, U)$, insofar as $Z \perp\!\!\!\perp U$ remains valid. In particular, the instruments are allowed to influence $Y$ through pathways independent of $U$ and $X$. This is an important generalisation, if one considers how difficult it is to corroborate the Exclusion Restriction condition, whether on the basis of empirical evidence or biological knowledge.

A general situation where the set of instruments $Z$ unconditionally satisfies Condition 2 is depicted by the conditional independence graph of Figure 1 where, for the time being, the reader is asked to ignore node $F_X$. One can use the $d$-separation rule [15], or moralisation [21], to check that this graph violates the Exclusion Restriction condition, due to the presence of a $Z \rightarrow Y$ arrow, but this condition is not required by our method. Hence, if the assumptions in Figure 1 hold and $Z$ is associated with $X$, then $Z$ unconditionally qualifies as an instrument for assessing the causal effect of $X$ on $Y$ through our method. While the example of Figure 2(a) is a special case of Figure 1, Figure 2(b) contains an instrument ($Z_3$) that violates Confounder Independence, which is not compatible with our method.

The node $F_X$ in Figure 1 represents an example of regime indicator [11] [12], and tells us whether the value of $X$ is set by a hypothetical exogenous intervention or
instead it arises from passive observation. Embodied in the graph is the relationship $F_X \perp (U, Z)$, stating that an intervention on $X$ will not affect $Z$ or $U$ – a sensible assumption if we accept that genetic variants cannot be causally affected by changes in $X$. Also expressed in the graph is the assumption $Y \perp F_X \mid (X, Z, U)$, stating that, conditional on $Z$ and $U$, the distribution of $Y$ given $X$ does not depend on whether the value of $X$ has been generated by passive observation or intervention. This implies that the $X \rightarrow Y$ arrow in the graph, and the coefficient of $X$ in a regression of $Y$ on $(X, Z, U)$, can be interpreted causally. By contrast, the method does not necessarily require the association between $Z$ and $X$ (represented in the graph by the $Z \rightarrow X$ arrow) to be causal.

3 The Model

3.1 The Likelihood

Assume each sample individual is characterized by a complete set of observed values for $X, Y$ and $Z \equiv (Z_1, \ldots, Z_J)$. According to the graph in Figure 1, the conditional distribution $P(X, Y, U \mid Z)$, factorizes as:

$$P(X, Y, U \mid Z) = P(U) \ P(X \mid Z, U) \ P(Y \mid X, Z, U).$$  \hspace{1cm} (1)

If we write $N(a, b)$ for the normal distribution with mean $a$ and variance $b$, our assumed model has form

$$P(U) = N(0, 1),$$ \hspace{1cm} (2)
$$P(X \mid Z, U) = N(\omega_X + \alpha Z^T + \delta_X U, \sigma_X^2),$$ \hspace{1cm} (3)
$$P(Y \mid X, Z, U) = N(\omega_Y + \theta X + \beta Z^T + \delta_Y U, \sigma_Y^2),$$ \hspace{1cm} (4)

or, equivalently,

$$P(X \mid Z) = \omega_X + \alpha Z^T + A,$$ \hspace{1cm} (5)
$$P(Y \mid X, Z) = \omega_Y + \theta X + \beta Z^T + B.$$ \hspace{1cm} (6)

with $A \sim N(0, \delta_X^2 + \sigma_X^2)$ $B \sim N(0, \delta_Y^2 + \sigma_Y^2)$ and $\text{cov}(A, B) = \delta_X \delta_Y$. We exclude a possible effect of $(X, Z, U)$ on the variance of $Y$. Equations (5–6) contain the $2J + 6$ parameters $(\omega_X, \omega_Y, \tau_X^2 \equiv \delta_X^2 + \sigma_X^2, \tau_Y^2 \equiv \delta_Y^2 + \sigma_Y^2, \lambda \equiv \delta_X \delta_Y, \theta, \alpha, \beta)$, which we shall refer to as the structural parametrization. Of inferential interest among these is parameter $\theta$ of Equation (4), which can be interpreted in terms of change in $Y$ due to an intervention on $X$. Not all of the
$2J + 6$ structural parameters are identified from the likelihood, for the following reason. The conditional expectation $E(X \mid Z) = \omega_X + \alpha Z^T$ and the conditional variance $\text{var}(X \mid Z) = \tau_X^2$ provide $J + 2$ conditions that make structural parameters $\omega_X, \alpha, \tau_X$ identifiable from the likelihood. The conditional expectation $E(Y \mid X, Z) = \omega_Y + \theta_X X + \beta Z^T$ provides additional $J + 2$ conditions: \( \omega_Y = \omega_Y - \omega_X \frac{\lambda}{\tau_X}, \theta' = \theta + \frac{\lambda}{\tau_X} \) and $\beta' = \beta - \alpha \frac{\lambda}{\tau_X}$. A further condition is provided by the conditional variance $\text{var}(Y \mid X, Z) = \left(1 - \left(\frac{\lambda}{\tau_Y \tau_X}\right)^2\right) (\tau_Y^2)$, for a total of $2J + 5$ conditions – insufficient to estimate the full set of $2J + 6$ structural parameters. The information contained in the data identifies the structural parameters $\omega_X, \alpha, \tau_X$, but fails to identify the remaining structural parameters, $(\omega_Y, \tau_Y, \lambda, \theta, \beta)$, including the parameter of inferential interest, $\theta$. Full parameter identifiability is achieved in the unlikely, and therefore uninteresting, situation where the values of the $J$ components of $\beta$ are supplied by external knowledge.

We tackle the problem from a Bayesian point of view, by designing a prior distribution that makes the posterior distribution proper. Let the symbol $D$ denote the data. Then it is helpful to express the posterior in the following product form:

$$
\pi \equiv P(\omega, \tau, \lambda, \theta, \alpha, \beta \mid D) = P(\omega_X, \alpha, \tau_X \mid D) P(\omega_Y, \theta, \tau_Y, \lambda \mid \beta, \omega_X, \alpha, \tau_X, D) P(\beta \mid \omega_X, \alpha, \tau_X, D)
$$

Because $\beta$ belongs to the unidentifiable subset of the model parameters, we have $P(\beta \mid \omega_X, \alpha, \tau_X, D) = P(\beta \mid \omega_X, \alpha, \tau_X)$, which leads to

$$
\pi = P(\omega_X, \alpha, \tau_X \mid D) P(\omega_Y, \theta, \tau_Y, \lambda \mid \beta, \omega_X, \alpha, \tau_X, D) P(\beta \mid \omega_X, \alpha, \tau_X) \quad (7)
$$

The data allow us to learn about parameters $\omega_X, \alpha, \tau_X$ (first term of the above product) and, conditional on $\beta, \omega_X, \alpha, \tau_X$, they allow us to learn about the remaining parameters in the model (second term of the product), but they provide no information about $\beta$ and, in particular, about the possible dependence between $\beta$ and $\alpha$. This is not a fatal flaw if we provide $\beta$ with a suitable, scientifically plausible, prior. One option consists of assuming $\beta = 0$. Reasons why we repute this an untenable assumption have been previously discussed. Another option is to impose inequalities based on the assumption that, say, the direct component of the effect of $Z_j$ on $Y$ is smaller in magnitude than the (indirect) effect mediated by $X$. In this paper we adopt a different approach, that requires us to introduce a further condition that is sometimes referred to as the Instrument Strength Independent of Direct Effect (INSIDE) condition.
Condition 3 (INSIDE) *The genetic associations with the exposure are independent of the direct effects of the genetic variants on the outcome: \( \beta_j \perp \alpha_j, \) for \( j = 1, \ldots, J \)*

Under Condition 3 we shape the conditional prior \( P(\beta \mid \omega_X, \alpha, \tau_X) = P(\beta) \) to express our prior belief that some of its components are zero. This is discussed in the next section.

### 3.2 The Prior

We shall now discuss the prior specifications for the parameters of model (2–4). Of special interest is the prior we impose on the vector \( \beta \). It is often assumed in the MR literature that all the components of \( \beta \) are zero. We replace this with the more realistic assumption that some of the components of this vector are zero, and incorporate this in our model by imposing on \( \beta \) the horseshoe shrinkage prior proposed by Carvalho [7]. With this prior, the components of \( \beta \) will be shrunk towards zero, but to different degrees inferred from the data: large components will be only moderately shrunk, while small components will be heavily shrunk towards zero. The prior mechanism may be informally described as follows. Those instruments whose effects on \( Y \) are irreconcilable with a no-pleiotropy model will have large corresponding \( \beta \) parameters. Our prior will leave these parameters relatively unshrunk, so that those instruments will have little impact on the estimated \( \theta \). By contrast, those instruments that are compatible with a no-pleiotropy model and a low-variance outcome error probability will have their corresponding \( \beta \) parameters heavily shrunk towards 0, so that the estimate of theta will predominantly depend on the information provided by these non-pleiotropic instruments.

We apply Carvalho’s horseshoe prior to \( \beta \) by writing:

\[
\begin{align*}
p(\beta_j \mid \phi_j) &= N(0, \phi_j^2), \\
p(\phi_j \mid \gamma) &= \text{Cauchy}^+(0, \gamma), \\
p(\gamma) &= \text{Cauchy}^+(0, 1),
\end{align*}
\]

for \( j = 1, \ldots, J \), where \( \text{Cauchy}^+(0, a) \) denotes the half-Cauchy distribution on the positive reals with scale parameter \( a \). Crucially, in the above prior, each \( \beta_j \) is mixed over its own unknown \( \phi_j \). The parameters \( \phi_j \)'s control the local degrees of shrinking, and are all independently drawn from a half-Cauchy prior with a
common, unknown global scale parameter $\gamma$, which controls the global degree of shrinking. By virtue of (8), small values of $\phi_j$ cause $\beta_j$ to shrink towards zero, whereas large values will prevent the estimate of $\beta_j$ from shrinking. Importantly, the horseshoe prior is free from user-chosen hyperparameters.

The shrinkage for instrument $j$ is measured by parameter $\kappa_j = 1/(1 + \phi_j^2)$, called the shrinkage weight, with $\kappa_j = 0$ (resp., $\kappa_j = 1$) indicating absence of (resp., near-total) shrinking. The shrinkage weights $\kappa_j$ are inferred from the data. Equations (8–10), with $\gamma = 1$, yield a horseshoe-shaped $Beta(.5,.5)$ prior for $\kappa_j$, peaking at $\kappa_j = 0$ and $\kappa_j = 1$. The ability of our model to discriminate between pleiotropic and non-pleiotropic instruments corresponds to the tendency of parameter $\kappa_j$ to be, on average, lower for the non-pleiotropic than for the pleiotropic instruments. In Section 4 we assess separation by a simulation experiment.

We are now going to discuss the prior specifications for the remaining model parameters. In our analyses, we have taken parameters $\omega_X$ and $\omega_Y$ to follow a priori independent uniform distributions. However, since these parameters are related to the global means of two observed variables, one may be able to shape informative priors for $\omega_X$ and $\omega_Y$ on the basis of external information. In our analyses we took each $\alpha_j$, for $j = 1, \ldots, J$, to be independently drawn from a normal $N(\mu_\alpha, \sigma_\alpha^2)$ population prior, with hyperparameters $\mu_\alpha$ and $\sigma_\alpha$ subject to uniform priors. However, under our $Z \perp U$ assumption one will often be able to shape an informative prior for the $\alpha$ parameters (for example a prior that imposes on these parameters specific signs) on the basis of external $(Z, X)$ data. Parameters $\sigma_X$ and $\sigma_Y$ are only partially identifiable. We assigned these two parameters uniform positive prior distributions, which did not cause mixing problems in our Markov chain Monte Carlo exploration of the model posterior distribution. We completed our prior specifications by taking the parameters $\eta_X$, $\eta_Y$ and $\theta$ to follow uniform independent priors.

There are situations where some instruments can be safely assumed to exert no pleiotropic effect. These instruments can be used to gather prior information about the value of $\tau_X$. By combining this information with the constraint $\tau_X^2 = \eta_X^2 + \sigma_X^2$, one may attempt to derive inequalities involving $\eta_X$ and $\sigma_X$ and use them to shape an informative joint prior for these two parameters.
Figure 3: We have selected at random one of the datasets generated in the simulation experiment of Section 4 and compared the distribution of the shrinkage parameter $\kappa_j$ over the set of the non-pleiotropic instruments (box on the left) with that over the set of pleiotropic instruments (box on the right). As expected, the components of $\beta$ associated with the pleiotropic instruments have values of $\kappa_j$ close to zero, which indicates that they tend to be left unshrunk, whereas the components of $\beta$ associated with the non-pleiotropic instruments have values of $\kappa_j$ closer to 1, which indicates that they are heavily shrunk.
4 Simulation Experiment

A simulation experiment was set up to comparatively assess the performance of the proposed method and of the weighted median estimator (WME) [6] [2]. Throughout the experiment, we set the number of instruments, $J$, to be equal to 20, with the instrumental variables representing "allele doses" (0, 1, 2), and we took the effect of each instrument on both $X$ and $Y$ to be linear in the allele dose. We imposed a pleiotropic effect on half of the instruments, the remaining instruments being treated as pleiotropic. We considered six simulation scenarios differing by type of pleiotropy (balanced, positive or negative) and sample size (100, 520). For each scenario, we simulated 1000 replicate datasets by setting $\theta = 0$ – the null hypothesis –, and further 1000 datasets by setting $\theta = 0.35$ – the alternative hypothesis. Each new simulation started with the generation of a configuration of values of $Z_1, \ldots, Z_{20}$ for each hypothetical individual, these values being drawn from $J$ independent trinomial distributions that mimicked the joint distribution of real SNP loci. Conditional on such values, the simulation proceeded with the generation of a configuration of values of $(X, Y, U)$ for each hypothetical individual, on the basis of Equations (2–4) with $\delta_X \sim N(-0.05, 0.0025), \delta_Y \sim N(-1.0025), \omega_Y \sim N(-3.7, 0.04), \omega_X = 3.3, \sigma_Y = 0.1, \sigma_X = 0.1$ and $\alpha_j \sim N(0.034, 0.0031), \beta_j \sim N(0.012\xi, 0.0025)$, for $j = 1, \ldots, 10$, where $\xi$ indicates balanced ($\xi = 0$), negative ($\xi = -1$) and positive ($\xi = 1$) pleiotropy, and $\beta_j = 0$, for $j = 11, \ldots, 20$.

Each simulated dataset was analyzed by using both the WME and the proposed method. In the latter case, inference was based on Markov chain Monte Carlo (MCMC) samples from the posterior distribution defined by Equations (2–4) jointly with the prior specifications of Section 3.2. These samples were generated by using the Hamiltonian dynamics MCMC techniques [22] [24] offered by the program Stan [26] [25]. Initial values for the Markov chains were generated automatically in STAN based on approximate posterior mean estimates obtained via variational inference techniques [27]. No Markov chain mixing problems were encountered. The WME analysis of each dataset produced a point estimate and a corresponding 95 percent confidence interval for $\theta$. Analysis by our method produced a posterior mean and a 95 percent Bayesian credible interval for $\theta$.

The two methods were comparatively assessed in terms of (i) coverage under the null, (ii) coverage under the alternative, (iii) power, (iv) bias under the null and (v) bias under the alternative. The estimated coverage under the null (resp., alter-
native) was the proportion of simulations performed under the null (resp., alternative) where the credible/confidence interval for $\theta$ contained the value 0 (resp., 0.35). Power was estimated as the proportion of simulations under the alternative hypothesis where the credible/confidence interval for $\theta$ was contained by the positive real axis. Bias was estimated as the average signed difference between the point estimate for $\theta$ and the corresponding true value of the parameter. A summary of the simulation results is given in Table 1. The proposed method appears to outperform the WME in terms of coverage under the null, especially in the presence of a larger sample size. It appears superior also in terms of coverage under the alternative, when the sample is small. The two methods appear to offer roughly the same power. As expected, in both methods, power appears to depend on sample size. The differences in bias between the two methods are minimal. Under the proposed method, coverage under the null appears to be slightly more robust to positive pleiotropy than with the WME, when the sample is small.

In Figure 3 we have selected at random one of the datasets generated in this simulation experiment, and compared the distribution of the shrinkage parameter $\kappa_j$ over the set of the non-pleiotropic instruments (box on the left) with that over the set of pleiotropic instruments (box on the right). As expected, the components of $\beta$ associated with the pleiotropic instruments have values of $\kappa_j$ close to zero, which indicates that they tend to be left unshrunk, whereas the components of $\beta$ associated with the non-pleiotropic instruments have values of $\kappa_j$ closer to 1, which indicates that they are heavily shrunk.

5 Sex-Dependent Causal Effect of Body Mass on Phenylalanine

A high body mass is associated with an increased risk of several chronic diseases. A better understanding of the underlying biology requires that we identify the metabolic mediators of this deleterious effect [23]. Within this perspective, Ho et al [16] have analyzed data from 2383 Framingham offspring cohort participants, and tested the association between the body mass index (BMI) and more than two hundred cardiometabolic traits and metabolites. As many as sixty metabolites were found to be significantly ($P < 0.00023$) associated with BMI. The next step is now to assess whether these associations are causal. We advocate a MR approach to the problem, where BMI acts as exposure and the individual metabolites, in turn, act as responses. SNPs associated with BMI are used as instruments to
Our method Weighted median estimator

| Scenario | Pleiotropy | Sample Size | Coverage under Null | Coverage under Alternative | Power | Bias under Null | Bias under Alternative | Coverage under Null | Coverage under Alternative | Power | Bias under Null | Bias under Alternative |
|----------|------------|-------------|---------------------|---------------------------|-------|----------------|------------------------|---------------------|--------------------------|-------|----------------|------------------------|
| 1 0 520  | .92 .9     | .89 .001    | .025                | .79 .79                   | .875 .002 | .007 |
| 2 − 520 | .89 .9     | .86 .028    | .008                | .77 .80                   | .85 .043 | .009 |
| 3 + 520 | .90 .86    | .89 .029    | -.017               | .79 .77                   | .91 .038 | .015 |
| 4 0 100 | .90 .92    | .57 .004    | .3                   | .88 .93                   | .53 .03  | .055 |
| 5 − 100 | .92 .91    | .54 .32     | -.024               | .89 .92                   | .55 .009 | -.02 |
| 6 + 100 | .89 .92    | .57 .029    | .06                  | .81 .84                   | .65 .07  | .06  |

Table 1: Results of a comparative assessment of the proposed and of the median estimator methods for causal effect estimation. Table rows correspond to six different simulation scenarios characterized by the presence of balanced (0), positive (+) or negative (−) pleiotropy and by the sample size (520 vs 100). Throughout the simulation, the number of instruments was kept equal to 20. Method performance was separately assessed under each of the 6 scenarios on the basis of 2000 simulated datasets, in terms of coverage under the null and under the alternative, power and bias. See main text for further details.

assess whether BMI is a causal influence on the metabolite of interest.

The idea can be effectively implemented by using our proposed method. To illustrate this, we shall now apply our method to the assessment of the putative causal effect of BMI on one of the metabolites highlighted by the Framingham study: the aromatic amino acid phenylalanine. This analysis we have carried out on the basis of data from 520 unrelated individuals, aged 25–74 years, sampled from a population-based Finnish cohort – the Dietary, Lifestyle and Genetic determinants of Obesity and Metabolic Syndrome (DILGOM) study[17]. The DILGOM data contain information about the individuals’ serum metabonomes, combined with the genome-wide profiles of genetic and transcriptional variation from blood
leukocytes of the same individuals. The data also contain individual-level measures of BMI, age and sex.

The first step of our analysis consisted of selecting a subset of 98 DILGOM-genotyped SNPs, based on a $p \leq 1 \times 10^{-5}$ significance threshold for the SNP’s association with BMI (more precisely, for the Wald test statistic for the regression of BMI on the SNP), and on a maximum between-SNP linkage disequilibrium score of $\leq 0.05$. We let the genotypes of the 98 selected SNPs act as instruments in our analysis, $(Z_1, \ldots, Z_{98})$, to be treated as continuous variables, with values $(0, 1, 2)$ corresponding to the number of minor alleles found at the SNP. We let the variable BMI act as exposure, $X$, and the concentration of phenylalanine, expressed on a log scale, act as outcome, $Y$. We incorporate in the analysis the variable sex, denoted as $W$, taking value 0 for female and 1 for male. The resulting problem structure is depicted in Figure 4.

The model specification (2-4) was modified to acknowledge the possible interaction between the effects of sex ($W$) and BMI ($X$) on phenylalanine concentration ($Y$). Such an elaboration was motivated by evidence [20] that sex and BMI interact in their effects on coronary artery disease and other clinical outcomes. The elaboration was straightforwardly implemented, as is often the case within
a Bayesian approach that keeps model specification and inference calculations independent of each other. All we had to do was to modify Equations (2-4) into:

\[

tilde{P}(U) = N(0,1),
\]

\[
P(X \mid Z,U) = N(\omega_X + \alpha Z^T + \psi_{XW}W + \delta_X U, \sigma_X^2),
\]

\[
P(Y \mid X,Z,U) = N(\omega_Y + \theta(X + \psi_{YXW}W) + \beta Z^T + \psi_{YW}W + \delta_Y U, \sigma_Y^2),
\]

where the BMI \times SEX interaction is represented by parameter \psi_{YXW}, so that the causal effect of BMI on log-concentration of phenylalanine is represented by \theta in the female stratum, and by \theta' \equiv \theta + \psi_{YXW} in the males.

We completed the model by specifying the priors as described in Section 3.2. We sampled the model posterior distribution by running 10000 iterations of a (Hamiltonian dynamics) Markov chain. The last 5000 samples were used to approximate the posterior marginal distributions and to obtain posterior means and credible intervals for the parameters of interest. Figure 5 shows the obtained marginal posterior distributions for parameters \theta and \psi_{YXW} of Equations (11). The parameter \theta' was included in the model as a derived quantity, so as to obtain samples from its marginal posterior distribution and to estimate its posterior mean and credible interval. The estimates for the parameters of interest are reported in Table 1. The 95 percent credible interval for \psi_{YXW} is contained by the positive real axis, which
Figure 6: In this plot, the black dots correspond to the instrumental SNPs in the analysis of Section 5, the horizontal coordinates to the SNP’s coefficient in the exposure regression (least-squares regression of BMI on that SNP), and their vertical coordinates to the SNP’s coefficient in the response regression. The 95 percent credible intervals for the coefficients are represented as dashed segments.
represents strong evidence of an interaction between the causal effects of BMI and sex on the concentration of phenylalanine. The causal effect of BMI on the log-concentration of phenylalanine was estimated to be 0.34 (95 percent credible interval 0.21 to 0.47) in the females, and 0.2 (95 percent credible interval 0.098 to 0.3) in the males.

It would have been possible to examine the interaction by running separate analyses within the male and female strata, although and the cost of a loss of statistical power. Figure 6 provides visual evidence of the causal effect of the BMI on phenylalanine. In this figure, each instrumental SNP appears as a black dot with the \( x \) and \( y \) coordinates corresponding to the coefficients of the SNP in the exposure and outcome regressions, respectively, and the corresponding 95% confidence intervals are represented by dashed segments. The emerging linear relationship can be interpreted to suggest that hypothetical perturbations of \( X \) would result in corresponding, proportional, perturbations in \( Y \).

By repeating the analysis on a large set of metabolites, we may aim to a classification of obesity based on the values of the molecular mediators that are responsible for its deleterious effects, for purposes of personalised medicine and drug target discovery.

| Parameter | Posterior Mean | Standard Deviation | 95 Percent Credible Interval |
|-----------|----------------|--------------------|-----------------------------|
| \( \theta \) | 0.34           | 0.068              | (0.21,0.47)                 |
| \( \psi_{YXW} \) | -0.14         | 0.072              | (-0.28,-0.0062)             |
| \( \theta' \) | 0.2           | 0.051              | (0.098,0.3)                 |

Table 2: Point and interval estimates for some parameters of model (11), based on the DILGOM dataset of Section 5. The causal effect of BMI on the log-concentration of phenylalanine is represented by parameter \( \theta \) in the female stratum, and by \( \theta' \equiv \theta + \psi_{YXW} \) in the males.

6 Discussion

Kang and colleagues [19] use the term ”invalid” (resp., ”valid”) to denote an instrument that violates (resp., obeys) the Exclusion Restriction condition. They
propose a LASSO-type procedure to identify the valid instruments from within a set of candidate instrumental variables. The idea, further elaborated by Windmeijer and colleagues [28], is to obtain a sparse estimate of the vector representing the pleiotropic effects by imposing on it an $l_1$ penalty. The null elements of the estimated vector should then correspond to the valid instruments. In our framework, we may construct a Bayesian analogue of Windmeijer’s approach by replacing the horseshoe prior on $\beta$ with a double-exponential prior. But this will make a big difference to the posterior means when $\beta$ is sparse. This is because our (horseshoe) prior presents superior tail robustness to the large signals introduced in the $\beta$ vector by the pleiotropic effects, and possesses the ability to shrink the components of $\beta$ near zero much more forcefully than those far from zero, thanks to the combined local and global shrinking. Our work differs from Windmeijer’s also from the point of view of the method justification, which in the present paper is based on Dawid’s decision-theoretic causal inference framework [12], rather than on the notion of potential outcome.

A number of method issues await investigation. Of foremost importance is to consider the method behaviour in the presence of collinearity of the instruments in the outcome regression. Our prior on $\beta$ should supply enough tail probability to produce a posterior distribution which preserves the pattern of correlation between the components of $\beta$.

Acknowledgments

The first two authors acknowledge partial support from the European Union’s Seventh Framework Programme FP7-Health- 2012-INNOVATION, under grant agreement number 305280 (MIMOmics). The DILGOM data resource exploited in Section 5 has been funded by the Sigrid Juselius and Yrjö Jahnsson Foundations and by the Finnish Academy grants no. 255935 and 269517. Our analysis of these data has benefitted from discussions with Drs. Xiaoguang Xu and Susana Conde.

References

[1] J Bowden, G Davey Smith, and S Burgess. Mendelian Randomization With Invalid Instruments: Effect Estimation and Bias Detection Through Egger Regression. International Journal of Epidemiology, 44(2):512525, 2015.
[2] Jack Bowden, George Davey Smith, Philip C Haycock, and Stephen Burgess. Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. *Genetic Epidemiology*, 40:304–314, 2016.

[3] S Burgess, A Butterworth, A Malarstig, and S. Thompson. Use of Mendelian Randomisation to Assess Potential Benefit of Clinical Intervention. *BMJ*, 345:e7325, 2012.

[4] Stephen Burgess, Jack Bowden, Tove Fall, Erik Ingelsson, and Simon G Thompson. Sensitivity analyses for robust causal inference from Mendelian randomization analyses with multiple genetic variants. *Epidemiology (in press)*, 2016.

[5] Stephen Burgess and Simon G. Thompson. *Mendelian Randomization: Methods for Using Genetic Variants in Causal Estimation*. Chapman and Hall, 2015.

[6] Han C. Detecting invalid instruments using l1-gmm. *Econ Lett*, 101:285–287, 2008.

[7] Carlos M Carvalho, Nicholas G Polson, and James G Scott. The horseshoe estimator for sparse signals. *Biometrika*, page asq017, 2010.

[8] G Davey Smith and S. Ebrahim. Mendelian Randomization: Can Genetic Epidemiology Contribute to Understanding Environmental Determinants of Disease? *International Journal of Epidemiology*, 32:122, 2003.

[9] G Davey Smith and G. Hemani. Mendelian Randomization: Genetic Anchors for Causal Inference in Epidemiological Studies. *Hum Mol Genet*, 23:89–98, 2014.

[10] A. P. Dawid. Conditional independence in statistical theory (with Discussion). *J. Roy. Statist. Soc. B*, 41:1–31, 1979.

[11] A. Philip Dawid. Influence diagrams for causal modelling and inference. *International Statistical Review*, 70:161–189, 2002. Corrigenda, *ibid.*, 437.

[12] A. Philip Dawid. Statistical causality from a decision-theoretic perspective. *Ann. Rev. Statist. Appl.*, 2:273–303, 2015.
[13] Vanessa Didelez and Nuala A. Sheehan. Mendelian randomisation as an instrumental variable approach to causal inference. *Statistical Methods in Medical Research*, 16:309–330, 2007.

[14] Vanessa Didelez and Nuala A. Sheehan. Mendelian randomisation: Why epidemiology needs a formal language for causality. In Federica Russo and Jon Williamson, editors, *Causality and Probability in the Sciences*, volume 5 of *Texts In Philosophy Series*, pages 263–292. College Publications, London, 2007.

[15] D. Geiger, T. Verma, and J. Pearl. Identifying independence in Bayesian networks. *Networks*, 20(5):507–534, 1990.

[16] JE Ho, MG Larson, A Gorbani, S Cheng, MH Chen, M Keyes, EP Rhee, CB Clish, RS Vasan, RE Gerszten, and Wang TJ. Metabolomic Profiles of Body Mass Index in the Framingham Heart Study Reveal Distinct Cardiometabolic Phenotypes. *PloS one*, 11, 2016.

[17] M. Inouye, J. Kettunen, P. Soininen, K. Silander, S. Ripatti, L.S. Kumpula, E. Hamalainen, P. Jousilahti, A.J. Kangas, S. Mannisto, M.J. Savolainen, A. Jula, J. Leiviska, A. Palotie, V. Salomaa, M. Perola, M. AlaKorpela, and L. Peltonen. Metabonomic, transcriptomic, and genomic variation of a population cohort. *Molecular Systems Biology*, 6:502513, 2010.

[18] E. M. Jones, J. R. Thompson, V. Didelez, and N. A. Sheehan. On the choice of parameterisation and priors for the bayesian analyses of mendelian randomisation studies. *Statistics in Medicine*, 31(14):1483–1501, 2012.

[19] Hyunseung Kang, Anru Zhang, T. Tony Cai, and Dylan S. Small. Instrumental variables estimation with some invalid instruments and its application to mendelian randomization. *Journal of the American Statistical Association*, 111(513):132–144, 2016.

[20] Robert C. Kaplan, M. Larissa Avils-Santa, Christina M. Parrinello, David B. Hanna, Molly Jung, Sheila F. Castaeda, Arlene L. Hankinson, Carmen R. Isasi, Orit Birnbaum-Weitzman, Ryung S. Kim, Martha L. Daviglus, Gregory A. Talavera, Neil Schneiderman, and Jianwen Cai. Body mass index, sex, and cardiovascular disease risk factors among hispanic/latino adults: Hispanic community health study/study of latinos. *Journal of the American Heart Association*, 3(4), 2014.
[21] S. L. Lauritzen, A. P. Dawid, B. N. Larsen, and H. G. Leimer. Independence properties of directed Markov fields. *Networks*, 20(5):491–505, 1990.

[22] N. Metropolis, A. Rosenbluth, M. Rosenbluth, M. Teller, and E. Teller. Equations of state calculations by fast computing machines. *Journal of Chemical Physics*, 21:1087–1092, 1953.

[23] Steven C. Moore, Charles E. Matthews, Joshua N. Sampson, Rachael Z. Stolzenberg-Solomon, Wei Zheng, Qiyun Cai, Yu Ting Tan, Wong-Ho Chow, Bu-Tian Ji, Da Ke Liu, Qian Xiao, Simina M. Boca, Michael F. Leitzmann, Gong Yang, Yong Bing Xiang, Rashmi Sinha, Xiao Ou Shu, and Amanda J Cross. Human metabolic correlates of body mass index. *Metabolomics*, 10:0, 2013.

[24] R. Neal. MCMC using hamiltonian dynamics. In Gelman A. Jones G. L. Brooks, S. and X.L. Meng, editors, *Handbook of Markov Chain Monte Carlo*, pages 116–162. Chapman and Hall/CRC, 2011.

[25] Stan Development Team. *RStan, version 2.2*. http://mc-stan.org/rstan.html, 2014.

[26] Stan Development Team. *Stan: A C++ library for probability and sampling, version 2.2*. http://mc-stan.org/, 2014.

[27] M. J. Wainwright and M. I. Jordan. Graphical models, exponential families, and variational inference. *Foundations and Trends in Machine Learning*, 1(1-2):1–305, 2008.

[28] Frank Windmeijer, Helmut Farbmacher, Neil Davies, and George Davey Smith. On the use of the Lasso for Instrumental Variables Estimation with Some Invalid Instruments. Bristol economics discussion papers, Department of Economics, University of Bristol, UK, 2016.