Identification and Estimation of the Bi-Directional MR with Some Invalid Instruments

Feng Xie[1], **Zhen Yao**[1], **Lin Xie**[1], **Yan Zeng**[1,*], **Zhi Geng**[1]

[1]Beijing Technology and Business University

Abstract

We consider the challenging problem of estimating causal effects from purely observational data in the bi-directional Mendelian randomization (MR), where some invalid instruments, as well as unmeasured confounding, usually exist. To address this problem, most existing methods attempt to find proper valid instrumental variables (IVs) for the target causal effect by expert knowledge or by assuming that the causal model is a one-directional MR model. As such, in this paper, we first theoretically investigate the identification of the bi-directional MR from observational data. In particular, we provide necessary and sufficient conditions under which valid IV sets are correctly identified such that the bi-directional MR model is identifiable, including the causal directions of a pair of phenotypes (i.e., the treatment and outcome). Moreover, based on the identification theory, we develop a cluster fusion-like method to discover valid IV sets and estimate the causal effects of interest. We theoretically demonstrate the correctness of the proposed algorithm. Experimental results show the effectiveness of our method for estimating causal effects in both one-directional and bi-directional MR models.

1 Introduction

Mendelian randomization (MR) is a powerful method for estimating the causal effect of a potentially modifiable risk factor (treatment) on disease (outcome) in observational studies, which has been used across a wide variety of contexts, such as clinic [Mokry et al., 2015, Carreras-Torres et al., 2017], socioeconomics [Cuellar-Partida et al., 2016, Brumpton et al., 2020], and drug targets [Ference et al., 2015, Li et al., 2020]. Most existing MR methods assume a one-directional causal relationship. However, bi-directional relationships are ubiquitous in real-life scenarios, for example, obesity and vitamin D status [Vimaleswaran et al., 2013], body mass index (BMI) and type 2 diabetes (T2D), etc. Understanding and analyzing bi-directional relationships can provide deeper insights into complex systems, leading to more effective interventions and solutions.

Within a causal inference framework, MR can be implemented as a form of instrumental variables (IVs) analysis in which genetic variants[2] serve as IVs for the modifiable risk factor. Specifically, as shown in Figure 1, suppose obesity (X) and Vitamin D status (Y) are the treatment and outcome of interest, respectively, and lifestyle factors $(\mathbf{U})$ are the unmeasured confounders between them. One can use genetic variants $\mathbf{G}$ as IVs to explore the causal effect of X on Y in observational data [Vimaleswaran et al., 2013] if $\mathbf{G}$ are valid IVs, i.e., $\mathbf{G}$ satisfy the following three assumptions [Wright, 1928, Goldberger, 1972, Bowden and Turkington, 1990, Hernán and Robins, 2006]:

A1. [*Relevance*] The genetic variants $\mathbf{G}$ are associated with the exposure X;

A2. [*Exclusion Restriction*] The genetic variants $\mathbf{G}$ have no direct pathway to the outcome Y;

[*] Corresponding author

[2] The genetic variants that act as IVs in MR studies are Single Nucleotide Polymorphisms (SNPs).

38th Conference on Neural Information Processing Systems (NeurIPS 2024).

A3. [*Randomness*] The genetic variants $\mathbf{G}$ are uncorrelated with unmeasured confounders $\mathbf{U}$.

Figure 1 illustrates these three assumptions for a genetic variant G that is a valid IV relative to the causal relationship $X \to Y$. Given a valid IV G in the linear model, one can estimate the causal effect of risk factor X on the outcome Y of interest consistently by using Two-Stage Least Squares (TSLS) [Burgess et al., 2017]. However, in most MR studies, the genetic variants may include some invalid IVs due to horizontal pleiotropy– where some genetic variants may have pleiotropic effects on both the treatment X and the outcome Y via different biological pathways [Davey Smith and Ebrahim, 2003, Lawlor et al., 2008]. How to select valid IVs from such genetic variants becomes the major issue in the MR study. In general, valid IVs need to be chosen based on domain knowledge or expert experience [Richmond et al., 2017, Martens et al., 2006, Zhao et al., 2023]. However, it is usually difficult to select appropriate valid IVs without precise prior knowledge of genetic variants, and an invalid IV may cause biased estimation of the effect of X on Y [Sanderson et al., 2022, Richmond and Smith, 2022]. Therefore, it is desirable to investigate ways of selecting genetic variants as valid IVs solely from observed variables.

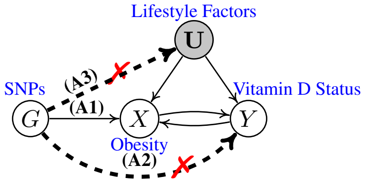


Figure 1: Graphical illustration of a valid IV model, where dashed lines indicate the absence of arrows. G is a valid IV relative to the causal relationship $X \to Y$.

Many contributions have been made to handle MR studies with some invalid IVs under specific assumptions. Existing methods can be roughly divided into four strategies. The first strategy assumes the *InSIDE assumption*, which states that the genetic variants' pleiotropic effects on the outcome Y are uncorrelated with their effects on the exposure X, and requires that the number of IVs increases with the sample size [Bowden et al., 2015]. The second strategy is based on the *Majority rule assumption*, which assumes that over 50% of the candidate IVs are valid [Kang et al., 2016, Bowden et al., 2016, Windmeijer et al., 2019, Hartford et al., 2021]. The third strategy assumes the *Plurality rule assumption*, which means that the number of valid IVs is larger than any number of invalid IVs with the same ratio estimator limit [Guo et al., 2018, Windmeijer et al., 2021]. The last strategy assumes the *Two-Valid IVs assumption*, which requires that the number of valid IVs is greater than or equal to 2, and the *Rank-faithfulness assumption*, which states that the probability distribution P is rank-faithful to a directed acyclic graph $\mathcal{G}$ if every rank constraint on a sub-covariance matrix that holds in P is entailed by every linear structural model with respect to $\mathcal{G}$ [Silva and Shimizu, 2017, Xie et al., 2022, Cheng et al., 2023]. Although these methods have been used in various fields, they assumed that the one-directional causal relationship between X and Y is known and may fail to handle scenarios where bi-directional relationships are present.

Recently, Darrous et al. [2021] proposed a latent heritable confounder MR method to estimate bi-directional causal effects with a hierarchical prior on the true parameters. However, their method is sensitive to prior misspecification. Later, Li and Ye [2022] introduced a focusing framework to test bi-directional causal effects under the *noise distribution of the effect estimates assumption*, which is exciting. However, this assumption is strictly parameterized (See Condition 1 in [Li and Ye, 2022] for more details). Moreover, they focus on the two-sample MR model that assumes homogeneity across samples, whereas we consider the one-sample MR model. See Appendix A for more details.

In this paper, we aim to investigate the identifiability of the one-sample bi-directional MR model and to provide an estimation method. Specifically, we make the following contributions:

1. We present sufficient and necessary conditions for the identifiability of the bi-directional MR model, enabling both valid IV sets for each direction and the causal effects of interests to be correctly identified.
2. We propose a practical and effective cluster fusion-like algorithm for unbiased estimation. This algorithm correctly identifies which IVs are valid, determines the causal directions to which the valid IV sets belong, and estimates the bi-directional causal effects.
3. Extensive experiments demonstrate the efficacy of the proposed algorithms in MR models.

2 Model Definition and IV Estimator

2.1 Bi-Directional MR Causal Models

Suppose we have n independent samples $(X_i, Y_i, \mathbf{G}_i)$ from the distribution of $(X, Y, \mathbf{G})$, where $X \in \mathbb{R}$ and $Y \in \mathbb{R}$ is a pair of phenotypes of interest, and $\mathbf{G} = (G_1, G_2, \ldots, G_g)^\intercal \in \mathbb{R}^g$ denotes measured genetic variants, which may include invalid IVs. Analogous to Li and Ye [2022], for each sample, indexed by i, the phenotype X_i is taken as a linear function of the phenotype Y_i, genetic variants $\mathbf{G}_i$, and an error term ε_{X_i}, while phenotype Y_i is modeled as a linear function of the phenotype X_i, genetic variants $\mathbf{G}_i$, and an error term ε_{Y_i}. Without loss of generality, we assume that all variables have a zero mean (otherwise can be centered). Specifically, the generating process of the data is given below:

$$\begin{aligned} X &= Y\beta_{Y\to X} + \mathbf{G}^\intercal \boldsymbol{\gamma}_X + \varepsilon_X, \\ Y &= X\beta_{X\to Y} + \mathbf{G}^\intercal \boldsymbol{\gamma}_Y + \varepsilon_Y, \end{aligned} \tag{1}$$

where $\beta_{Y\to X}$ is the causal effect of Y on X and $\beta_{X\to Y}$ is that of X on Y. $\boldsymbol{\gamma}_X = (\gamma_{X,1}, ..., \gamma_{X,g})^\intercal$ and $\boldsymbol{\gamma}_Y = (\gamma_{Y,1}, ..., \gamma_{Y,g})^\intercal$ are the direct effects of genetic variants $\mathbf{G}$ on X and Y, respectively. Note that ε_X and ε_Y are error terms that are correlated due to unmeasured confounders $\mathbf{U}$ between X and Y. Besides, there may exist a single genetic variant $G_i \in \mathbf{G}$ with both $\gamma_{X,i} \neq 0$ and $\gamma_{Y,i} \neq 0$, which implies that G_i also has a direct pathway to the outcome, violating Assumption A2 [*Exclusion Restriction*]. Like Li and Ye [2022], we here restrict the independence between any two genetic variants in $\mathbf{G}$ (i.e., genetic variants are randomized). In Section 5, we discuss the situation where this restriction is violated. Unlike Li and Ye [2022], we allow genetic variants to cause unmeasured confounders (partially violating Assumption A3 [*Randomness*]).

Following Hausman [1983], we assume that $\beta_{X\to Y}\beta_{Y\to X} \neq 1$. Then let $\Delta = 1/(1-\beta_{X\to Y}\beta_{Y\to X})$, Eq.(1) can be reorganized to avoid recursive formulations as follows:

$$\begin{aligned} X &= (\mathbf{G}^\intercal \boldsymbol{\gamma}_X + \mathbf{G}^\intercal \boldsymbol{\gamma}_Y \beta_{Y\to X} + \varepsilon_X + \varepsilon_Y \beta_{Y\to X})\Delta, \\ Y &= (\mathbf{G}^\intercal \boldsymbol{\gamma}_X \beta_{X\to Y} + \mathbf{G}^\intercal \boldsymbol{\gamma}_Y + \varepsilon_X \beta_{X\to Y} + \varepsilon_Y)\Delta. \end{aligned} \tag{2}$$

If $\beta_{X\to Y}\beta_{Y\to X} = 1$, the causal effects $\beta_{X\to Y}$ and $\beta_{Y\to X}$ are not identifiable, even in the presence of a valid IV.

Goal. In this paper, we aim to address whether the bi-directional MR model in Eq.(1) is identifiable; that is, whether we can estimate the causal effects $\beta_{X\to Y}$ and $\beta_{Y\to X}$ given infinite data, even without prior knowledge about which candidate IVs are valid or invalid.

2.2 IV Estimator

In this section, we briefly describe the classical IV estimator, the two-stage least squares (TSLS) estimator, which is capable of consistently estimating the causal effects $\beta_{X\to Y}$ and $\beta_{Y\to X}$ of interest in the above bi-directional MR causal model of Eq.(1) when the valid IVs are known [Wooldridge, 2010]. We denote by $\mathbf{G}_{\mathcal{V}}^{X\to Y}$ the set consisting of all valid IVs in $\mathbf{G}$ relative to $X \to Y$, and $\mathbf{G}_{\mathcal{I}}^{X\to Y}$ the set that consists of at least one invalid IV in $\mathbf{G}$ relative to $X \to Y$. Similar notations are applied to the inverse causal relationship $Y \to X$, i.e., $\mathbf{G}_{\mathcal{V}}^{Y\to X}$ and $\mathbf{G}_{\mathcal{I}}^{Y\to X}$.

Proposition 1 (Two Stage Least Square (TSLS) Estimator)**.** *Assume the system is a linear bi-directional causal model 1. For a given causal relationship $X \to Y$ in the system, the causal effect of X on Y can be identified by*

$$\hat{\beta}_{X\to Y} = \left[X^\intercal \mathbf{P} X\right]^{-1} X^\intercal \mathbf{P} Y = \beta_{X\to Y}, \tag{3}$$

where $\mathbf{P} = (\mathbf{G}_{\mathcal{V}}^{X\to Y})^\intercal \left[\mathbf{G}_{\mathcal{V}}^{X\to Y}(\mathbf{G}_{\mathcal{V}}^{X\to Y})^\intercal\right]^{-1} \mathbf{G}_{\mathcal{V}}^{X\to Y}$ is the projection matrix.

Remark 1. *Note that, when utilizing the TSLS estimator, the causal effect is biased if the candidate set $\mathbf{G}$ includes invalid IVs. For instance, consider the causal relationship $X \to Y$, given an invalid IV set $\mathbf{G}_{\mathcal{I}}^{X\to Y}$, the causal effect of X on Y is given by*

$$\hat{\beta}_{X\to Y} = \left[X^\intercal \tilde{\mathbf{P}} X\right]^{-1} X^\intercal \tilde{\mathbf{P}} Y \quad = \beta_{X\to Y} + \underbrace{\left[X^\intercal \tilde{\mathbf{P}} X\right]^{-1} X^\intercal \tilde{\mathbf{P}} (\mathbf{G}^\intercal \boldsymbol{\gamma}_Y + \varepsilon_Y)}_{\beta_{bias}},$$

where $\tilde{\mathbf{P}} = (\mathbf{G}_{\mathcal{I}}^{X\to Y})^\intercal \left[\mathbf{G}_{\mathcal{I}}^{X\to Y}(\mathbf{G}_{\mathcal{I}}^{X\to Y})^\intercal\right]^{-1} \mathbf{G}_{\mathcal{I}}^{X\to Y}$.

In the remaining of the paper, we denote such a procedure by $\hat{\beta}_{X\to Y} = \mathrm{TSLS}(X, Y, \mathbf{G}^{X\to Y})$. Similarly, for causal relationship $Y \to X$, one can also have the corresponding causal effect of Y on X given the set of IVs, i.e., $\hat{\beta}_{Y\to X} = \mathrm{TSLS}(Y, X, \mathbf{G}^{Y\to X})$. For details about the proof of Proposition 1 and Remark 1, please refer to Appendix G.1 and G.2.

3 Identifiability of Bi-Directional MR Model

In this section, we first show by a simple example that the valid and invalid IV sets can impose different constraints. Then, we formulate these constraints and present the necessary and sufficient conditions that render the model identifiable.

3.1 A Motivating Example

Figure 2 gives an illustration of our basic idea. Suppose there are 2 valid IVs, i.e., G_1 and G_3, and 3 invalid IVs, i.e., G_2, G_4 and G_5, relative to the causal relationship $X \to Y$. For the inverse $Y \to X$, identical conclusions can be derived. Assume the generating process of X and Y follows Eq.(1), where specifically we set all variables to have a zero mean and unit variance and $X = Y\beta_{Y\to X} + G_1\gamma_{X,1} + G_2\gamma_{X,2} + G_3\gamma_{X,3} + G_4\gamma_{X,4} + G_5\gamma_{X,5} + \varepsilon_X$, and $Y = X\beta_{X\to Y} + G_2\gamma_{Y,2} + G_4\gamma_{Y,4} + G_5\gamma_{Y,5} + \varepsilon_Y$, where $\beta_{X\to Y} = \beta_{Y\to X} = 0.6, \gamma_{X,1} = \gamma_{X,2} = \gamma_{X,3} = 1, \gamma_{X,4} = 1.8, \gamma_{X,5} = 1.2, \gamma_{Y,2} = 0.5, \gamma_{Y,4} = 0.6, \gamma_{Y,5} = 0.3$.

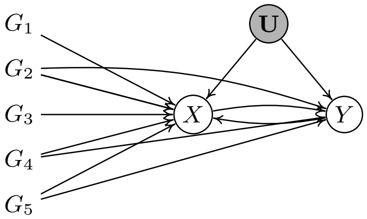


Figure 2: An illustrative example where valid and invalid IV sets induce distinct constraints, where $\mathbf{G}_{\mathcal{V}}^{X\to Y} = (G_1, G_3)^\intercal$ is a valid IV set, while $\mathbf{G}_{\mathcal{I}}^{X\to Y} = (G_2, G_4, G_5)^\intercal$ is invalid due to pathways $G_2 \to Y$, $G_4 \to Y$ and $G_5 \to Y$.

Interestingly, we have the following observations:

Observation 1. Given a valid IV set where there are at least two IVs , e.g., $\mathbf{G}_{\mathcal{V}}^{X\to Y} = (G_1, G_3)^\intercal$, we have:

$$\operatorname{corr}(Y - X\omega_{\{G_3\}}, G_1) = 0, \qquad \operatorname{corr}(Y - X\omega_{\{G_1\}}, G_3) = 0,$$

where $\operatorname{corr}(\cdot)$ denotes the Pearson's correlation coefficient between two random variables, and $\omega_{\{G_i\}} = \operatorname{TSLS}(X, Y, \{G_i\})$ with $i \in \{1, 3\}$.

Observation 2. However, given an invalid IV set, e,g., $\mathbf{G}_{\mathcal{I}}^{X\to Y} = (G_2, G_4, G_5)^\intercal$, we have:

$$\operatorname{corr}(Y - X\omega_{\{G_4,G_5\}}, G_2) \neq 0, \operatorname{corr}(Y - X\omega_{\{G_2,G_5\}}, G_4) \neq 0, \operatorname{corr}(Y - X\omega_{\{G_2,G_4\}}, G_5) \neq 0,$$

where $\omega_{\{G_i,G_j\}} = \operatorname{TSLS}(X, Y, \{G_i, G_j\})$ with $i \neq j$ and $i, j \in \{2, 4, 5\}$.

Based on these two observations, we can see that the valid and invalid IV sets entail clearly different constraints regarding the correlation coefficients[3], which inspires us to further derive our identification analysis. For details about the observations, please refer to Appendix C.

3.2 Main Identification Results

We begin with the following definition and the main assumptions.

Definition 1. *(Pseudo-Residual) Let $\mathbb{G}$ be a subset of candidate genetic variants. A pseudo-residual of $\{X, Y\}$ relative to $\mathbb{G}$ is defined as*

$$\mathcal{PR}_{(X,Y\,|\,\mathbb{G})} := Y - X\omega_{\mathbb{G}}, \tag{4}$$

where $\omega_{\mathbb{G}} = \operatorname{TSLS}(X, Y, \mathbb{G})$.

This "pseudo-residual" is applied to measure the uncorrelated relationship with some genetic variants. Note that concepts to "pseudo-residual" have been developed to address different tasks [Drton and Richardson, 2004, Chen et al., 2017, Cai et al., 2019, Xie et al., 2020], but our formalization is different from theirs in terms of the parameter $\omega_{\mathbb{G}}$. To the best of our knowledge, it has not been realized that the uncorrelated property involving such pseudo-residuals reflects the validity of the IVs in the bi-directional MR causal model (see Propositions 2 $\sim$ 3).

As analyzed by Chu et al. [2001], within the framework of linear models, a variable being a valid IV imposes no constraints on the joint marginal distribution of the observed variables. In other words, there is no available test to determine whether a variable is a valid IV without making further assumptions. Therefore, we introduce the following assumption.

Assumption 1 (Valid IV Set). *For a given causal relationship (if the relationship exists), there exists a valid IV set that consists of at least two valid IVs. For example, for the causal relationship $X \to Y$, $|\mathbf{G}_{\mathcal{V}}^{X\to Y}| \geq 2$.*

[3] Please note that these constraints can be tested easily by observed data.

Assumption 1 is the same as in [Silva and Shimizu, 2017, Cheng et al., 2023] if the model is a one-directional MR model. Notice that this assumption is much milder than the *Majority rule* assumption [Kang et al., 2016, Bowden et al., 2016, Windmeijer et al., 2019, Hartford et al., 2021] and *Plurality rule* assumption [Guo et al., 2018, Windmeijer et al., 2021]: Assumption 1 does not rely on the total number of genetic variants, while *Majority rule* and *Plurality rule* assumptions do.

We now show that under Assumption 1, one can identify the class of invalid IV sets.

Proposition 2 (Identifying Invalid IV Sets)**.** *Let $\mathbb{G} = \{G_1, \dots, G_p\}, p \geq 2$ be a subset of candidate genetic variants $\mathbf{G}$. Suppose that Assumption 1 and the size of participants $n \to \infty$ hold. If there exists a $G_j \in \mathbb{G}$ such that,*

$$\operatorname{corr}(\mathcal{PR}_{(X,Y \,|\, \mathbb{G} \setminus G_j)}, G_j) \neq 0, \tag{5}$$

then $\mathbb{G}$ is an invalid IV set for any one of the causal relationships.

Proposition 2 is valuable when given a set of genetic variants but lack prior knowledge of the validity of IV sets. By testing specific correlations in Eq.(5), we can conclude that the current IV set is invalid.

Example 1. *Consider the example in Figure 2. Suppose $\mathbb{G} = \{G_1, G_2\}$, according to Proposition 2 we have $\operatorname{corr}(\mathcal{PR}_{(X,Y \,|\, \{G_2\})}, G_1) \neq 0$. Thus $\mathbb{G}$ is an invalid IV set.*

One may naturally raise the following question: Can all the invalid IV sets be identified by Proposition 2? In other words, can we identify all the valid IV sets? Unfortunately, Assumption 1 is an insufficient condition for identifying the sets of valid IVs. See an illustrative example below.

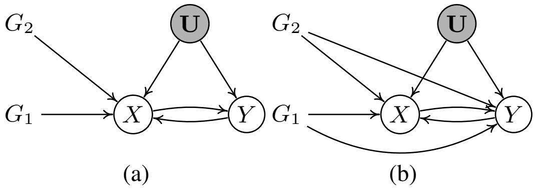


Figure 3: An illustrative example that valid and invalid IV sets may induce the same constraints in Eq.(5) of Proposition 2, where $\{G_1, G_2\}$ is the set of valid IVs in (a), while invalid in (b). It implies Assumption 1 is not sufficient to find valid IV sets.

Example 2 (Counterexample)**.** *Consider the example in Figure 3. Suppose $\mathbb{G} = \{G_1, G_2\}$. In subgraph (a), for $G_1 \in \mathbb{G}$, according to Proposition 2 we obtain*

$$\operatorname{corr}(\mathcal{PR}_{(X,Y \,|\, \{G_2\})}, G_1) = 0 \tag{6}$$

Similarly, for $G_2 \in \mathbb{G}$, we have

$$\operatorname{corr}(\mathcal{PR}_{(X,Y \,|\, \{G_1\})}, G_2) = 0 \tag{7}$$

In subgraph (b), for $G_1 \in \mathbb{G}$, we check the condition of Proposition 2 and obtain

$$\operatorname{corr}(\mathcal{PR}_{(X,Y \,|\, \{G_2\})}, G_1) = \frac{\gamma_{Y,1}\gamma_{X,2} - \gamma_{Y,2}\gamma_{X,1}}{\beta_{Y \to X}\gamma_{Y,2} + \gamma_{X,2}}. \tag{8}$$

Similarly, for $G_2 \in \mathbb{G}$, we have

$$\operatorname{corr}(\mathcal{PR}_{(X,Y \,|\, \{G_1\})}, G_2) = \frac{\gamma_{Y,2}\gamma_{X,1} - \gamma_{Y,1}\gamma_{X,2}}{\beta_{Y \to X}\gamma_{Y,1} + \gamma_{X,1}}. \tag{9}$$

We know that $\{G_1, G_2\}$ is an invalid IV set in this case. However, if the proportion of effects of G_1 on X and Y is equal to the proportion of the effects of G_2 on X and Y, i.e., $\gamma_{X,1}\gamma_{Y,2} = \gamma_{Y,1}\gamma_{X,2}$, we have

$$\operatorname{corr}(\mathcal{PR}_{(X,Y \,|\, \{G_2\})}, G_1) = 0, \qquad \operatorname{corr}(\mathcal{PR}_{(X,Y \,|\, \{G_1\})}, G_2) = 0,$$

which is consistent with the conclusion of subgraph (a). These observations imply that one can not identify valid IV sets under only Assumption 1.

To give sufficient conditions for identifying valid IV sets, we first introduce the following assumption.

Assumption 2 (Generic Identifiability)**.** *For a given MR causal model, parameters γ and β live in a set of Lebesgue measure non-zero.*

In other words, Assumption 2 specifically implies that given a general subset of candidate genetic variants $\mathbb{G}$, there exists a $G_j \in \mathbb{G}$ that satisfies $|\sum_{G_i \in \mathbb{G}/G_j} \bar{\beta}_i cov(G_i, G_i)[(\gamma_{X,i} + \gamma_{X,U}\gamma_{U,i})(\gamma_{Y,j} + \gamma_{Y,U}\gamma_{U,j}) - (\gamma_{Y,i} + \gamma_{Y,U}\gamma_{U,i})(\gamma_{X,j} + \gamma_{X,U}\gamma_{U,j})]| \neq 0$, where $\bar{\beta}_i \neq 0$ is the estimated coefficient between G_i and X. For instance, in Example 2, such an assumption simplifies to $\gamma_{X,1}\gamma_{Y,2} \neq \gamma_{Y,1}\gamma_{X,2}$. Whenever $\gamma_{X,1}\gamma_{Y,2} = \gamma_{Y,1}\gamma_{X,2}$, parameters γ and β would fall into a set of Lebesgue measure zero, rendering non-identifiable of the model. It is worth noting that in real life, although we cannot obtain the ground truths of causal effects between variables, especially when latent confounders are involved, Assumption 2 is generally satisfied. This is because the set of conditions to violate it occupies a very small portion of the entire space.

With Assumption 2, we now derive sufficient conditions for generic identifiability in Proposition 3.

Proposition 3 (Identifying Valid IV Sets)**.** *Let $\mathbb{G} = \{G_1, \ldots, G_p\}, p \geq 2$ be a subset of candidate genetic variants $\mathbf{G}$. Suppose that Assumptions 1 and 2, and the size of participants $n \to \infty$ hold. If each $G_j \in \mathbb{G}$ satisfies*

$$\mathrm{corr}(\mathcal{PR}_{(X,Y\,|\,\mathbb{G}\setminus G_j)}, G_j) = 0, \tag{10}$$

then $\mathbb{G}$ is a proper valid IV set for one of the causal relationships, i.e., $\mathbb{G} \subseteq \mathbf{G}_{\mathcal{V}}^{X\to Y}$ or $\mathbb{G} \subseteq \mathbf{G}_{\mathcal{V}}^{Y\to X}$.

Proposition 3 indicates that, under Assumptions 1 and 2, we are able to identify a subset that consists of valid IVs for one of the relationships, from the candidate genetic variants $\mathbf{G}$. Here, it should be noted that in a bi-directional MR model (with both $\beta_{X\to Y} \neq 0$ and $\beta_{Y\to X} \neq 0$), one cannot determine whether the identified IV set $\mathbb{G}$ is related to the causal relationship $X \to Y$ or $Y \to X$. To address this, we here introduce the following conditions that allow the estimated valid IV sets to determine the direction.

Assumption 3. *In a bi-directional MR model, for a given causal relationship $X \to Y$, $\beta^2_{\mathrm{X\to Y}} \cdot Var(X) < Var(Y)$. Similarly, for a given causal relationship $Y \to X$, $\beta^2_{\mathrm{Y\to X}} \cdot Var(Y) \leq Var(X)$.*

Assumption 3 is a very natural condition that one expects to hold for the unique identifiability of valid IVs for the bi-directional model. This assumption is often reasonable in MR models as discussed in Xue and Pan [2020]. One may refer to Pages 4∼5 in Xue and Pan [2020] for more details.

Proposition 4 (Identifying Direction of Causal Influences)**.** *Suppose Assumption 3 holds. Given a valid IV set denoted as $\mathbb{G}$, if each $G_j \in \mathbb{G}$ satisfies the condition $|\mathrm{corr}(G_j, Y)/\mathrm{corr}(G_j, X)| < 1$, then $\mathbb{G}$ is a valid IV set for the causal relationship $X \to Y$, i.e., $\mathbb{G} \subseteq \mathbf{G}_{\mathcal{V}}^{X\to Y}$. Conversely, if this condition is not satisfied, $\mathbb{G}$ is a valid IV set for the causal relationship $Y \to X$, i.e., $\mathbb{G} \subseteq \mathbf{G}_{\mathcal{V}}^{Y\to X}$.*

Proposition 4 indicates that, under Assumption 3, it is possible to ascertain the directional orientation of the identified IV sets. Thus, with Propositions 2∼4, we have sufficient and necessary conditions under which the bi-directional MR model is fully identifiable, formalized as follows:

Theorem 1 (Identifiability of Bi-directional MR model)**.** *Suppose that Assumptions 1 ∼ 3, and the size of participants $n \to \infty$ hold, the Bi-directional MR model is fully identifiable, which includes the identification of valid IV sets, the causal relationships the identified sets relate to, the causal directions between X and Y, and the causal effects of X on Y as well as of Y on X.*

4 PReBiM Algorithm

In this section, we leverage the above theoretical results and propose a data-driven algorithm, PReBiM (**P**seudo-**Re**sidual-based **Bi**-directional **MR**), for estimating the causal effects of interest. It contains two key steps, finding valid IV sets (Step I), and inferring causal direction and estimating the causal effects given the identified valid IV sets (Step II). The algorithm is designed with the following rules, which are proved correct: (1) valid IV sets can be correctly discovered given the measured genetic variants (Section 4.1), and (2) the causal direction and causal effects can be uniquely identified (Section 4.2). The entire process is summarized in Algorithm 1.

Algorithm 1 PReBiM

```
Input: A dataset of measured genetic variants $\mathbf{G} = (G_1, ..., G_g)^\intercal$, two phenotypes $X$ and $Y$,
    significance level $\alpha$, and parameter $W$, maximum number of IVs to consider.
Valid IV sets $\mathcal{V} \leftarrow$ FindValidIVSets($\mathbf{G}$, $X$, $Y$, $\alpha$, $W$);                ▷ Step I
($\hat{\beta}_{X\to Y}, \hat{\beta}_{Y\to X}$) $\leftarrow$ InferCausalDirectionEffects($X$, $Y$, $\mathcal{V}$);      ▷ Step II
Output: $\hat{\beta}_{X\to Y}$ and $\hat{\beta}_{Y\to X}$, the causal effects of $X$ on $Y$ and $Y$ on $X$, respectively.
```

4.1 Step I: Finding Valid IV Sets

Propositions 2 and 3 have paved the way to distinguish the invalid and valid IV sets, respectively. This enables us to use a cluster fusion-like method to discover the valid IV sets[4]. To improve the algorithm's effectiveness with a finite sample size, especially when the pool of candidate genetic variants $\mathbf{G}$ is substantial, we introduce a parameter W, representing the maximum number of instrumental variables (IVs) to consider. This approach aims to circumvent the necessity of identifying the largest IV set within the collection, thereby minimizing the need for IV validity testing.

The basic process is provided in Algorithm 2. Due to limited space, the specific details of algorithm execution are provided in Appendix E. In practice, we check for the valid IV test, i.e., Eq.(10), with the Pearson Correlation Test using the Fisher transformation [Anderson, 2003], denoted by PCT.

Algorithm 2 FindValidIVSets

```
Input: A dataset of measured genetic variants $\mathbf{G} = (G_1, ..., G_g)^\intercal$, two phenotypes $X$ and $Y$,
    significance level $\alpha$, and parameter $W$, maximum number of IVs to consider.
1. Initialize valid IV sets $\mathcal{V} = \emptyset$ and $\tilde{\mathbf{G}} = \mathbf{G}$.
2. Find $\mathcal{V}_{new}$ with $|\mathbb{G}| = 2$ according to minimize the sum of correlation between pseudo-residual
    $\mathcal{PR}_{(X,Y\,|\,\mathbb{G}\setminus G_i)}$ and $G_i$, where $G_i \in \mathbb{G}$ and $\mathbb{G} \in \tilde{\mathbf{G}}$.
3. Update $\mathcal{V}_{\text{new}}$ by incrementally adding genetic variant $G_k$ until it is impossible to add variables
    without passing PCT or the length of the set $\mathcal{V}_{\text{new}}$ reaches our predetermined threshold $W$.
4. Repeat Step 1 and Step 2 to find another $\mathcal{V}'_{\text{new}}$. If $\mathcal{V}$ is empty, add $\mathcal{V}'_{\text{new}}$ to $\mathcal{V}$. If not, and
    the combined set $\{\mathcal{V} \cup \mathcal{V}'_{\text{new}}\}$ passes the PCT, merge them; otherwise, discard $\mathcal{V}'_{\text{new}}$. Stop the
    iteration when $\mathcal{V}$ contains two sets of IVs or when there is one or fewer genetic variants left in
    $\tilde{\mathbf{G}}$.
Output: $\mathcal{V}$, a set that collects the valid IV sets.
```

4.2 Step II: Inferring Causal Direction and Estimating the Causal Effects

In this section, we infer the causal direction and estimate the causal effects given the identified valid IV sets. The basic process is provided in Algorithm 3. Due to limited space, the specific details of algorithm execution are provided in Appendix F.

Algorithm 3 InferCausalDirectionEffects

```
Input: Two phenotypes $X$ and $Y$, Valid IV sets $\mathcal{V}$.
1. Infer the causal direction corresponding to the valid IV set $\mathcal{V}$ based on Proposition 4.
2. Calculate the final causal effects $\hat{\beta}_{X\to Y}$ and $\hat{\beta}_{Y\to X}$ by $\mathrm{TSLS}(\cdot)$.
Output: $\hat{\beta}_{X\to Y}$ and $\hat{\beta}_{Y\to X}$
```

4.3 Correctness of PReBiM Algorithm

In this section, we show that, in the large sample limit, for the causal relationships of interest $X \leftrightarrow Y$, the causal effects $\hat{\beta}_{X\to Y}$ and $\hat{\beta}_{Y\to X}$ obtained through the proposed method are unbiased.

Theorem 2 (Correctness)**.** *Assume that the data $\{X, Y\}$ and $\mathbf{G}$ strictly follow Eq.*(1) *and Assumptions 1 $\sim$ 3 hold. Given infinite samples, the PReBiM algorithm outputs the true causal effects $\beta_{X\to Y}$ and $\beta_{Y\to X}$ correctly.*

4.4 Complexity of PReBiM Algorithm

We give the computational complexity analysis as follows. First, the complexity of finding a valid IV set $\mathcal{V}_{new}$ of length 2 is $\mathcal{O}\left(2\binom{g}{2}\right)$, where g is the number of IVs. Then, the complexity of expanding $\mathcal{V}_{new}$ to the length W is $\mathcal{O}\left(\frac{(2g-W-2)(W-1)}{2}\right)$, where W is the maximum length of the IV set. For finding additional valid IV sets, the number of loops, t, must satisfy $t \leq \frac{g-4}{W}$. The complexity of finding the second valid IV set of length W is given by $\mathcal{O}\left(\sum_{k=1}^{t}\left(2\binom{g-kW}{2} + \frac{(2g-(2k+1)W-2)(W-1)}{2}\right) + 2W(t-1) + 1\right)$.

[4] A cluster is considered a valid IV set, and the term "fusion-like" refers to the specific process of identifying and merging these clusters.

Therefore, the total computational complexity of the PReBiM algorithm is $\mathcal{O}\left(\sum_{k=0}^{t}\left(2\binom{g-kW}{2}+\frac{(2g-(2k+1)W-2)(W-1)}{2}\right)+2W(t-1)+1\right)$.

5 Discussion

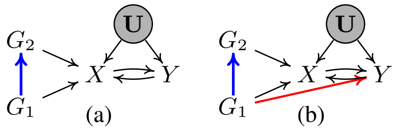


Figure 4: Simple examples, where $\{G_1, G_2\}$ is a valid IV set in (a), whereas invalid in (b).

The preceding sections demonstrate that a valid IV set can be identified when any two genetic variants in $\mathbf{G}$ are independent. In this section, we explore whether the main results of Propositions 2 and 3 remain applicable when some genetic variants in $\mathbf{G}$ are dependent. As shown in Figure 4 (b), we evaluate the condition of Proposition 2 and find that $\mathrm{corr}(\mathcal{PR}_{(X,Y,|G_2)}, G_1) \neq 0$ and $\mathrm{corr}(\mathcal{PR}_{(X,Y,|G_1)}, G_2) \neq 0$. This indicates that $\{G_1, G_2\}$ is an invalid IV set. Conversely, in Figure 4 (a), when assessing the condition of Proposition 3, we observe that $\mathrm{corr}(\mathcal{PR}_{(X,Y,|G_2)}, G_1) = 0$ and $\mathrm{corr}(\mathcal{PR}_{(X,Y,|G_1)}, G_2) = 0$, suggesting that $\{G_1, G_2\}$ is a valid IV set. Consequently, it is interesting to note that even with such dependence between genetic variants, our main results may still be effective in identifying valid IV sets. In Appendix H.1 $\sim$ H.2, we further demonstrate the practicality of our method for this example. As for the complex scenarios where there is confounding among genetic variants or between the genetic variants and some phenotype, or where there exist genetic variants that are associated with another phenotype while this phenotype causes X and Y, we leave them into our future work.

6 Experimental Results

In this section, we conduct various simulation studies to evaluate the performance of the proposed PReBiM method. The methods we compare against are: 1) NAIVE, the least-squares regression method; 2) MR-Egger [Bowden et al., 2015]; 3) sisVIVE algorithm [Kang et al., 2016] [5]; 4) IV-TETRAD algorithm[Silva and Shimizu, 2017] [6]; 5) TSHT algorithm [Guo et al., 2018] [7]; and 6) PReBiM, our method. The second method, MR-Egger, is specifically for MR studies with invalid IVs. The last four methods are capable of handling the one-sample MR model in the presence of unmeasured confounders. Our source code can be found in the Supplementary Materials.

Experimental setup. To compare the performance of these methods in a realistic setting, analogous to Slob and Burgess [2020], the genetic variants are modeled as Single Nucleotide Polymorphisms (SNPs), with a varying minor allele frequency maf_j, and take values 0, 1, or 2. The minor allele frequencies are drawn from a uniform distribution. Specifically, the data generation process for the bi-directional model is as follows:

$$
\begin{aligned}
U &= \mathbf{G}^{\intercal}\gamma_U + \varepsilon_1, && (11)\\
X &= Y\beta_{Y\to X} + \mathbf{G}^{\intercal}\gamma_X + U\gamma_{X,U} + \varepsilon_2, && (12)\\
Y &= X\beta_{X\to Y} + \mathbf{G}^{\intercal}\gamma_Y + U\gamma_{Y,U} + \varepsilon_3, && (13)\\
G_{ij} &\sim \mathit{Binomial}(2, maf_j),\ maf_j \sim \mathcal{U}(0.1, 0.5), && (14)
\end{aligned}
$$

where the error terms $\varepsilon_1, \varepsilon_2, \varepsilon_3$ each follow an independent normal distribution with mean 0 and unit variance. The causal effects $\beta_{Y\to X}$ and $\beta_{X\to Y}$ are generated from a uniform distribution between $[-1, -0.5] \cup [0.5, 1]$. Note that by setting $\beta_{Y\to X} = 0$ in Eq.(12), the data generation process for the one directional model can be obtained.

We here conducted experiments with the following tasks.

- **T1: Sensitivity to Sample Size.** We evaluated the impact of different sample sizes: $n = 2k, 5k$, and $10k$, where k equals $1,000$.

[5] For sisVIVE algorithm, we used the implementations in the R sisVIVE package, which can be downloaded at `https://cran.r-project.org/web/packages/sisVIVE/`.

[6] For IV-TETRAD method, we used the implementations in the R package, which can be downloaded at `https://www.homepages.ucl.ac.uk/~ucgtrbd/code/iv_discovery/`.

[7] For the TSHT algorithm, we used the implementations in the R RobustIV package, which can be downloaded at `https://cran.r-project.org/web/packages/RobustIV/`.

- **T2: Sensitivity to the Number of Valid IVs.** We explored three distinct IV combination scenarios: $\mathcal{S}(2, 2, 6)$, $\mathcal{S}(3, 3, 8)$, and $\mathcal{S}(4, 4, 10)$. The first two elements in the parentheses represent the number of valid instrumental variables for causal relationships $X \to Y$ and $Y \to X$, respectively. The last element in the parentheses represents the total number of genetic variants.

For a comprehensive analysis, we examined the data from the Bi-directional MR model and the One-directional MR model, as detailed in Section 6.1 and 6.2, respectively. For each experimental setting, we repeated the simulation 500 times and averaged the results.

Metrics: We adopted the following evaluation metrics to evaluate the results of all methods.

- **(i) Correct-Selecting Rate (CSR)**: the number of correctly identified valid IVs divided by the total number of genetic variants, for the direction $X \to Y$ or $Y \to X$.
- **(ii) Mean Squared Error (MSE)**: The squared difference between the estimated causal effect and the true causal effect.

To further validate the effectiveness and practicality of our algorithm, we have expanded our experimental settings to include additional scenarios such as small sample sizes, different numbers of valid IVs, large-scale datasets, and cases where all IVs are valid. Within these settings, we compare our algorithm with the five aforementioned methods to assess algorithm performance. Detailed experimental results are provided in Appendix H.3 $\sim$ H.6.

6.1 Evaluation on Bi-Directional MR Model

In this section, we evaluate the performance of six methods on bi-directional MR data, i.e., $\beta_{X \to Y} \neq 0$ and $\beta_{Y \to X} \neq 0$. Table 1 summarizes the results of metrics CSR and MSE in a bi-directional MR model with various sample sizes. It is noted that sisVIVE, IV-TETRAD, and TSHT are not specifically designed for the bi-directional model, so we run them in both forward and reverse directions to obtain the corresponding results. As expected, our proposed PReBiM method gives the best results in all three scenarios, with all sample sizes, indicating that it can identify valid IVs and derive consistent causal effects from purely observational data, even without knowledge of the causal direction between X and Y. Furthermore, the performance of the other three comparison methods of selecting IVs was poor, indicating that they are not suitable for bi-directional MR models. The MSE of the NAIVE method does not tend toward 0, indicating that if unobserved confounding is not considered, the estimated causal effect is certainly biased. Similarly, the MSE of MR-Egger is poor if estimated with all instrumental variables.

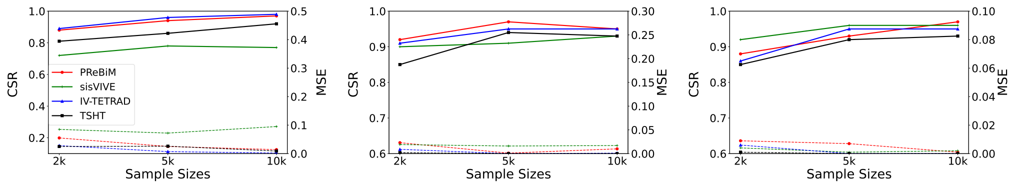
Table 1: Performance comparison of NAIVE, MR-Egger, sisVIVE, IV-TETRAD, TSHT, and PReBiM in estimating bi-directional MR models across various sample sizes and three scenarios.

		$\mathcal{S}(2, 2, 6)$				$\mathcal{S}(3, 3, 8)$				$\mathcal{S}(4, 4, 10)$			
		$X \to Y$		$Y \to X$		$X \to Y$		$Y \to X$		$X \to Y$		$Y \to X$	
Size	Algorithm	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**
2k	NAIVE	-	0.354	-	0.349	-	0.351	-	0.320	-	0.335	-	0.304
	MR-Egger	-	0.800	-	0.734	-	0.571	-	0.569	-	0.457	-	0.494
	sisVIVE	0.30	0.398	0.25	0.447	0.34	0.379	0.32	0.379	0.37	0.346	0.38	0.330
	IV-TETRAD	0.60	0.859	0.30	0.867	0.60	0.773	0.28	0.782	0.67	0.688	0.23	0.622
	TSHT	0.07	0.606	0.06	0.660	0.07	0.549	0.07	0.613	0.12	0.653	0.11	0.689
	PReBiM	**0.85**	**0.046**	**0.85**	**0.070**	**0.89**	**0.083**	**0.87**	**0.075**	**0.88**	**0.039**	**0.89**	**0.057**
5k	NAIVE	-	0.350	-	0.339	-	0.347	-	0.319	-	0.357	-	0.306
	MR-Egger	-	0.737	-	0.836	-	0.604	-	0.508	-	0.515	-	0.520
	sisVIVE	0.32	0.421	0.30	0.407	0.33	0.378	0.35	0.384	0.39	0.439	0.38	0.365
	IV-TETRAD	0.62	0.804	0.31	0.844	0.63	0.836	0.29	0.659	0.67	0.686	0.25	0.640
	TSHT	0.04	0.544	0.06	0.565	0.08	0.528	0.06	0.570	0.10	0.549	0.07	0.541
	PReBiM	**0.93**	**0.020**	**0.91**	**0.027**	**0.90**	**0.019**	**0.92**	**0.020**	**0.90**	**0.009**	**0.91**	**0.010**
10k	NAIVE	-	0.366	-	0.348	-	0.319	-	0.342	-	0.349	-	0.300
	MR-Egger	-	0.800	-	0.763	-	0.524	-	0.620	-	0.487	-	0.424
	sisVIVE	0.31	0.457	0.29	0.503	0.37	0.383	0.31	0.394	0.41	0.399	0.41	0.328
	IV-TETRAD	0.64	0.811	0.31	0.804	0.64	0.748	0.29	0.696	0.71	0.635	0.24	0.577
	TSHT	0.04	0.449	0.02	0.475	0.05	0.525	0.05	0.466	0.05	0.479	0.07	0.498
	PReBiM	**0.95**	**0.044**	**0.93**	**0.018**	**0.93**	**0.026**	**0.93**	**0.039**	**0.93**	**0.027**	**0.94**	**0.011**

Note: The symbol "$-$" means methods have no output. "↑" means a higher value is better, and vice versa.

6.2 Evaluation on One-Directional MR Model

In this section, we evaluate the performance of six methods on one-directional MR data, e.g., $\beta_{X \to Y} \neq 0$ and $\beta_{Y \to X} = 0$. For fairness, we assume that the causal direction $X \to Y$ is known for all methods. Figure 5 summarizes the results of metrics CSR (solid lines) and MSE (dashed lines) for all methods in a one-directional MR model with different scenarios. As expected, the metrics CSR and MSE of our method approach the expected value as the sample size increases. The overall results are comparable to the IV-TETRAD algorithm and superior to the sisVIVE algorithm and TSHT algorithm. This is because our method, similar to the IV-TETRAD method, requires fewer valid IVs in the system (at least 2), whereas the other two methods require the number of valid IVs that are related to the overall genetic variants, namely the majority rule assumption (over 50% of the candidate IVs are valid) and plurality rule assumption (the number of valid IVs is larger than any number of invalid IVs). It has been noted that under the IV-TETRAD method for scenario $\mathcal{S}(2,0,6)$, the metrics CSR and MSE outperform our method. This is because the IV-TETRAD method requires a predetermined number of IV sets to be specified in advance, and in this case, we have predetermined the number of valid IVs for it. However, our method does not have this prior information.



(a) $\mathcal{S}(2,0,6)$ (b) $\mathcal{S}(3,0,8)$ (c) $\mathcal{S}(4,0,10)$

Figure 5: Performance comparison of sisVIVE, IV-TETRAD, TSHT, and PReBiM in estimating one-directional MR models across various sample sizes and three scenarios.

6.3 Evaluation on Real-World Data

We first apply our method to analyze the bi-directional causal relationships between obesity and vitamin D status using the GWAS data from Vimaleswaran et al. [2013]. Note that the original data only consists of summary data, and thus we generate individual-level data based on the data generation mechanism described in Eq.(1). The data we used comprises 16 related SNPs as candidate IVs, including seven SNPs associated with obesity (BMI): rs9939609 (FTO), rs2867125 (TMEM18), rs4074134 (BDNF), rs7647305 (ETV5), rs7138803 (FAIM2), rs3101336 (NEGR1), and rs10938397 (GNPDA2); four SNPs related to 25-hydroxyvitamin D (25(OH)D): rs12785878 (DHCR7), rs10741657 (CYP2R1), rs2282679 (GC), and rs6013897 (CYP24A1); and five SNPs associated with BMI and 25(OH)D: rs4498364, rs1381660, rs4549702, rs12760109, and rs77913838. We observed that FTO and FAIM2 serve as valid IVs for the $X \to Y$, while DHCR7 and CYP24A1 are valid IVs for the $Y \to X$, with estimated causal effects of -1.15 and -0.05, respectively. These findings are consistent with those findings in [Vimaleswaran et al., 2013].

Next, we apply our method to analyze the causal effect of institutions on economic development using the Colonial Origins dataset from [Acemoglu et al., 2001]. The data includes eight candidate IVs: absolute latitude (lat_abst), the density of European settlements in 1900 (euro1900), the level of democracy in 1900 (democ1), constitutional constraints in 1900 (cons1), the timing of industrialization (indtime), democracy in 2000 (democ00a), constitutional constraints in 2000 (cons00a), and log-transformed European settler mortality rates (logem4). Our method identifies euro1900 and logem4 as valid IVs, with an estimated causal effect of 0.861, which is consistent with the findings reported in Acemoglu et al. [2001].

7 Conclusion

We investigated the identifiability conditions for the bi-directional MR model using purely observational data. First, we proposed a testable constraint for identifying valid IV sets, and we demonstrated that, under appropriate conditions, these valid IV sets can be partially or even fully identified by checking the proposed constraints. Experimental results on simulation data further verified the effectiveness of our algorithm. Currently, we assume that genetic variants are randomized. Allowing for general dependent genetic variants is a direction for future work. Additionally, while we focus on a linear bi-directional MR model, in future research, we will generalize to address nonlinear or even more complex data.

Acknowledgements

FX would like to acknowledge the support by the Natural Science Foundation of China (62306019). YZ would like to acknowledge the support of the Beijing Municipal Education Commission Science and Technology Program General Project (KM202410011016). We appreciate the constructive comments from all anonymous reviewers, which greatly helped to improve this paper.

References

Daron Acemoglu, Simon Johnson, and James A Robinson. The colonial origins of comparative development: An empirical investigation. *American economic review*, 91(5):1369–1401, 2001.

TW Anderson. An introduction to multivariate statistical analysis. *Wiley series in probability and statistics Show all parts in this series*, 2003.

Jack Bowden, George Davey Smith, and Stephen Burgess. Mendelian randomization with invalid instruments: effect estimation and bias detection through egger regression. *International journal of epidemiology*, 44(2):512–525, 2015.

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(4):304–314, 2016.

Roger J Bowden and Darrell A Turkington. *Instrumental variables*. Number 8. Cambridge university press, 1990.

Ben Brumpton, Eleanor Sanderson, Karl Heilbron, Fernando Pires Hartwig, Sean Harrison, Gunnhild Åberge Vie, Yoonsu Cho, Laura D Howe, Amanda Hughes, Dorret I Boomsma, et al. Avoiding dynastic, assortative mating, and population stratification biases in mendelian randomization through within-family analyses. *Nature communications*, 11(1):3519, 2020.

Stephen Burgess, Dylan S Small, and Simon G Thompson. A review of instrumental variable estimators for mendelian randomization. *Statistical methods in medical research*, 26(5):2333–2355, 2017.

Ruichu Cai, Feng Xie, Clark Glymour, Zhifeng Hao, and Kun Zhang. Triad constraints for learning causal structure of latent variables. *Advances in neural information processing systems*, 32, 2019.

Robert Carreras-Torres, Mattias Johansson, Valerie Gaborieau, Philip C Haycock, Kaitlin H Wade, Caroline L Relton, Richard M Martin, George Davey Smith, and Paul Brennan. The role of obesity, type 2 diabetes, and metabolic factors in pancreatic cancer: a mendelian randomization study. *JNCI: Journal of the National Cancer Institute*, 109(9), 2017.

Robert Carreras-Torres, Mattias Johansson, Philip C Haycock, Caroline L Relton, George Davey Smith, Paul Brennan, and Richard M Martin. Role of obesity in smoking behaviour: Mendelian randomisation study in uk biobank. *bmj*, 361, 2018.

Bryant Chen, Daniel Kumor, and Elias Bareinboim. Identification and model testing in linear structural equation models using auxiliary variables. In *ICML*, pages 757–766, 2017.

Debo Cheng, Jiuyong Li, Lin Liu, Kui Yu, Thuc Duy Le, and Jixue Liu. Discovering ancestral instrumental variables for causal inference from observational data. *IEEE Transactions on Neural Networks and Learning Systems*, pages 1–11, 2023.

Tianjiao Chu, Richard Scheines, and Peter Spirtes. Semi-instrumental variables: a test for instrument admissibility. In *Proceedings of the Seventeenth conference on Uncertainty in artificial intelligence*, pages 83–90, 2001.

Gabriel Cuellar-Partida, Yi Lu, Pik Fang Kho, Alex W Hewitt, H-Erich Wichmann, Seyhan Yazar, Dwight Stambolian, Joan E Bailey-Wilson, Robert Wojciechowski, Jie Jin Wang, et al. Assessing the genetic predisposition of education on myopia: a mendelian randomization study. *Genetic epidemiology*, 40(1):66–72, 2016.

Liza Darrous, Ninon Mounier, and Zoltán Kutalik. Simultaneous estimation of bi-directional causal effects and heritable confounding from gwas summary statistics. *Nature communications*, 12(1): 7274, 2021.

George Davey Smith and Shah Ebrahim. mendelian randomization: can genetic epidemiology contribute to understanding environmental determinants of disease? *International journal of epidemiology*, 32(1):1–22, 2003.

Mathias Drton and Thomas S Richardson. Iterative conditional fitting for gaussian ancestral graph models. In *UAI*, pages 130–137. AUAI Press, 2004.

Brian A Ference, Faisal Majeed, Raju Penumetcha, John M Flack, and Robert D Brook. Effect of naturally random allocation to lower low-density lipoprotein cholesterol on the risk of coronary heart disease mediated by polymorphisms in npc1l1, hmgcr, or both: a 2× 2 factorial mendelian randomization study. *Journal of the American College of Cardiology*, 65(15):1552–1561, 2015.

Xue Gao, Ling-Xian Meng, Kai-Li Ma, Jie Liang, Hui Wang, Qian Gao, and Tong Wang. The bidirectional causal relationships of insomnia with five major psychiatric disorders: a mendelian randomization study. *European Psychiatry*, 60:79–85, 2019.

Arthur S Goldberger. Structural equation methods in the social sciences. *Econometrica: Journal of the Econometric Society*, pages 979–1001, 1972.

Zijian Guo, Hyunseung Kang, T Tony Cai, and Dylan S Small. Confidence intervals for causal effects with invalid instruments by using two-stage hard thresholding with voting. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 80(4):793–815, 2018.

Jason S Hartford, Victor Veitch, Dhanya Sridhar, and Kevin Leyton-Brown. Valid causal inference with (some) invalid instruments. In *International Conference on Machine Learning*, pages 4096–4106. PMLR, 2021.

Jerry A Hausman. Specification and estimation of simultaneous equation models. *Handbook of econometrics*, 1:391–448, 1983.

Miguel A Hernán and James M Robins. Instruments for causal inference: an epidemiologist's dream? *Epidemiology*, pages 360–372, 2006.

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.

Debbie A Lawlor, Roger M Harbord, Jonathan AC Sterne, Nic Timpson, and George Davey Smith. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Statistics in medicine*, 27(8):1133–1163, 2008.

Gloria Hoi-Yee Li, Ching-Lung Cheung, Philip Chun-Ming Au, Kathryn Choon-Beng Tan, Ian Chi-Kei Wong, and Pak-Chung Sham. Positive effects of low ldl-c and statins on bone mineral density: an integrated epidemiological observation analysis and mendelian randomization study. *International Journal of Epidemiology*, 49(4):1221–1235, 2020.

Sai Li and Ting Ye. A focusing framework for testing bi-directional causal effects with gwas summary data. *arXiv preprint arXiv:2203.06887*, 2022.

Edwin P Martens, Wiebe R Pestman, Anthonius de Boer, Svetlana V Belitser, and Olaf H Klungel. Instrumental variables: application and limitations. *Epidemiology*, pages 260–267, 2006.

Lauren E Mokry, Stephanie Ross, Omar S Ahmad, Vincenzo Forgetta, George Davey Smith, Aaron Leong, Celia MT Greenwood, George Thanassoulis, and J Brent Richards. Vitamin d and risk of multiple sclerosis: a mendelian randomization study. *PLoS medicine*, 12(8):e1001866, 2015.

Joris M Mooij, Dominik Janzing, and Bernhard Schölkopf. From ordinary differential equations to structural causal models: the deterministic case. *arXiv preprint arXiv:1304.7920*, 2013.

RC Richmond, KH Wade, Laura Corbin, Jack Bowden, Gibran Hemani, NJ Timpson, and G Davey Smith. Investigating the role of insulin in increased adiposity: bi-directional mendelian randomization study. *BioRxiv*, page 155739, 2017.

Rebecca C Richmond and George Davey Smith. Mendelian randomization: concepts and scope. *Cold Spring Harbor Perspectives in Medicine*, 12(1):a040501, 2022.

Eleanor Sanderson, M Maria Glymour, Michael V Holmes, Hyunseung Kang, Jean Morrison, Marcus R Munafò, Tom Palmer, C Mary Schooling, Chris Wallace, Qingyuan Zhao, et al. Mendelian randomization. *Nature Reviews Methods Primers*, 2(1):6, 2022.

Ricardo Silva and Shohei Shimizu. Learning instrumental variables with structural and non-gaussianity assumptions. *Journal of Machine Learning Research*, 18(120):1–49, 2017.

Eric AW Slob and Stephen Burgess. A comparison of robust mendelian randomization methods using summary data. *Genetic epidemiology*, 44(4):313–329, 2020.

Duncan C Thomas and David V Conti. Commentary: the concept of mendelian randomization. *International journal of epidemiology*, 33(1):21–25, 2004.

Karani S Vimaleswaran, Diane J Berry, Chen Lu, Emmi Tikkanen, Stefan Pilz, Linda T Hiraki, Jason D Cooper, Zari Dastani, Rui Li, Denise K Houston, et al. Causal relationship between obesity and vitamin d status: bi-directional mendelian randomization analysis of multiple cohorts. *PLoS medicine*, 10(2):e1001383, 2013.

Frank Windmeijer, Helmut Farbmacher, Neil Davies, and George Davey Smith. On the use of the lasso for instrumental variables estimation with some invalid instruments. *Journal of the American Statistical Association*, 114(527):1339–1350, 2019.

Frank Windmeijer, Xiaoran Liang, Fernando P Hartwig, and Jack Bowden. The confidence interval method for selecting valid instrumental variables. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 83(4):752–776, 2021.

Jeffrey M Wooldridge. *Econometric analysis of cross section and panel data*. 2010.

Philip G Wright. *Tariff on animal and vegetable oils*. Macmillan Company, New York, 1928.

Feng Xie, Ruichu Cai, Biwei Huang, Clark Glymour, Zhifeng Hao, and Kun Zhang. Generalized independent noise conditionfor estimating latent variable causal graphs. In *Advances in Neural Information Processing Systems*, pages 14891–14902, 2020.

Feng Xie, Yangbo He, Zhi Geng, Zhengming Chen, Ru Hou, and Kun Zhang. Testability of instrumental variables in linear non-gaussian acyclic causal models. *Entropy*, 24(4):512, 2022.

Haoran Xue and Wei Pan. Inferring causal direction between two traits in the presence of horizontal pleiotropy with gwas summary data. *PLoS genetics*, 16(11):e1009105, 2020.

Haoran Xue and Wei Pan. Robust inference of bi-directional causal relationships in presence of correlated pleiotropy with gwas summary data. *PLoS genetics*, 18(5):e1010205, 2022.

Guorui Zhao, Zhe Lu, Yaoyao Sun, Zhewei Kang, Xiaoyang Feng, Yundan Liao, Junyuan Sun, Yuyanan Zhang, Yu Huang, and Weihua Yue. Dissecting the causal association between social or physical inactivity and depression: a bidirectional two-sample mendelian randomization study. *Translational Psychiatry*, 13(1):194, 2023.

A More Details on MR

The basic goal of epidemiologic studies is to assess the effect of changes in exposure on outcomes. The causal effect of exposure on outcome is often different from the observed correlation due to confounding factors. Correlations between exposure and outcome cannot be used as reliable evidence for inferring causality. In contrast, **Mendelian Randomization** (MR) studies use genetic variants to infer the causal effect of exposure on outcome. The idea behind MR studies is to find a genetic variant (or multiple genetic variants) that is associated with exposure but not with other confounders and that does not directly affect the outcome. Such a genetic variant in principle fulfills the basic assumptions of instrumental variables (IVs). It is then used to assess the causal effect of the exposure on the outcome [Thomas and Conti, 2004]. Since the assumptions of IVs cannot be fully tested and may be violated during IVs' selection, a number of methods have emerged to identify valid IVs.

MR studies can be conducted using a single sample, i.e., **one-sample Mendelian Randomization**, in which individuals are tested for genetic variation, exposure, and outcome in the same population. On the contrary, in **two-sample Mendelian Randomization**, the association between genetic variation and exposure is estimated in one dataset while that between genetic variation and outcome is estimated in another dataset. Compared with the Two-sample MR, one-sample MR provides more direct evidence by eliminating potential biases that can arise from individual-level data, which turns out to be more meaningful yet challenging.

Additionally, most existing MR methods assume a one-directional causal relationship between exposure and outcome, whereas bi-directional relationships are ubiquitous in real-life scenarios. For instance, there exist bi-directional relationships between obesity and vitamin D status [Vimaleswaran et al., 2013], body mass index (BMI) and type 2 diabetes (T2D), diastolic blood pressure and stroke [Xue and Pan, 2022], insomnia and five major psychiatric disorders [Gao et al., 2019], smoking and BMI [Carreras-Torres et al., 2018], etc. It is thus desirable to take further research on bi-directional MR. **Bi-directional Mendelian Randomization** assesses not only the causal effect of the exposure on the outcome but also the effect of the outcome on the exposure. To achieve this, valid IVs for both the exposure and the outcome are needed. However, this is tough because genetic variants associated with the exposure are often also associated with the outcome, and vice versa. Our goal here is to identify and differentiate valid IVs for each direction within a one-sample MR framework and infer bi-directional causal effects.

Regarding our bi-directional MR causal model, we give further relative descriptions in the following. **(i)** Similar to Li and Ye [2022], our model in Eq.(1) describes bi-directional causality in equilibrium, and in econometrics, it is known as the simultaneous equation model. According to Hausman [1983], to avoid the recursive formalization, Eq.(1) equivalently is transformed into Eq.(2) with $\beta_{X\to Y}\beta_{Y\to X} \neq 1$. **(ii)** For such a bi-directional (cyclic) structure, Mooij et al. [2013] take an Ordinary Differential Equation (ODEs) perspective and show under which conditions the equilibrium state of a system of the first-order ODEs can be described by a deterministic structural causal model (SCM). This is a very interesting work. Please note that our setting is different from those in Mooij et al. [2013]: our model is motivated by bi-directional MR studies, other than a dynamical system from the control field. Further, due to the specificity of MR studies, we can only obtain the snapshot data or equilibrium data, other than dynamical ones for the treatment, the outcome as well as genetic variants.

B Notation List

Table 2: List of major notations with descriptions.

Notation	**Description**
$\mathbf{U}$	Unmeasured Confounders
$\mathbf{G}$	Genetic variants
$\mathbb{G} \subset \mathbf{G}$	Candidate genetic variants
X	Exposure or treatment
Y	Outcome
n	Sample size
$\boldsymbol{\gamma}_X, \boldsymbol{\gamma}_Y, \boldsymbol{\gamma}_U$	Effects of $\mathbf{G}$ on X, $\mathbf{G}$ on Y, and of $\mathbf{G}$ on U, respectively
Δ	A reduction factor calculated with $1 - \beta_{X\to Y}\beta_{Y\to X}$
$\varepsilon_X, \varepsilon_Y$	Error terms of X, and of Y, respectively
$\beta_{X\to Y}, \beta_{Y\to X}$	True effects of X on Y, and of Y on X, respectively
$\hat{\beta}_{X\to Y}, \hat{\beta}_{Y\to X}$	Estimated causal effects from candidate IVs for the directions $X \to Y$ and $Y \to X$, respectively
$\mathbf{G}_{\mathcal{V}}^{X\to Y}, \mathbf{G}_{\mathcal{V}}^{Y\to X}$	A set consisting of all valid IVs in $\mathbf{G}$ relative to $X \to Y$, and $Y \to X$, respectively
$\mathbf{G}_{\mathcal{I}}^{X\to Y}, \mathbf{G}_{\mathcal{I}}^{Y\to X}$	A set consisting at least one invalid IV in $\mathbf{G}$ relative to $X \to Y$ or $Y \to X$, respectively
$\mathrm{TSLS}(\cdot)$	The procedure of estimating causal effects using two-stage least square method
$\omega_{\mathbb{G}}$	Estimated causal effect derived from $\mathbb{G}$
$\mathcal{PR}_{(X,Y\,\mid\,\mathbb{G}\backslash G_j)}$	Pseudo-residual of $\{X, Y\}$ relative to $\mathbb{G}\backslash G_j$
PCT	Pearson Correlation Test

C More Details on Observations 1 and 2

C.1 Observation 1

Since $\mathbf{G}_{\mathcal{V}}^{X\to Y} = (G_1, G_3)^\intercal$ is a valid IV set, employing G_1 or G_3 in $\mathrm{TSLS}(\cdot)$ entails unbiased causal effects, i.e., $\omega_{\{G_i\}} = \mathrm{TSLS}(X, Y, \{G_i\}) = \beta_{X\to Y}$ with $i \in \{1, 3\}$. Thus, we have,

$$
\begin{aligned}
Y - X\omega_{\{G_1\}} &= Y - X\beta_{X\to Y} = G_2\gamma_{Y,2} + G_4\gamma_{Y,4} + G_5\gamma_{Y,5} + \varepsilon_Y, \\
Y - X\omega_{\{G_3\}} &= Y - X\beta_{X\to Y} = G_2\gamma_{Y,2} + G_4\gamma_{Y,4} + G_5\gamma_{Y,5} + \varepsilon_Y.
\end{aligned}
$$

Because both G_1 and G_3 are valid IVs, they are independent of ε_Y; and any two genetic variants are assumed to be independent of each other, we get,

$$
\begin{aligned}
\mathrm{corr}(Y - X\omega_{\{G_3\}}, G_1) = 0, \\
\mathrm{corr}(Y - X\omega_{\{G_1\}}, G_3) = 0.
\end{aligned}
$$

C.2 Observation 2

Without loss of generality, we here give details about how $\mathrm{corr}(Y - X\omega_{\{G_4,G_5\}}, G_2) \neq 0$ is derived. The other two inequalities could be obtained in the same way. Following the procedure of $\mathrm{TSLS}(\cdot)$, we first get the estimate of X with $\{G_4, G_5\}$, denoted by $\hat{X}$, and obtain $\omega_{\{G_4,G_5\}}$ using $\hat{X}$ and Y.

$$
\begin{aligned}
\hat{X} &= G_4\hat{\beta}_4 + G_5\hat{\beta}_5 \\
&= G_4(\gamma_{X,4} + \gamma_{Y,4}\beta_{Y\to X})\Delta + G_5(\gamma_{X,5} + \gamma_{Y,5}\beta_{Y\to X})\Delta \\
&= (G_4\gamma_{X,4} + G_4\gamma_{Y,4}\beta_{Y\to X} + G_5\gamma_{X,5} + G_5\gamma_{Y,5}\beta_{Y\to X})\Delta,
\end{aligned}
$$

where since G_4 and G_5 are neither correlated with the latent confounder U nor the other IVs as shown in Figure 2, the second equality holds. Then, we could get the estimate of $\omega_{\{G_4,G_5\}}$, i.e.,

$$
\begin{aligned}
\omega_{\{G_4,G_5\}} = &\frac{cov(G_4, G_4)(\gamma_{X,4} + \gamma_{Y,4}\beta_{Y\to X})(\gamma_{Y,4} + \gamma_{X,4}\beta_{X\to Y})}{cov(G_4, G_4)(\gamma_{X,4} + \gamma_{Y,4}\beta_{Y\to X})^2 + cov(G_5, G_5)(\gamma_{X,5} + \gamma_{Y,5}\beta_{Y\to X})^2} \\
&+ \frac{cov(G_5, G_5)(\gamma_{X,5} + \gamma_{Y,5}\beta_{Y\to X})(\gamma_{Y,5} + \gamma_{X,5}\beta_{X\to Y})}{cov(G_4, G_4)(\gamma_{X,4} + \gamma_{Y,4}\beta_{Y\to X})^2 + cov(G_5, G_5)(\gamma_{X,5} + \gamma_{Y,5}\beta_{Y\to X})^2}.
\end{aligned}
$$

Then we get,

$$\begin{aligned}
&\operatorname{corr}(Y - X\omega_{\{G_4,G_5\}}, G_2)\\
&= (\gamma_{Y,2} + \gamma_{X,2}\beta_{X\to Y})\Delta - (\gamma_{X,2} + \gamma_{Y,2}\beta_{Y\to X})\Delta\omega_{\{G_4,G_5\}}\\
&= [\gamma_{X,2}(\beta_{X\to Y} - \omega_{\{G_4,G_5\}}) + \gamma_{Y,2}(1 - \beta_{Y\to X}\omega_{\{G_4,G_5\}})]\Delta.
\end{aligned}$$

Since,

$$\begin{aligned}
&\beta_{X\to Y} - \omega_{\{G_4,G_5\}}\\
=&\ \frac{\beta_{X\to Y}(\gamma_{X,4} + \gamma_{Y,4}\beta_{Y\to X})^2 cov(G_4,G_4) + \beta_{X\to Y}(\gamma_{X,5} + \gamma_{Y,5}\beta_{Y\to X})^2 cov(G_5,G_5)}{(\gamma_{X,4} + \gamma_{Y,4}\beta_{Y\to X})^2 cov(G_4,G_4) + (\gamma_{X,5} + \gamma_{Y,5}\beta_{Y\to X})^2 cov(G_5,G_5)}\\
-&\ \frac{(\gamma_{X,4} + \gamma_{Y,4}\beta_{Y\to X})(\gamma_{Y,4} + \gamma_{X,4}\beta_{X\to Y}) cov(G_4,G_4)}{(\gamma_{X,4} + \gamma_{Y,4}\beta_{Y\to X})^2 cov(G_4,G_4) + (\gamma_{X,5} + \gamma_{Y,5}\beta_{Y\to X})^2 cov(G_5,G_5)}\\
-&\ \frac{(\gamma_{X,5} + \gamma_{Y,5}\beta_{Y\to X})(\gamma_{Y,5} + \gamma_{X,5}\beta_{X\to Y}) cov(G_5,G_5)}{(\gamma_{X,4} + \gamma_{Y,4}\beta_{Y\to X})^2 cov(G_4,G_4) + (\gamma_{X,5} + \gamma_{Y,5}\beta_{Y\to X})^2 cov(G_5,G_5)}\\
=&\ \frac{(\beta_{X\to Y}\beta_{Y\to X} - 1)[\gamma_{Y,4}(\gamma_{X,4} + \gamma_{Y,4}\beta_{Y\to X}) + \gamma_{Y,5}(\gamma_{X,5} + \gamma_{Y,5}\beta_{Y\to X})]}{(\gamma_{X,4} + \gamma_{Y,4}\beta_{Y\to X})^2 + (\gamma_{X,5} + \gamma_{Y,5}\beta_{Y\to X})^2}\\
=&\ \frac{(\beta_{X\to Y}\beta_{Y\to X} - 1)(\mathbf{C}_{44}\Gamma_{X,4}\gamma_{Y,4} + \mathbf{C}_{55}\Gamma_{X,5}\gamma_{Y,5})}{\mathbf{C}_{44}\Gamma^2_{X,4} + \mathbf{C}_{55}\Gamma^2_{X,5}},
\end{aligned}$$

and

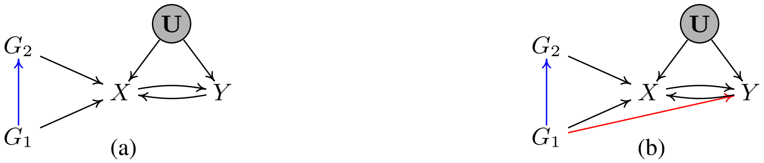
$$\begin{aligned}
&1 - \beta_{Y\to X}\omega_{\{G_4,G_5\}}\\
=&\ \frac{(\gamma_{X,4} + \gamma_{Y,4}\beta_{Y\to X})^2 cov(G_4,G_4) + (\gamma_{X,5} + \gamma_{Y,5}\beta_{Y\to X})^2 cov(G_5,G_5)}{(\gamma_{X,4} + \gamma_{Y,4}\beta_{Y\to X})^2 cov(G_4,G_4) + (\gamma_{X,5} + \gamma_{Y,5}\beta_{Y\to X})^2 cov(G_5,G_5)}\\
-&\ \frac{\beta_{Y\to X}(\gamma_{X,4} + \gamma_{Y,4}\beta_{Y\to X})(\gamma_{Y,4} + \gamma_{X,4}\beta_{X\to Y}) cov(G_4,G_4)}{(\gamma_{X,4} + \gamma_{Y,4}\beta_{Y\to X})^2 cov(G_4,G_4) + (\gamma_{X,5} + \gamma_{Y,5}\beta_{Y\to X})^2 cov(G_5,G_5)}\\
-&\ \frac{\beta_{Y\to X}(\gamma_{X,5} + \gamma_{Y,5}\beta_{Y\to X})(\gamma_{Y,5} + \gamma_{X,5}\beta_{X\to Y}) cov(G_5,G_5)}{(\gamma_{X,4} + \gamma_{Y,4}\beta_{Y\to X})^2 cov(G_4,G_4) + (\gamma_{X,5} + \gamma_{Y,5}\beta_{Y\to X})^2 cov(G_5,G_5)}\\
=&\ \frac{[\gamma_{X,4}(\gamma_{X,4} + \gamma_{Y,4}\beta_{Y\to X}) cov(G_4,G_4) + \gamma_{X,5}(\gamma_{X,5} + \gamma_{Y,5}\beta_{Y\to X}) cov(G_5,G_5)]\Delta}{(\gamma_{X,4} + \gamma_{Y,4}\beta_{Y\to X})^2 cov(G_4,G_4) + (\gamma_{X,5} + \gamma_{Y,5}\beta_{Y\to X})^2 cov(G_5,G_5)}\\
=&\ \frac{\Delta(\mathbf{C}_{44}\Gamma_{X,4}\gamma_{X,4} + \mathbf{C}_{55}\Gamma_{X,5}\gamma_{X,5})}{\mathbf{C}_{44}\Gamma^2_{X,4} + \mathbf{C}_{44}\Gamma^2_{X,5}},
\end{aligned}$$

Where we define $\Gamma_{X,i} = \gamma_{X,i} + \gamma_{Y,i}\beta_{Y\to X}$, $\Gamma_{Y,j} = \gamma_{Y,j} + \gamma_{X,j}\beta_{X\to Y}$, $\mathbf{C}_{ij} = cov(G_i, G_j)$ and $\Delta \triangleq 1 - \beta_{Y\to X}\beta_{X\to Y}$. we can finally obtain $\operatorname{corr}(Y - X\omega_{\{G_4,G_5\}}, G_2)$, that is,

$$\begin{aligned}
&\operatorname{corr}(Y - X\omega_{\{G_4,G_5\}}, G_2)\\
=&\ \frac{\gamma_{X,2}(\beta_{X\to Y}\beta_{Y\to X} - 1)(\mathbf{C}_{44}\Gamma_{X,4}\gamma_{Y,4} + \mathbf{C}_{55}\Gamma_{X,5}\gamma_{Y,5})\Delta}{\mathbf{C}_{44}\Gamma^2_{X,4} + \mathbf{C}_{55}\Gamma^2_{X,5}}\\
+&\ \frac{\gamma_{Y,2}(1 - \beta_{Y\to X}\beta_{X\to Y})(\mathbf{C}_{44}\Gamma_{X,4}\gamma_{X,4} + \mathbf{C}_{55}\Gamma_{X,5}\gamma_{X,5})\Delta}{\mathbf{C}_{44}\Gamma^2_{X,4} + \mathbf{C}_{55}\Gamma^2_{X,5}}\\
=&\ \frac{\mathbf{C}_{44}\Gamma_{X,4}(\gamma_{X,2}\gamma_{Y,4} - \gamma_{X,4}\gamma_{Y,2}) + \mathbf{C}_{55}\Gamma_{X,5}(\gamma_{X,2}\gamma_{Y,5} - \gamma_{X,5}\gamma_{Y,2})}{\mathbf{C}_{44}\Gamma^2_{X,4} + \mathbf{C}_{55}\Gamma^2_{X,5}} \neq 0.
\end{aligned}$$

D More Details on the Example Provided in Section 5

Figure 6 gives an illustration of our idea, demonstrating that even when IVs are correlated, we can still identify them as valid IVs using our proposed method. In subgraph (a), there are two valid IVs: G_1 and G_2. However, in subgraph (b), these two IVs become invalid as G_1 is correlated with Y, rendering them invalid.



(a)

(b)

Figure 6: A simple example, where the set $\{G_1, G_2\}$ is a valid IV set in subgraph (a), whereas it is not valid in subgraph (b).

Assume the generating process of X and Y in subgraph (a) follows:

$$\begin{aligned} X &= Y\beta_{Y\to X} + G_1\gamma_{X,1} + G_2\gamma_{X,2} + \varepsilon_X, \\ Y &= X\beta_{X\to Y} + \varepsilon_Y, \\ G_2 &= G_1\gamma_{1,2} + \varepsilon_2. \end{aligned} \tag{15}$$

where ε_X and ε_Y are **correlated**, and ε_2 represents the independent error term.
For $G_1 \in \mathbb{G}$, we check the condition of Proposition 3:

$$\begin{aligned} \omega_{\{G_1\}} &= \text{TSLS}(X, Y, \{G_1\}) = \frac{\text{cov}(Y, G_1)}{\text{cov}(X, G_1)} = \beta_{X\to Y} + \frac{\text{cov}(\varepsilon_Y, G_1)}{\text{cov}(X, G_1)} = \beta_{X\to Y} \\ \mathcal{PR}_{(X,Y\,|\,\{G_1\})} &= Y - \omega_{\{G_1\}}X = \varepsilon_Y \\ \text{corr}(\mathcal{PR}_{(X,Y\,|\,\{G_1\})}, G_2) &= 0 \end{aligned}$$

Similarly, for $G_2 \in \mathbb{G}$, we check the condition of Proposition 3:

$$\begin{aligned} \omega_{\{G_2\}} &= \text{TSLS}(X, Y, \{G_2\}) = \frac{\text{cov}(Y, G_2)}{\text{cov}(X, G_2)} = \beta_{X\to Y} + \frac{\text{cov}(\varepsilon_Y, G_2)}{\text{cov}(X, G_2)} = \beta_{X\to Y} \\ \mathcal{PR}_{(X,Y\,|\,\{G_2\})} &= Y - \omega_{\{G_2\}}X = \varepsilon_Y \\ \text{corr}(\mathcal{PR}_{(X,Y\,|\,\{G_2\})}, G_1) &= 0 \end{aligned}$$

Assume the generating process of X and Y in subgraph (b) follows Equation 16:

$$\begin{aligned} X &= Y\beta_{Y\to X} + G_1\gamma_{X,1} + G_2\gamma_{X,2} + \varepsilon_X, \\ Y &= X\beta_{X\to Y} + G_1\gamma_{Y,1} + \varepsilon_Y, \\ G_2 &= G_1\gamma_{1,2} + \varepsilon_2. \end{aligned} \tag{16}$$

where ε_X and ε_Y are **correlated**, and ε_2 represents the independent error term.
Then, Equation 16 can be reorganized to avoid recursive formulations as follows:

$$\begin{aligned} X &= \Delta\left(G_1(\gamma_{X,1} + \gamma_{1,2}\gamma_{X,2} + \gamma_{Y,1}\beta_{Y\to X}) + \varepsilon_2\gamma_{X,2} + \varepsilon_X + \varepsilon_Y\beta_{Y\to X}\right) \\ &= \Delta\left(G_1\Gamma_{X,1} + \varepsilon_2\gamma_{X,2} + \varepsilon_X + \varepsilon_Y\beta_{Y\to X}\right) \\ Y &= \Delta\left(G_1(\gamma_{Y,1} + \beta_{X\to Y}(\gamma_{X,1} + \gamma_{X,2}\gamma_{1,2})) + \varepsilon_2\gamma_{X,2}\beta_{X\to Y} + \varepsilon_X\beta_{X\to Y} + \varepsilon_Y\right) \\ &= \Delta\left(G_1\Gamma_{Y,1} + \varepsilon_2\gamma_{X,2}\beta_{X\to Y} + \varepsilon_X\beta_{X\to Y} + \varepsilon_Y\right) \end{aligned} \tag{17}$$

where $\Gamma_{X,1} = \gamma_{X,1} + \gamma_{1,2}\gamma_{X,2} + \gamma_{Y,1}\beta_{Y\to X}$ and $\Gamma_{Y,1} = \gamma_{Y,1} + \beta_{X\to Y}(\gamma_{X,1} + \gamma_{X,2}\gamma_{1,2})$. It is noted that $\Gamma_{X,1} \neq 0$ and $\Gamma_{Y,1} \neq 0$.
In subgraph (b), for $G_2 \in \mathbb{G}$, we check the condition of Proposition 3:

$$
\begin{aligned}
\omega_{\{G_2\}} &= \mathrm{TSLS}(X, Y, \{G_2\}) = \frac{\mathrm{cov}(Y, G_2)}{\mathrm{cov}(X, G_2)} = \beta_{X\to Y} + \gamma_{Y,1}\frac{\mathrm{cov}(G_1, G_2)}{\mathrm{cov}(X, G_2)} \\
&= \beta_{X\to Y} + \frac{\gamma_{Y,1}\gamma_{1,2}}{\Delta}\frac{\mathrm{cov}(G_1, G_1)}{\mathrm{cov}(G_1, G_1)(\gamma_{1,2}\Gamma_{X,1}) + \mathrm{cov}(\varepsilon_2, \varepsilon_2)\gamma_{X,2}} \\
&= \beta_{X\to Y} + \frac{\gamma_{Y,1}\gamma_{1,2}}{\Delta}\frac{1}{\gamma_{1,2}\Gamma_{X,1} + \gamma_{X,2}\mathcal{M}}, \\
\mathcal{PR}_{(X,Y\,|\,\{G_2\})} &= Y - \omega_{\{G_2\}}X \\
&= G_1\gamma_{Y,1} + \varepsilon_Y - \frac{\gamma_{Y,1}\gamma_{1,2}}{\Delta}\frac{1}{\gamma_{1,2}\Gamma_{X,1} + \gamma_{X,2}\mathcal{M}}X \\
&= G_1\gamma_{Y,1} + \varepsilon_Y - \frac{\gamma_{Y,1}\gamma_{1,2}(G_1\Gamma_{X,1} + \varepsilon_2\gamma_{X,2} + \varepsilon_X + \varepsilon_Y\beta_{Y\to X})}{\gamma_{1,2}\Gamma_{X,1} + \gamma_{X,2}\mathcal{M}}, \\
\mathrm{corr}(\mathcal{PR}_{(X,Y\,|\,\{G_2\})}, G_1) &= \gamma_{Y,1} - \frac{\gamma_{Y,1}\gamma_{1,2}\Gamma_{X,1}}{\gamma_{1,2}\Gamma_{X,1} + \gamma_{X,2}\mathcal{M}} \\
&= \frac{\gamma_{Y,1}\gamma_{1,2}\Gamma_{X,1} + \gamma_{Y,1}\gamma_{X,2}\mathcal{M} - \gamma_{Y,1}\gamma_{1,2}\Gamma_{X,1}}{\gamma_{1,2}\Gamma_{X,1} + \gamma_{X,2}\mathcal{M}} \\
&= \frac{\gamma_{Y,1}\gamma_{X,2}\mathcal{M}}{\gamma_{1,2}\Gamma_{X,1} + \gamma_{X,2}\mathcal{M}}
\end{aligned}
\tag{18}
$$

where $\mathcal{M} = \frac{\mathrm{cov}(\varepsilon_2,\varepsilon_2)}{\mathrm{cov}(G_1,G_1)} \neq 0$.

Based on these two observations, we can conclude that the two IVs in subgraph (a) can be deemed valid. However, in subgraph (b), they can be deemed invalid.

E More Details on FindValidIVSets Algorithm (in Section 4.1)

It is noteworthy that, to mitigate the unreliability of statistical tests in finite samples, in practice, we choose to take the smallest correlation coefficient to select a valid IV set, as in Line 4 or 10 of Algorithm 4.

Algorithm 4 FindValidIVSets

```
Input: A dataset of measured genetic variants $\mathbf{G} = (G_1, ..., G_g)^\intercal$, two phenotypes $X$ and $Y$,
    significance level $\alpha$, and parameter $W$, maximum number of IVs to consider.
 1: Initialize valid IV sets $\mathcal{V} = \emptyset$ and $\tilde{\mathbf{G}} = \mathbf{G}$.
 2: repeat
 3:   For all subsets $\mathbb{G} \in \tilde{\mathbf{G}}$ with $|\mathbb{G}| = 2$, compute the correlation between pseudo-residual
      $\mathcal{PR}_{(X,Y \,|\, \mathbb{G} \setminus G_i)}$ and $G_i$, where $G_i \in \mathbb{G}$.
 4:   $\mathcal{V}_{new} \leftarrow \arg\min_{\mathbb{G} \in \mathbf{G}} \sum_{i=1}^{2} \mathrm{corr}(\mathcal{PR}_{(X,Y \,|\, \mathbb{G} \setminus G_i)}, G_i)$.
 5:   repeat
 6:     $\tilde{\mathbf{G}}' \leftarrow \tilde{\mathbf{G}}$
 7:     For each variable $G_k \in \tilde{\mathbf{G}}'$, remove all variables from $\tilde{\mathbf{G}}'$ corresponding to those that set
        $\{\mathcal{V}, G_k\}$ fail to the PCT.
 8:     if $\tilde{\mathbf{G}}' \neq \emptyset$ then
 9:       Compute the correlation between pseudo-residual $\mathcal{PR}_{(X,Y \,|\, \mathcal{V})}$ and $G_k$.
10:       $G' \leftarrow \arg\min_{G_k \in \tilde{\mathbf{G}}'} \mathrm{corr}(\mathcal{PR}_{(X,Y \,|\, \mathcal{V})}, G_k)$.
11:       $\mathcal{V}_{new} \leftarrow \mathcal{V}_{new} \cup \{G_k\}$.
12:     else
13:       Break the loop of line 5;
14:     end if
15:   until the length of the set $\mathcal{V}_{new}$ has reached our predefined threshold $W$.
16:   if Set $\mathcal{V} = \emptyset$ then
17:     Add set $\mathcal{V}_{new}$ into $\mathcal{V}$.
18:   else
19:     if Set $\{\mathcal{V} \cup \mathcal{V}_{new}\}$ fail to PCT then
20:       Add set $\mathcal{V}_{new}$ into $\mathcal{V}$.
21:     else
22:       Delete set $\mathcal{V}_{new}$ from $\tilde{\mathbf{G}}$.
23:     end if
24:   end if
25: until $\mathcal{V}$ contains two sets or $|\tilde{\mathbf{G}}| \leq 1$.
Output: $\mathcal{V}$, a set that collects the valid IV sets.
```

F More Details on InferCausalDirectionEffects Algorithm (in Section 4.2)

Algorithm 5 InferCausalDirectionEffects

```
Input: Two phenotypes $X$ and $Y$, Valid IV sets $\mathcal{V}$.
Initialize sets $\mathbf{G}_{\mathcal{V}}^{X\to Y} = \emptyset$ and $\mathbf{G}_{\mathcal{V}}^{Y\to X} = \emptyset$, and the causal effects $\hat{\beta}_{X\to Y} = \emptyset$ and $\hat{\beta}_{Y\to X} = \emptyset$.
for each $G_j \in \mathcal{V}$ do
    if $|\mathrm{corr}(G_j, Y)/\mathrm{corr}(G_j, X)| < 1$ then
        Add $G_j$ into $\mathbf{G}_{\mathcal{V}}^{X\to Y}$;
    else
        Add $G_j$ into $\mathbf{G}_{\mathcal{V}}^{Y\to X}$;
    end if
end for
$\hat{\beta}_{X\to Y} \leftarrow \mathrm{TSLS}(X, Y, \mathbf{G}_{\mathcal{V}}^{X\to Y})$.
$\hat{\beta}_{Y\to X} \leftarrow \mathrm{TSLS}(Y, X, \mathbf{G}_{\mathcal{V}}^{Y\to X})$.
Output: $\hat{\beta}_{X\to Y}$ and $\hat{\beta}_{Y\to X}$
```

G Proofs

G.1 Proof of Proposition 1

Proof. From procedure "two-stage least squares", we obtained the fitted values $\hat{X}$ from the regression in the first stage: $\hat{X} = (\mathbf{G}_{\mathcal{V}}^{X\to Y})^{\intercal}\hat{\alpha}$. According to OLS regression,

$$\begin{aligned}\hat{X} &= (\mathbf{G}_{\mathcal{V}}^{X\to Y})^{\intercal}\left[(\mathbf{G}_{\mathcal{V}}^{X\to Y}(\mathbf{G}_{\mathcal{V}}^{X\to Y})^{\intercal})^{-1}\mathbf{G}_{\mathcal{V}}^{X\to Y}X\right]\\ &= \left[(\mathbf{G}_{\mathcal{V}}^{X\to Y})^{\intercal}(\mathbf{G}_{\mathcal{V}}^{X\to Y}(\mathbf{G}_{\mathcal{V}}^{X\to Y})^{\intercal})^{-1}\mathbf{G}_{\mathcal{V}}^{X\to Y}\right]X\\ &= \mathbf{P}X.\end{aligned}$$

Then run the OLS regression for Y on $\hat{X}$ in second stage: $Y = \hat{\beta}\hat{X}$. where:

$$\begin{aligned}\hat{\beta} &= (\hat{X}^{\intercal}\hat{X})^{-1}(\hat{X}^{\intercal}Y)\\ &= ((\mathbf{P}X)^{\intercal}\mathbf{P}X)^{-1}((\mathbf{P}X)^{\intercal}Y)\\ &= (X^{\intercal}\mathbf{P}X)^{-1}(X^{\intercal}\mathbf{P}Y)\\ &= (X^{\intercal}\mathbf{P}X)^{-1}(X^{\intercal}\mathbf{P})\left(X\beta_{X\to Y} + (\mathbf{G}_{\mathcal{V}}^{X\to Y})^{\intercal}\gamma_Y + \varepsilon_Y\right)\\ &= \beta_{X\to Y} + (X^{\intercal}\mathbf{P}X)^{-1}(X^{\intercal}\mathbf{P}(\mathbf{G}_{\mathcal{V}}^{X\to Y})^{\intercal}\gamma_Y) + (X^{\intercal}\mathbf{P}X)^{-1}(X^{\intercal}\mathbf{P}\varepsilon_Y)\end{aligned}$$

Since $\mathbf{G}_{\mathcal{V}}^{X\to Y}$ is a valid IV set, for $G_j \in \mathbf{G}_{\mathcal{V}}^{X\to Y}$, both $\gamma_{Y,j} = 0$ ($A2$) and $cov(G_j, \varepsilon_Y) = 0$ ($A3$). Hence, we obtained

$$\begin{aligned}&(X^{\intercal}\mathbf{P}X)^{-1}(X^{\intercal}\mathbf{P}(\mathbf{G}_{\mathcal{V}}^{X\to Y})^{\intercal}\gamma_Y) = 0\\ &(X^{\intercal}\mathbf{P}X)^{-1}(X^{\intercal}\mathbf{P}\varepsilon_Y) = (X^{\intercal}\mathbf{P}X)^{-1}(X^{\intercal}(\mathbf{G}_{\mathcal{V}}^{X\to Y})^{\intercal}(\mathbf{G}_{\mathcal{V}}^{X\to Y}(\mathbf{G}_{\mathcal{V}}^{X\to Y})^{\intercal})^{-1}\mathbf{G}_{\mathcal{V}}^{X\to Y}\varepsilon_Y = 0,\end{aligned}$$

which implies that $\hat{\beta} = \beta_{X\to Y}$. □

G.2 Proof of Remark 1

Proof. Similar to G.1, from procedure "two-stage least squares", we obtained the fitted values $\hat{X}$ from the regression in the first stage: $\hat{X} = (\mathbf{G}_{\mathcal{I}}^{X\to Y})^{\intercal}\hat{\alpha}$. According to OLS regression,

$$\begin{aligned}\hat{X} &= (\mathbf{G}_{\mathcal{I}}^{X\to Y})^{\intercal}\left[(\mathbf{G}_{\mathcal{I}}^{X\to Y}(\mathbf{G}_{\mathcal{I}}^{X\to Y})^{\intercal})^{-1}\mathbf{G}_{\mathcal{I}}^{X\to Y}X\right]\\ &= \left[(\mathbf{G}_{\mathcal{I}}^{X\to Y})^{\intercal}(\mathbf{G}_{\mathcal{I}}^{X\to Y}(\mathbf{G}_{\mathcal{I}}^{X\to Y})^{\intercal})^{-1}\mathbf{G}_{\mathcal{I}}^{X\to Y}\right]X\\ &= \tilde{\mathbf{P}}X.\end{aligned}$$

Then run the OLS regression for Y on $\hat{X}$ in second stage: $Y = \hat{\beta}\hat{X}$. where:

$$
\begin{aligned}
\hat{\beta} &= (\hat{X}^\intercal \hat{X})^{-1}(\hat{X}^\intercal Y) \\
&= ((\tilde{\mathbf{P}}X)^\intercal \tilde{\mathbf{P}}X)^{-1}((\tilde{\mathbf{P}}X)^\intercal Y) \\
&= (X^\intercal \tilde{\mathbf{P}}X)^{-1}(X^\intercal \tilde{\mathbf{P}}Y) \\
&= (X^\intercal \tilde{\mathbf{P}}X)^{-1}(X^\intercal \tilde{\mathbf{P}}) \left(X\beta_{X\to Y} + (\mathbf{G}_{\mathcal{I}}^{X\to Y})^\intercal \boldsymbol{\gamma}_Y + \varepsilon_Y\right) \\
&= \beta_{X\to Y} + \underbrace{\left[X^\intercal \tilde{\mathbf{P}}X\right]^{-1} X^\intercal \tilde{\mathbf{P}}(\mathbf{G}_{\mathcal{I}}^{X\to Y})^\intercal \boldsymbol{\gamma}_Y + \varepsilon_Y)}_{\beta_{bias}} \\
&= \beta_{X\to Y} + (X^\intercal \tilde{\mathbf{P}}X)^{-1}(X^\intercal \tilde{\mathbf{P}}(\mathbf{G}_{\mathcal{I}}^{X\to Y})^\intercal \gamma_Y) + (X^\intercal \tilde{\mathbf{P}}X)^{-1}(X^\intercal \tilde{\mathbf{P}}\varepsilon_Y)
\end{aligned}
$$

Since $\mathbf{G}_{\mathcal{I}}^{X\to Y}$ is a valid IV set, for each $G_j \in \mathbf{G}_{\mathcal{I}}^{X\to Y}$, either $\gamma_{Y,j} \neq 0$ ($A2$), or $cov(G_j, \varepsilon_Y) \neq 0$ ($A3$), or both $\gamma_{Y,j} \neq 0$ and $cov(G_j, \varepsilon_Y) \neq 0$ ($A2$ and $A3$).
Hence, we obtained

$$
\begin{aligned}
&(X^\intercal \tilde{\mathbf{P}}X)^{-1}(X^\intercal \tilde{\mathbf{P}}(\mathbf{G}_{\mathcal{I}}^{X\to Y})^\intercal \gamma_Y) \neq 0 \\
&(X^\intercal \tilde{\mathbf{P}}X)^{-1}(X^\intercal \tilde{\mathbf{P}}\varepsilon_Y) = (X^\intercal \tilde{\mathbf{P}}X)^{-1}(X^\intercal (\mathbf{G}_{\mathcal{I}}^{X\to Y})^\intercal (\mathbf{G}_{\mathcal{I}}^{X\to Y}(\mathbf{G}_{\mathcal{I}}^{X\to Y})^\intercal)^{-1}\mathbf{G}_{\mathcal{I}}^{X\to Y}\varepsilon_Y \neq 0,
\end{aligned}
$$

which implies that $\beta_{bias} \neq 0$. That is to say the estimated causal effect $\hat{\beta} = \beta_{X\to Y} + \beta_{bias}$ is biased. □

G.3 Proof of Proposition 2

Proof. We prove it by contradiction, i.e., if $\mathbb{G}$ is a valid IV set for one of the causal relationships, then for each $G_j \in \mathbb{G}$, $\mathrm{corr}(\mathcal{PR}_{(X,Y\,|\,\mathbb{G}\backslash G_j)}, G_j) = 0$. Without loss of generality, we consider the case for $X \to Y$. The proof with the inverse causal relationship can be derived accordingly.

i) assume that $\mathbb{G}$ is the valid IV set relative to the causal relationship $X \to Y$, i.e., $\mathbb{G} \subseteq \mathbf{G}_{\mathcal{V}}^{X\to Y}$. Let G_j be a genetic variant in $\mathbb{G}$. We can see that $\mathbb{G}\backslash G_j$ is also a valid IV set. Because the size of participants $n \to \infty$, and according to the consistent estimator of TSLS, we have

$$\omega_{\{\mathbb{G}\backslash G_j\}} = \mathrm{TSLS}(X, Y, \mathbb{G}\backslash G_j) = \beta_{X\to Y}.$$

Based on Eq.(1), we have

$$\mathcal{PR}_{(X,Y\,|\,\mathbb{G}\backslash G_j)} = Y - X\omega_{\{\mathbb{G}\backslash G_j\}} = \mathbf{G}^\intercal \boldsymbol{\gamma}_Y + \varepsilon_Y$$

Because $\mathbb{G}$ is a valid IV set relative to $X \to Y$, for $G_k \in \mathbf{G}, k \neq j$, either $\gamma_{Y,k} = 0$ (if $G_k \in \mathbb{G}$) or $\mathrm{corr}(G_k, G_j) = 0$ (if $G_k \notin \mathbb{G}$). It is noted that G_k can not be correlated with G_j, otherwise, the genetic variant G_j will dissatisfy $A2$ or $A3$. Hence, we obtain $\mathrm{corr}(\mathbf{G}^\intercal \boldsymbol{\gamma}_Y + \varepsilon_Y, G_j) = 0$, which implies that $\mathrm{corr}(\mathcal{PR}_{(X,Y\,|\,\mathbb{G}\backslash G_j)}, G_j) = 0$.

ii) assume that $\mathbb{G}$ is the valid IV set relative to $Y \to X$, i.e., $\mathbb{G} \subseteq \mathbf{G}_{\mathcal{V}}^{Y\to X}$. Let G_j be a genetic variant in $\mathbb{G}$. We can see that $\mathbb{G}\backslash G_j$ is also a valid IV set relative to $Y \to X$. It is noted that we here still need to verify Eq.(5). According to the TSLS estimator and Eq.(1), we have

$$
\begin{aligned}
\omega_{\{\mathbb{G}\backslash G_j\}} &= \mathrm{TSLS}(X, Y, \mathbb{G}\backslash G_j) \\
&= \left[X^\intercal \tilde{\mathbf{P}}X\right]^{-1} X^\intercal \tilde{\mathbf{P}}Y \\
&= \left[X^\intercal \tilde{\mathbf{P}}X\right]^{-1} X^\intercal \tilde{\mathbf{P}}(1/\beta_{Y\to X})(X - \mathbf{G}^\intercal \boldsymbol{\gamma}_X - \varepsilon_X) \\
&= (1/\beta_{Y\to X})\left(1 - \left[X^\intercal \tilde{\mathbf{P}}X\right]^{-1} X^\intercal \tilde{\mathbf{P}}(\mathbf{G}^\intercal \boldsymbol{\gamma}_X + \varepsilon_X)\right), \\
&= \left(1 - \left[X^\intercal \tilde{\mathbf{P}}X\right]^{-1} X^\intercal \tilde{\mathbf{P}}(\mathbf{G}^\intercal \boldsymbol{\gamma}_X + \varepsilon_X)\right)\beta_{Y\to X}^{-1},
\end{aligned}
$$

where $\tilde{\mathbf{P}} = \{\mathbb{G}\backslash G_j\}\left[\{\mathbb{G}\backslash G_j\}^\intercal \{\mathbb{G}\backslash G_j\}\right]^{-1}\{\mathbb{G}\backslash G_j\}^\intercal$, X, Y and ε_X are $n \times 1$ vectors, $\mathbb{G}$ is $n \times p$ matrix and $\boldsymbol{\gamma}_X$ is a $g \times 1$ vector.

Hence, we have

$$\begin{aligned}
\mathcal{PR}_{(X,Y\,|\,\mathbb{G}\backslash G_j)} &= Y - X\omega_{\{\mathbb{G}\backslash G_j\}} \\
&= Y - X\left(1 - \left[X^{\intercal}\tilde{\mathbf{P}}X\right]^{-1} X^{\intercal}\tilde{\mathbf{P}}(\mathbf{G}^{\intercal}\boldsymbol{\gamma}_X + \varepsilon_X)\right)\beta^{-1}_{Y\to X} \\
&= Y - X\beta^{-1}_{Y\to X} + X\left[X^{\intercal}\tilde{\mathbf{P}}X\right]^{-1} X^{\intercal}\tilde{\mathbf{P}}(\mathbf{G}^{\intercal}\boldsymbol{\gamma}_X + \varepsilon_X)\beta^{-1}_{Y\to X} \\
&= -(\mathbf{G}^{\intercal}\boldsymbol{\gamma}_X + \varepsilon_X)\beta^{-1}_{Y\to X} + X\left[X^{\intercal}\tilde{\mathbf{P}}X\right]^{-1} X^{\intercal}\tilde{\mathbf{P}}(\mathbf{G}^{\intercal}\boldsymbol{\gamma}_X + \varepsilon_X)\beta^{-1}_{Y\to X} \\
&= \left(-\boldsymbol{I} + X\left[X^{\intercal}\tilde{\mathbf{P}}X\right]^{-1} X^{\intercal}\tilde{\mathbf{P}}\right)(\mathbf{G}^{\intercal}\boldsymbol{\gamma}_X + \varepsilon_X)\,\beta^{-1}_{Y\to X},
\end{aligned}$$

where $\boldsymbol{I}$ is a $n \times n$ identity matrix.
Because $\mathbb{G}$ is a valid IV set relative to $Y \to X$, for $G_k \in \mathbf{G}, k \neq j$, either $\gamma_{X,k} = 0$ (if $G_k \in \mathbb{G}$) or $\mathrm{corr}(G_k, G_j) = 0$ (if $G_k \notin \mathbb{G}$).

Hence,

$$\mathrm{corr}(\mathbf{G}^{\intercal}\boldsymbol{\gamma}_X + \varepsilon_X), G_j) = 0$$

Therefore, we obtain

$$\mathrm{corr}((X/\beta_{Y\to X})\left[X^{\intercal}\tilde{\mathbf{P}}X\right]^{-1} X^{\intercal}\tilde{\mathbf{P}}(\mathbf{G}^{\intercal}\boldsymbol{\gamma}_X + \varepsilon_X), G_j) = 0$$

which implies that $\mathrm{corr}(\mathcal{PR}_{(X,Y\,|\,\mathbb{G}\backslash G_j)}, G_j) = 0$. □

G.4 Proof of Proposition 3

Proof. We prove it by contradiction, i.e., if $\mathbb{G}$ is an invalid IV set for one of the causal relationships, then there exists at least one $G_j \in \mathbb{G}$ such that $\mathrm{corr}(\mathcal{PR}_{(X,Y\,|\,\mathbb{G}\backslash G_j)}, G_j) \neq 0$. Without loss of generality, we consider the case for $X \to Y$. The proof with the inverse causal relationship $Y \to X$ can be derived accordingly. There are three cases to be considered. i) Suppose G_j is an invalid IV in $\mathbb{G}$ and $\mathbb{G}\backslash G_j$ is a valid IV set; ii) Suppose G_j is an invalid IV in $\mathbb{G}$ and $\mathbb{G}\backslash G_j$ is an invalid IV set; iii) Suppose G_j is a valid IV in $\mathbb{G}$ and $\mathbb{G}\backslash G_j$ is an invalid IV set.

i) Suppose G_j is invalid and all IVs in $\mathbb{G}\backslash G_j$ are valid. Due to the validity of all IVs in $\mathbb{G}\backslash G_j$, according to the consistent estimator of TSLS, we have,

$$\omega_{\{\mathbb{G}\backslash G_j\}} = \mathrm{TSLS}(X, Y, \mathbb{G}\backslash G_j) = \beta_{X\to Y}.$$

In order to consider the case of all violating assumptions for IVs, we extend Eq.(1) to Eq.(6), we have

$$\mathcal{PR}_{(X,Y\,|\,\mathbb{G}\backslash G_j)} = Y - X\omega_{\{\mathbb{G}\backslash G_j\}} = \mathbf{G}^{\intercal}\boldsymbol{\gamma}_Y + \varepsilon_Y = \mathbf{G}^{\intercal}\boldsymbol{\gamma}_Y + U\gamma_{Y,U} + \varepsilon_3,$$

where we make $\varepsilon_Y = U\gamma_{Y,U} + \varepsilon_3$ to tell the influential difference between the latent confounder U and the external noise ε_2 on Y. Here $G_j \perp\!\!\!\perp \varepsilon_3$ but G_j may be correlated with U by $\gamma_{U,j}$. Denote by G_i the other IV with $i \neq j$, and we have $G_j \perp\!\!\!\perp G_i$. Hence,

$$\begin{aligned}
&\mathrm{corr}(\mathcal{PR}_{(X,Y\,|\,\mathbb{G}\backslash G_j}, G_j) \\
&= \gamma_{Y,j}\mathrm{corr}(G_j, G_j) + \gamma_{Y,U}\mathrm{corr}(U, G_j) \\
&= \gamma_{Y,j} + \gamma_{Y,U}\gamma_{U,j}.
\end{aligned}$$

Due to the faithfulness assumption, $\mathrm{corr}(\mathcal{PR}_{(X,Y\,|\,\mathbb{G}\backslash G_j}, G_j) \neq 0$.

ii) Suppose G_j is invalid and $\mathbb{G}\backslash G_j$ is an invalid IV set, where there are m genetics in $\mathbb{G}\backslash G_j = \{G_1, ..., G_m\}$. Following the procedure of TSLS, we first get the estimate of X with $\mathbb{G}\backslash G_j$, denoted by $\hat{X}$, and obtain $\omega_{\{\mathbb{G}\backslash G_j\}}$ using $\hat{X}$ and Y.

$$\hat{X} = \sum_{k=1}^{m} G_k\hat{\beta}_k = \sum_{k=1}^{m} G_k\Delta[(\gamma_{X,k} + \gamma_{Y,k}\beta_{Y\to X}) + (\gamma_{X,U} + \gamma_{Y,U}\beta_{Y\to X})\gamma_{U,k}].$$

$$
\begin{aligned}
\omega_{\{\mathbb{G}\backslash G_j\}} &= \frac{\sum_{k=1}^{m}[\hat{\beta}_k(\gamma_{Y,k}+\gamma_{X,k}\beta_{X\to Y})+\hat{\beta}_k\gamma_{U,k}(\gamma_{Y,U}+\gamma_{X,U}\beta_{X\to Y})]\mathbf{C}_{kk}\Delta}{\sum_{k=1}^{m}(\hat{\beta}_k)^2} \\
&= \frac{\sum_{k=1}^{m}[\bar{\beta}_k(\gamma_{Y,k}+\gamma_{X,k}\beta_{X\to Y})+\bar{\beta}_k\gamma_{U,k}(\gamma_{Y,U}+\gamma_{X,U}\beta_{X\to Y})]\mathbf{C}_{kk}}{\sum_{k=1}^{m}(\bar{\beta}_m)^2}, \\
&= \frac{\sum_{k=1}^{m}\bar{\beta}_k[(\gamma_{Y,k}+\gamma_{X,k}\beta_{X\to Y})+\gamma_{U,k}(\gamma_{Y,U}+\gamma_{X,U}\beta_{X\to Y})]\mathbf{C}_{kk}}{\sum_{k=1}^{m}(\bar{\beta}_k)^2} \\
&= \frac{\sum_{k=1}^{m}(A_{X,k}+A_{X,U}\gamma_{U,k})(A_{Y,k}+A_{Y,U}\gamma_{U,k})\mathbf{C}_{kk}}{\sum_{k=1}^{m}(\bar{\beta}_k)^2},
\end{aligned}
$$

where $\bar{\beta}_k = \hat{\beta}_k/\Delta = (\gamma_{X,k}+\gamma_{Y,k}\beta_{Y\to X})+\gamma_{U,k}(\gamma_{X,U}+\gamma_{Y,U}\beta_{Y\to X}) = A_{X,k}+A_{X,U}\gamma_{U,k}$, $A_{X,k} = \gamma_{X,k}+\gamma_{Y,k}\beta_{Y\to X}$ and $A_{X,U} = \gamma_{X,U}+\gamma_{Y,U}\beta_{Y\to X}$. $A_{Y,k} = \gamma_{Y,k}+\gamma_{X,k}\beta_{X\to Y}$ and $A_{Y,U} = \gamma_{Y,U}+\gamma_{X,U}\beta_{X\to Y}$ and $\mathbf{C}_{kk} = cov(G_k, G_k)$. Note that such notations $A.$ enjoy some great properties shown as below,

$$
\begin{aligned}
A_{X,k} - A_{Y,k}\beta_{Y\to X} &= \gamma_{X,k}(1-\beta_{X\to Y}\beta_{Y\to X}), \\
A_{X,k}\beta_{X\to Y} - A_{Y,k} &= \gamma_{Y,k}(\beta_{X\to Y}\beta_{Y\to X}-1), \\
A_{X,1}A_{Y,2} - A_{X,2}A_{Y,1} &= (1-\beta_{X\to Y}\beta_{Y\to X})(\gamma_{X,1}\gamma_{Y,2}-\gamma_{X,2}\gamma_{Y,1}).
\end{aligned}
\tag{19}
$$

Hence,

$$
\begin{aligned}
&\operatorname{corr}(\mathcal{PR}_{(X,Y\,|\,\mathbb{G}\backslash G_j)}, G_j) \\
&= (\gamma_{Y,j}+\gamma_{X,j}\beta_{X\to Y})\Delta - (\gamma_{X,j}+\gamma_{Y,j}\beta_{Y\to X})\Delta\omega_{\{\mathbb{G}\backslash G_j\}} \\
&+ \gamma_{U,j}(\gamma_{Y,U}+\gamma_{X,U}\beta_{X\to Y})\Delta - \gamma_{U,j}(\gamma_{X,U}+\gamma_{Y,U}\beta_{Y\to X})\Delta\omega_{\{\mathbb{G}\backslash G_j\}} \\
&= \Delta\{[\gamma_{Y,j}(1-\beta_{Y\to X}\omega_{\{\mathbb{G}\backslash G_j\}})+\gamma_{X,j}(\beta_{X\to Y}-\omega_{\{\mathbb{G}\backslash G_j\}})] \\
&+ \gamma_{U,j}[\gamma_{Y,U}(1-\beta_{Y\to X}\omega_{\{\mathbb{G}\backslash G_j\}})+\gamma_{X,U}(\beta_{X\to Y}-\omega_{\{\mathbb{G}\backslash G_j\}})]\} \\
&= \Delta[(1-\beta_{Y\to X}\omega_{\{\mathbb{G}\backslash G_j\}})(\gamma_{Y,j}+\gamma_{Y,U}\gamma_{U,j})+(\beta_{X\to Y}-\omega_{\{\mathbb{G}\backslash G_j\}})(\gamma_{X,j}+\gamma_{X,U}\gamma_{U,j})].
\end{aligned}
$$

Employing the properties in Eqs.(19), we get

$$
\begin{aligned}
&1-\beta_{Y\to X}\omega_{\{\mathbb{G}\backslash G_j\}} \\
&= \frac{\sum_{k=1}^{m}(A_{X,k}+A_{X,U}\gamma_{U,k})^2\mathbf{C}_{kk} - \beta_{Y\to X}(A_{X,k}+A_{X,U}\gamma_{U,k})(A_{Y,k}+A_{Y,U}\gamma_{U,k})\mathbf{C}_{kk}}{\sum_{k=1}^{m}(\bar{\beta}_k)^2\mathbf{C}_{kk}} \\
&= \frac{(1-\beta_{X\to Y}\beta_{Y\to X})\sum_{k=1}^{m}(A_{X,k}+A_{X,U}\gamma_{U,k})(\gamma_{X,k}+\gamma_{X,U}\gamma_{U,k})\mathbf{C}_{kk}}{\sum_{k=1}^{m}(\bar{\beta}_k)^2\mathbf{C}_{kk}},
\end{aligned}
$$

and

$$
\begin{aligned}
&\beta_{X\to Y}-\omega_{\{\mathbb{G}\backslash G_j\}} \\
&= \frac{\beta_{X\to Y}\sum_{k=1}^{m}(A_{X,k}+A_{X,U}\gamma_{U,k})^2\mathbf{C}_{kk} - \sum_{k=1}^{m}(A_{X,k}+A_{X,U}\gamma_{U,k})(A_{Y,k}+A_{Y,U}\gamma_{U,k})\mathbf{C}_{kk}}{\sum_{k=1}^{m}(\bar{\beta}_k)^2\mathbf{C}_{kk}} \\
&= \frac{(\beta_{X\to Y}\beta_{Y\to X}-1)\sum_{k=1}^{m}(A_{X,k}+A_{X,U}\gamma_{U,k})(\gamma_{Y,k}+\gamma_{Y,U}\gamma_{U,k})\mathbf{C}_{kk}}{\sum_{k=1}^{m}(\bar{\beta}_k)^2\mathbf{C}_{kk}}.
\end{aligned}
$$

Thus,

$$
\begin{aligned}
&\operatorname{corr}(\mathcal{PR}_{(X,Y\,|\,\mathbb{G}\backslash G_j)}, G_j) \\
&= \frac{\sum_{k=1}^{m}\mathbf{C}_{kk}(A_{X,k}+A_{X,U}\gamma_{U,k})(\gamma_{X,k}+\gamma_{X,U}\gamma_{U,k})}{\sum_{k=1}^{m}(\bar{\beta}_k)^2\mathbf{C}_{kk}}(\gamma_{Y,j}+\gamma_{Y,U}\gamma_{U,j}) \\
&\quad - \frac{\sum_{k=1}^{m}\mathbf{C}_{kk}(A_{X,k}+A_{X,U}\gamma_{U,k})(\gamma_{Y,k}+\gamma_{Y,U}\gamma_{U,k})}{\sum_{k=1}^{m}(\bar{\beta}_k)^2\mathbf{C}_{kk}}(\gamma_{X,j}+\gamma_{X,U}\gamma_{U,j}) \\
&= \frac{\sum_{k=1}^{m}\bar{\beta}_k\mathbf{C}_{kk}[(\gamma_{X,k}+\gamma_{X,U}\gamma_{U,k})(\gamma_{Y,j}+\gamma_{Y,U}\gamma_{U,j})-(\gamma_{Y,k}+\gamma_{Y,U}\gamma_{U,k})(\gamma_{X,j}+\gamma_{X,U}\gamma_{U,j})]}{\sum_{k=1}^{m}(\bar{\beta}_k)^2\mathbf{C}_{kk}} \\
&= \frac{\sum_{k=1}^{m}\bar{\beta}_k\mathbf{C}_{kk}[(\gamma_{X,k}\gamma_{Y,j}-\gamma_{Y,k}\gamma_{X,j})+\gamma_{Y,U}(\gamma_{X,k}\gamma_{U,j}-\gamma_{U,k}\gamma_{X,j})+\gamma_{X,U}(\gamma_{U,k}\gamma_{Y,j}-\gamma_{Y,k}\gamma_{U,j})]}{\sum_{k=1}^{m}(\bar{\beta}_k)^2\mathbf{C}_{kk}} \neq 0.
\end{aligned}
$$

Because of the faithfulness assumption, $\bar{\beta}_k \neq 0$. Due to Assumption 2, for $G_k \in \mathbb{G}\backslash G_j$ and the confounder U, $\sum_{k=1}^{m} \bar{\beta}_k \mathbf{C}_{kk}[(\gamma_{X,k}\gamma_{Y,j}-\gamma_{Y,k}\gamma_{X,j})+\gamma_{Y,U}(\gamma_{X,k}\gamma_{U,j}-\gamma_{U,k}\gamma_{X,j})+\gamma_{X,U}(\gamma_{U,k}\gamma_{Y,j}-\gamma_{Y,k}\gamma_{U,j})] \neq 0$.

iii) Suppose G_j is a valid IV in $\mathbb{G}$ and $\mathbb{G}\backslash G_j$ is an invalid IV set. Similar to ii), we get $\omega_{\{\mathbb{G}\backslash G_j\}}$:

$$\omega_{\{\mathbb{G}\backslash G_j\}} = \frac{\sum_{k=1}^{m}(A_{X,k} + A_{X,U}\gamma_{U,k})(A_{Y,k} + A_{Y,U}\gamma_{U,k})\mathbf{C}_{kk}}{\sum_{k=1}^{m}(\bar{\beta}_k)^2\mathbf{C}_{kk}}.$$

Since the valid IV G_j is uncorrelated with neither other invalid IVs nor the confounder, we then derive,

$$\begin{aligned}
&\operatorname{corr}(\mathcal{PR}_{(X,Y \mid \mathbb{G}\backslash G_j)}, G_j) \\
&= (\gamma_{Y,j} + \gamma_{X,j}\beta_{X\to Y})\Delta - (\gamma_{X,j} + \gamma_{Y,j}\beta_{Y\to X})\Delta\omega_{\{\mathbb{G}\backslash G_j\}} \\
&= \Delta\gamma_{X,j}(\beta_{X\to Y} - \omega_{\{\mathbb{G}\backslash G_j\}}).
\end{aligned}$$

where:

$$\begin{aligned}
&\beta_{X\to Y} - \omega_{\{\mathbb{G}\backslash G_j\}} \\
&= \frac{\beta_{X\to Y}\sum_{k=1}^{m}\mathbf{C}_{kk}[(A_{X,k} + A_{X,U}\gamma_{U,k})^2 - (A_{X,k} + A_{X,U}\gamma_{U,k})(A_{Y,k} + A_{Y,U}\gamma_{U,k})]}{\sum_{k=1}^{m}(\bar{\beta}_k)^2\mathbf{C}_{kk}} \\
&= \frac{(\beta_{X\to Y}\beta_{Y\to X} - 1)\sum_{k=1}^{m}\mathbf{C}_{kk}(A_{X,k} + A_{X,U}\gamma_{U,k})(\gamma_{Y,k} + \gamma_{Y,U}\gamma_{U,k})}{\sum_{k=1}^{m}(\bar{\beta}_k)^2\mathbf{C}_{kk}}.
\end{aligned}$$

Thus, we get

$$\begin{aligned}
&\operatorname{corr}(\mathcal{PR}_{(X,Y \mid \mathbb{G}\backslash G_j)}, G_j) = \Delta\gamma_{X,j}(\beta_{X\to Y} - \omega_{\{\mathbb{G}\backslash G_j\}}) \\
&= -\frac{\sum_{k=1}^{m}\mathbf{C}_{kk}(A_{X,k} + A_{X,U}\gamma_{U,k})(\gamma_{Y,k} + \gamma_{Y,U}\gamma_{U,k})\gamma_{X,j}}{\sum_{k=1}^{m}(\bar{\beta}_k)^2\mathbf{C}_{kk}} \\
&= -\frac{\sum_{k=1}^{m}\bar{\beta}_k\mathbf{C}_{kk}(\gamma_{Y,k} + \gamma_{Y,U}\gamma_{U,k})\gamma_{X,j}}{\sum_{k=1}^{m}(\bar{\beta}_k)^2\mathbf{C}_{kk}}.
\end{aligned}$$

Since G_j is a valid IV ($\gamma_{Y,j} = \gamma_{U,j} = 0$), and from Assumption 2, we have $\sum_{k=1}^{m}\bar{\beta}_k\mathbf{C}_{kk}(\gamma_{Y,k} + \gamma_{Y,U}\gamma_{U,k})\gamma_{X,j} \neq 0$. Proposition 3 is proved. □

G.5 Proof of Proposition 4

Proof. We prove this proposition by contradiction, i.e., i) if $\mathbb{G}$ is the valid IV set relative to the causal relationship $Y \to X$, then $\exists\, G_j \in \mathbb{G}$ satisfies $|\frac{\operatorname{corr}(G_j,Y)}{\operatorname{corr}(G_j,X)}| \geq 1$; and ii) if $\mathbb{G}$ is the valid IV set relative to the causal relationship $X \to Y$, then $\exists\, G_j \in \mathbb{G}$ satisfies $|\frac{\operatorname{corr}(G_j,Y)}{\operatorname{corr}(G_j,X)}| < 1$.

i) Suppose $\mathbb{G}$ is the valid IV set relative to the causal relationship $Y \to X$. According to Assumption 3, we have $|\beta_{Y\to X}| \leq \sqrt{\frac{\operatorname{Var}(X)}{\operatorname{Var}(Y)}}$. Hence,

$$\begin{aligned}
\left|\frac{\operatorname{corr}(G_j,Y)}{\operatorname{corr}(G_j,X)}\right| &= \left|\frac{\operatorname{Cov}(G_j,Y)}{\sqrt{\operatorname{Var}(G_j)\operatorname{Var}(Y)}}\frac{\sqrt{\operatorname{Var}(G_j)\operatorname{Var}(X)}}{\operatorname{Cov}(G_j,X)}\right| \\
&= \left|\frac{\gamma_{Y,j}\Delta}{\sqrt{\operatorname{Var}(Y)}}\frac{\sqrt{\operatorname{Var}(X)}}{\gamma_{Y,j}\Delta\beta_{Y\to X}}\right| \\
&= \left|\frac{1}{\beta_{Y\to X}}\sqrt{\frac{\operatorname{Var}(X)}{\operatorname{Var}(Y)}}\right| \geq 1,
\end{aligned}$$

which proves case i).

ii) Suppose $\mathbb{G}$ is the valid IV set relative to the causal relationship $X \to Y$. According to Assumption 3, we have $|\beta_{X\to Y}| < \sqrt{\frac{\mathrm{Var}(Y)}{\mathrm{Var}(X)}}$. Hence,

$$\begin{aligned}
\left|\frac{\mathrm{corr}(G_j, Y)}{\mathrm{corr}(G_j, X)}\right| &= \left|\frac{\mathrm{Cov}(G_j, Y)}{\sqrt{\mathrm{Var}(G_j)\mathrm{Var}(Y)}} \frac{\sqrt{\mathrm{Var}(G_j)\mathrm{Var}(X)}}{\mathrm{Cov}(G_j, X)}\right| \\
&= \left|\frac{\gamma_{X,j}\Delta\beta_{X\to Y}}{\sqrt{\mathrm{Var}(Y)}} \frac{\sqrt{\mathrm{Var}(X)}}{\gamma_{X,j}\Delta}\right| \\
&= \left|\beta_{X\to Y}\sqrt{\frac{\mathrm{Var}(X)}{\mathrm{Var}(Y)}}\right| < 1,
\end{aligned}$$

which proves case ii) and concludes the proposition. □

G.6 Proof of Theorem 1

Proof. Firstly, given Assumptions 1 and 2, in light of Propositions 2 and 3, we can identify all sets of valid instrumental variables (IVs). Next, given Assumption 3, by Proposition 4, we can further identify what the causal relationships corresponding to these IV sets. It is important to note that if all the IV sets correspond to a single causal relationship, such as $X \to Y$, we can conclude that the model is a one-directional MR model. Finally, with the corresponding IV set identified for each causal influence, we can employ the classical IV estimator, namely the two-stage least squares (TSLS) estimator, to accurately estimate the causal effects.

Based on the above analysis, we can conclude that the bi-directional MR model is fully identifiable.

□

G.7 Proof of Theorem 2

Proof. The correctness of PReBiM originates from the following observations:

- Firstly, in Step 1 (Algorithm 4), by Propositions 2 and 3, valid IV sets in $\mathbf{G}$ have been exactly discovered in $\mathcal{V}$ (Lines 2 $\sim$ 25 of Algorithm 4).
- Secondly, in Step 2 (Algorithm 5), by the condition of Proposition 4, the direction of causal influence can be determined (Line 2 $\sim$ 8 of Algorithm 5).
- Lastly, by Eq.(1) of Proposition 1, unbiased causal effects can be estimated exactly given the identified IV sets (Lines 9 $\sim$ 10 of Algorithm 5).

Based on the above analysis, we can identify all valid IV sets and obtain the causal effects correctly. □

H More Experimental Results

H.1 Evaluating the Performance on Bi-directional MR Model with Dependent Valid IVs

Table 3 summarizes the CSR and MSE metrics' results across six methods within a bi-directional MR model with varying sample sizes. As expected, our proposed method exhibits superior performance, even in scenarios where the included valid instrumental variables (IVs) are correlated. This highlights its capability to accurately identify effective IVs and provide consistent causal effect estimates solely from observational data, regardless of whether the relevant IVs are correlated. Importantly, this effectiveness persists without prior knowledge of the causal direction between X and Y. Conversely, the performance of the other three methods remains suboptimal in such contexts, indicating their limited applicability in cases with correlated valid IVs.

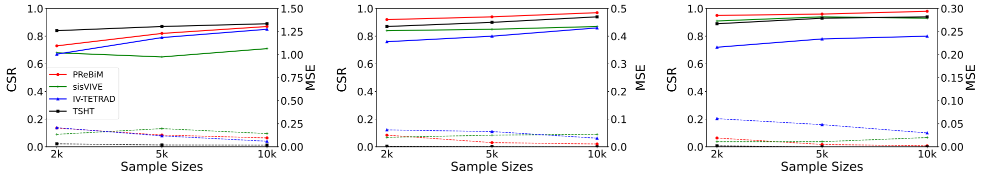
Table 3: Performance comparison of NAIVE, MR-Egger, sisVIVE, IV-TETRAD, TSHT, and PReBiM in estimating bi-directional MR models across various sample sizes and three scenarios.

		$\mathcal{S}(2,2,6)$				$\mathcal{S}(3,3,8)$				$\mathcal{S}(4,4,10)$			
		$X \rightarrow Y$		$Y \rightarrow X$		$X \rightarrow Y$		$Y \rightarrow X$		$X \rightarrow Y$		$Y \rightarrow X$	
Size	Algorithm	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**
2k	NAIVE	-	0.409	-	0.341	-	0.350	-	0.372	-	0.409	-	0.314
	MR-Egger	-	1.198	-	1.320	-	1.033	-	1.322	-	1.087	-	1.391
	sisVIVE	0.31	0.478	0.29	0.395	0.34	0.408	0.34	0.388	0.35	0.450	0.36	0.328
	IV-TETRAD	0.40	1.224	0.42	0.900	0.52	0.830	0.29	0.903	0.44	1.033	0.32	0.779
	TSHT	0.09	0.657	0.04	0.636	0.10	0.696	0.08	0.699	0.12	0.804	0.10	0.708
	PReBiM	**0.84**	**0.014**	**0.79**	**0.167**	**0.89**	**0.058**	**0.88**	**0.097**	**0.84**	**0.053**	**0.83**	**0.079**
5k	NAIVE	-	0.399	-	0.326	-	0.371	-	0.362	-	0.391	-	0.333
	MR-Egger	-	1.000	-	1.204	-	1.171	-	1.181	-	0.971	-	1.358
	sisVIVE	0.30	0.484	0.31	0.426	0.35	0.452	0.34	0.381	0.38	0.375	0.37	0.327
	IV-TETRAD	0.50	1.042	0.40	0.700	0.49	1.041	0.38	0.778	0.47	0.977	0.36	0.778
	TSHT	0.06	0.701	0.05	0.531	0.09	0.689	0.06	0.660	0.11	0.653	0.09	0.589
	PReBiM	**0.90**	**0.113**	**0.84**	**0.081**	**0.91**	**0.050**	**0.90**	**0.061**	**0.88**	**0.048**	**0.89**	**0.061**
10k	NAIVE	-	0.378	-	0.358	-	0.408	-	0.323	-	0.401	-	0.339
	MR-Egger	-	1.052	-	1.307	-	1.017	-	1.313	-	1.185	-	1.303
	sisVIVE	0.33	0.465	0.34	0.427	0.35	0.448	0.34	0.358	0.38	0.431	0.41	0.299
	IV-TETRAD	0.54	0.995	0.39	0.839	0.52	1.092	0.41	0.637	0.51	0.963	0.38	0.553
	TSHT	0.04	0.641	0.03	0.543	0.04	0.734	0.04	0.449	0.09	0.654	0.07	0.567
	PReBiM	**0.90**	**0.058**	**0.87**	**0.089**	**0.94**	**0.018**	**0.93**	**0.026**	**0.93**	**0.022**	**0.92**	**0.056**

Note: This scenario represents a bi-directional model with correlated valid IVs. The symbol "$-$" means that methods do not output information. "↑" means a higher value is better, and vice versa.

H.2 Evaluating the Performance on One-directional MR Model with Dependent Valid IVs

In this section, we assess the efficacy of four methods within a one-directional Mendelian Randomization (MR) framework. For a fair comparison, we operate under the assumption that the causal pathway from X to Y is established for all methods. Figure 7 displays the CSR and MSE metrics for these methods, considering diverse sample sizes and numbers of valid instrumental variables (IVs). As expected, our approach maintains strong performance, even amidst correlated valid IVs. The outcomes are comparable with those of the TSHT algorithm, with our method notably surpassing both the sisVIVE and IV-TETRAD algorithms under various conditions.



(a) $\mathcal{S}(2,0,6)$

(b) $\mathcal{S}(3,0,8)$

(c) $\mathcal{S}(4,0,10)$

Figure 7: Performance comparison of sisVIVE, IV-TETRAD, TSHT, and PReBiM in estimating one-directional MR models incorporating valid IVs across various sample sizes and three scenarios.

H.3 Evaluating the Performance on Bi-directional MR Model with Small Sample Sizes

In this section, we will evaluate the performance of these six methods in a bi-directional Mendelian randomization framework with small samples. Table 4 displays the CSR and MSE metrics for these methods, considering three scenarios with a sample size of 200. We find that though the performances of all four methods are not satisfactory, ours still outperforms other baselines. It also reflects an open problem of our work with small sample sizes. We leave it as our future in-depth direction.

H.4 Evaluating the Performance on Bi-directional MR Model with Different Numbers of Valid IVs

Table 5 summarizes the CSR and MSE metrics' results across six methods within a bi-directional MR model with different numbers of valid IVs. Specifically, $\mathcal{S}(2,3,7)$ indicates that in the bi-directional model, there are two valid instrumental variables estimated for the direction $X \rightarrow Y$, and three valid instrumental variables estimated for the direction $Y \rightarrow X$, with the remaining two

Table 4: Performance comparison of NAIVE, MR-Egger, sisVIVE, IV-TETRAD, TSHT, and PReBiM in estimating bi-directional MR models across small sample size (200) and three scenarios.

		$\mathcal{S}(2,2,6)$				$\mathcal{S}(3,3,8)$				$\mathcal{S}(4,4,10)$			
		$X \to Y$		$Y \to X$		$X \to Y$		$Y \to X$		$X \to Y$		$Y \to X$	
Size	Algorithm	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**
200	NAIVE	-	0.360	-	0.330	-	0.343	-	0.331	-	0.320	-	0.336
	MR-Egger	-	0.941	-	0.657	-	0.579	-	0.594	-	0.433	-	0.535
	sisVIVE	0.21	0.389	0.24	0.383	0.29	0.331	0.28	0.336	0.34	0.318	0.30	0.329
	IV-TETRAD	0.30	1.057	0.26	0.797	0.26	0.811	0.20	0.886	0.15	0.723	0.12	0.787
	TSHT	0.17	0.677	0.16	0.642	0.22	0.504	0.24	0.534	0.26	0.493	0.23	0.452
	PReBiM	**0.54**	**0.339**	**0.55**	**0.350**	**0.55**	**0.313**	**0.57**	**0.281**	**0.51**	**0.270**	**0.52**	**0.288**

Note: The symbol "$-$" means that methods do not output this information. "↑" means a higher value is better, and vice versa.

being invalid instrumental variables. The same interpretation applies to $\mathcal{S}(2,4,8)$ and $\mathcal{S}(3,5,10)$. It can be seen that whether the number of valid IVs in these two directions is the same or not does not affect the performance of our algorithm theoretically. The experimental results also empirically verify it. Overall, In cases where the number of IVs in both the $X \to Y$ and $Y \to X$ directions are different, our PReBiM algorithm outperforms other baselines in terms of CSR and MSE.

Table 5: Performance comparison of NAIVE, MR-Egger, sisVIVE, IV-TETRAD, TSHT, and PReBiM in estimating bi-directional MR models across various sample sizes and three scenarios.

		$\mathcal{S}(2,3,7)$				$\mathcal{S}(2,4,8)$				$\mathcal{S}(3,5,10)$			
		$X \to Y$		$Y \to X$		$X \to Y$		$Y \to X$		$X \to Y$		$Y \to X$	
Size	Algorithm	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**
2k	NAIVE	-	0.433	-	0.267	-	0.464	-	0.227	-	0.431	-	0.237
	MR-Egger	-	0.702	-	0.646	-	0.560	-	0.610	-	0.465	-	0.476
	sisVIVE	0.16	0.746	0.52	0.170	0.11	0.958	0.68	0.093	0.14	0.907	0.65	0.099
	IV-TETRAD	0.37	1.490	0.55	0.368	0.24	1.886	0.71	0.188	0.35	1.474	0.56	0.150
	TSHT	0.00	2.226	0.72	0.066	0.00	2.467	0.85	0.004	0.00	2.453	0.84	0.003
	PReBiM	**0.81**	**0.062**	**0.89**	**0.036**	**0.78**	**0.063**	**0.89**	**0.031**	**0.80**	**0.053**	**0.87**	**0.038**
5k	NAIVE	-	0.394	-	0.307	-	0.479	-	0.228	-	0.457	-	0.228
	MR-Egger	-	0.509	-	0.691	-	0.593	-	0.546	-	0.540	-	0.486
	sisVIVE	0.20	0.611	0.49	0.274	0.09	1.085	0.72	0.113	0.13	0.917	0.66	0.089
	IV-TETRAD	0.37	1.479	0.56	0.312	0.25	1.869	0.69	0.165	0.30	1.641	0.63	0.164
	TSHT	0.00	2.296	0.80	0.027	0.00	2.476	0.90	0.001	0.00	2.477	0.90	0.001
	PReBiM	**0.86**	**0.067**	**0.93**	**0.008**	**0.83**	**0.035**	**0.93**	**0.023**	**0.86**	**0.021**	**0.91**	**0.003**
10k	NAIVE	-	0.434	-	0.273	-	0.463	-	0.234	-	0.434	-	0.226
	MR-Egger	-	0.646	-	0.593	-	0.550	-	0.560	-	0.525	-	0.443
	sisVIVE	0.17	0.807	0.50	0.230	0.10	1.083	0.71	0.088	0.15	0.932	0.77	0.079
	IV-TETRAD	0.38	1.495	0.59	0.322	0.26	1.753	0.69	0.244	0.34	1.429	0.62	0.204
	TSHT	0.00	2.370	0.85	0.022	0.00	2.494	0.92	0.001	0.00	2.486	0.93	0.000
	PReBiM	**0.90**	**0.022**	**0.97**	**0.005**	**0.91**	**0.013**	**0.95**	**0.009**	**0.92**	**0.038**	**0.93**	**0.008**

Note: The symbol "$-$" means that methods do not output this information. "↑" means a higher value is better, and vice versa.

H.5 Evaluating the Performance on Bi-directional MR Model with Large-Scale Datasets

In this section, we evaluate the performance of these methods in a bi-directional MR framework with large-scale datasets. Table 6 show results of the settings $\mathcal{S}(10,10,30)$ and $\mathcal{S}(15,15,40)$. We observe that the overall performances of all methods decrease with large-scale datasets, whereas our method still performs more superior than other baselines.

H.6 Evaluating the Performance on Bi-directional MR Model with All IVs Being Valid

In this section, we evaluate the performance of these methods in a bi-directional MR framework with all IVs being valid. That is, only valid IVs are included in the model, either to estimate the direction $X \to Y$ or the direction $Y \to X$. The results in Table 7 below show the settings $\mathcal{S}(2,2,4)$. To ensure the thoroughness of the experiment, we've added another setting, $\mathcal{S}(3,3,6)$. As expected, our method gives the best results across all sample sizes and directions. As the sample size increases, the metric CSR approaches 1, indicating that our method can identify valid IVs and also validating our theoretical guarantees.

Table 6: Performance comparison of NAIVE, MR-Egger, sisVIVE, IV-TETRAD, TSHT, and PReBiM in estimating bi-directional MR models with large-scale datasets.

		$\mathcal{S}(10,10,30)$				$\mathcal{S}(15,15,40)$			
		$X \to Y$		$Y \to X$		$X \to Y$		$Y \to X$	
Size	Algorithm	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**
2k	NAIVE	-	0.298	-	0.292	-	0.288	-	0.299
	MR-Egger	-	0.337	-	0.316	-	0.276	-	0.285
	sisVIVE	0.15	0.275	0.15	0.246	0.24	0.188	0.22	0.223
	IV-TETRAD	0.22	0.802	0.22	0.647	0.11	0.666	0.07	0.700
	TSHT	0.18	1.029	0.28	0.874	0.27	1.012	0.28	0.995
	PReBiM	**0.59**	**0.244**	**0.57**	**0.173**	**0.67**	**0.152**	**0.71**	**0.157**
5k	NAIVE	-	0.297	-	0.299	-	0.301	-	0.285
	MR-Egger	-	2.307	-	0.323	-	0.293	-	0.278
	sisVIVE	0.15	0.247	0.14	0.281	0.23	0.236	0.23	0.200
	IV-TETRAD	0.49	0.635	0.48	0.495	0.38	0.572	0.36	0.546
	TSHT	0.20	1.020	0.21	1.083	0.22	0.967	0.19	1.042
	PReBiM	**0.72**	**0.079**	**0.73**	**0.102**	**0.81**	**0.094**	**0.77**	**0.075**
10k	NAIVE	-	0.301	-	0.284	-	0.307	-	0.279
	MR-Egger	-	0.338	-	0.325	-	0.280	-	0.272
	sisVIVE	0.16	0.271	0.17	0.264	0.24	0.216	0.25	0.196
	IV-TETRAD	0.58	0.443	0.62	0.390	0.53	0.535	0.53	0.432
	TSHT	0.19	0.957	0.20	0.863	0.22	0.886	0.18	1.024
	PReBiM	**0.80**	**0.062**	**0.80**	**0.062**	**0.85**	**0.061**	**0.84**	**0.075**

Note: The symbol "$-$" means that methods do not output this information. "↑" means a higher value is better, and vice versa.

Table 7: Performance comparison of NAIVE, MR-Egger, sisVIVE, IV-TETRAD, TSHT, and PReBiM in estimating bi-directional MR models across various sample sizes and three scenarios.

		$\mathcal{S}(2,2,4)$				$\mathcal{S}(3,3,6)$			
		$X \to Y$		$Y \to X$		$X \to Y$		$Y \to X$	
Size	Algorithm	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**	**CSR↑**	**MSE↓**
2k	NAIVE	-	0.413	-	0.349	-	0.351	-	0.353
	MR-Egger	-	1.993	-	2.067	-	0.852	-	0.981
	sisVIVE	0.70	0.532	0.72	0.450	0.75	0.367	0.74	0.414
	IV-TETRAD	0.63	0.822	0.35	0.792	0.68	0.651	0.29	0.716
	TSHT	0.02	0.412	0.02	0.388	0.02	0.372	0.02	0.373
	PReBiM	**0.98**	**0.003**	**0.98**	**0.003**	**0.98**	**0.010**	**0.98**	**0.008**
5k	NAIVE	-	0.386	-	0.364	-	0.369	-	0.342
	MR-Egger	-	2.145	-	2.570	-	0.943	-	0.952
	sisVIVE	0.71	0.578	0.74	0.502	0.79	0.383	0.73	0.442
	IV-TETRAD	0.66	0.811	0.33	0.899	0.68	0.714	0.29	0.596
	TSHT	0.01	0.415	0.02	0.387	0.01	0.355	0.01	0.370
	PReBiM	**0.99**	**0.009**	**0.99**	**0.008**	**0.99**	**0.001**	**0.99**	**0.001**
10k	NAIVE	-	0.390	-	0.374	-	0.336	-	0.364
	MR-Egger	-	2.015	-	2.902	-	1.051	-	0.994
	sisVIVE	0.74	0.538	0.72	0.497	0.78	0.384	0.78	0.437
	IV-TETRAD	0.65	0.812	0.35	0.877	0.74	0.630	0.25	0.792
	TSHT	0.02	0.423	0.02	0.398	0.01	0.335	0.01	0.387
	PReBiM	**0.99**	**0.001**	**0.979**	**0.000**	**0.99**	**0.008**	**0.99**	**0.009**

Note: The symbol "$-$" means that methods do not output this information. "↑" means a higher value is better, and vice versa.

NeurIPS Paper Checklist

1. **Claims**

   Question: Do the main claims made in the abstract and introduction accurately reflect the paper's contributions and scope?

   Answer: [Yes]

   Justification: We thoroughly elaborate on our contributions and their relevance to specific application domains in both the abstract and introduction sections.

   Guidelines:

   - The answer NA means that the abstract and introduction do not include the claims made in the paper.
   - The abstract and/or introduction should clearly state the claims made, including the contributions made in the paper and important assumptions and limitations. A No or NA answer to this question will not be perceived well by the reviewers.
   - The claims made should match theoretical and experimental results, and reflect how much the results can be expected to generalize to other settings.
   - It is fine to include aspirational goals as motivation as long as it is clear that these goals are not attained by the paper.

2. **Limitations**

   Question: Does the paper discuss the limitations of the work performed by the authors?

   Answer: [Yes]

   Justification: We mentioned in Section 5 and Section 7 the limitations, i.e., whether our algorithms are still feasible when the instrumental variables are dependent of each other, and that at present our work is still limited to the case where the causal relationship is linear. These two main issues are our future research direction.

   Guidelines:

   - The answer NA means that the paper has no limitation while the answer No means that the paper has limitations, but those are not discussed in the paper.
   - The authors are encouraged to create a separate "Limitations" section in their paper.
   - The paper should point out any strong assumptions and how robust the results are to violations of these assumptions (e.g., independence assumptions, noiseless settings, model well-specification, asymptotic approximations only holding locally). The authors should reflect on how these assumptions might be violated in practice and what the implications would be.
   - The authors should reflect on the scope of the claims made, e.g., if the approach was only tested on a few datasets or with a few runs. In general, empirical results often depend on implicit assumptions, which should be articulated.
   - The authors should reflect on the factors that influence the performance of the approach. For example, a facial recognition algorithm may perform poorly when image resolution is low or images are taken in low lighting. Or a speech-to-text system might not be used reliably to provide closed captions for online lectures because it fails to handle technical jargon.
   - The authors should discuss the computational efficiency of the proposed algorithms and how they scale with dataset size.
   - If applicable, the authors should discuss possible limitations of their approach to address problems of privacy and fairness.
   - While the authors might fear that complete honesty about limitations might be used by reviewers as grounds for rejection, a worse outcome might be that reviewers discover limitations that aren't acknowledged in the paper. The authors should use their best judgment and recognize that individual actions in favor of transparency play an important role in developing norms that preserve the integrity of the community. Reviewers will be specifically instructed to not penalize honesty concerning limitations.

3. **Theory Assumptions and Proofs**

Question: For each theoretical result, does the paper provide the full set of assumptions and a complete (and correct) proof?

Answer: [Yes]

Justification: We provided detailed proofs in Appendix C, Appendix D and Appendix G, for our provided examples, propositions, and theorems, respectively.

Guidelines:

- The answer NA means that the paper does not include theoretical results.
- All the theorems, formulas, and proofs in the paper should be numbered and cross-referenced.
- All assumptions should be clearly stated or referenced in the statement of any theorems.
- The proofs can either appear in the main paper or the supplemental material, but if they appear in the supplemental material, the authors are encouraged to provide a short proof sketch to provide intuition.
- Inversely, any informal proof provided in the core of the paper should be complemented by formal proofs provided in appendix or supplemental material.
- Theorems and Lemmas that the proof relies upon should be properly referenced.

4. **Experimental Result Reproducibility**

Question: Does the paper fully disclose all the information needed to reproduce the main experimental results of the paper to the extent that it affects the main claims and/or conclusions of the paper (regardless of whether the code and data are provided or not)?

Answer: [Yes]

Justification: We show our experimental settings as well as some of the experimental results in Section 6. In our supplementary materials, we provided the code for our algorithm as well as a simple example. If the data is generated following our model assumptions in Section 6, the results can be reproduced with the specified experimental settings.

Guidelines:

- The answer NA means that the paper does not include experiments.
- If the paper includes experiments, a No answer to this question will not be perceived well by the reviewers: Making the paper reproducible is important, regardless of whether the code and data are provided or not.
- If the contribution is a dataset and/or model, the authors should describe the steps taken to make their results reproducible or verifiable.
- Depending on the contribution, reproducibility can be accomplished in various ways. For example, if the contribution is a novel architecture, describing the architecture fully might suffice, or if the contribution is a specific model and empirical evaluation, it may be necessary to either make it possible for others to replicate the model with the same dataset, or provide access to the model. In general. releasing code and data is often one good way to accomplish this, but reproducibility can also be provided via detailed instructions for how to replicate the results, access to a hosted model (e.g., in the case of a large language model), releasing of a model checkpoint, or other means that are appropriate to the research performed.
- While NeurIPS does not require releasing code, the conference does require all submissions to provide some reasonable avenue for reproducibility, which may depend on the nature of the contribution. For example
  (a) If the contribution is primarily a new algorithm, the paper should make it clear how to reproduce that algorithm.
  (b) If the contribution is primarily a new model architecture, the paper should describe the architecture clearly and fully.
  (c) If the contribution is a new model (e.g., a large language model), then there should either be a way to access this model for reproducing the results or a way to reproduce the model (e.g., with an open-source dataset or instructions for how to construct the dataset).

(d) We recognize that reproducibility may be tricky in some cases, in which case authors are welcome to describe the particular way they provide for reproducibility. In the case of closed-source models, it may be that access to the model is limited in some way (e.g., to registered users), but it should be possible for other researchers to have some path to reproducing or verifying the results.

5. **Open access to data and code**

   Question: Does the paper provide open access to the data and code, with sufficient instructions to faithfully reproduce the main experimental results, as described in supplemental material?

   Answer: [Yes]

   Justification: We anonymized and packaged our code and data, and put them in supplementary materials.

   Guidelines:

   - The answer NA means that paper does not include experiments requiring code.
   - Please see the NeurIPS code and data submission guidelines (`https://nips.cc/public/guides/CodeSubmissionPolicy`) for more details.
   - While we encourage the release of code and data, we understand that this might not be possible, so No is an acceptable answer. Papers cannot be rejected simply for not including code, unless this is central to the contribution (e.g., for a new open-source benchmark).
   - The instructions should contain the exact command and environment needed to run to reproduce the results. See the NeurIPS code and data submission guidelines (`https://nips.cc/public/guides/CodeSubmissionPolicy`) for more details.
   - The authors should provide instructions on data access and preparation, including how to access the raw data, preprocessed data, intermediate data, and generated data, etc.
   - The authors should provide scripts to reproduce all experimental results for the new proposed method and baselines. If only a subset of experiments are reproducible, they should state which ones are omitted from the script and why.
   - At submission time, to preserve anonymity, the authors should release anonymized versions (if applicable).
   - Providing as much information as possible in supplemental material (appended to the paper) is recommended, but including URLs to data and code is permitted.

6. **Experimental Setting/Details**

   Question: Does the paper specify all the training and test details (e.g., data splits, hyperparameters, how they were chosen, type of optimizer, etc.) necessary to understand the results?

   Answer: [Yes]

   Justification: We placed the detailed experimental settings of the experiments in Section 6 of the paper and the complete details with the code in the supplementary materials.

   Guidelines:

   - The answer NA means that the paper does not include experiments.
   - The experimental setting should be presented in the core of the paper to a level of detail that is necessary to appreciate the results and make sense of them.
   - The full details can be provided either with the code, in appendix, or as supplemental material.

7. **Experiment Statistical Significance**

   Question: Does the paper report error bars suitably and correctly defined or other appropriate information about the statistical significance of the experiments?

   Answer: [Yes]

   Justification: Our experiments included mean square error (MSE) for the evaluation metrics, which expresses the statistical significance of the experiment. We show it in all the tables in the paper. It is obtained by taking the mean by calculating the square of the difference between the estimated causal effect and the true value.

Guidelines:

- The answer NA means that the paper does not include experiments.
- The authors should answer "Yes" if the results are accompanied by error bars, confidence intervals, or statistical significance tests, at least for the experiments that support the main claims of the paper.
- The factors of variability that the error bars are capturing should be clearly stated (for example, train/test split, initialization, random drawing of some parameter, or overall run with given experimental conditions).
- The method for calculating the error bars should be explained (closed form formula, call to a library function, bootstrap, etc.)
- The assumptions made should be given (e.g., Normally distributed errors).
- It should be clear whether the error bar is the standard deviation or the standard error of the mean.
- It is OK to report 1-sigma error bars, but one should state it. The authors should preferably report a 2-sigma error bar than state that they have a 96% CI, if the hypothesis of Normality of errors is not verified.
- For asymmetric distributions, the authors should be careful not to show in tables or figures symmetric error bars that would yield results that are out of range (e.g. negative error rates).
- If error bars are reported in tables or plots, The authors should explain in the text how they were calculated and reference the corresponding figures or tables in the text.

8. **Experiments Compute Resources**

   Question: For each experiment, does the paper provide sufficient information on the computer resources (type of compute workers, memory, time of execution) needed to reproduce the experiments?

   Answer: [Yes]

   Justification: All experiments were conducted using AMD Ryzen 7 7735H with Radeon Graphics processors, operating at a base speed of 3.20 GHz, and equipped with 16.0 GB (15.2 GB available) of RAM.

   Guidelines:

   - The answer NA means that the paper does not include experiments.
   - The paper should indicate the type of compute workers CPU or GPU, internal cluster, or cloud provider, including relevant memory and storage.
   - The paper should provide the amount of compute required for each of the individual experimental runs as well as estimate the total compute.
   - The paper should disclose whether the full research project required more compute than the experiments reported in the paper (e.g., preliminary or failed experiments that didn't make it into the paper).

9. **Code Of Ethics**

   Question: Does the research conducted in the paper conform, in every respect, with the NeurIPS Code of Ethics `https://neurips.cc/public/EthicsGuidelines`?

   Answer: [Yes]

   Justification: Our research complies with the NeurIPS Code of Ethics.

   Guidelines:

   - The answer NA means that the authors have not reviewed the NeurIPS Code of Ethics.
   - If the authors answer No, they should explain the special circumstances that require a deviation from the Code of Ethics.
   - The authors should make sure to preserve anonymity (e.g., if there is a special consideration due to laws or regulations in their jurisdiction).

10. **Broader Impacts**

    Question: Does the paper discuss both potential positive societal impacts and negative societal impacts of the work performed?

Answer: [NA]

Justification: Our papers are basic research.

Guidelines:

- The answer NA means that there is no societal impact of the work performed.
- If the authors answer NA or No, they should explain why their work has no societal impact or why the paper does not address societal impact.
- Examples of negative societal impacts include potential malicious or unintended uses (e.g., disinformation, generating fake profiles, surveillance), fairness considerations (e.g., deployment of technologies that could make decisions that unfairly impact specific groups), privacy considerations, and security considerations.
- The conference expects that many papers will be foundational research and not tied to particular applications, let alone deployments. However, if there is a direct path to any negative applications, the authors should point it out. For example, it is legitimate to point out that an improvement in the quality of generative models could be used to generate deepfakes for disinformation. On the other hand, it is not needed to point out that a generic algorithm for optimizing neural networks could enable people to train models that generate Deepfakes faster.
- The authors should consider possible harms that could arise when the technology is being used as intended and functioning correctly, harms that could arise when the technology is being used as intended but gives incorrect results, and harms following from (intentional or unintentional) misuse of the technology.
- If there are negative societal impacts, the authors could also discuss possible mitigation strategies (e.g., gated release of models, providing defenses in addition to attacks, mechanisms for monitoring misuse, mechanisms to monitor how a system learns from feedback over time, improving the efficiency and accessibility of ML).

11. **Safeguards**

    Question: Does the paper describe safeguards that have been put in place for responsible release of data or models that have a high risk for misuse (e.g., pretrained language models, image generators, or scraped datasets)?

    Answer: [NA]

    Justification: The study does not address this issue.

    Guidelines:

    - The answer NA means that the paper poses no such risks.
    - Released models that have a high risk for misuse or dual-use should be released with necessary safeguards to allow for controlled use of the model, for example by requiring that users adhere to usage guidelines or restrictions to access the model or implementing safety filters.
    - Datasets that have been scraped from the Internet could pose safety risks. The authors should describe how they avoided releasing unsafe images.
    - We recognize that providing effective safeguards is challenging, and many papers do not require this, but we encourage authors to take this into account and make a best faith effort.

12. **Licenses for existing assets**

    Question: Are the creators or original owners of assets (e.g., code, data, models), used in the paper, properly credited and are the license and terms of use explicitly mentioned and properly respected?

    Answer: [NA]

    Justification: The study does not address this issue.

    Guidelines:

    - The answer NA means that the paper does not use existing assets.
    - The authors should cite the original paper that produced the code package or dataset.
    - The authors should state which version of the asset is used and, if possible, include a URL.

- The name of the license (e.g., CC-BY 4.0) should be included for each asset.
- For scraped data from a particular source (e.g., website), the copyright and terms of service of that source should be provided.
- If assets are released, the license, copyright information, and terms of use in the package should be provided. For popular datasets, `paperswithcode.com/datasets` has curated licenses for some datasets. Their licensing guide can help determine the license of a dataset.
- For existing datasets that are re-packaged, both the original license and the license of the derived asset (if it has changed) should be provided.
- If this information is not available online, the authors are encouraged to reach out to the asset's creators.

13. **New Assets**

    Question: Are new assets introduced in the paper well documented and is the documentation provided alongside the assets?

    Answer: [NA]

    Justification: The study does not address this issue.

    Guidelines:

    - The answer NA means that the paper does not release new assets.
    - Researchers should communicate the details of the dataset/code/model as part of their submissions via structured templates. This includes details about training, license, limitations, etc.
    - The paper should discuss whether and how consent was obtained from people whose asset is used.
    - At submission time, remember to anonymize your assets (if applicable). You can either create an anonymized URL or include an anonymized zip file.

14. **Crowdsourcing and Research with Human Subjects**

    Question: For crowdsourcing experiments and research with human subjects, does the paper include the full text of instructions given to participants and screenshots, if applicable, as well as details about compensation (if any)?

    Answer: [NA]

    Justification: The study does not address this issue.

    Guidelines:

    - The answer NA means that the paper does not involve crowdsourcing nor research with human subjects.
    - Including this information in the supplemental material is fine, but if the main contribution of the paper involves human subjects, then as much detail as possible should be included in the main paper.
    - According to the NeurIPS Code of Ethics, workers involved in data collection, curation, or other labor should be paid at least the minimum wage in the country of the data collector.

15. **Institutional Review Board (IRB) Approvals or Equivalent for Research with Human Subjects**

    Question: Does the paper describe potential risks incurred by study participants, whether such risks were disclosed to the subjects, and whether Institutional Review Board (IRB) approvals (or an equivalent approval/review based on the requirements of your country or institution) were obtained?

    Answer: [NA]

    Justification: The study does not address this issue.

    Guidelines:

    - The answer NA means that the paper does not involve crowdsourcing nor research with human subjects.

- Depending on the country in which research is conducted, IRB approval (or equivalent) may be required for any human subjects research. If you obtained IRB approval, you should clearly state this in the paper.
- We recognize that the procedures for this may vary significantly between institutions and locations, and we expect authors to adhere to the NeurIPS Code of Ethics and the guidelines for their institution.
- For initial submissions, do not include any information that would break anonymity (if applicable), such as the institution conducting the review.