

# Contents

<b>1</b>	<b>Introduction</b>	<b>2</b>
1.1	Prior Work and Our Contributions . . . . .	2
<b>2</b>	<b>Setup</b>	<b>3</b>
2.1	Notation and Definitions . . . . .	3
2.2	IV Assumptions and Two-Sample MR . . . . .	3
2.3	Bounds on Average Treatment Effect . . . . .	5
<b>3</b>	<b>Properties of Bounds from Summary-Level Data</b>	<b>6</b>
3.1	Bounds from Bivariate Data . . . . .	7
<b>4</b>	<b>Improving Bounds With Multiple IVs</b>	<b>9</b>
<b>5</b>	<b>What can you do with summary-level data for bounds? A Quasi-Bayesian Path to More Information</b>	<b>11</b>
5.1	Sampling Procedure . . . . .	11
5.2	Single IV Case . . . . .	13
5.3	Multiple IV Case . . . . .	15
<b>6</b>	<b>Data Analysis</b>	<b>15</b>
6.1	Smoking effect on depression . . . . .	16
6.2	Smoking effect on lung cancer . . . . .	22
<b>7</b>	<b>Conclusion and Practical Considerations</b>	<b>25</b>
<b>A</b>	<b>Proof of Theorem 3.1</b>	<b>27</b>
<b>B</b>	<b>Exploration of Scenarios Where Bounds are Flipped</b>	<b>29</b>
<b>C</b>	<b>More details for smoking on depression example</b>	<b>29</b>
<b>References</b>		<b>30</b>

# 1 Introduction

In many research settings, the end goal is often to assess the treatment (or causal) effect of some treatment or exposure on a specific outcome. The challenges present when estimating causal effects are great and many. The Gold Standard for obtaining good estimates of causal effects is the completely randomized trial, where the treatment is randomly assigned to half the subjects, but in many settings, such as epidemiological studies, such a design is not feasible. For example, a study exploring the negative effects of smoking on depression (Wootton et al. 2019) would not be possible to conduct through a completely randomized trial due to ethical concerns. In such settings, epidemiologists have to rely on observational data, which introduces the concern of unmeasured confounders.

To combat unmeasured confounders, Instrumental Variable (IV) methods have been utilized in many fields. The IV model itself is rather simple, but powerful. With few assumptions, it enables us to find non-parametric bounds on the average treatment effect which, in a setting where instrument, exposure and outcome all are binary, rule out at least half of the possible values. While instrumental variable methods have historically been very popular in the field of Economics, lately they have gained traction in the field of epidemiology through Mendelian randomization (MR) studies.

MR studies use genetic variants as instruments to estimate the causal effect of an exposure, or risk factor, on an outcome, often a disease. The cornerstone of Mendelian randomization is the idea that genotypes are randomly assigned when passed on from parents to offspring at meiosis. This makes genetic variants excellent candidates for instruments when the exposure of interest is environmental, and in the world of epidemiology, where the complexity of problems only increases with the inclusion of genetic variants, the non-parametric nature of IV bounds provide a unique opportunity to avoid various modeling assumptions that are often hard to check and justify. Non-parametric bounds also only rely on summary statistics, making this approach very desirable when utilizing genetic variants as we avoid the privacy concerns that often arise when dealing with genetic data.

Another benefit to MR methods that is often highlighted in the literature is the ability to work with two separate data sources, one providing observations of the exposure and instrument, and one providing observations of the outcome and instrument (Davies, Holmes, and Smith 2018). This enables researchers to draw on the already very large number of available data sets from GWAS studies, which often include data on just one variable together with genetic markers. Most work in deriving non-parametric bounds is based on the assumption that observations of the triplet of variables are available. I.e. for traditional bounds to be useful, values of exposure, instrument, and outcome have to be observed from the same subjects. For us to be able to utilize non-parametric methods bounds in an MR analysis based on results from GWAS studies, these need to be expressed in terms of summary data from two sets of bivariate data sources. Fortunately, flexible methods for finding non-parametric bounds exist, and these allow us to obtain and calculate such bounds.

The combination of two sample MR data and non-parametric bounds is a very intriguing one. The vast amount of already available summary statistics from GWAS studies enables us to explore a lot of interesting questions. The minimal set of assumptions needed for non-parametric bounds is a stark contrast to many other approaches utilizing genetic markers as instrumental variables. Minimizing the set of assumptions, which are often very hard to verify or even justify, is a definite plus, especially when trying to combine different data sources, as this can often lead to necessitate an even larger set.

## 1.1 Prior Work and Our Contributions

The use of non-parametric bounds is not new. Swanson et al. (2018) provide a nice overview of these, and include sets of bounds derived from different sets of assumptions. These assumptions vary substantially, and the resulting bounds come with different characteristics. The weakest set of assumptions result in what is known as the Balke-Pearl bounds, first presented by Balke and Pearl (1993), for which the width is always  $1 - ST$ , while the strongest set of assumptions allow for point identification of the average treatment effect.

The work presented here mainly focus on a framework with assumptions similar to those used to obtain the Balke-Pearl bounds.

Common for all the scenarios covered by Swanson et al. (2018) is that they are all based on joint observations of exposure, outcome, and instrument, and all consider only binary instruments. Though non-parametric bounds of the average treatment effect have been presented in scenarios where the instrument is categorical with an arbitrary number of categories (Richardson and Robins 2014), and in a scenario where observations on exposure and instrument, and outcome and instrument are obtained separately (Ramsahai 2012), a description of the behavior of these bounds seems to be missing from the literature.

In this paper, we will explore the behavior of non-parametric bounds of the average treatment effect in settings inspired by the practical constraints present in Mendelian randomization studies. That is, we will keep our focus on data obtained from two bivariate sources, and where the instrument is not restricted to be binary. Particularly, we provide a more in-depth exploration of the width of these bounds, what we can expect to learn, and if we stand to gain information by utilizing multiple IVs, as in the case of Mendelian randomization, many potential IVs are available.

## 2 Setup

### 2.1 Notation and Definitions

In the following, let  $X$  and  $Y$  be binary exposure and outcome, respectively,  $Z$  be a categorical instrumental variable taking values in  $\{0, 1, \dots, k - 1\}$ , and  $U$  an unmeasured confounder for the effect of  $X$  on  $Y$ . No assumptions about the structure of  $U$  are made.

We are interested in bounding the average treatment effect (ATE)

$$\text{ATE} = E[Y^1 - Y^0],$$

where  $Y^1$  is the counterfactual outcome for a subject had the subject been exposed ( $X = 1$ ), and  $Y^0$  is the counterfactual outcome had the subject not been exposed ( $X = 0$ ). The counterfactual outcomes of  $X$  are denoted similarly using  $X^z$  for the counterfactual outcome of  $X$  if  $Z = z$ .

Furthermore, we will be working with a simple measure of strength of the IV  $Z$  on the exposure  $X$ . We say that the strength of  $Z$  on  $X$  is  $\text{ST} = \max_{z_1, z_2} |P(X = 1|Z = z_1) - P(X = 1|Z = z_2)|$ .

### 2.2 IV Assumptions and Two-Sample MR

Although bounds can be derived in settings where some of the following assumptions are relaxed (Ramsahai 2012), we will be working with the following set of assumptions:

- the instrumental variable  $Z$  is relevant, i.e. correlated with the exposure  $X$ ,

$$Z \not\perp X \tag{A1}$$

- the instrumental variable  $Z$  is independent of the confounder  $U$ ,

$$Z \perp U \tag{A2}$$

which implies  $Z \perp Y^{z,x}$  for all  $x, z$ .

- Marginal Stochastic Exclusion,

$$E[Y^{z,x}] = E[Y^{z',x}] \text{ for all } x, z, z', \quad (\text{A3})$$

where  $Y^{z,x}$  is the counterfactual outcome if  $X = x$  and  $Z = z$ ,

- Stable Unit Treatment Value Assumption (SUTVA)

$$Y = \sum_{x,z} I[Z = z, X = x] Y^{x,z} \quad (\text{A4})$$

For Mendelian randomization studies based on GWAS results, the credibility of assumption (A1) can be based on the seemingly high replicability of GWAS findings (Marigorta et al. 2018).

Assumption (A2) can be justified, at least to some extent, in many cases based on biological reasons. Since an individual's genotype is, in many cases, independently assigned at conception, the independence of a genetic variant from a large set of potential confounders can be argued to be a reasonable assumption. For example, many socioeconomic and behavioral characteristics that often confound exposure/outcome relationships can be reasonably assumed independent of genetic variants. It is important to note that a similar argument cannot always be made for other potential confounders.

Assumption (A3), which states that there is no effect of the instrument  $Z$  on the outcome  $Y$  other than that through the exposure  $X$ , is potentially violated through Linkage Disequilibrium (LD). LD refers to the correlation of allelic states at different loci. If the genetic variant that is proposed to be an instrument is in LD with another genetic variant, which in turn is correlated with the outcome, assumption (A3) could be violated.

The validity of assumptions (A4) and (??) is harder, if not impossible, to establish through data, and both may be viewed as necessary assumptions that must be justified based on a more heuristic argument.

For a more in-depth discussion of the validity of some of these assumptions in a Mendelian randomization setting, see Lawlor et al. (2008).

In the following, we will refer to two different data settings: the typical MR setting, where we have two separate data sources, one providing information of  $(X, Z)$  and one providing information of  $(Y, Z)$ , and the setting that has traditionally been explored using non-parametric bounds, where we have information on the triplet of variables  $(X, Y, Z)$ . We will refer to the former as bivariate data, and the latter as trivariate data.

Two additional assumptions will be referenced throughout this paper. Monotonicity of the effect of  $Z$  on  $X$  assumes

$$P(X = 1|Z = z, U) \leq P(X = 1|Z = z + 1, U), \quad (1)$$

and monotonicity of the effect of  $Z$  on  $Y$  assumes

$$P(Y = 1|Z = z, U) \leq P(Y = 1|Z = z + 1, U), \quad (2)$$

Both of these assumptions are fairly common in general IV literature, and often implicitly assumed in Mendelian randomization analyses through the models utilized (though the direction might be flipped in some cases).

### 2.3 Bounds on Average Treatment Effect

We will briefly review the method presented by Ramsahai (2012). Since our main focus is the bivariate data setting, we will demonstrate the method in this setting here. Similar arguments can be made to arrive at bounds from trivariate data.

Let  $\vec{\tau}^* = \left( P(Y = 1|X = 0, U), P(Y = 1|X = 1, U), P(X = 1|Z = 0, U), \dots, P(X = 1|Z = k - 1, U) \right) \in [0, 1]^{2+k}$  and  $\vec{v}^* = \left( P(Y = 0|Z = 0, U), \dots, P(Y = 1|Z = k - 1, U), P(X = 0|Z = 0, U), \dots, P(X = 1|Z = k - 1, U), \alpha^* \right)$  where

$$\alpha^* = P(Y = 1|X = 1, U) - P(Y = 1|X = 0, U).$$

Since  $U \perp Z$ ,  $E_U[P(X = x|Z = z, U)] = P(X = x|Z = z)$  and  $E_U[P(Y = y|Z = z, U)] = P(Y = y|Z = z)$ . Let  $\vec{v} = E_U[\vec{v}^*] = \left( P(Y = 0|Z = 0), \dots, P(Y = 1|Z = k - 1), P(X = 0|Z = 0), \dots, P(X = 1|Z = k - 1), \alpha \right)$ , where

$$\begin{aligned} \alpha &= E_U[P(Y = 1|X = 1, U) - P(Y = 1|X = 0, U)] \\ &= E[Y^1] - E[Y^0] = \text{ATE}. \end{aligned}$$

Note that while  $\vec{\tau}^*$  and  $\vec{v}^*$  are both entirely unobservable,  $\vec{v}$  consists of  $k$  observable values, and one unobservable value, the ATE.

By Marginal Exchangeability of  $Y^{z,x}$  (A2),

$$P(X = x, Y = y|Z = z, U) = P(Y = 1|X = x, U)P(X = x|Z = z, U),$$

which means we can define a mapping  $f : [0, 1]^{2+k} \mapsto \mathcal{V}$  such that  $f(\vec{\tau}^*) = \vec{v}^*$  as

$$f(y_0, y_1, x_0, x_1, \dots, x_{k-1}) = \begin{pmatrix} (1 - y_0) \cdot (1 - x_0) + (1 - y_1) \cdot x_0 \\ y_0 \cdot (1 - x_0) + y_1 \cdot x_0 \\ \vdots \\ (1 - y_0) \cdot (1 - x_{k-1}) + (1 - y_1) \cdot x_{k-1} \\ y_0 \cdot (1 - x_{k-1}) + y_1 \cdot x_{k-1} \end{pmatrix}$$

We define  $\mathcal{V} = f([0, 1]^{2+k})$ .

Since  $\vec{v} = E_U[\vec{v}^*]$ ,  $\vec{v}$  must be a convex combination of  $\vec{v}^*$ . Let  $\mathcal{H}$  be the convex hull of  $\mathcal{V}$ . Then  $\vec{v}$  will be in  $\mathcal{H}$ .

Now, let  $\hat{\mathcal{T}}$  be the set of extreme vertices of  $[0, 1]^{2+k}$ ,  $\hat{\mathcal{V}} = f(\hat{\mathcal{T}})$ , and  $\hat{\mathcal{H}}$  be the convex hull of  $\hat{\mathcal{V}}$ . By Theorem 1 in Appendix B of Ramsahai (2012),  $\mathcal{H} = \hat{\mathcal{H}}$ . This means that  $\vec{v} \in \hat{\mathcal{H}}$ . Utilizing a program such as Polymake, we can describe  $\mathcal{H}$  with a set of inequalities, which give us constraints that  $\vec{v}$  must satisfy.

This means that we can obtain inequalities that the components of  $\vec{v}$  must satisfy by describing the extreme vertices of  $[0, 1]^{2+k}$ , map them to  $\mathcal{V}$  using the relatively simple function  $f$ , and then use polymake to find inequalities that characterize the convex hull of  $f([0, 1]^{2+k})$ . This gives us a set of inequalities involving the components of  $\vec{v}$ . Some of these will be verifiable, as they will not include the only unobservable quantity  $\alpha$ . Others will not be verifiable, but will allow us to obtain bounds on the unobservable quantity  $\alpha$  using the observable entries of  $\vec{v}$ .

This exact same approach can be used in the trivariate setting, and when imposing different extra assumptions, such as monotonicity of the effect of  $Z$  on  $X$  (1) or  $Z$  on  $Y$  (2). The latter is done by imposing these assumption on  $\hat{\mathcal{V}}$  by removing vectors that violate these extra assumptions.

One important thing to note here is that these expressions do not always result in a valid set of bounds. In our simulations we found that a small fraction of the simulated probability distributions result in bounds where the lower limit is larger than the upper limit. Whether this is a problem in practice remains to be seen, but we are not aware of any real life data sets giving rise to bounds with this behavior. The cause for this is not clear, but among possible explanations is the existence of an assumption that is not captured in the checkable constraints. It is only natural to conclude that one or more assumptions are violated when one encounters a scenario where the bounds are flipped. For more, see Appendix B.

We implemented this approach using R version 4.0.2 (R Core Team 2020) for the high level calculations, and Polymake (Assarf et al. 2017) to obtain the inequalities.

### 3 Properties of Bounds from Summary-Level Data

Non-parametric bounds obtained from trivariate data sources have been thoroughly explored in the past for binary instruments. These bounds come with a few very desirable properties. For one, under the assumptions presented in Section 2.2, the width is guaranteed to be less than  $1 - ST = P(X = 0|Z = 1) - P(X = 1|Z = 0)$  (Balke and Pearl 1993). The bounds are computationally easy to calculate, and rely only on summary level data. In particular, with values of  $P(X = x, Y = y|Z = z)$ , non-parametric bounds can be obtained. As mentioned, this allows us to avoid many of the privacy concerns that often arise when handling genetic data.

Scenarios where  $k > 2$  has, to our knowledge, not been thoroughly explored. Richardson and Robins (2014) provide bounds for a general categorical instrumental variable, but the behavior of the bounds in this settings is not described in detail. Since the main scope of this paper is to explore bounds from bivariate data sources, we will not spend much time on the trivariate case, but will note that from simulations, it seems that the width of trivariate bounds are indeed still bounded by  $1 - ST$  for  $k = 3$  and  $k = 4$  (Figure 1).

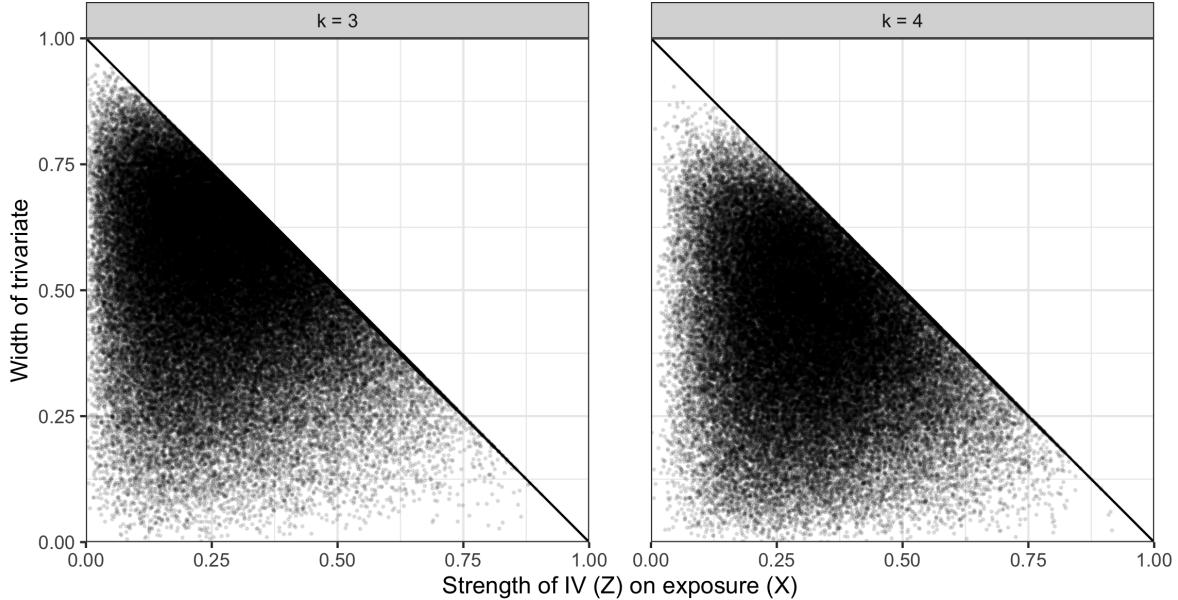


Figure 1: The results of calculating widths of bounds.  $10^5$  distributions of  $(X, Y|Z)$  were randomly generated for both  $k = 3$  and  $k = 4$ . For  $k = 3$ , 11,741 of these violated one or more of the constraints. For  $k = 4$ , 21,779 violated one or more of the constraints, and 37 resulted in an upper bound that is smaller than the lower bound. These are not included here. Black line indicates Width =  $1 - ST$ .

In Mendelian randomization, trivariate data sources are scarce. Bivariate data sources, on the other hand, are plentiful. The rest of this section is dedicated to explore the behavior of non-parametric bounds derived from bivariate data sources. These were first introduced by Ramsahai (2007).

### 3.1 Bounds from Bivariate Data

First, we seek to examine the information one can potentially obtain from bounds found using a single instrumental variable, when only summaries from bivariate data are available. We are particularly interested in whether we can gain any insights into the direction and magnitude of the ATE. One crucial quantity in this quest is the width of the bounds obtained. Wide bounds provide less information about the magnitude, and are much less likely to provide any information regarding direction as compared to narrower bounds. Here, we will construct bounds from many sets of randomly generated values of  $P(X = 1|Z = z)$  and  $P(Y = 1|Z = z)$ .

Following the approach from Ramsahai (2012) as outlined in Section 2.3, we obtain the following bounds on the average treatment effect from the quantities  $P(X = 1|Z = z)$  and  $P(Y = 1|Z = z)$ ,  $z = 0, 1, 2$ :

$$\max \left\{ \begin{array}{ll} \max_{i \neq j} & P(Y = 1|Z = i) - 2 \cdot P(Y = 1|Z = j) - 2 \cdot P(X = 1|Z = j) \\ \max_{i \neq j} & P(Y = 1|Z = i) + P(X = 1|Z = i) - P(Y = 1|Z = j) - P(X = 1|Z = j) - 1 \\ \max_{i \neq j} & 2 \cdot P(Y = 1|Z = i) + 2 \cdot P(X = 1|Z = i) - P(Y = 1|Z = j) - 3 \\ \max_i & -P(Y = 1|Z = i) - P(X = 1|Z = i) \\ \max_i & P(Y = 1|Z = i) + P(X = 1|Z = i) - 2 \end{array} \right\}$$

$$\leq \alpha \leq$$

$$\min \left\{ \begin{array}{ll} \min_{i \neq j} & P(Y = 1|Z = i) - 2 \cdot P(Y = 1|Z = j) + 2 \cdot P(X = 1|Z = j) + 1 \\ \min_{i \neq j} & P(Y = 1|Z = i) + 2 \cdot P(Y = 1|Z = j) - 2 \cdot P(X = 1|Z = j) + 1 \\ \min_{i \neq j} & P(Y = 1|Z = i) - P(X = 1|Z = i) + P(X = 1|Z = j) - P(Y = 1|Z = j) + 1 \\ \min_i & P(X = 1|Z = i) - P(Y = 1|Z = i) + 1 \\ \min_i & P(Y = 1|Z = i) - P(X = 1|Z = i) + 1 \end{array} \right\}$$

Furthermore, we obtain the following checkable constraints:

$$\min \left\{ \begin{array}{ll} \min_{i \neq j} & P(Y = 1|Z = i) - P(X = 1|Z = i) - P(Y = 1|Z = j) - P(X = 1|Z = j) + 2 \\ \min_{i \neq j} & P(Y = 1|Z = i) + P(X = 1|Z = i) - P(Y = 1|Z = j) + P(X = 1|Z = j) \\ \min_i & P(X = 1|Z = i) \\ \min_i & P(Y = 1|Z = i) \\ \min_i & 1 - P(X = 1|Z = i) \\ \min_i & 1 - P(Y = 1|Z = i) \end{array} \right\} \geq 0 \quad (3)$$

We notice that the constraints from the law of probability are recovered (the last four expressions above) along with 12 non-trivial constraints.

These bounds involve 24 different expressions on both the lower and upper end, making an algebraic exploration of the width very challenging. However, by imposing the two monotonicity assumptions (1) and (2), the bounds reduce to just three on the lower end and three on the upper end:

$$\begin{aligned}
& \max \left\{ \begin{array}{l} -P(Y = 0|Z = 2) - P(Y = 1|Z = 0) + P(X = 0|Z = 0) - P(X = 0|Z = 2) \\ P(Y = 0|Z = 0) - 2 \cdot P(Y = 0|Z = 2) - P(X = 0|Z = 2) \\ -P(Y = 0|Z = 2) - 2 \cdot P(Y = 1|Z = 0) + P(X = 0|Z = 0) \end{array} \right\} \\
& \leq ATE \leq \\
& \min \left\{ \begin{array}{l} 1 + P(Y = 0|Z = 0) - P(X = 0|Z = 0) \\ 1 + P(Y = 0|Z = 0) - P(Y = 0|Z = 2) - P(X = 0|Z = 0) + P(X = 0|Z = 2) \\ 1 - P(Y = 0|Z = 2) + P(X = 0|Z = 2) \end{array} \right\}
\end{aligned}$$

From these, the following result follows:

**Theorem 3.1.** *If the effects of  $Z$  on  $X$  and of  $Z$  on  $Y$  are both monotonically increasing (that is, (1) and (2) hold), the width of the bounds obtained from bivariate data is bounded from above by  $2 - 2 \cdot ST$ . In particular, the width of the bounds is guaranteed to be less than 1 only when the strength is greater than 0.5.*

*Proof.* The proof is presented in Appendix A. It is a brute force proof relying on going through all possible pairs of upper and lower bounds. With the two monotonicity assumptions the number of expressions in the upper and lower bounds is only three for each leading to only nine possible expressions for the width.  $\square$

Note that this result does not rule out the possibility that the bounds from bivariate data with weak IVs have width less than 1. It simply states that, for weak IVs, there are no guarantees.

To explore the behavior of the width of the bounds without imposing the two monotonicity assumptions, we turn to numerical simulations. We randomly generate 10,000 sets of values of  $P(X = 1|Z = z)$  and  $P(Y = 1|Z = z)$ , and calculate the corresponding bounds. Figure 2 shows the bounds for 9,877 of these. The remaining 123 resulted in scenarios where the lower bounds were larger than the upper bounds.

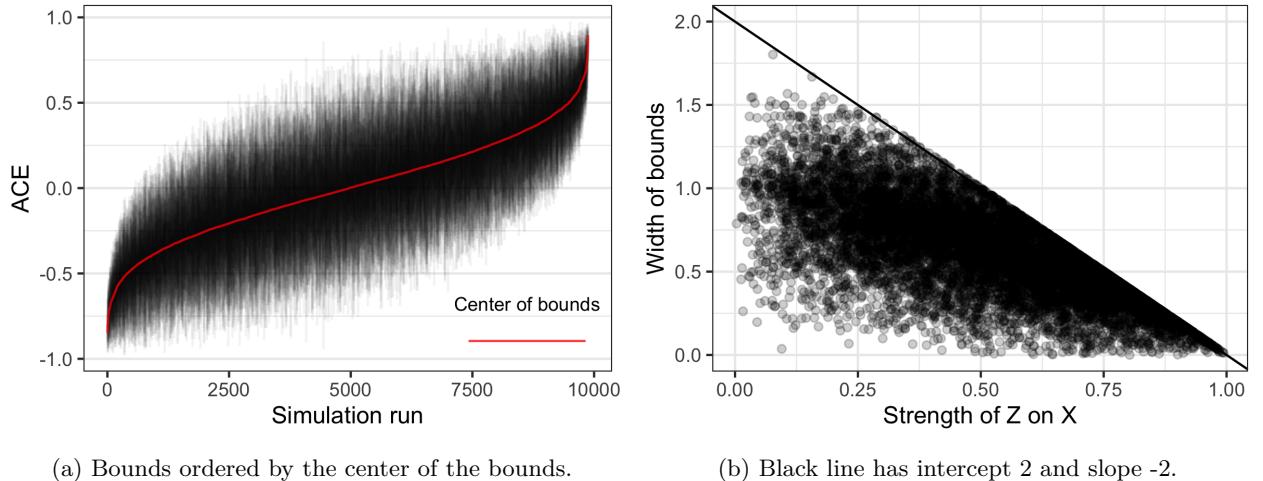


Figure 2: 10,000 values for bivariate distributions were randomly generated such that no constraints were violated. Of these, 123 resulted in bounds where the lower bound was greater than the upper bounds. These have been removed from these plots.

Figure 2a show all bounds sorted by the center of the bounds. What is interesting about this figure is that the entire interval -1 to 1 is covered, and the widths of the bounds vary quite a bit. In many cases, we do indeed see widths greater than 1. It is important to note that the center of the bounds carry no real significance in this context, but is simply used to sort these bounds for illustrative purposes.

Figure 2b show the widths of the same 9,877 bounds plotted against the strength of the instruments. The black line overlaid the plot has intercept 2 and slope -2, which is the upper bound for the width found

when including the two monotonicity assumptions. Here we see that this upper bound might very well hold even when we do not include these two assumptions. Here, it is even more evident that the width exceeds 1 in many cases.

In Table 1, we see the proportion of the intervals presented on Figure 2 with width greater than 1, 0.75, and 0.5, stratified by strength. This shows that while not guaranteed, it is not impossible to observe bounds with width less than 1. However, for IVs with strength less than 0.1, it is just above 46% of the randomly generated distributions that lead to widths greater than 1, while only  $\approx 10\%$  result in intervals with width less than 0.5.

Strength	Proportion of bounds with width greater than...		
	1	0.75	0.5
[0,0.05]	0.470	0.783	0.892
(0.05,0.1]	0.461	0.722	0.894
(0.1,0.25]	0.323	0.703	0.922
(0.25,0.5]	0.136	0.495	0.836
(0.5,1]	0.000	0.074	0.371

Table 1: Proportion of bounds from distributions where width is greater than 1, 0.75, and 0.5 stratified by strength of the instrument  $Z$  on the exposure  $X$ .

In the context of MR analyses, this is a rather depressing result. Most IVs encountered in MR analyses are very weak, which means that the chances that bivariate bounds from MR analyses are informative with width less than 1 are very slim. It should also be noted that while a set of bounds with width greater than 1 provides basically no information, a set of bounds with width just below 1 does not provide much more information. Due to the non-parametric nature of the bounds, the interval  $[-0.1, 0.8]$  does not indicate that the average treatment effect is more likely to be positive than the interval  $[-0.7, 0.2]$ .

## 4 Improving Bounds With Multiple IVs

In Section 3, we found that non-parametric bounds derived from bivariate data require rather strong instrumental variables to guarantee useful results. It seems that there simply is not enough information in bivariate data. One natural question is to ask is whether we can aggregate the information from multiple instrumental variables to obtain a set of improved bounds. In this section, we will consider one approach to do just that, and try to characterize what gains can be expected.

To maintain the close connection to MR analyses, we will consider a logistic model that is often used in MR analyses. Specifically, let

$$\text{logit}(P(X = 1|Z_1 = z_1, \dots, Z_n = z_n)) = \beta_0 + \sum_i \beta_i z_i$$

$$\text{logit}(P(Y = 1|X = x)) = \gamma_0 + \gamma_1 x,$$

where  $\text{logit}(a) = \frac{1}{1+\exp(-a)}$ ,  $y \in \{0, 1\}$ ,  $x \in \{0, 1\}$ ,  $z_i \in \{0, 1, 2\}$ , and  $\beta_i, \gamma_j \in \mathbb{R}$ . This particular model is often used in GWAS studies that focus on associations between genetic variants and binary phenotypes [REFERENCE NEEDED, MAYBE REFERENCE PLINK SOFTWARE?]. Furthermore,  $P(Z_j = 0) = P(Z_j = 2) = 0.25$  and  $P(Z_j = 1) = 0.5$ , which is in line with what would be expected in a Mendelian randomization scenario where pairs of binary alleles are randomly chosen. Here, we will use  $\gamma_0 = -2$ ,  $\gamma_1 = 0.2$ .

To avoid any unpleasant surprises due to randomness from simulating actual data, we decided to integrate (either exactly or numerically depending on the value of  $n$ ) to find the probabilities  $P(Y = 1|Z_j = z_j)$  and  $P(X = 1|Z_j = z_j)$ . We draw the coefficients  $\beta_i \sim \text{Uniform}(0, 1/n)$ . This is a scenario similar to what we

encounter in the MR setting. Figure 3 shows the resulting bounds for the three different values of  $n$  plotted against the strengths of the IVs.

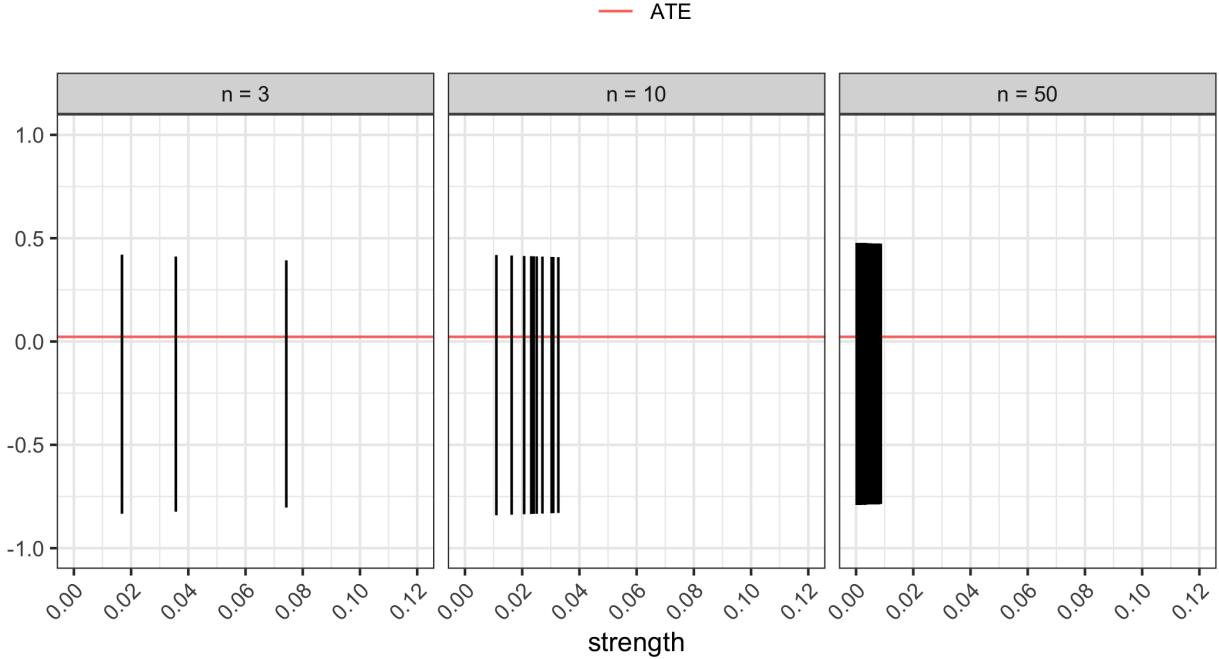


Figure 3: Bounds based on probabilities derived from the logistic model. Here, the coefficients are randomly chosen as  $\text{Uniform}(0, 1/n)$  for different values of  $n$ .

Figure 3 shows that when many valid IVs are present, the individual bivariate upper and lower bounds seems to be monotonically decreasing and increasing, respectively, as the strength of the IV increases. This means intersections of intervals from many IVs will result in an interval very similar, if not identical, to the most narrow of the individual bounds, which in turn will be the interval derived using the strongest of the IVs.

Another interesting, although not surprising, observation is the shrinking of the strengths of the individual instruments when the total number of instruments included increases. With many instruments, the linear combination  $\beta_0 + \sum_i \beta_i z_i$  will generally be relatively large, simply by chance. This means that the effect on  $P(X = 1|Z_1, \dots, Z_n)$  of a single instrument being 1 instead of 0 is quite small. This is important. In Section 3.1, we saw that chances of obtaining informative bounds with weak instruments are slim. If one believes the true model includes many instruments, chances are that these are relatively weak.

In MR analyses based on bivariate data from GWAS results, this indicates that aggregating information from multiple instruments in a simple manor, such as taking interceptions, will not result in more information than simply using the best of the individual bounds. This strategy is only appropriate in a situation where all the proposed instruments are valid. If we on the other hand want to protect ourselves against using bounds from a potentially invalid instrument by taking the union of the bounds from many proposed instruments, we would end up with very conservative bounds. This would in turn provide even less information about the target, namely the ATE. This is partly due to the lack of guarantees on the width of the bounds obtained from bivariate data (Section 3.1), which means it is very unlikely that a collection of instruments all provide informative bounds. When combining bounds through unions, only attributes shared among all bounds will be preserved, so if just one weak instrument is included, the resulting union bounds will provide very little information.

## 5 What can you do with summary-level data for bounds? A Quasi-Bayesian Path to More Information

Although bivariate data does not provide enough information for the derived bounds to guarantee the same desirable and useful qualities as their trivariate counterparts, they still provide some information about the trivariate data distribution. In this section, we will demonstrate a simple approach to use the bivariate data to describe the set of possible trivariate distributions, and their bounds.

The idea is relatively simple: we wish to use the known quantities  $P(X = x|Z = z)$  and  $P(Y = y|Z = z)$  to get a sense of which possible distributions  $P(X = x, Y = y|Z = z)$  marginalize to the known distributions, while satisfying the constraints obtained from the polymake program. By repeatedly, and independently, drawing such trivariate distributions, we can get a sense of the bounds trivariate data could give. Using this, questions about the potential information one could gain from knowing the full trivariate distribution can be answered.

### 5.1 Sampling Procedure

The joint conditional distribution  $P(X = x, Y = y|Z = z)$  can be constructed from the marginal conditional distributions  $P(X = x|Z = z)$  and  $P(Y = y|Z = z)$  if we know the values of  $\text{Cov}(X, Y|Z = z)$  for each  $z$ , since

$$P(X = x, Y = y|Z = z) = P(X = x|Z = z)P(Y = y|Z = z) + (2 \cdot I[x = y] - 1)\text{Cov}(X, Y|Z = z). \quad (4)$$

Since these covariances are essentially completely unknown to us, we draw them uniformly from the set of values that result in the joint conditional distribution of  $(X, Y|Z)$  being an actual probability distribution satisfying the verifiable constraints from (3).

This set of values is not trivial, but fortunately we can find a superset of values that is much smaller than  $[-1, 1]^k$ . When implementing this approach, we propose a set of covariances by sampling from this superset, construct the trivariate distribution, and check if any constraints are violated. If there are any violations, the proposed set of covariances is discarded, and a new set proposed.

Combining  $0 \leq P(X = x, Y = y|Z = z) \leq 1$  for all values of  $z = 0, 1, \dots, k - 1$  with (4), we see that

$$-P(X = x|Z = z)P(Y = y|Z = z) \leq \text{Cov}(X, Y|Z = z) \leq 1 - P(X = x|Z = z)P(Y = y|Z = z)$$

when  $x = y$ , and

$$P(X = x|Z = z)P(Y = y|Z = z) - 1 \leq \text{Cov}(X, Y|Z = z) \leq P(X = x|Z = z)P(Y = y|Z = z)$$

when  $x \neq y$ . Since this holds for all  $z = 0, 1, \dots, k - 1$ , we find that  $\text{Cov}(X, Y|Z = z)$  must be such that

$$\begin{aligned} \max_z \left\{ \begin{array}{l} -P(X = 1|Z = z)P(Y = 1|Z = z) \\ -P(X = 0|Z = z)P(Y = 0|Z = z) \\ P(X = 1|Z = z)P(Y = 0|Z = z) - 1 \\ P(X = 0|Z = z)P(Y = 1|Z = z) - 1 \end{array} \right\} \\ \leq \text{Cov}(X, Y|Z = z) \leq \\ \min_z \left\{ \begin{array}{l} 1 - P(X = 1|Z = z)P(Y = 1|Z = z) \\ 1 - P(X = 0|Z = z)P(Y = 0|Z = z) \\ P(X = 1|Z = z)P(Y = 0|Z = z) \\ P(X = 0|Z = z)P(Y = 1|Z = z) \end{array} \right\} \end{aligned}$$

Furthermore, enforcing the IV inequalities  $\max_x \sum_y \max_z P(X = x, Y = y | Z = z) \leq 1$ , we get constraints on the differences between  $\text{Cov}(X, Y | Z = z_1)$  and  $\text{Cov}(X, Y | Z = z_2)$ . For any  $x = 0, 1$ , and any pair  $(z_1, z_2) \in \{0, 1, \dots, k - 1\} \times \{0, 1, \dots, k - 1\}$ , we see that  $0 \leq P(X = x, Y = 0 | Z = z_1) + P(X = x, Y = 1 | Z = z_2) \leq 1$  (where the first inequality is a result of summing two positive quantities). Again, using (4), we see that for  $x = 0$ ,

$$0 \leq P(X = 0 | Z = z_1)P(Y = 0 | Z = z_1) + \text{Cov}(X, Y | Z = z_1) + P(X = 0 | Z = z)P(Y = 1 | Z = z_2) - \text{Cov}(X, Y | Z = z_2) \leq 1, \quad (5)$$

which is equivalent to

$$\begin{aligned} & -P(X = 0 | Z = z_1)P(Y = 0 | Z = z_1) - P(X = 0 | Z = z)P(Y = 1 | Z = z_2) \\ & \leq \text{Cov}(X, Y | Z = z_1) - \text{Cov}(X, Y | Z = z_2) \leq \\ & \quad 1 - P(X = 0 | Z = z_1)P(Y = 0 | Z = z_1) - P(X = 0 | Z = z)P(Y = 1 | Z = z_2). \end{aligned}$$

A similar exercise can be done for  $x = 1$ . The result is that, for any pair of  $(z_1, z_2) \in \{0, 1, \dots, k - 1\} \times \{0, 1, \dots, k - 1\}$ , the values of  $\text{Cov}(X, Y | Z = z_1)$  and  $\text{Cov}(X, Y | Z = z_2)$  must satisfy

$$\begin{aligned} \max \left\{ \begin{array}{l} -P(X = 0 | Z = z_1)P(Y = 0 | Z = z_1) - P(X = 0 | Z = z_2)P(Y = 1 | Z = z_2) \\ P(X = 1 | Z = z_1)P(Y = 0 | Z = z_1) + P(X = 1 | Z = z_2)P(Y = 1 | Z = z_2) - 1 \\ P(X = 0 | Z = z_2)P(Y = 0 | Z = z_2) + P(X = 0 | Z = z_1)P(Y = 1 | Z = z_1) - 1 \\ -P(X = 1 | Z = z_2)P(Y = 0 | Z = z_2) - P(X = 1 | Z = z_1)P(Y = 1 | Z = z_1) \end{array} \right\} \\ \leq \text{Cov}(X, Y | Z = z_1) - \text{Cov}(X, Y | Z = z_2) \leq \\ \min \left\{ \begin{array}{l} 1 - P(X = 0 | Z = z_1)P(Y = 0 | Z = z_1) - P(X = 0 | Z = z_2)P(Y = 1 | Z = z_2) \\ P(X = 1 | Z = z_1)P(Y = 0 | Z = z_1) + P(X = 1 | Z = z_2)P(Y = 1 | Z = z_2) \\ P(X = 0 | Z = z_2)P(Y = 0 | Z = z_2) + P(X = 0 | Z = z_1)P(Y = 1 | Z = z_1) \\ 1 - P(X = 1 | Z = z_2)P(Y = 0 | Z = z_2) - P(X = 1 | Z = z_1)P(Y = 1 | Z = z_1) \end{array} \right\} \end{aligned}$$

To create a possible set of values of  $P(X = x, Y = y | Z = z)$ , we sequentially draw values for  $\text{Cov}(X, Y | Z = 0)$ ,  $\text{Cov}(X, Y | Z = 1), \dots, \text{Cov}(X, Y | Z = k - 1)$ , such that the above inequalities hold, calculate the values of  $P(X = x, Y = y | Z = z)$  using (4), and check that the constraints in (3) are satisfied. If any of the constraints are violated, the values are rejected, and the procedure repeated until we have a set of values for  $\text{Cov}(X, Y | Z = 0), \text{Cov}(X, Y | Z = 1), \dots, \text{Cov}(X, Y | Z = k - 1)$  that result in a trivariate probability distribution that satisfies the constraints in (3).

The ultimate goal of this exercise is to try to assess whether knowledge about the full trivariate probabilities would allow us to determine direction of the ATE. In most cases there is not a firm answer to this question, as some trivariate probabilities result in bounds that would, while other trivariate probability distributions result in bounds that would not. So, we are really trying to assess questions such as “given the bivariate probabilities, what is the chance that the trivariate data would allow us to determine direction?”

The approach presented here can, under the right set of assumptions, be interpreted as generating a sample from the posterior distribution over all possible trivariate distributions given the marginalized probabilities, and a uniform prior on the unknown quantities  $\text{Cov}(X, Y | Z = z)$ . This means that we can obtain posterior probabilities of certain events. In particular, we will be interested in the posterior probability that the trivariate bounds contain 0. We will use this as a heuristic measure of the loss of information in going from trivariate to bivariate data.

## 5.2 Single IV Case

To illustrate the method described in the previous section, we start with considering the single IV case. This allows us to easily explore the behavior of this method, and present a few different scenarios. In Section 5.3, we describe how this method can be used if multiple instruments are available.

Depending on the values of  $P(X = 1|X = z)$  and  $P(Y = 1|Z = z)$ , the picture this approach paints can vary dramatically, which in turn leads to very different conclusions. Here, we will consider nine different sets of values of these marginal distributions that illustrate a few different scenarios one can end up in when using this quasi-bayesian approach. The marginal distributions are presented in Table 2 below, while Table 3 shows the estimated posterior probability of the trivariate bounds containing 0 based on 1000 trivariate distributions sampled as described in Section 5.1. All trivariate bounds are shown on Figure 4.

	Column 1	Column 2	Column 3
Row a	{0.125, 0.399, 0.080}	{0.244, 0.275, 0.185}	{0.603, 0.469, 0.310}
	{0.699, 0.840, 0.742}	{0.238, 0.089, 0.146}	{0.638, 0.346, 0.719}
Row b	{0.886, 0.968, 0.874}	{0.139, 0.441, 0.334}	{0.901, 0.909, 0.935}
	{0.805, 0.822, 0.951}	{0.179, 0.359, 0.559}	{0.821, 0.810, 0.905}
Row c	{0.175, 0.079, 0.365}	{0.493, 0.911, 0.085}	{0.434, 0.045, 0.733}
	{0.599, 0.358, 0.087}	{0.360, 0.480, 0.441}	{0.747, 0.370, 0.169}

Table 2: Values of  $P(X = 1|Z = z)$  and  $P(Y = 1|Z = z)$  used to illustrate our quasi-bayesian approach. These are presented with  $\{P(X = 1|Z = 0), P(X = 1|Z = 1), P(X = 1|Z = 2)\}$  on the first row, and  $\{P(Y = 1|Z = 0), P(Y = 1|Z = 1), P(Y = 1|Z = 2)\}$  on the second row.

	Column 1	Column 2	Column 3
Row a	[-0.583, 0.338]	[-0.331, 0.814]	[-0.574, 0.468]
	100.00%	76.00%	63.20%
Row b	[-0.156, 0.758]	[-0.077, 0.693]	[-0.129, 0.897]
	100.00%	11.00%	98.00%
Row c	[-0.275, 0.24]	[-0.136, 0.214]	[-0.083, 0.112]
	100.00%	88.30%	41.00%

Table 3: For each of the nine panels displayed in figure 4, this table includes lower and upper bounds based on the bivariate data, and proportion of trivariate distributions overlapping 0.

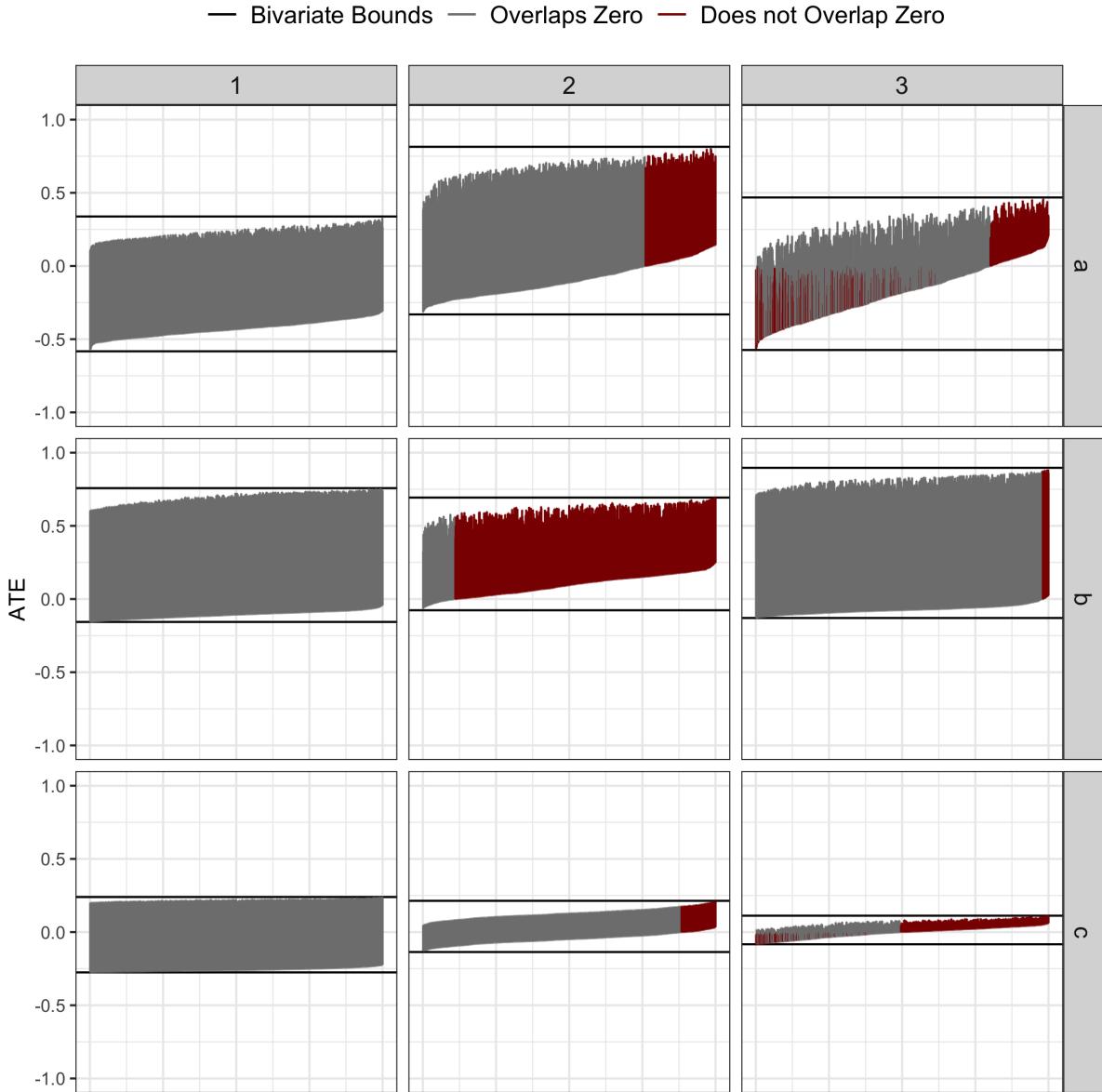


Figure 4: Trivariate bounds are constructed from the bivariate distribution by drawing values for  $\text{Cov}(X, Y|Z = z)$ ,  $z = 0, 1, 2$ . Even similar bivariate distributions can result in very different insights.

Row a shows three scenarios where the bivariate bounds are all more or less centered around zero with similar widths. However, the conclusions are rather different. Column 1 shows no trivariate distribution would allow us to determine the direction of the ATE using bounds. Column 2 indicates that about 24% of the possible trivariate distributions would allow us to determine direction, while for column 3 that number is approximately 36.8%. However, while the direction is always the same for column 2 (positive), it varies for column 3.

Row b illustrates three scenarios where the bivariate bounds are centered well above zero, and all of similar large widths. Here, we see one case where we have no hope of determining direction from trivariate bounds (column 1), one case where we are most likely to be able to determine the direction of the ATE to be positive from trivariate bounds (column 2), and one case where we are rather unlikely to be able to determine the

direction of the ATE from trivariate bounds (column 3).

Row c is similar to row a in that all bivariate bounds are centered around 0, but here all bivariate bounds are rather narrow. The three columns indicate similar conclusions as seen in row a. This shows that even with rather narrow bivariate bounds centered around 0, the intuitive conclusion that trivariate bounds would not be able to detect direction is nowhere near guaranteed to be correct.

The nine panels sets of values here indicate that there is no simple way to determine whether trivariate bounds would be useful from just the bivariate bounds. There is a wide variety of possible scenarios where similar bivariate bounds correspond to posterior distributions of trivariate distributions that indicate very different potentials of the trivariate bounds.

It is important to reflect on the interpretation of posterior probabilities. A scenario like the one resulting in the bounds presented in row b, column 2 only provides information about the trivariate bounds under the assumption that all possible valid trivariate probability distributions are equally likely. Under this assumption, it tells us that it is much more likely that the ATE is positive. It does not, however, rule out a negative value of the ATE. What it does tell us is that trivariate bounds will not be able to determine direction *if the ATE is in fact negative*. This conclusion only hinges on the correctness of the marginal probabilities,  $P(X = 1|Z = z)$  and  $P(Y = 1|Z = z)$ , and the assumptions presented in Section 2.2.

### 5.3 Multiple IV Case

Although the bivariate bounds often do not provide much information themselves, as we saw in the previous section, the little information available can sometimes provide some insights. The approach presented draws on the fact that trivariate bounds are guaranteed to be much narrower than bivariate bounds. It remains to be seen if utilizing such an approach while aggregating information from multiple IVs through intersecting bounds.

The simplest extension to the multiple IV scenario, is to simply repeat the sampling procedure presented in Section 5.1 for each proposed instrument before creating the combined bounds by taking the intersection of the pairwise bounds. This builds on one main assumption in that the two sampling procedures are done independently, and so implicitly assume that the covariances of  $X$  and  $Y$  given  $Z_1$  are independent of the covariance of  $X$  and  $Y$  given  $Z_2$ .

Specifically, say we get bounds  $(LB_{1i}, UB_{1i}), i = 1, 2, \dots, m$  by sampling  $m$  trivariate distributions based on the information we have on  $(X, Z_1)$  and  $(Y, Z_1)$ , and lower bounds  $(LB_{2i}, UB_{2i}), i = 1, 2, \dots, m$  by sampling  $m$  trivariate distributions based on the information we have on  $(X, Z_2)$  and  $(Y, Z_2)$ . We then create the intersection bounds as  $(\max_{z \in 1,2} LB_{zi}, \min_{z \in 1,2} UB_{zi}), i = 1, 2, \dots, m$ . This, under the assumption that  $\text{Cov}(X, Y|Z_1 = z)$  and  $\text{Cov}(X, Y|Z_2 = z)$  are independent of each other, gives us a sample from the posterior distribution of intersection bounds. We can use this to assess the potential usefulness of aggregating information from two sets of trivariate data,  $(X, Y, Z_1)$  and  $(X, Y, Z_2)$ , using intersection bounds.

We will illustrate this approach in the next section using data obtained from MRBase.

## 6 Data Analysis

In this section we will consider two example analyses demonstrating the approaches presented above. The data was obtained using the IEU GWAS database, which is available in R through the `TwoSampleMR` package. (Hemani et al. 2018) We will explore the non-parametric bounds obtained from bivariate data sources, and what conclusions are attainable based on our quasi-bayesian approach. To do so, we consider two examples: the effect of smoking on depression, and the effect of smoking on lung cancer.

To be able to find non-parametric bounds, we need estimates of the marginal probabilities  $P(Y = 1|Z = z)$  and  $P(X = 1|Z = z)$ . To do so, we use the `TwoSampleMR` R-package. This allows us to find studies that have explored the effects of genetic variants on the exposure and outcome variables we are interested

in. Instruments were extracted, and LD based clumping ( $r^2 \geq 0.001$  within a 10,000 kb window using  $p < 5 \times 10^{-8}$  as the level of significance) performed such that only independent instruments with significant associations are returned. The data is harmonized to make sure that the effects of the SNPs on exposure and outcome were measured with the same allele as reference. We obtain coefficients from GWAS experiments corresponding to the effects of the SNPs on the exposure, and the outcome from a logistic model. Since no intercept for these models are included in the reported results, but marginal proportions of the outcome, exposure, and allele frequencies are, we find the intercepts by solving  $P(X = 1) = \sum_{z=0}^2 \text{logit}(\beta_0 + \hat{\beta}_1 \cdot z) \cdot P(Z = z)$  and  $P(Y = 1) = \sum_{z=0}^2 \text{logit}(\gamma_0 + \hat{\gamma}_1 \cdot z) \cdot P(Z_j = z)$  for  $\beta_0$  and  $\gamma_0$ , respectively. This allows us to calculate  $P(Y = 1|Z_j = z)$  and  $P(X = 1|Z_j = z)$  for every  $j$  and  $z = 0, 1, 2$ . With these quantities, non-parametric bounds on the ATE can be calculated.

For complete and reproducible code, see [[link to vignette showing analysis on pkgdown page](#)].

## 6.1 Smoking effect on depression

In our first example, we explore the effect smoking has as an exposure on the outcome depression.[reference] Data on  $(X|Z)$  is obtained from the experiment with id ukb-d-20116\_0 in the MRBase database, and data on  $(Y|Z)$  is obtained from the experiment with id ukb-d-20544\_11. We find 84 genetic variants that can be used as instruments for the effect of smoking on depression. Using these 84 genetic variants, we want to first explore if non-parametric bounds can be used to obtain any information about the average treatment effect of smoking on the chances of developing depression. We will follow up on this with an exploration of the conclusions our quasi-bayesian approach can provide in this specific example. Finally, we will take a look at intersections of these bounds, and comment on the usefulness of this approach in this practical setting.

The genetic markers that were identified here as potential instruments all look very similar in terms of the estimated conditional distributions of exposure and outcome given instruments. Figure 5 shows histograms of the values of  $P(X = 1|Z = z)$  and  $P(Y = 1|Z = z), z = 0, 1, 2$ , for all 84 instruments. As you can see, there is very little variation in the actual values. Especially the small change when moving from  $z = 0$  through  $z = 1$  to  $z = 2$  on the three left panels is of interest here, as this is our first indication that these instruments might be rather weak.

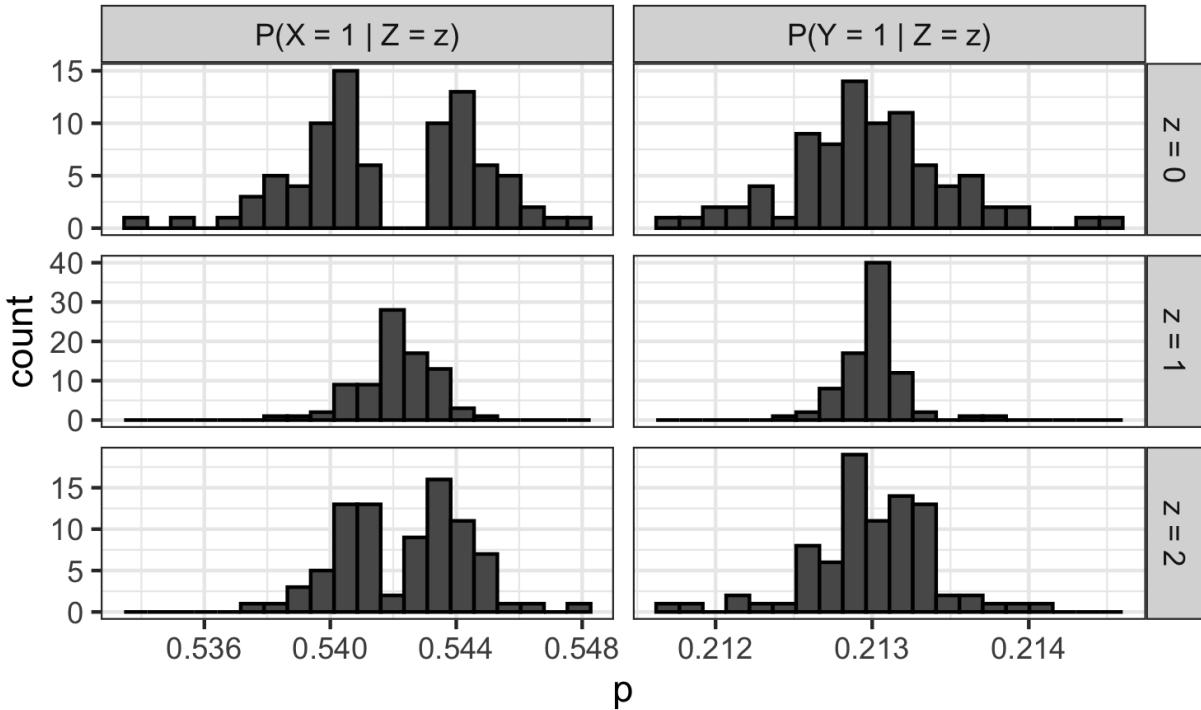


Figure 5: Histograms of the marginal conditional probabilities  $P(X = 1|Z = z)$ ,  $z = 0, 1, 2$  and  $P(Y = 1|Z = z)$ ,  $z = 0, 1, 2$ .

Figure 6 shows a histogram of the strength of all the potential instruments. We see here that the strength of the strongest instrument is less than 0.01, which is much smaller than the 0.5 needed to guarantee narrow bounds, and well in line with the observation on Figure 5. More information on the instruments and summary statistics can be found in Appendix C.

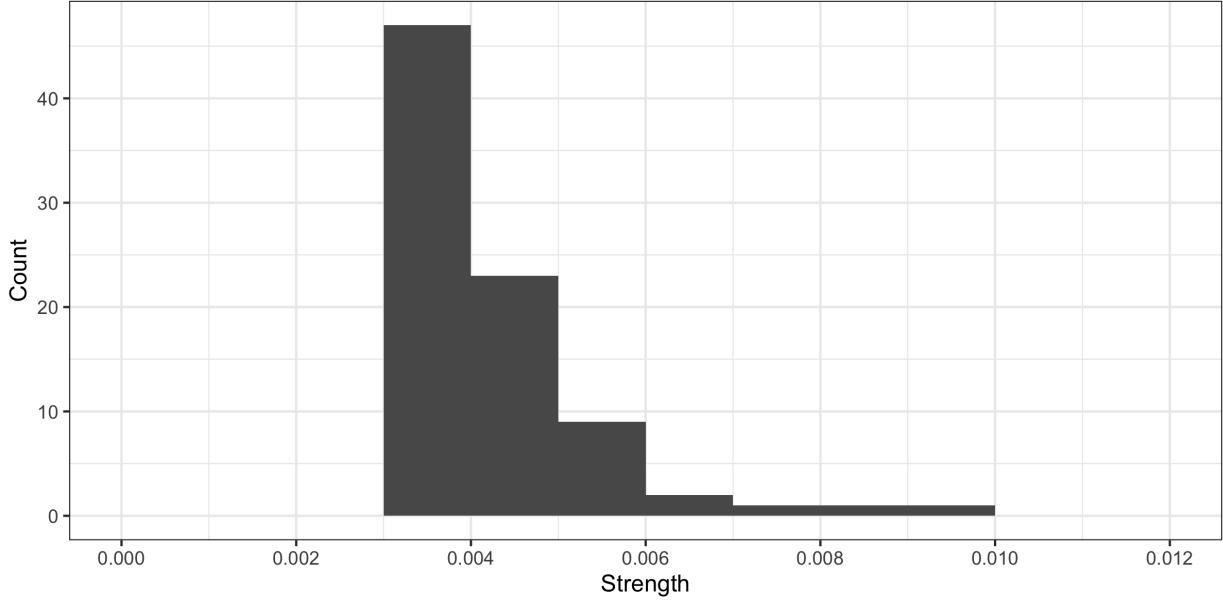


Figure 6: Histogram of strengths of IVs on the exposure. Here, SNPs are IVs, and smoking status (ever/never) is exposure. We see that all IVs are very weak, with the largest value just below 0.01.

From the 84 instrumental variables found, we obtain 84 sets of bounds using the values of  $P(X = 1|Z_j = z), P(Y = 1|Z_j = z), z = 0, 1, 2, j = 1, 2, \dots, 84$ . These are shown on Figure 7. From this figure, it is immediately clear that all the intervals are practically identical. This means that none of these instruments result in bounds that can help us determine direction of the ATE, and, in general, the amount of information they provide on the magnitude of the ATE is limited. This also tells us that trying to aggregate information from these instruments by simply creating intersection bounds will lead to essential no gains.

The very minimal amount of information we get from these bounds is no surprise. As already mentioned, all instruments are very weak, which as we saw in Section 3.1 tend to lead to wide bounds.

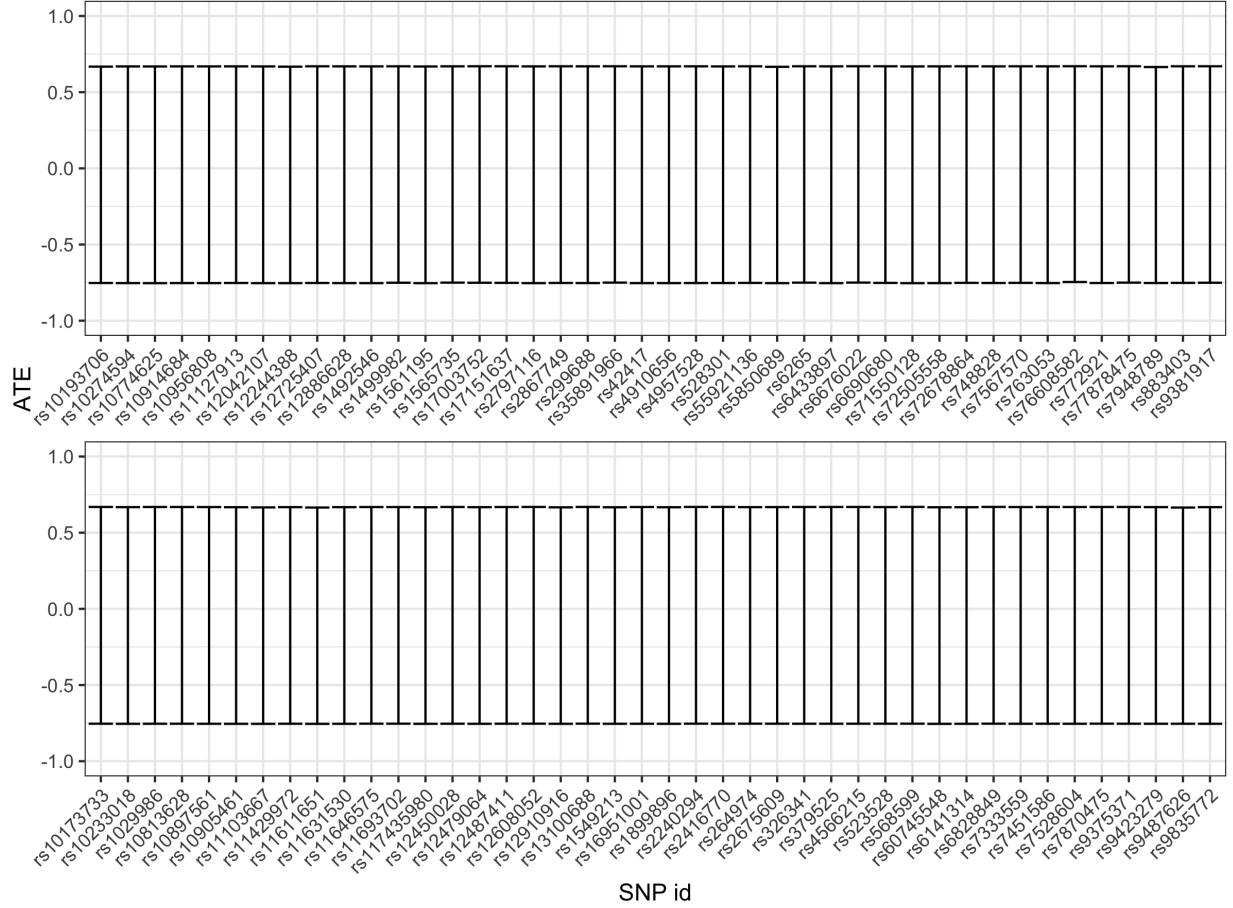


Figure 7: Non-parametric bounds for the 84 genetic variants identified as potential instruments for the effect of smoking on depression created based on the bivariate probabilities found from GWAS summary statistics.

With this in mind, we proceed to explore our quasi-bayesian approach. For each of the 84 genetic variants, we sample 500 potential trivariate distributions as described in Section 5. From these 500 trivariate distributions, non-parametric bounds are created. Figure 8 shows the resulting bounds.

It is clear that while the trivariate bounds are much narrower than the corresponding bivariate bounds. This is very much so in line with our expectations. Unfortunately, all the bounds found based on potential trivariate distributions overlap 0. This means that we will not be able to use non-parametric bounds to determine the direction of the ATE of smoking on the chances of developing depression, even if we were to obtain trivariate data.

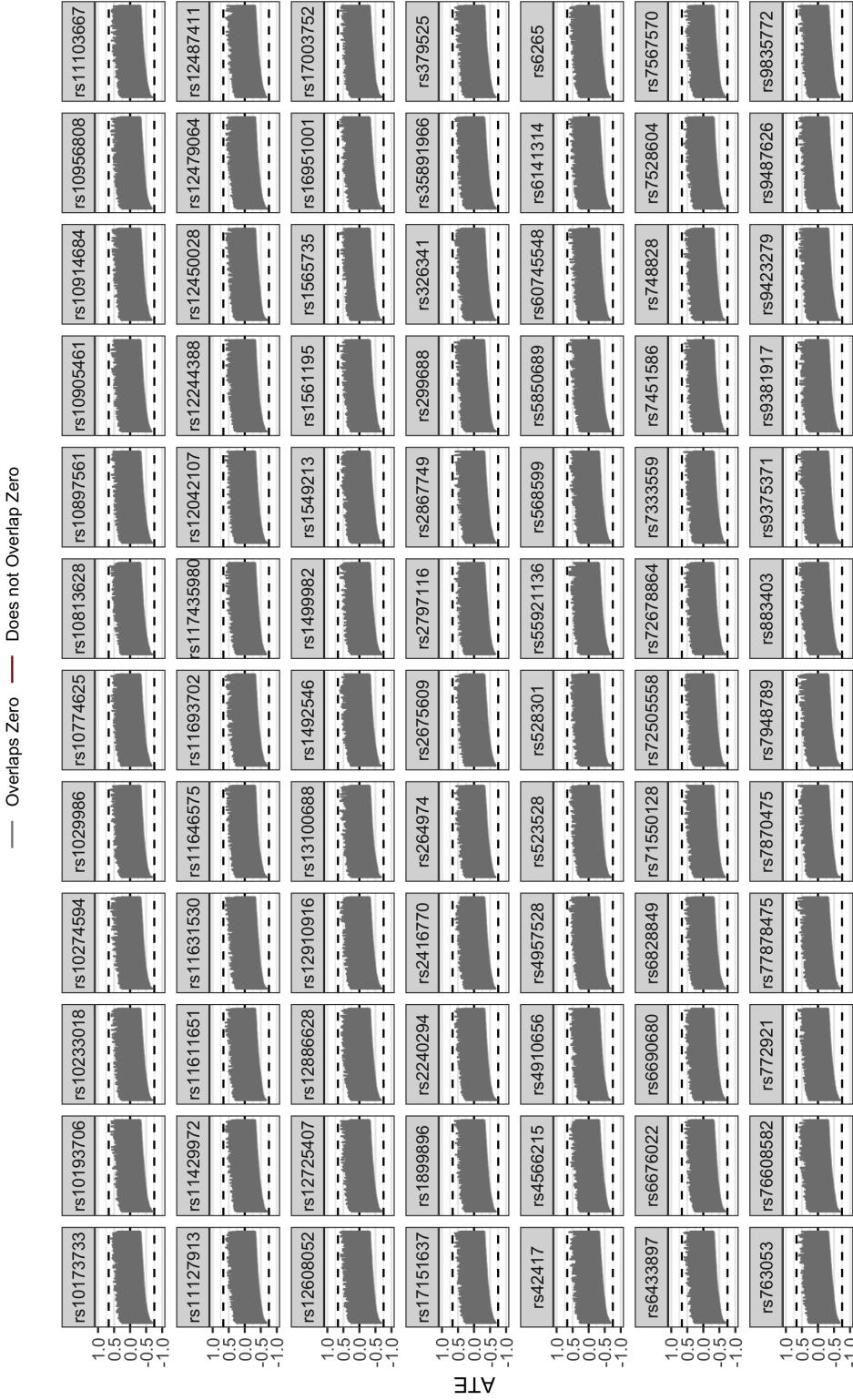


Figure 8: 500 bounds for each of the 84 SNPs. Each bound is based on a set of values for the trivariate distribution randomly sampled. Bounds are color coded to show if they overlap 0 (grey) or do not (red). All bounds overlap 0.

Aggregating the information from multiple IVs through intersections is a simple idea, but everything we have seen so far points to this not being useful in practice. Figure 9 shows the results from doing exactly this for 9 pairs of SNPs, both when simply creating intersection of the bivariate bounds, and when using our quasi-bayesian approach to estimate the distribution of intersections of bounds from trivariate distributions as described in Section 5.3. Comparing Figure 9 to Figure 8, we notice that the intersection bounds are essentially the same width. As for intersections of trivariate bounds, these are narrower than the corresponding intersections of bivariate bounds, but we do not see any scenario where intersections of trivariate bounds would help us determine direction of the ATE.

Again, the conclusion is that no sets of trivariate distributions allows us to determine direction of the average treatment effect through the use of non-parametric bounds.

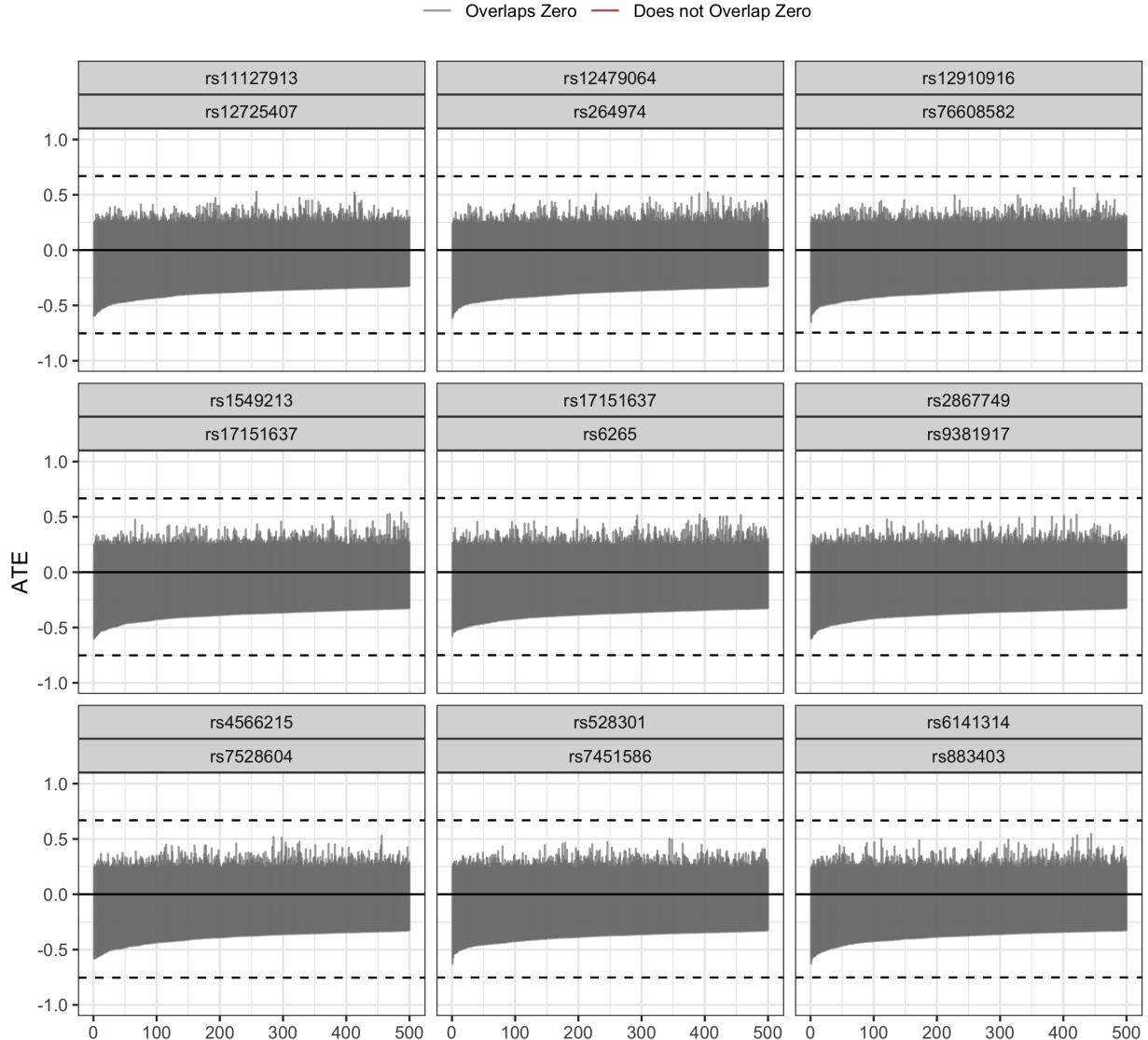


Figure 9: Intersection bounds based on randomly sampled trivariate distributions from pairs of SNPs. These 9 pairs were randomly chosen from all possible pairs.

It is very important to keep in mind that this conclusion is only valid as long as the probabilities obtained are the true population probabilities. If this is the case, then non-parametric bounds simply will not allow us to determine direction of the ATE. The accuracy of the probabilities can be questioned, as these are derived from logistic regression results.

## 6.2 Smoking effect on lung cancer

As a positive control, we consider the effect of smoking on lung cancer. The general approach is a replicate of the previous section. Here, we obtain data on  $(Y|Z)$  from the experiment in MRBase with id ukb-d-40001\_C349, while the data on  $(X|Z)$  is again from the experiment with id ukb-d-20116\_0.

As before, the bivariate bounds (figure 10) are rather wide (all have width greater than 1) meaning they convey no truly useful information about the ATE, and even if we were to obtain trivariate data, we will not be able to determine the direction of the ATE (figure 11). Aggregating through intersections (figure 12) does not lead to real gain in information, even if this is done using bounds based on trivariate distributions.

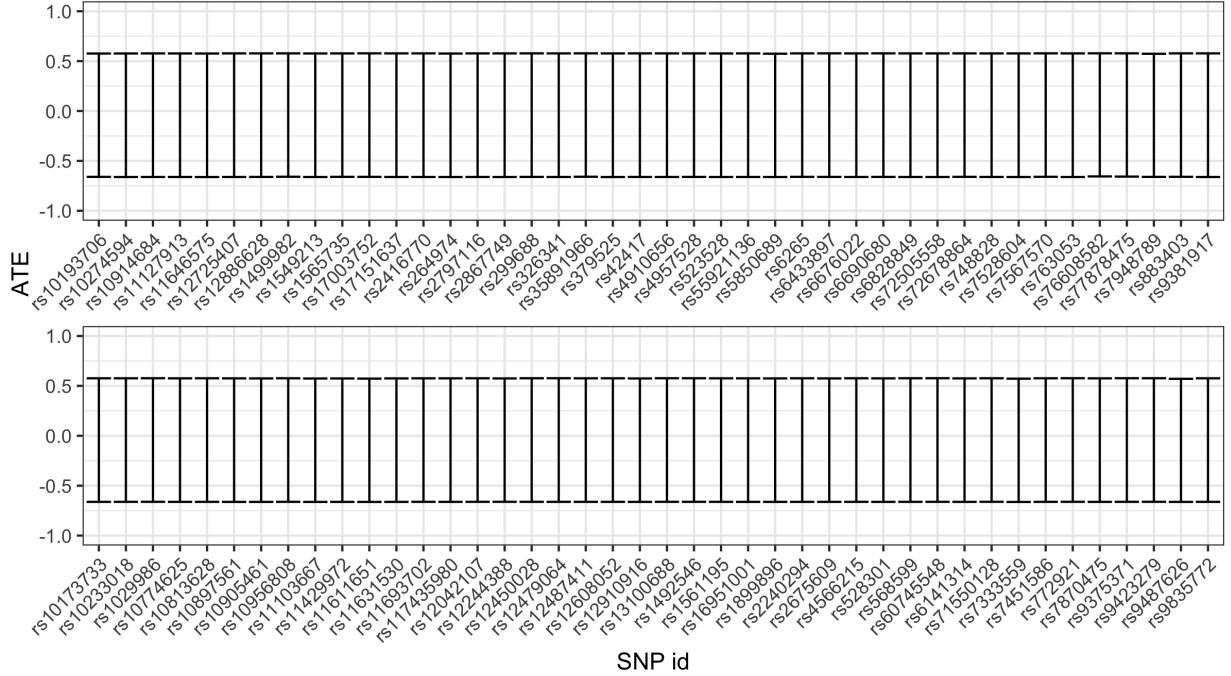


Figure 10: Non-parametric bounds on the average treatment effect of smoking on lung cancer.

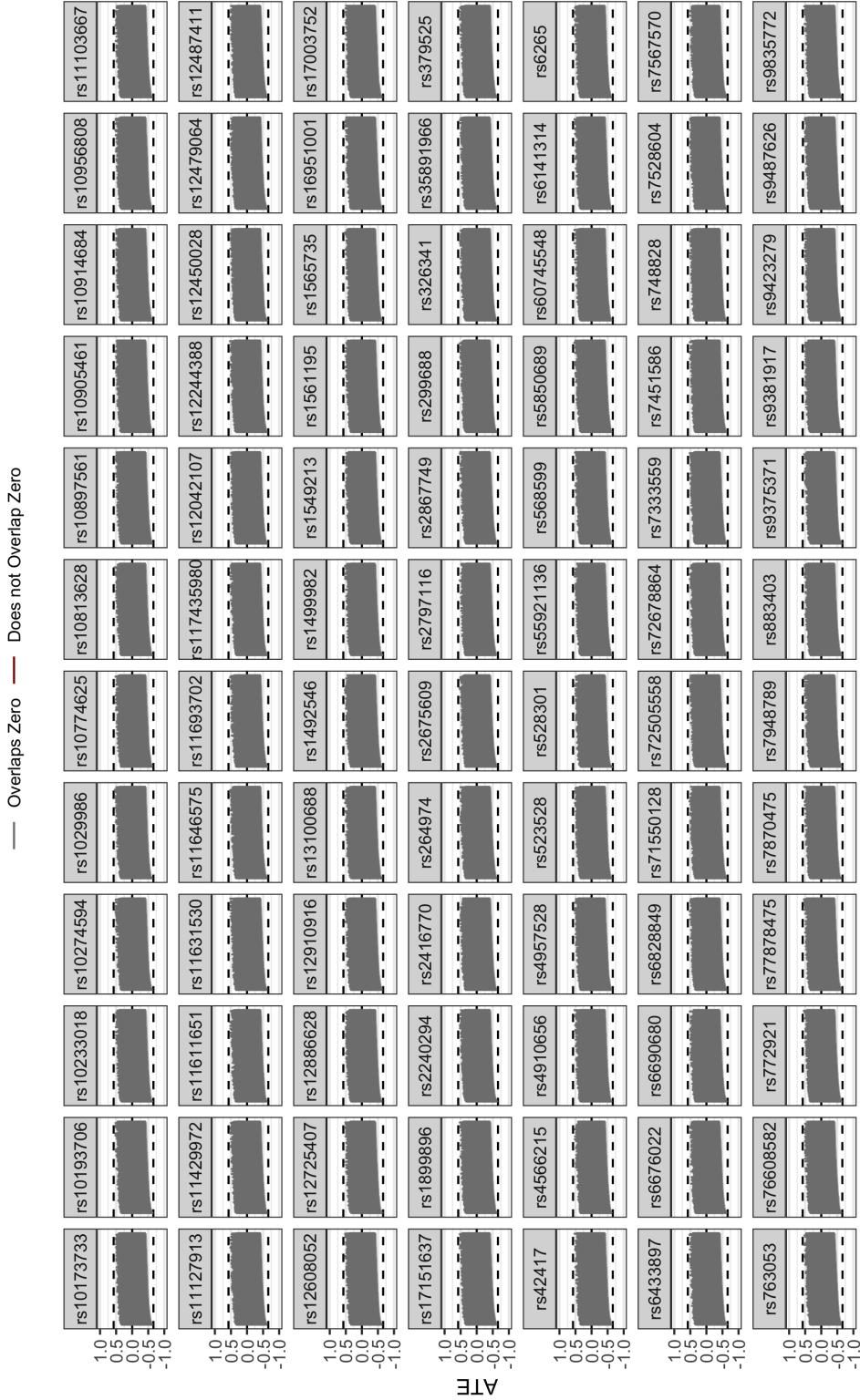


Figure 11: 500 bounds for each of the 84 SNPs. Each bound is based on a set of values for the trivariate distribution randomly sampled. Bounds are color coded to show if they overlap 0 (grey) or do not (red). All bounds overlap 0.

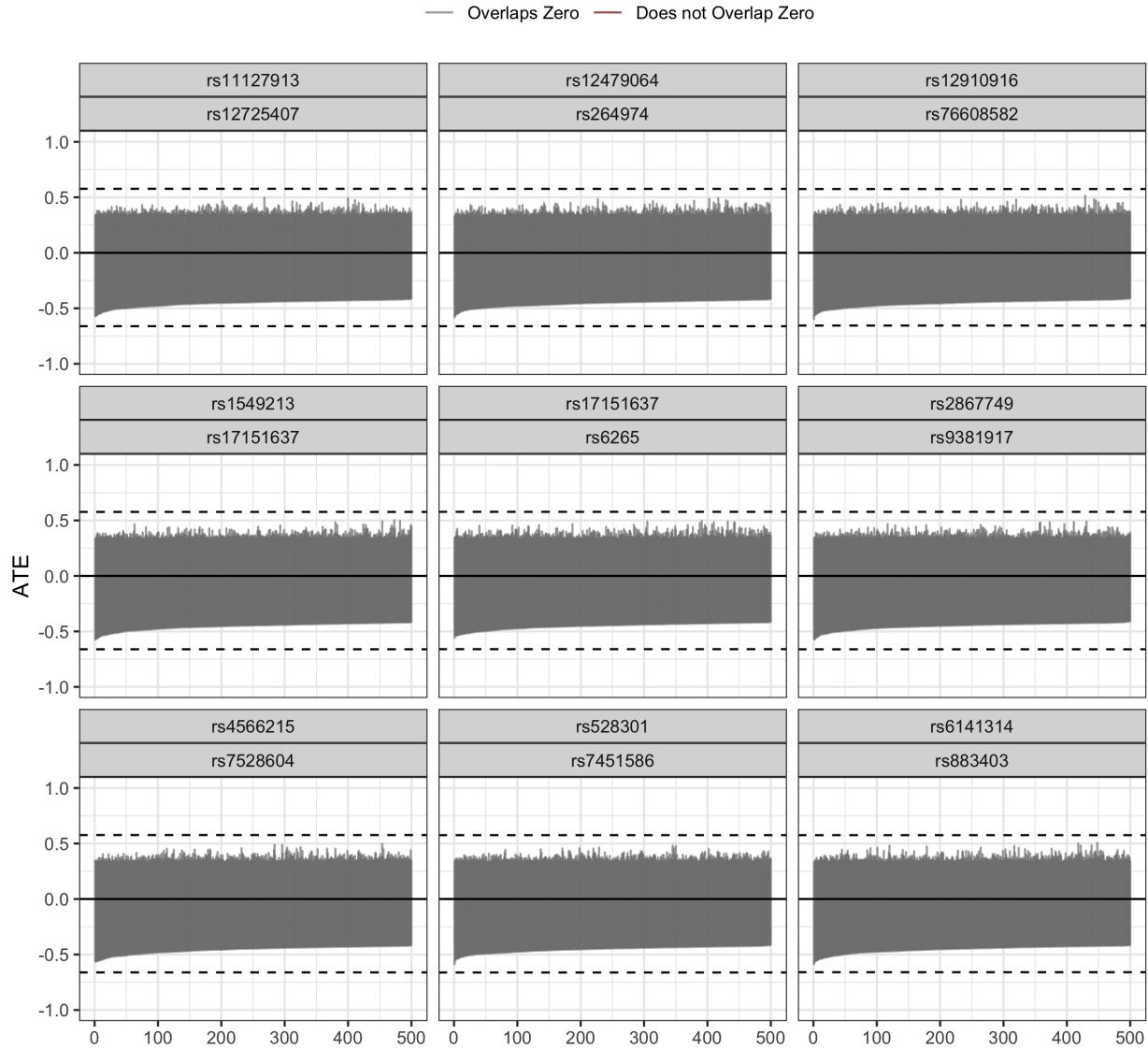


Figure 12: Intersection bounds based on randomly sample trivariate distributions from pairs of SNPs. These 9 pairs were randomly chosen from all possible pairs.

This is a very concerning result. It is well established that smoking has a strong causal effect on the chances of developing lung cancer [references...]. The fact that we are unable to say anything about the ATE in this case does not leave much hope in terms of future discoveries based on non-parametric bounds obtained using bivariate data. Even more concerning is the fact that trivariate distributions also are unsuccessful in determining the direction of the effect. Non-parametric bounds alone seem unable to give information about the direction of the effect, whether based on bivariate or trivariate data.

## 7 Conclusion and Practical Considerations

Non-parametric bounds are without a doubt an attractive concept. With a minimal set of assumptions they let us obtain bounds on the average treatment effect in a deterministic way – no probabilistic interpretations needed. It almost sounds to good to be true. As we have seen here, it turns out, in certain settings, it is.

While non-parametric bounds based on trivariate data come with very nice guarantees, such as the width always being less than 1, they are not applicable in Mendelian randomization analyses based on the kind of data that are made readily available through the many databases full of GWAS results. These databases contain information about bivariate data rather than trivariate data.

Fortunately, a framework for working out non-parametric bounds in this setting does exist (Ramsahai 2012), and it can be easily extended to many other scenarios, for example working with Instrumental Variables with more than two levels. Unfortunately, we lose the strong guarantees on the maximum width of the bounds we know from the trivariate bounds. To regain these guarantees, we need rather strong assumptions about the strength of the IV. Depending on the specific context, such strong IVs are very unlikely to be available.

Though information from bounds based on bivariate data might be limited, some is still available. Aggregating information from many instruments can be done in a simple fashion using intersections of individual bounds. This simple approach is only valid when all instruments are valid. In that case, it is a very reasonable way of aggregating information, but this will only result in significant gains of information when the individual bounds are shifted from one another, and not almost identical or nested. The problem with these non-parametric bounds is that the upper and lower bounds are close to monotonically decreasing and increasing, respectively, as a function of the strength. This means that intersections of bounds results in the set of bounds obtained from the strongest instrument, which leaves us with no more information than had we simply used the strongest instrument.

In a last effort to fully utilize the information we do have from bivariate data, we outline an approach to explore the potential trivariate distributions that are in agreement with the bivariate data at hand, and the bounds these potential trivariate distributions lead to. This gives us the opportunity to assess the conclusions non-parametric bounds from trivariate data could potentially lead to. One can use this to assess a posterior probability of the trivariate bounds containing zero, something that tells us if trivariate bounds are likely to be useful in determining direction of the average treatment effect, and could help guide a decision to further pursue an experiment aimed at collecting trivariate data. We considered a few different scenarios that provide different potential conclusions, and saw how diverse conclusions one can get to even when the original bivariate bounds are relatively similar. This suggests that we do indeed lose a lot of information in summarizing a trivariate distribution with only two bivariate distributions.

To demonstrate the use of non-parametric bounds in Mendelian randomization analyses, we considered two examples. In the first example, we aimed at finding bounds on the effect of smoking on the chances of developing depression. Unfortunately, all instruments available were very week with the strongest instrument having a strength of less than 0.01. This results in bounds that provide very little information. Our quasi-bayesian approach suggests that even trivariate bounds would not be able to provide much extra information.

In our second example, we explored the effect of smoking on the chances of developing lung cancer. It has been well established that there is a rather strong causal effect of smoking on the chances of developing lung cancer. Unfortunately, our non-parametric bounds were not able to determine the direction of this effect, and our quasi-bayesian approach once again suggests that trivariate bounds would only bring a marginal improvement.

In this context, it is important to note that the conclusions made about the trivariate distributions only hold if the bivariate probabilities are correct. Whether that is the case here is questionable, as these probabilities are estimated based on logistic regression models.

Using genetic variants as instrumental variables is a very intriguing idea, but combining this setting with non-parametric bounds seems to give very few results. One potential use case of non-parametric bounds in a Mendelian randomization analysis could be when one has prior knowledge about the direction of the effect, but wish to get a better sense of the magnitude. Non-parametric bounds can provide an upper limit

on this magnitude, which might in some scenarios be of use. For example in our second example, where the direction of the effect of smoking on lung cancer is well known, non-parametric bounds might help in providing an upper bound for the effect.

## A Proof of Theorem 3.1

First of all, we note that the bounds found using the approach previously described when we impose both of the mentioned monotonicity assumptions are as follows:

$$\begin{aligned} \max & \left\{ \begin{array}{l} -P(Y = 0|Z = 2) - P(Y = 1|Z = 0) + P(X = 0|Z = 0) - P(X = 0|Z = 2) \\ P(Y = 0|Z = 0) - 2 \cdot P(Y = 0|Z = 2) - P(X = 0|Z = 2) \\ -P(Y = 0|Z = 2) - 2 \cdot P(Y = 1|Z = 0) + P(X = 0|Z = 0) \end{array} \right\} (L1) \\ & \left\{ \begin{array}{l} 1 + P(Y = 0|Z = 0) - P(X = 0|Z = 0) \\ 1 - P(Y = 0|Z = 2) + P(X = 0|Z = 2) \end{array} \right\} (L2) \\ & \leq ATE \leq (L3) \\ \min & \left\{ \begin{array}{l} 1 + P(Y = 0|Z = 0) - P(Y = 0|Z = 2) - P(X = 0|Z = 0) + P(X = 0|Z = 2) \\ 1 - P(Y = 0|Z = 2) + P(X = 0|Z = 2) \end{array} \right\} (U1) \\ & \left\{ \begin{array}{l} 1 + P(Y = 0|Z = 0) - P(Y = 0|Z = 2) - P(X = 0|Z = 0) + P(X = 0|Z = 2) \\ 1 - P(Y = 0|Z = 2) + P(X = 0|Z = 2) \end{array} \right\} (U2) \\ & \left\{ \begin{array}{l} 1 + P(Y = 0|Z = 0) - P(X = 0|Z = 0) + P(X = 0|Z = 2) \\ 1 - P(Y = 0|Z = 2) + P(X = 0|Z = 2) \end{array} \right\} (U3) \end{aligned}$$

This gives us a total of nine different expressions for the width of the bounds. Since we assume monotonicity of the effect of  $Z$  on  $X$ , the strength simplifies to  $ST = P(X = 1|Z = 2) - P(X = 1|Z = 0)$ .

### Width = U1 - L1

If the upper bound is  $U1$ ,  $U1 \leq U2$ , which implies  $P(Y = 0|Z = 2) - P(X = 0|Z = 2) \leq 0$ . Therefore,

$$\begin{aligned} U1 - L1 &= 1 + P(Y = 0|Z = 0) - P(X = 0|Z = 0) + P(Y = 0|Z = 2) + P(Y = 1|Z = 0) - P(X = 0|Z = 0) + P(X = 0|Z = 2) \\ &= 2 - ST + P(Y = 0|Z = 2) - P(X = 0|Z = 0) \\ &= 2 - 2 \cdot ST + P(Y = 0|Z = 2) - P(X = 0|Z = 2) \leq 2 - 2 \cdot ST. \end{aligned}$$

### Width = U2 - L1

$$\begin{aligned} U2 - L1 &= 1 + P(Y = 0|Z = 0) - P(Y = 0|Z = 2) - P(X = 0|Z = 0) + P(X = 0|Z = 2) \\ &\quad + P(Y = 0|Z = 2) + P(Y = 1|Z = 0) - P(X = 0|Z = 0) + P(X = 0|Z = 2) \\ &= 2 - 2 \cdot ST \end{aligned}$$

### Width = U3 - L1

Since the upper bound is  $U3$ ,  $U3 \leq U2$ , which implies  $P(X = 0|Z = 0) - P(Y = 0|Z = 0) \leq 0$ . Therefore,

$$\begin{aligned} U3 - L1 &= 1 - P(Y = 0|Z = 2) + P(X = 0|Z = 2) + P(Y = 0|Z = 2) + P(Y = 1|Z = 0) - P(X = 0|Z = 0) + P(X = 0|Z = 2) \\ &= 1 + P(Y = 1|Z = 0) - ST + P(X = 0|Z = 2) \\ &= 2 - 2 \cdot ST + P(X = 0|Z = 0) - P(Y = 0|Z = 0) \leq 2 - 2 \cdot ST. \end{aligned}$$

### Width = U1 - L2

Since the upper bound is  $U1$ ,  $P(Y = 0|Z = 2) \leq P(X = 0|Z = 2)$ . Since the lower bound is  $L2$ ,  $L2 \geq L1$ , which gives us  $1 - P(X = 0|Z = 0) \geq P(Y = 0|Z = 2)$ . Therefore,

$$\begin{aligned} U1 - L2 &= 1 + P(Y = 0|Z = 0) - P(X = 0|Z = 0) - P(Y = 0|Z = 0) + 2 \cdot P(Y = 0|Z = 2) + P(X = 0|Z = 2) \\ &= 1 - ST + 2P(Y = 0|Z = 2) \\ &\leq 2 - ST - P(X = 0|Z = 0) + P(X = 0|Z = 2) = 2 - 2 \cdot ST. \end{aligned}$$

### Width = U2 - L2

Since the lower bound is  $L2$ ,  $1 - P(X = 0|Z = 0) \geq P(Y = 0|Z = 2)$ . So,

$$\begin{aligned} U2 - L2 &= 1 - P(X = 0|Z = 0) + P(X = 0|Z = 2) + P(Y = 0|Z = 2) + P(X = 0|Z = 2) \\ &= 1 - ST + P(Y = 0|Z = 2) + P(X = 0|Z = 2) \\ &\leq 2 - 2 \cdot ST. \end{aligned}$$

### Width = U3 - L2

Since the lower bound is  $L2$ ,  $1 - P(X = 0|Z = 0) \geq P(Y = 0|Z = 2)$ . Since the upper bound is  $U3$ ,  $P(X = 0|Z = 0) \leq P(Y = 0|Z = 0)$ . Therefore,

$$\begin{aligned} U3 - L2 &= 1 - P(Y = 0|Z = 2) + P(X = 0|Z = 2) - P(Y = 0|Z = 0) + 2 \cdot P(Y = 0|Z = 2) + P(X = 0|Z = 2) \\ &= 1 + 2 \cdot P(X = 0|Z = 2) + P(Y = 0|Z = 2) - P(Y = 0|Z = 0) \\ &= 1 - 2 \cdot ST + 2P(X = 0|Z = 0) + P(Y = 0|Z = 2) - P(Y = 0|Z = 0) \\ &\leq 2 - 2 \cdot ST \end{aligned}$$

### Width = U1 - L3

Since the upper bound is  $U1$ ,  $P(Y = 0|Z = 2) \leq P(X = 0|Z = 2)$ . Since the lower bound is  $L3$ ,  $L3 \geq L1$ , which implies  $P(Y = 1|Z = 0) \leq P(X = 0|Z = 2)$ . So,

$$\begin{aligned} U1 - L3 &= 2 - P(X = 0|Z = 0) + P(Y = 0|Z = 2) + P(Y = 1|Z = 0) - P(X = 0|Z = 0) \\ &= 2 - 2 \cdot ST - 2 \cdot P(X = 0|Z = 2) + P(Y = 0|Z = 2) + P(Y = 1|Z = 0) \\ &\leq 2 - 2 \cdot ST \end{aligned}$$

### Width = U2 - L3

Since the lower bound is  $L3$ ,  $P(Y = 1|Z = 0) \leq P(X = 0|Z = 2)$

$$\begin{aligned} U2 - L3 &= 2 - 2 \cdot P(X = 0|Z = 0) + P(X = 0|Z = 2) + P(Y = 1|Z = 0) \\ &= 2 - ST + P(Y = 1|Z = 0) - P(X = 0|Z = 0) \\ &= 2 - 2 \cdot ST + P(Y = 1|Z = 0) - P(X = 0|Z = 2) \leq 2 - 2 \cdot ST \end{aligned}$$

### Width = U3 - L3

Since the lower bound is  $L3$ ,  $P(Y = 1|Z = 0) \leq P(X = 0|Z = 2)$ . Since the upper bound is  $U3$ ,  $1 - P(X = 0|Z = 0) \geq P(Y = 1|Z = 0)$ . Therefore,

$$\begin{aligned} U3 - L3 &= 1 + P(X = 0|Z = 2) + 2 \cdot P(Y = 1|Z = 0) - P(X = 0|Z = 0) \\ &\leq 1 - ST + P(X = 0|Z = 2) + 1 - P(X = 0|Z = 0) \\ &= 2 - 2 \cdot ST. \end{aligned}$$

## B Exploration of Scenarios Where Bounds are Flipped

## C More details for smoking on depression example

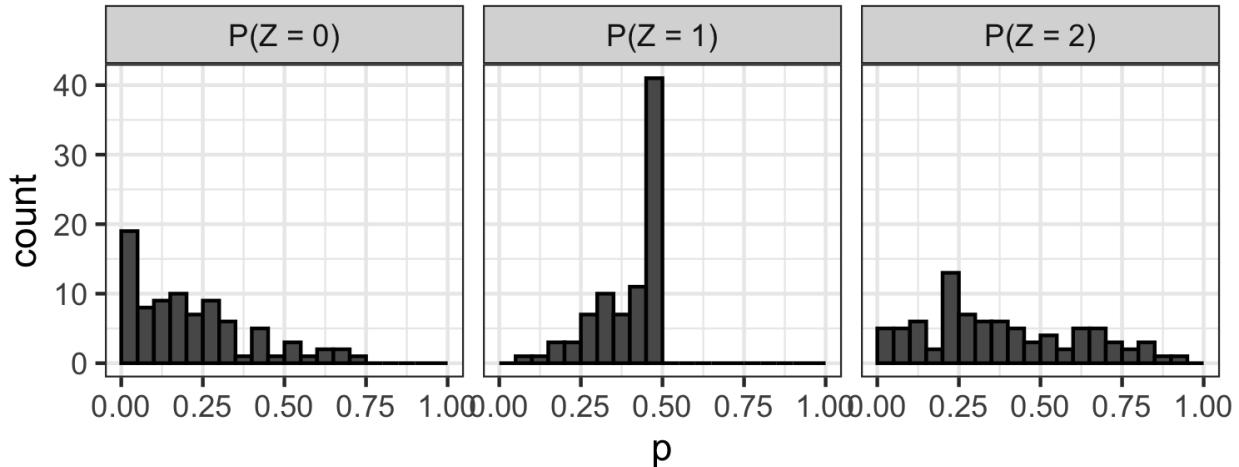


Figure 13: Histograms of the marginal distribution of instruments,  $P(Z = z)$ ,  $z = 0, 1, 2$ .

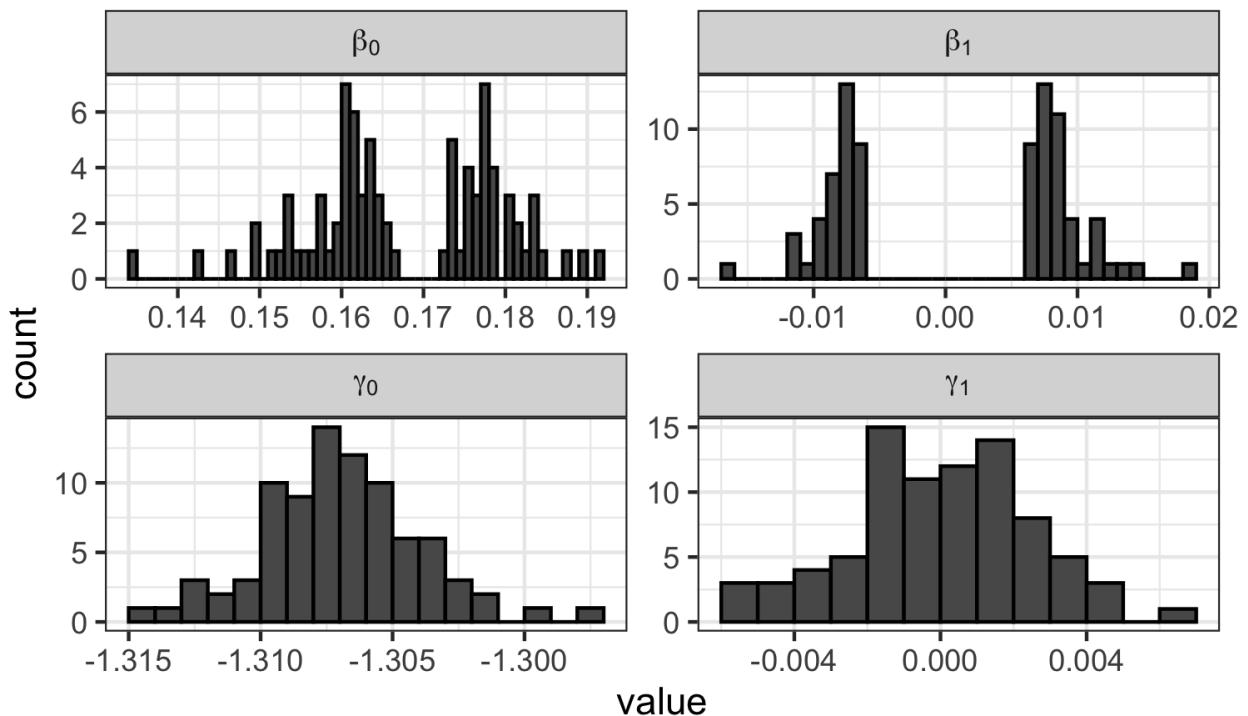


Figure 14: Histograms of the coefficients from GWAS results of logistic regression of the SNPs on exposure and outcome. Intercepts ( $\beta_0$  and  $\gamma_0$ ) are inferred, while slopes ( $\beta_1$  and  $\gamma_1$ ) are as reported.

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