

# Non-parametric Bounds in Two-Sample Summary-Data Mendelian Randomization: Some Cautionary Tales for Practice

## **Abstract**

Recently, in genetic epidemiology, Mendelian randomization (MR) has become a popular approach to estimate causal exposure effects by using single nucleotide polymorphisms from genome-wide association studies (GWAS) as instruments. The most popular type of MR study, a two-sample summary-data MR study, relies on having summary statistics from two independent GWAS and using parametric methods for estimation. However, little is understood about using a nonparametric bound-based analysis, a popular approach in traditional instrumental variables frameworks, to study causal effects in two-sample MR. In this work, we explore using a bound-based analysis in two-sample MR studies. We also propose a framework to assess how likely one can obtain more informative bounds on the causal effect if we used a different MR design, notably a one-sample MR design. We conclude by demonstrating our findings through two real data analyses concerning the causal effect of smoking on lung cancer and the causal effect of high cholesterol on heart attacks. Overall, our results suggest that while a bound-based analysis may be appealing due to its nonparametric nature, it is rarely suitable as a method of analysis to bound the causal exposure effect in two-sample MR studies unless strong assumptions are met.

# 1 Introduction

In recent years, genetic variants have been used as instrumental variables (IV) to estimate causal effects in epidemiological studies, often referred to as Mendelian randomization (MR) studies [17, 24, 10]. Typically, MR studies are based on a two-sample study design where published summary statistics from two independent genome wide association studies (GWAS), with one providing information about the exposure and instrument and the other about the outcome and instrument, are used [7, 11, 18]. Under a two-sample study design, investigators frequently use parametric methods to study exposure effects. Notable examples include the IVW estimator [7], MR-Egger regression [4], weighted median [5], MR-PRESSO [44] and MR-RAPS [49], to name a few; see Burgess and Thompson [10], Burgess, Small, and Thompson [8] and Slob and Burgess [38] for recent reviews.

An alternative approach to study exposure effects in instrumental variables without parametric assumptions is through nonparametric IV bounds [3, 12, 26, 31, 33]. Briefly, nonparametric IV bounds use a minimum set of assumptions to provide a range of plausible values for the exposure effect. They are typically used when the outcome, the exposure, and the instrument are all binary and are simultaneously observed; we refer to this setting as the one-sample setting to contrast it from the two-sample setting. Arguably, the most well-known IV bounds are the Balke-Pearl bounds [3] for the average treatment effect. Cheng and Small [12] and Richardson and Robins [31] extended the Balke-Pearl bounds to allow for a non-binary instrument. Ramsahai [30] derived bounds under two-sample study designs; see Swanson et al. [43] and references therein for a recent summary of IV bounds.

Using IV bounds can be an attractive alternative to study exposure effects in non-MR, one-sample settings [42, 43] and some [19, 41] have suggested using IV bounds to study exposure effects in MR studies given the strong parametric assumptions accompanying most MR analyses. Despite these suggestions, to the best of our knowledge, there is little work on using bounds in typical MR settings, i.e. two-sample study designs with summary statistics. For example, what kind of genetic variants provide the most informative conclusions about the exposure effect in terms of the bounds not containing the null effect? Can combining multiple variants lead to shorter and tighter bounds? How do the bounds change if many instruments are weak, which is typical in MR studies from two-sample designs? The overall goal of this paper is to offer some practical guidance on using IV bounds in two-sample MR studies. We focus on two aspects: (1) the length of the bounds and (2) whether bounds cover the null effect of zero, both of which inform MR investigators about the direction and relative magnitude of the exposure effect.

Our overall takeaway message for investigators using two-sample MR studies is that unless the candidate

instruments are very strong, a bound-based analysis will often be non-informative. Instead, investigators should either try to use one-sample MR studies or use well-informed parametric approaches to ascertain the exposure effect.

## 2 Methods

### 2.1 Review: Notation, Definitions, and Assumptions

Let  $X$  and  $Y$  be binary exposure and outcome variables, respectively,  $Z$  be a categorical instrumental variable taking values in  $\{0, 1, 2\}$ , and  $U$  be an unmeasured confounder for the effect of  $X$  on  $Y$ . Let  $Y^{z,x}$  be the potential outcome [34, 39] had the subject received exposure value  $X = x$  and instrument value  $Z = z$ . We assume the stable unit treatment value assumption (SUTVA) [16, 35], formalized as  $Y = \sum_{x,z} I[Z = z, X = x] Y^{x,z}$  where  $I[\cdot]$  is the indicator function.

We make the following set of assumptions about  $X, Y, Z$ , and  $U$  that are typical in MR studies; see Didelez and Sheehan [19] and Wang and Tchetgen Tchetgen [46] for details.

- (A1) (*Relevance*):  $Z \not\perp X$
- (A2) (*Independent instrument*):  $Z \perp U$
- (A3) (*Exclusion restriction*):  $Y^{z,x} = Y^{z',x} = Y^x$  for all  $x, z, z'$
- (A4) (*Conditional ignorability of  $X, Z$  given  $U$* ):  $Y^{z,x} \perp Z, X | U$

Briefly, (A1) can be satisfied by finding SNPs that have been consistently associated with the exposure. (A2) and (A3) are justified by scientific theory and can be violated if the SNP is (i) in linkage disequilibrium with an unmeasured SNP that affects the exposure and the outcome or (ii) has multiple functions beyond affecting the exposure (i.e. pleiotropic), to name a few. Finally, (A4) states that if  $U$  is observed, then it is sufficient to unconfound the relationship between  $X$  and  $Y$ .

Throughout the paper, we will assume (A1)-(A4) hold to focus the discussion on the bounds, even though they are important to assess in practice. We make some additional remarks about assumptions (A1)-(A4). First, in practice, most MR studies only explicitly state assumptions (A1)-(A3) along with some parametric modeling assumptions [10]. Second, Richardson and Robins [31] showed that one can remove (A4) and strengthen (A2) with  $Z \perp U, Y^{z,x}$  without consequence on the IV bounds. Third, under SUTVA and assumptions (A3)-(A4), we have  $Y \perp Z | X, U$ , which is another common way to express the exclusion

restriction in MR studies [19, 43]. Fourth, for simplicity, we do not assume the existence of a potential treatment  $X^z$ .

Next, we introduce the following assumptions (A5) and (A6); these assumptions are not necessary to construct bounds, but they will help characterize IV bounds in two-sample studies.

$$(A5) \text{ (Monotonicity between } Z \text{ and } X) P(X = 1|Z = z, U) \leq P(X = 1|Z = z + 1, U) \text{ for } z = 0, 1, 2$$

$$(A6) \text{ (Monotonicity between } Z \text{ and } Y) P(Y = 1|Z = z, U) \leq P(Y = 1|Z = z + 1, U) \text{ for } z = 0, 1, 2$$

A variant of (A5) is common in the IV literature to study noncompliance [1, 2]. (A6) is an extension of (A5) to the outcome variable. (A5) or (A6) is plausible in MR if the direction of the genetic instrument's effect on the exposure or the outcome is well-established from scientific theory.

We also define instrument strength ST as

$$ST = \max_{z_1 \neq z_2} |P(X = 1|Z = z_1) - P(X = 1|Z = z_2)| \quad (1)$$

ST reduces to the definition of instrument strength in Balke and Pearl [3] when the instrument is binary; Balke and Pearl [3] used ST to characterize the width of their IV bounds. Also, (1) differs from other definitions of instrument strength based on a parametric model between the exposure and the outcome, say the concentration parameter; see Stock, Wright, and Yogo [40] for an overview.

## 2.2 IV Bounds Under Two-Sample Designs and Goals of Paper

The most popular design in MR studies is a two-sample design which has two separate data sources, one providing information about  $(X, Z)$  in the form of  $P(X = 1|Z = z)$ ,  $z \in \{0, 1, 2\}$ , and another providing information about  $(Y, Z)$  in the form of  $P(Y = 1|Z = z)$ ,  $z \in \{0, 1, 2\}$ . A two-sample design differs from a more traditional one-sample design which has a single data source providing information on all observed variables  $(X, Y, Z)$  in the form of  $P(Y = y, X = x|Z = z)$ . IV bounds have been well-studied in one-sample designs and there is a rich array of practical guidance for practitioners interested in using them in their studies [3, 31, 43]. However, as noted in the introduction, not much is known about the behavior of IV bounds under a two-sample design, especially how (or when) MR investigators should use them in their own studies.

Formally, the goal of this paper is to offer concrete practical advice on using IV bounds to study the average treatment effect (ATE), defined as

$$\text{ATE} = E[Y^1 - Y^0] = \int P(Y = 1 | X = 1, U = u)P(U = u)du - \int P(Y = 1 | X = 0, U = u)P(U = u)du$$

based on using  $P(Y = 1|Z = z)$  and  $P(X = 1|Z = z)$  for each  $z = 0, 1, 2$  obtained from a two-sample design. Specifically, under a two-sample design and assumptions (A1)-(A4), Ramsahai [30] derived a sharp bound for the ATE (see eAppendix A.1 for a detailed review and a discussion of “IV Inequalities” [3, 20] in two-sample MR studies).

$$\max \left\{ \begin{array}{ll} \max_{z_1 \neq z_2} & P(Y = 1|Z = z_1) - 2 \cdot P(Y = 1|Z = z_2) - 2 \cdot P(X = 1|Z = z_2) \\ \max_{z_1 \neq z_2} & P(Y = 1|Z = z_1) + P(X = 1|Z = z_1) - P(Y = 1|Z = z_2) - P(X = 1|Z = z_2) - 1 \\ \max_{z_1 \neq z_2} & 2 \cdot P(Y = 1|Z = z_1) + 2 \cdot P(X = 1|Z = z_1) - P(Y = 1|Z = z_2) - 3 \\ \max_z & -P(Y = 1|Z = z) - P(X = 1|Z = z) \\ \max_z & P(Y = 1|Z = z) + P(X = 1|Z = z) - 2 \end{array} \right\} \leq \text{ATE} \leq \quad (2)$$

$$\min \left\{ \begin{array}{ll} \min_{z_1 \neq z_2} & P(Y = 1|Z = z_1) - 2 \cdot P(Y = 1|Z = z_2) + 2 \cdot P(X = 1|Z = z_2) + 1 \\ \min_{z_1 \neq z_2} & P(Y = 1|Z = z_1) + 2 \cdot P(Y = 1|Z = z_2) - 2 \cdot P(X = 1|Z = z_2) + 1 \\ \min_{z_1 \neq z_2} & P(Y = 1|Z = z_1) - P(X = 1|Z = z_1) + P(X = 1|Z = z_2) - P(Y = 1|Z = z_2) + 1 \\ \min_z & P(X = 1|Z = z) - P(Y = 1|Z = z) + 1 \\ \min_z & P(Y = 1|Z = z) - P(X = 1|Z = z) + 1 \end{array} \right\}$$

This paper studies arguably the two most relevant properties of the above bounds that can guide practice: (1) the length of the bounds and (2) the ability to obtain bounds not covering the null effect of zero. To better understand bound-specific characteristics not due to sampling errors, we will assume we have population-level quantities of  $P(Y = 1|Z = z)$  and  $P(X = 1|Z = z)$ ; in practice, these are estimated summary GWAS statistics from logistic models [24, 6, 45, 27, 23] and eAppendix A.2 contains additional details.

### 3 Properties of IV Bounds

#### 3.1 Length of Bounds and Coverage of Null Effect

Theorem 3.1 characterizes the length of the IV bound in equation (2) under two-sample designs and assumptions (A1)-(A6); the extra assumptions (A5)-(A6) simplify the formula for the length of the bound to be an interpretable, linear function of instrument strength ST.

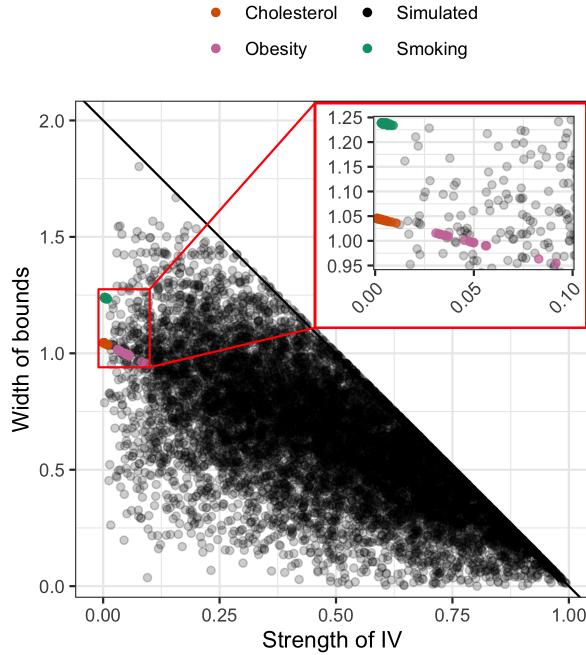
**Theorem 3.1.** *Under assumptions (A1)-(A6), a sharp upper bound on the length of the bound in equation (2) is  $2 - 2 \cdot ST$ , i.e. there exists a data generating process satisfying (A1)-(A6) and has width equal to  $2 - 2 \cdot ST$ .*

See eAppendix A.3 for the proof, which extends Theorem 3.1 to instruments with 2, 3, or 4 categories. Compared to the Balke-Pearl IV bounds with a binary IV in single-sample designs whose width is  $1 - ST$  [3], the length of the two-sample bounds can be twice as long. Also, the length of two-sample IV bounds is only guaranteed to be less than 1 if instrument strength ST is greater than 0.5; note that this does not imply that instruments with ST less than 0.5 has length greater than 1. In contrast, one-sample IV bounds always have length less than 1 unless ST is zero. In short, there is a cost, in length, of using a two-sample design instead of a one-sample design when performing a bound-based analysis of the ATE in MR.

Figure 1A numerically illustrates the consequences of Theorem 3.1 by calculating the bounds in equation (2) from 10,000 randomly generated sets of values of  $P(X = 1|Z = z)$  and  $P(Y = 1|Z = z)$  that satisfy the IV inequalities and assumptions (A1)-(A4). We also use three real-world data examples where the causal effect is known to exist: the effect of high cholesterol on incidence of heart attacks [14], the effect of smoking on incidence of lung cancer [15], and the effect of obesity on incidence of heart attacks [48]. The first two studies are discussed in detail in Section 5. We see that the width of the bounds often exceed 1 as the instrument strength decreases. Also, the three real-world studies generally do not lead to bounds with length less than 1. Figure 1B further illustrates this point by characterizing the relationship between instrument strength ST and the summary statistic coefficient  $\gamma_1$  from a logistic exposure model  $\text{logit}(P(X = 1|Z = z, U = u)) = \gamma_0 + \gamma_1 z + \gamma_U u$  commonly used in parametric approaches to analyzing two-sample MR studies; see eAppendix A.4 for details. We see that instrument strength ST of 0.5 corresponds to a regression coefficient  $\gamma_1$  of approximately 1.1, 1.16, 1.4 and 1.8 if  $\gamma_U$  is 0.1, 0.5, 1 and 2, respectively. Coefficients with such magnitudes are rare in GWAS where genetic variants often explain a small amount of variation in the exposure. To better contextualize this observation, we note that these values of  $\gamma_1$  correspond to odds ratios between 3 and 6 whereas the strong causal effect of exposure to ultraviolet light

on the incidence of skin cancer is estimated be in the range from 1.4 to 2.22 [36].

A



B

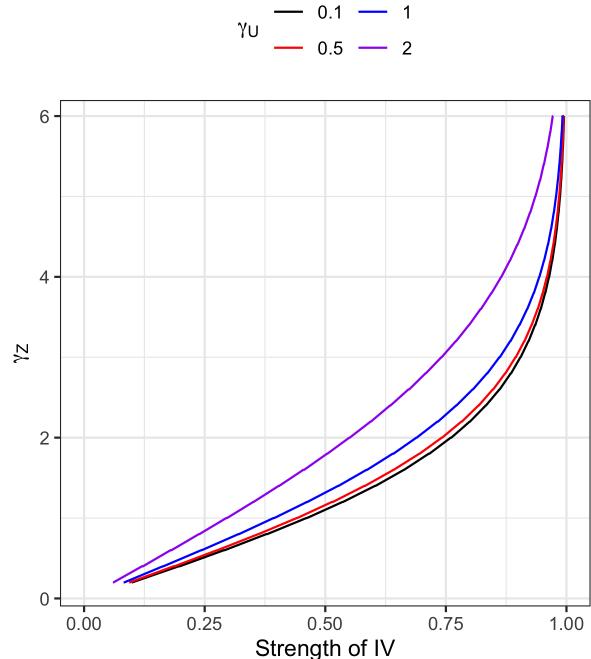


Figure 1: Illustration of the relationship between instrument strength, width of bounds obtained from two-sample design, and coefficients from logistic regression model. A: Relationship between instrument strength (ST) and width of the IV bounds. Black line is the upper bound on the two-sample IV bounds from Theorem 1. Black dots indicate one of the 10,000 IV bounds. Colored dots indicate bounds from real data; see Section 5 for details. B: Coefficients from logistic regression model and instrument strength (ST).

Next, for bounds with length less than 1, we examine what kind of  $\gamma_1$  is needed in order for the two-sample IV bounds to exclude 0 for an anticipated effect size of the ATE. This question is akin to computing the power of bounds but with population-level quantities. We reuse the same logistic model above for the exposure and the outcome; see eAppendix A.4 for details on this setup. Figure 2 shows the smallest  $\gamma_1$  needed to exclude 0 for different values of the ATE. Even for moderate effect sizes of 0.4, the corresponding  $\gamma_1$  must be around 2, a tall order for most GWAS. Also, as the effect of unmeasured confounding increases via  $\gamma_U$ , a larger  $\gamma_1$  is needed to exclude 0.

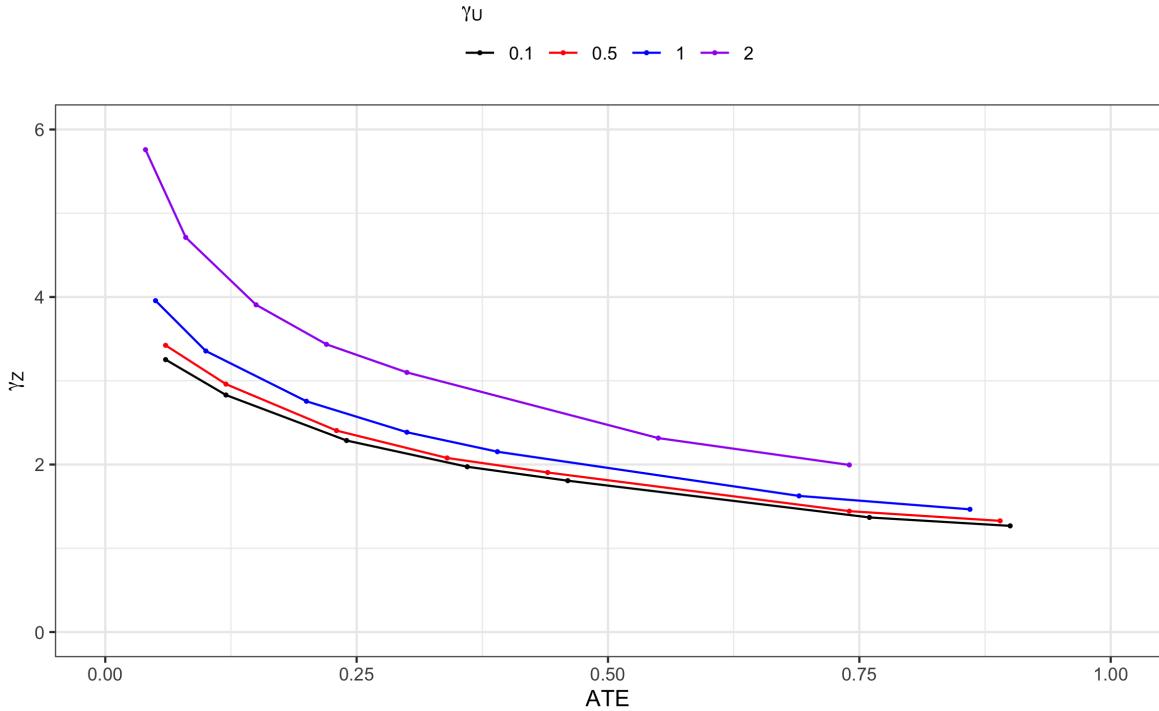


Figure 2: The smallest  $\gamma_1$  needed for a two-sample IV bound to exclude 0.

Overall, using two-sample MR studies with a bound-based analysis is unlikely to be informative. The bounds will often have length greater than 1 and rarely exclude 0 unless very strong genetic variants are used.

### 3.2 Would Multiple Instruments Help?

Based on the results above with a single instrument, a natural question from investigators is whether using multiple instruments can lead to more informative bounds for the ATE; see Swanson [41] for a recent discussion on this point. For example, suppose we aggregate two-sample IV bounds across multiple instruments by taking intersections of individual IV bounds. This approach may be inferior to another alternative where we expand the levels of  $Z$  from 0, 1, 2 to accommodate multiple instruments [41], but has the benefit of being applicable to most two-sample MR studies. However, as we show in eAppendix A.5, the strongest instrument essentially determines the length of the intersection bound because the bounds from each instrument exhibit a nesting property. In short, using a bound based on the strong instrument provides the same amount of information about the ATE as the intersection of individual IV bounds from multiple instruments.

## 4 Characterizing the Loss of Information in Two-Sample MR Studies

As hinted in Theorem 3.1, the increase in the bound’s length is an inevitable “cost” of using two-sample designs instead of one-sample designs in MR studies. This section investigates this loss of information in a bit more detail by creating a plausible range of the joint distribution of the outcome and the exposure given the instrument,  $P(X = x, Y = y|Z = z)$ , based on the observed data from two-sample MR studies. Specifically, using  $P(X = x|Z = z)$  and  $P(Y = y|Z = z)$ , and a uniform prior over the values of the unknown quantities  $\text{Cov}(X = x, Y = y|Z = z)$  that make up a joint distribution  $P(X, Y|Z)$  which satisfy the IV assumptions, we compute  $P(X = x, Y = y|Z = z)$  and its corresponding one-sample IV bounds of Balke and Pearl [3] and Richardson and Robins [31]; see eAppendix A.6 for details and also the connection to empirical Bayesian frameworks. If a large number of the one-sample IV bounds obtained from this procedure do not cover zero, then there is some evidence for a non-zero exposure effect and a one-sample MR study may yield informative bounds on the ATE. However, if a large number of the one-sample IV bounds cover zero, there is little hope of obtaining information about the ATE from bound-based approaches even if we used a one-sample MR design; in other words, the one-sample IV bounds are likely as conservative as the two-sample IV bounds.

Table 1 presents nine different sets of values of the marginal distributions  $P(Y|Z)$  and  $P(X|Z)$  that investigators could theoretically obtain from hypothetical two-sample MR studies. Figure 3 shows the one-sample IV bounds from the procedure we illustrated above.

Table 1: Values of  $P(X = 1|Z = z)$  and  $P(Y = 1|Z = z)$  used to illustrate our approach. For each cell (e.g. row A, column 1), we have  $\{P(X = 1|Z = 0), P(X = 1|Z = 1), P(X = 1|Z = 2)\}$  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	$\{0.125, 0.399, 0.080\}$	$\{0.244, 0.275, 0.185\}$	$\{0.603, 0.469, 0.310\}$
	$\{0.699, 0.840, 0.742\}$	$\{0.238, 0.089, 0.146\}$	$\{0.638, 0.346, 0.719\}$
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	$\{0.175, 0.079, 0.365\}$	$\{0.493, 0.911, 0.085\}$	$\{0.434, 0.045, 0.733\}$
	$\{0.599, 0.358, 0.087\}$	$\{0.360, 0.480, 0.441\}$	$\{0.747, 0.370, 0.169\}$

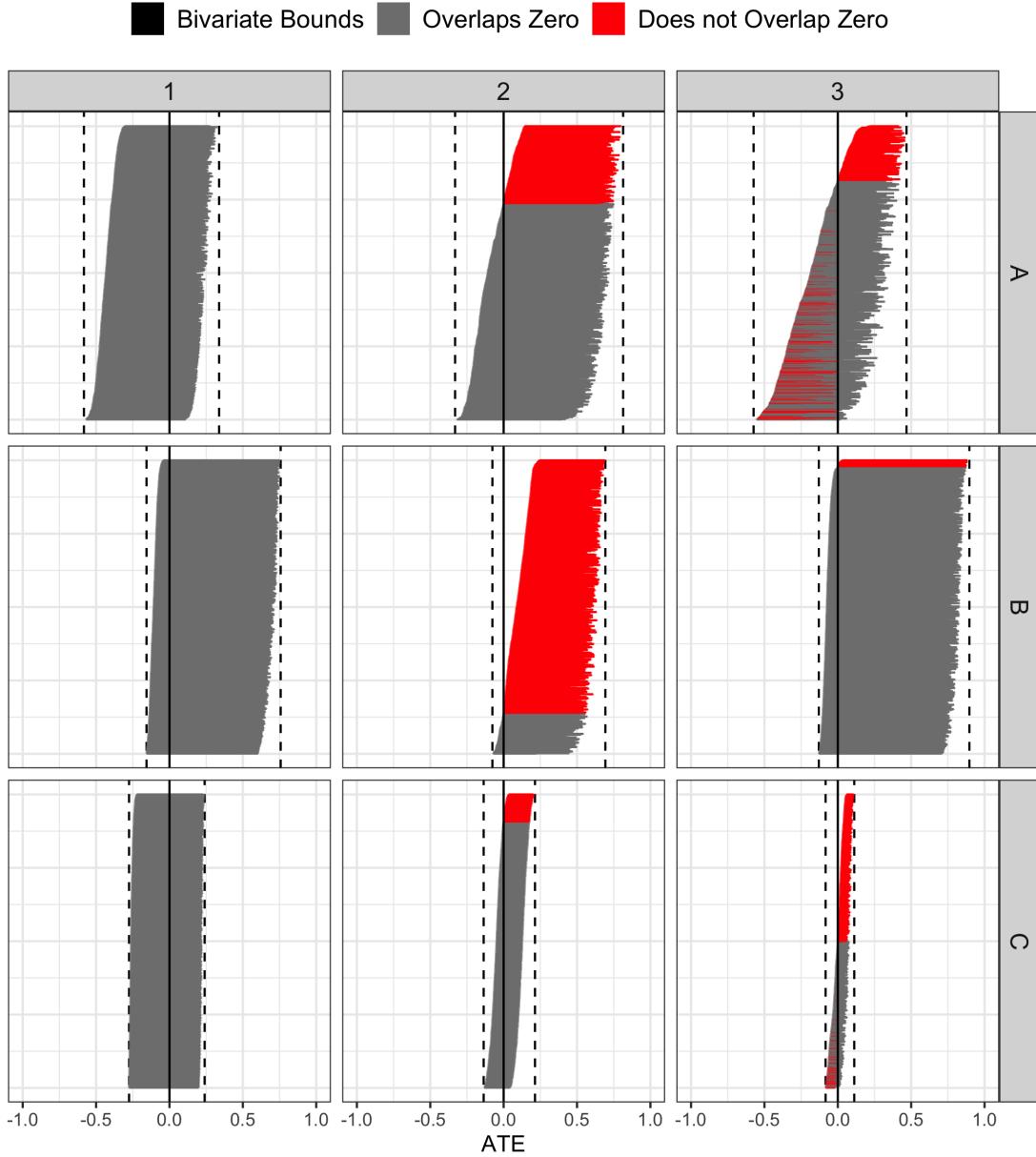


Figure 3: One-sample bounds (horizontal lines) and two-sample bounds (vertical dotted lines). Red color represents one-sample bounds that do not cover zero and gray color represents one-sample bounds that do cover zero.

Row A of Figure 3 shows three scenarios where the two-sample bounds are all centered close to zero with similar widths. But, the conclusions from the one-sample bound analysis are rather different. Column 1 shows no one-sample bounds would allow us to determine the presence of a non-zero exposure effect. Column 2 indicates that about 26.3% of the one-sample IV bounds does not contain 0 while for column 3 that number is approximately 35.9%. However, the latter includes one-sample bounds entirely below 0 and one-sample

bounds entirely above 0.

Row B illustrates three scenarios where the two-sample bounds are centered well above zero and have large widths. We see one case where we have no hope of determining direction of the ATE from the one-sample bounds (column 1), one case where we are most likely to determine the ATE’s direction (column 2), and one case where we are unlikely to determine the ATE’s direction (column 3).

Row C is similar to row A in that all the two-sample bounds are centered around 0, but the widths of the two-sample bounds are narrow. The three columns indicate similar conclusions as row A, showing that even with rather narrow two-sample bounds centered around 0, the one-sample bounds may still reveal some information about presence as well as the direction of the exposure effect.

Overall, our results above show that some two-sample MR studies could potentially reveal something useful about the ATE had we used a one-sample design. Nevertheless, we mention a word of caution when interpreting the results above, especially concerning the flat prior on the covariances. For example, a scenario like the one resulting in the bounds presented in row B, column 2 only provides honest information about the one-sample bounds if our prior on  $\text{Cov}(X, Y|Z)$  is correctly specified. If the prior is mis-specified whereby most one-sample bounds cover negative values of the ATE, a negative value of the ATE is possible. But in this case, if the ATE is in fact negative, our method does rule out the possibility of one-sample bounds being able to ascertain this because all one-sample bounds covering a negative ATE also covers 0.

## 5 Using Bound-Based Analysis in Two, Positive Control Examples

We demonstrate our findings about the behavior of two-sample IV bounds on two real MR studies. Our first study examines the effect of smoking on incidence of lung cancer and our second study examines the effect of self-reported high cholesterol on incidence of heart attack. The effect of smoking on lung cancer is known to be strong and positive [29]. Also, while the exact mechanism between high cholesterol and heart disease is still being discussed [22, 32], some meta-analyses of randomized clinical trials of the effect of cholesterol-lowering medication suggest a strong causal relationship [13, 14]. In both cases, we assess what conclusions are attainable based on bound-based analyses in studies where the causal effects are known to be strong and positive.

The study data were obtained from the UK Biobank data stored in the Integrative Epidemiology Unit (IEU) GWAS database. Specifically, data on smoking was obtained from the data entry ID ukb-d-20116\_0, data

on lung cancer was from data entry ID ukb-d-40001\_C349, data on cholesterol was from data entry ID ukb-a-108, and data on heart attack was from data entry ID ukb-a-434. We use the `TwoSampleMR` R package [21] with the recommended defaults to extract and clean the data. For more details, see eAppendix A.7.

For the effect of smoking on lung cancer, we used 84 genetic instruments, and for the effect of cholesterol on heart attack, we used 54 genetic instruments. The average instrument strengths were 0.0042 (range: 0.0032 to 0.0091) for smoking and 0.0005 (range: 0.0002 to 0.0022) for cholesterol; these values are much smaller than the  $ST = 0.5$  needed to guarantee narrow bounds. As such, the two-sample bounds in Figure 4 are rather wide; all of them have width greater than 1 and they convey no information about the causal effects of interest. Additionally, using our method from Section 4, the direction of the ATE may be difficult to determine had we had one-sample IV bounds; see Figure 5. eAppendix A.7 contains additional analysis, notably demonstrating that aggregating multiple bounds through intersections are also non-informative.

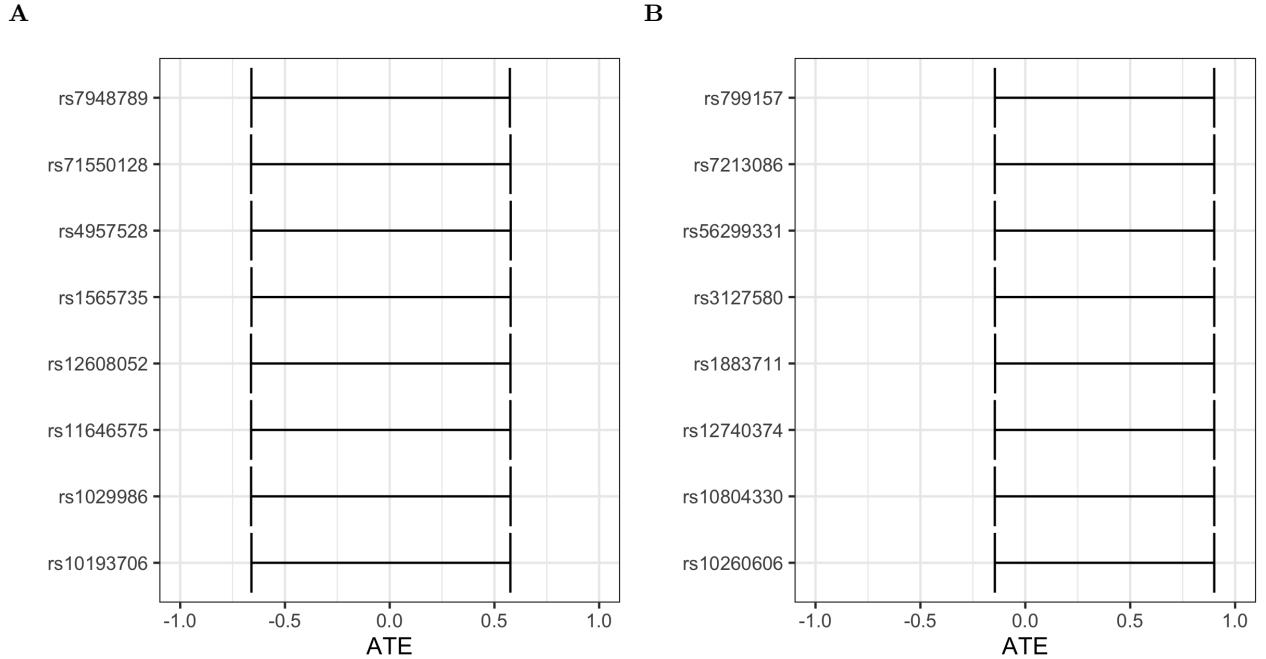


Figure 4: Two-sample IV bounds for the two real data examples with 8 SNPs from each data set. A: Two-sample IV bounds for the ATE of smoking on the incidence of lung cancer. B: Two-sample IV bounds for the ATE of high cholesterol on the incidence of heart attack.

Overall, while nonparametric bounds allow us to not make parametric assumptions frequent in two-sample MR analyses, they may be too conservative and provide little, if any, information about the exposure effects, even if the exposure effect is known to be positive and strong. Additionally, since many MR studies involve weak instruments, we believe bound-based approaches will likely have limited practical value to uncover causal effects.

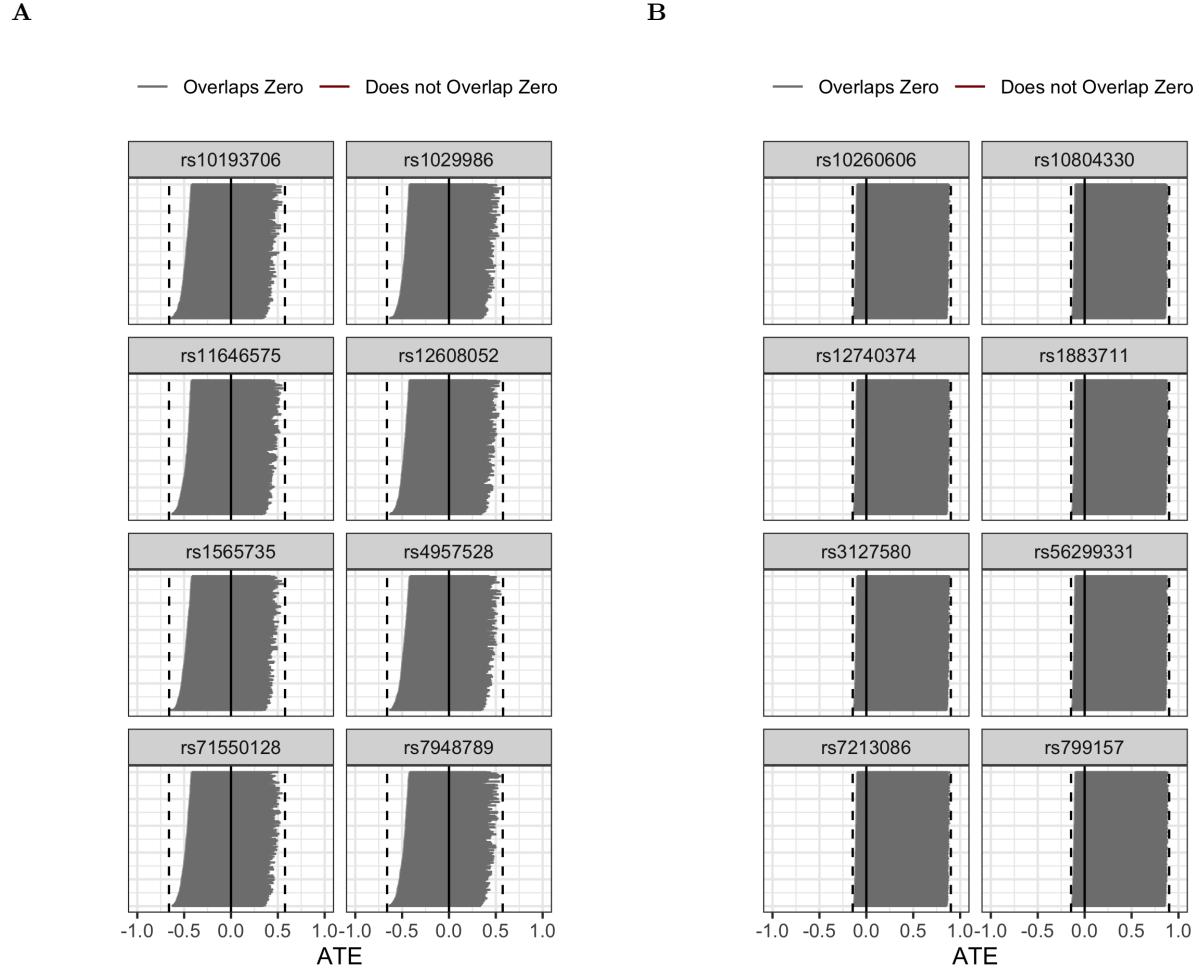


Figure 5: Potential one-sample IV bounds for the two real data examples using the method described in Section 4. A: One-sample IV bounds for the ATE of smoking on the incidence of lung cancer from 500 potential one-sample distributions for each SNP. B: One-sample IV bounds for the ATE of high cholesterol on the incidence of heart attack from 500 potential one-sample distributions for each SNP.

## 6 Discussion

Nonparametric bounds are without a doubt an attractive concept. With a minimal set of assumptions, they let investigators obtain bounds on the average treatment effect. However, as we have seen above, in typical MR studies with two-sample summary data, a bound-based analysis may generally be uninformative for two reasons. First, while IV bounds in one-sample settings have length always less than 1, in two-sample settings, this is not always the case. Second, many genetic variants in MR studies are too weakly associated with the exposure to produce bounds with length less than 1 or bounds that exclude 0. Indeed, our two real data examples showed that despite having strong causal effects, bound-based analyses were unable to detect these effects.

We also outlined an approach to roughly quantify the information loss going from one-sample designs to two-sample designs and to assess the range of conclusions that can be drawn from bound-based approaches if we had one-sample data. We demonstrate our method to a few different settings of two-sample data and showed the range of conclusions that can be drawn about the ATE.

What do our results suggest for bound-based analysis in two-sample MR settings in practice? Overall, our general recommendation is that unless investigators have a very strong instrument, ideally exceeding  $ST > 0.5$ , bounds will unlikely be useful as a nonparametric analysis of the ATE. Even if  $ST > 0.5$ , one would need strong IVs and/or strong effect sizes to make sure that the bounds do not cover 0. Indeed, in most cases, we believe investigators should use well-informed parametric methods to analyze the ATE. Nevertheless, there may be few limited, but meaningful use cases for bounds in two-sample MR studies. First when one has prior knowledge about the direction of the effect, but wish to get a better sense of the magnitude, nonparametric bounds can provide an upper limit on this magnitude. This is especially useful in cases where the exposure is known to cause harm or benefit, for example in our smoking on lung cancer example where the direction of the effect of smoking on lung cancer is well known and an upper bound on this effect would tell investigators about the maximum possible effect that smoking could have on increasing the incidence of lung cancer. Second, two-sample IV bounds can be used to check estimates from parametric methods to see if they lie inside of the bounds; if the estimates lie outside of the bounds, then the parametric models underlying the estimates are likely mis-specified.

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# A Supplemental Digital Content to “Non-parametric Bounds in Two-Sample Summary-Data Mendelian Randomization: Some Cautionary Tales for Practice”

This document contains the Supplemental Digital Content to our paper “Non-parametric Bounds in Two-Sample Summary-Data Mendelian Randomization: Some Cautionary Tales for Practice”. This includes additional details on how we obtain bounds on the Average Treatment Effect, more on the logistic models we used for simulating data, proof of Theorem 3.1, additional details and results for the “power” analysis presented in Section 3.1, exploration of the use of multiple IVs in two-sample MR analysis, details on the reconstruction of one-sample distributions introduced in Section 4, and details, summary statistics, and complete results for the two example analyses presented in Section 5.

## A.1 Bounds on Average Treatment Effect

We briefly review the method presented by Ramsahai [30] to bound the average treatment effect using two-sample summary 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 the exclusion restriction, we have

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

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 [30],  $\mathcal{H} = \hat{\mathcal{H}}$ . 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  $\vec{v}$ .

Following the approach from Ramsahai (2012) as outlined above, we obtain bounds on the average treatment effect from the quantities  $P(X = 1 | Z = z)$  and  $P(Y = 1 | Z = z)$ ,  $z = 0, 1, 2$ . To do so, we first write down the most extreme values of each of  $P(Y = 1 | X = x, U)$  and  $P(X = x | Z = z, U)$  for all  $x = 0, 1$ ,  $z = 0, 1, 2$ . Since these are probabilities, the extreme values are 0 and 1.

eTable 1: Most extreme values of  $P(Y = 1 | X = x, U)$  and  $P(X = 1 | Z = z, U)$ . Here, PY1XxU =  $P(Y = 1 | X = x, U)$  and PX1ZzU =  $P(X = 1 | Z = z, U)$ .

PY1X0U	PY1X1U	PY1Z0U	PX1Z1U	PX1Z2U
0	0	0	0	0

PY1X0U	PY1X1U	PY1Z0U	PX1Z1U	PX1Z2U
0	0	0	0	1
0	0	0	1	0
0	0	0	1	1
0	0	1	0	0
0	0	1	0	1
0	0	1	1	0
0	0	1	1	1
0	1	0	0	0
0	1	0	0	1
0	1	0	1	0
0	1	0	1	1
0	1	1	0	0
0	1	1	0	1
0	1	1	1	0
0	1	1	1	1
1	0	0	0	0
1	0	0	0	1
1	0	0	1	0
1	0	0	1	1
1	0	1	0	0
1	0	1	0	1
1	0	1	1	0
1	0	1	1	1
1	1	0	0	0

PY1X0U	PY1X1U	PY1Z0U	PX1Z1U	PX1Z2U
1	1	0	0	1
1	1	0	1	0
1	1	0	1	1
1	1	1	0	0
1	1	1	0	1
1	1	1	1	0
1	1	1	1	1

By applying the function  $f$  to each row, we get the most extreme vertices of  $P(X = x|Z = z, U)$ ,  $P(Y = y|Z = z, U)$ , and  $\alpha$  for all  $x = 0, 1$ ,  $y = 0, 1$  and  $z = 0, 1, 2$ .

eTable 2: Most extreme values of  $P(Y = y|Z = z)$  and  $P(X = x|Z = z)$ . Here, PYyZz =  $P(Y = y|Z = z)$ , PXxZz =  $P(X = x|Z = z)$ , and  $\alpha = P(Y = 1|X = 1, U) - P(Y = 1|X = 0, U)$ .

PY0Z0	PY0Z1	PY0Z2	PY1Z0	PY1Z1	PY1Z2	PX0Z0	PX0Z1	PX0Z2	PX1Z0	PX1Z1	PX1Z2	$\alpha$
1	1	1	0	0	0	1	1	1	0	0	0	0
0	0	0	1	1	1	1	1	1	0	0	0	-1
1	1	1	0	0	0	1	1	1	0	0	0	1
0	0	0	1	1	1	1	1	1	0	0	0	0
1	1	1	0	0	0	0	1	1	1	0	0	0
1	0	0	0	1	1	0	1	1	1	0	0	-1
0	1	1	1	0	0	0	1	1	1	0	0	1
0	0	0	1	1	1	0	1	1	1	0	0	0
1	1	1	0	0	0	1	0	1	0	1	0	0
0	1	0	1	0	1	1	0	1	0	1	0	-1
1	0	1	0	1	0	1	0	1	0	1	0	1
0	0	0	1	1	1	1	0	1	0	1	0	0

PY0Z0	PY0Z1	PY0Z2	PY1Z0	PY1Z1	PY1Z2	PX0Z0	PX0Z1	PX0Z2	PX1Z0	PX1Z1	PX1Z2	$\alpha$
1	1	1	0	0	0	0	0	1	1	1	0	0
1	1	0	0	0	1	0	0	1	1	1	0	-1
0	0	1	1	1	0	0	0	1	1	1	0	1
0	0	0	1	1	1	0	0	1	1	1	0	0
1	1	1	0	0	0	1	1	0	0	0	1	0
0	0	1	1	1	0	1	1	0	0	0	1	-1
1	1	0	0	0	1	1	1	0	0	0	1	1
0	0	0	1	1	1	1	1	0	0	0	1	0
1	1	1	0	0	0	0	1	0	1	0	1	0
1	0	1	0	1	0	0	0	1	0	1	0	-1
0	1	0	1	0	1	0	1	0	1	0	1	1
0	0	0	1	1	1	0	1	0	1	0	1	0
1	1	1	0	0	0	1	0	0	0	1	1	0
0	1	1	1	0	0	1	0	0	0	1	1	-1
1	0	0	0	1	1	1	0	0	0	1	1	1
0	0	0	1	1	1	1	0	0	0	1	1	0
1	1	1	0	0	0	0	0	0	0	1	1	0
1	1	1	0	0	0	0	0	0	0	1	1	-1
0	0	0	1	1	1	0	0	0	1	1	1	1
0	0	0	1	1	1	0	0	0	1	1	1	0

Theorem 1 of Ramsahai (2012) tells us that the values of  $P(X = 1|Z = z), P(Y = 1|Z = z)$ ,  $z = 0, 1, 2$  must lie in the convex hull of the vertices given by the rows in eTable 2. This means that the vector of these values must be a convex combination of the rows in said table. Using this with the fact that they must sum to 1 is what enables us to use polymake to find inequalities that the values of  $P(X = 1|Z = z)$ ,

$P(Y = 1|Z = z)$ , and  $\alpha$  must satisfy. In this particular case, these are as presented below. This table should be read as rows of coefficients for which it holds that  $\sum_{z=0}^2 c_{X1Zz} \cdot P(X = 1|Z = z) + \sum_{z=0}^2 c_{Y0Zz} \cdot P(Y = 0|Z = z) + c_{Y1Z0} \cdot P(Y = 1|Z = 0) + c_\alpha \alpha \geq 0$ .

eTable 3: Results from polymake. Columns with all zeroes have been removed.

c_{Y0Z0}	c_{Y0Z1}	c_{Y0Z2}	c_{Y1Z0}	c_{X1Z0}	c_{X1Z1}	c_{X1Z2}	c <sub><math>\alpha</math></sub>
2	0	-1	0	2	0	0	-1
1	0	-1	1	0	0	0	0
1	-1	0	1	0	0	0	0
1	-1	0	0	1	1	0	0
1	0	-1	0	1	0	1	0
2	0	-1	1	1	0	-1	-1
2	-1	0	1	1	-1	0	-1
2	0	-2	1	0	0	2	1
2	-1	0	1	-1	1	0	1
4	0	-2	3	0	0	-2	-1
2	-2	0	1	0	2	0	1
4	-1	0	2	-2	0	0	1
4	0	-1	2	-2	0	0	1
2	0	-1	1	-1	0	1	1
1	0	-1	1	0	0	1	1
3	-1	0	2	-1	-1	0	0
2	-1	0	0	2	0	0	-1
4	-2	0	3	0	-2	0	-1
3	0	-1	2	-1	0	-1	0
1	-1	0	1	0	1	0	1
1	-1	1	1	0	1	-1	1

$c_{\{Y_0Z_0\}}$	$c_{\{Y_0Z_1\}}$	$c_{\{Y_0Z_2\}}$	$c_{\{Y_1Z_0\}}$	$c_{\{X_1Z_0\}}$	$c_{\{X_1Z_1\}}$	$c_{\{X_1Z_2\}}$	$c_\alpha$
1	0	0	1	0	-1	0	0
1	0	0	1	0	0	-1	0
1	0	1	1	0	0	-1	1
2	-1	2	2	0	0	-2	1
1	1	0	1	0	-1	0	1
0	1	0	1	1	-1	0	1
0	0	1	1	1	0	-1	1
2	2	-1	2	0	-2	0	1
2	1	-1	2	0	-1	-1	0
2	-1	1	2	0	-1	-1	0
0	0	0	1	1	0	0	1
1	1	-1	1	0	-1	1	1
0	0	0	0	1	0	0	0
2	0	0	1	-1	0	0	1
0	0	1	1	-1	0	1	-1
0	0	0	0	0	1	0	0
1	-1	1	1	0	-1	1	-1
-1	2	0	0	0	2	0	-1
2	0	-1	2	0	0	-1	-1
1	0	1	3	-2	0	0	-1
1	1	0	2	-1	-1	0	0
0	1	-1	0	0	1	1	0
0	1	0	1	-1	1	0	-1
0	0	1	0	0	0	0	0

$c_{\{Y_0Z_0\}}$	$c_{\{Y_0Z_1\}}$	$c_{\{Y_0Z_2\}}$	$c_{\{Y_1Z_0\}}$	$c_{\{X_1Z_0\}}$	$c_{\{X_1Z_1\}}$	$c_{\{X_1Z_2\}}$	$c_\alpha$
-1	0	1	1	2	0	0	1
3	-2	1	3	0	-2	0	-1
0	0	0	0	0	0	1	0
0	-1	1	0	0	1	1	0
0	1	0	0	0	0	0	0
1	1	0	3	-2	0	0	-1
1	0	0	1	-1	0	0	0
0	2	-1	0	0	2	0	-1
1	0	2	2	0	0	-2	1
0	0	0	1	0	0	0	0
1	-2	1	1	0	2	0	1
2	-1	0	2	0	-1	0	-1
1	1	-1	1	0	1	-1	-1
-1	0	1	0	1	0	1	0
1	0	0	0	1	0	0	-1
-1	0	2	0	0	0	2	-1
1	2	0	2	0	-2	0	1
1	1	-2	1	0	0	2	1
-1	1	0	0	1	1	0	0
0	1	0	0	0	1	0	-1
0	0	1	0	0	0	1	-1
1	0	0	2	-1	0	0	-1
-1	1	0	1	2	0	0	1
3	1	-2	3	0	0	-2	-1

c_{YZ0}	c_{YZ1}	c_{YZ2}	c_{Y1Z0}	c_{X1Z0}	c_{X1Z1}	c_{X1Z2}	$c_\alpha$
0	-1	2	0	0	0	2	-1
1	0	1	2	-1	0	-1	0
1	0	0	0	0	0	0	0

The matrix presented in the table above simplifies to the following set of bounds on the average treatment effect. These are obtained by considering the rows above where  $c_\alpha \neq 0$ .

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

$$\leq \alpha \leq$$

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

Furthermore, we obtain the following checkable constraints from the rows where  $\alpha = 0$ :

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

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 (A5) and (A6), the bounds reduce to just three on the lower end and three on the upper end. This is done by removing rows in the matrix of extreme vertices where the monotonicity assumptions are violated before using Polymake to get the inequalities. The resulting bounds are presented below.

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

We encountered one surprise when studying the behavior of the bounds in (A.1). Of 10,123 randomly generated sets of values for  $P(X = 1|Z = z), P(Y = 1|Z = z)$ ,  $z = 0, 1, 2$ , 123 resulted in bounds where the upper limit is smaller than the lower limit without violating any of the verifiable constraints presented in (3). eTable 4 gives the values of the marginal conditional distributions with the strength of the IV, the corresponding bounds, and the width. It is notable that the IVs are rather strong in all cases where we see the bounds flip, but the bounds themselves and the widths vary quite a bit.

We first attributed this to the transition from one-sample to two-sample bounds, but later realized similar scenarios arise when dealing with one-sample bounds from four category IVs. Of 100,000 randomly generated

sets of values for  $P(X = x, Y = y|Z = z)$ ,  $x = 0, 1$ ,  $y = 0, 1$ ,  $z = 0, 1, 2, 3, 37$  result in bounds where the upper limit is smaller than the lower limit without any violation of the verifiable constraints. It is also worth noting that in a similar number of one-sample distributions randomly generated with a trichotomous instrument, we did not see any cases of flipped bounds without a violation of one or more of the verifiable constraints. eTable 5 show the bounds from the one-sample distributions with the strengths of the IVs, and the width. Again, it is interesting to see the large span of widths and strengths present.

We have been unable to unearth a reason for why we see this phenomenon. One possible explanation is that the distributions that result in flipped bounds violate some uncheckable assumption.

eTable 4: Marginal conditional probabilities resulting in bounds where the upper bound is smaller than the lower bound.

	P(X=1 Z=0)	P(X=1 Z=1)	P(X=1 Z=2)	P(Y=1 Z=0)	P(Y=1 Z=1)	P(Y=1 Z=2)	Strength	Lower Bound	Upper Bound	Width
12	0.2309955	0.3669268	0.9387298	0.8850137	0.3013143	0.9801302	0.7077343	0.5364056	-0.0067221	-0.5431277
	0.9404491	0.4742722	0.1448868	0.0262469	0.5741507	0.1155472	0.7955623	0.0532826	-0.4025552	-0.4558377
	0.8243777	0.0826950	0.6396267	0.0984834	0.0536095	0.6267494	0.7416826	0.3541403	-0.0785379	-0.4326782
	0.6253430	0.7940521	0.0769966	0.7125237	0.1332569	0.0937761	0.7170556	0.3709784	-0.0341142	-0.4050925
	0.4687418	0.9885571	0.0147455	0.4269904	0.0952051	0.1145516	0.9738116	0.1683963	-0.2136943	-0.3820906
	0.2384690	0.9589127	0.4551064	0.9411639	0.8220534	0.2995920	0.7204437	0.2623402	-0.1057977	-0.3681380
	0.1201855	0.5087544	0.6903413	0.1553146	0.7813318	0.0153936	0.5701558	0.2303316	-0.1312272	-0.3615588
	0.0558596	0.8249922	0.5150187	0.1693588	0.0317164	0.6019942	0.7691326	0.1515574	-0.1885458	-0.3401031
	0.0601930	0.7105220	0.7764157	0.0349669	0.6138605	0.1288649	0.7162227	0.4235408	0.0910378	-0.3325030
	0.9689451	0.3369273	0.0921191	0.9728974	0.3379845	0.6435396	0.8768260	0.5457005	0.2351435	-0.3105570
	0.0272617	0.9602504	0.7090107	0.9941238	0.7603751	0.5393045	0.9329888	-0.0980534	-0.3944198	-0.2963664
	0.8593575	0.5455747	0.0954651	0.7493743	0.2343858	0.8692962	0.7638924	-0.0169223	-0.3132765	-0.2963542
	0.0051370	0.7930864	0.6854693	0.0171757	0.5039197	0.0258429	0.7879494	0.4592943	0.1768274	-0.2824669
	0.8095621	0.0899196	0.7315497	0.1398438	0.0112235	0.5721541	0.7196425	0.3698677	0.0884094	-0.2814583
	0.0312864	0.5136612	0.7187288	0.1782691	0.7144743	0.0839332	0.6874423	0.2953632	0.0159345	-0.2794287
	0.2841081	0.4642261	0.9303618	0.9272837	0.3015191	0.8563395	0.6462537	0.2718836	0.0151680	-0.2567156
	0.7020589	0.0426525	0.7537495	0.8146495	0.9551254	0.3030152	0.7110970	-0.2695984	-0.5219304	-0.2523321
	0.7299439	0.7079992	0.0126445	0.4179246	0.9411138	0.9059591	0.7172993	-0.1196986	-0.3687044	-0.2490059
	0.8553215	0.1611814	0.3987327	0.0868026	0.0650961	0.5766878	0.6941401	0.1241329	-0.1137256	-0.2378585
	0.7503627	0.8262444	0.0255938	0.9023691	0.4826617	0.9697816	0.8006505	-0.1771982	-0.4057139	-0.2285157
	0.7516532	0.1293625	0.6636683	0.2319998	0.0773707	0.8011377	0.6222907	0.3876713	0.1595554	-0.2281159

eTable 4: Marginal conditional probabilities resulting in bounds where the upper bound is smaller than the lower bound. (*continued*)

	P(X=1 Z=0)	P(X=1 Z=1)	P(X=1 Z=2)	P(Y=1 Z=0)	P(Y=1 Z=1)	P(Y=1 Z=2)	Strength	Lower Bound	Upper Bound	Width
E <sup>T</sup>	0.1892072	0.6542341	0.6029697	0.9717090	0.8941221	0.2186525	0.4650268	-0.1219402	-0.3463509	-0.2244107
	0.9351863	0.1648035	0.3655840	0.1803887	0.1576169	0.6793117	0.7703828	0.0344709	-0.1889068	-0.2233777
	0.8913881	0.2924893	0.1391987	0.0678851	0.5562612	0.1311623	0.7521894	0.0155394	-0.2032671	-0.2188065
	0.2004629	0.8817321	0.4467427	0.2410824	0.0446975	0.7057212	0.6812692	-0.1773694	-0.3797903	-0.2024209
	0.2713706	0.9177118	0.2155938	0.0584116	0.0235335	0.5341155	0.7021180	-0.1254488	-0.3224721	-0.1970232
	0.1716186	0.9793879	0.4387238	0.0758875	0.0913810	0.4572813	0.8077692	-0.0377310	-0.2332949	-0.1955639
	0.0346134	0.8601421	0.5243412	0.7170224	0.9940138	0.4402146	0.8255286	0.2680971	0.0753966	-0.1927005
	0.0517557	0.9490455	0.4763609	0.2257054	0.0428283	0.4666474	0.8972898	-0.0882749	-0.2790819	-0.1908070
	0.2097271	0.7849572	0.5591844	0.9851851	0.7694310	0.2353843	0.5752301	-0.1266079	-0.3155315	-0.1889237
	0.8533233	0.5437889	0.3202183	0.0278734	0.0138157	0.8263378	0.5331050	-0.2888714	-0.4772378	-0.1883664
	0.0781475	0.4316186	0.9562902	0.6056942	0.2534086	0.8616394	0.8781427	0.3824505	0.1983152	-0.1841354
	0.7343532	0.7111032	0.0863323	0.4004145	0.9342732	0.9323079	0.6480209	-0.1096618	-0.2915366	-0.1818748
	0.4855778	0.2600183	0.9736867	0.3390356	0.9283873	0.7874292	0.7136685	0.1831962	0.0022975	-0.1808987
	0.6368154	0.0572293	0.8159708	0.5109590	0.0158577	0.1663634	0.7587416	0.3647850	0.1898262	-0.1749588
	0.8824330	0.1367268	0.3081087	0.0653359	0.1951474	0.6000460	0.7457061	-0.0637026	-0.2342401	-0.1705375
	0.8090247	0.3226145	0.5675011	0.9402684	0.9741885	0.3180210	0.4864103	0.1805653	0.0148730	-0.1656923
	0.4510693	0.0872080	0.9033969	0.5323388	0.1710303	0.0969452	0.8161888	0.0158620	-0.1452420	-0.1611040
	0.1518352	0.6975145	0.6509167	0.0629987	0.8097783	0.1657477	0.5456793	0.3801104	0.2198838	-0.1602266
	0.0653620	0.3813488	0.9612892	0.9275631	0.4953530	0.7515764	0.8959272	-0.0696219	-0.2290492	-0.1594273
	0.2032074	0.7755576	0.4991361	0.7865987	0.9554554	0.2348516	0.5723502	0.2271745	0.0680689	-0.1591056
	0.0233274	0.6660489	0.8176706	0.8429973	0.2798561	0.7213751	0.7943432	-0.2017648	-0.3594838	-0.1577189

eTable 4: Marginal conditional probabilities resulting in bounds where the upper bound is smaller than the lower bound. (*continued*)

	P(X=1 Z=0)	P(X=1 Z=1)	P(X=1 Z=2)	P(Y=1 Z=0)	P(Y=1 Z=1)	P(Y=1 Z=2)	Strength	Lower Bound	Upper Bound	Width
14	0.9294752	0.2110150	0.4387583	0.1560685	0.0882931	0.6040925	0.7184602	0.0054762	-0.1509059	-0.1563822
	0.1670113	0.6894123	0.4795673	0.0041910	0.8002859	0.0345400	0.5224010	0.4578813	0.3096595	-0.1482218
	0.3785346	0.9143229	0.1322393	0.3764540	0.9927913	0.6755701	0.7820836	0.4377743	0.2897923	-0.1479819
	0.1776605	0.3763786	0.8762187	0.2525663	0.7852824	0.1601145	0.6985582	-0.0751713	-0.2174909	-0.1423196
	0.7676593	0.0086728	0.5238627	0.3109642	0.8841540	0.9821670	0.7589865	-0.2989048	-0.4399984	-0.1410937
	0.8834087	0.2154675	0.5237259	0.9402145	0.9094435	0.4479360	0.6679412	0.1993104	0.0599839	-0.1393265
	0.2128945	0.6634662	0.7020688	0.9859116	0.2297734	0.8227277	0.4891743	-0.1801804	-0.3162608	-0.1360804
	0.8197957	0.4539939	0.2933378	0.1292782	0.6944266	0.0241216	0.5264579	0.0595077	-0.0754615	-0.1349692
	0.8932091	0.2573860	0.3789772	0.8683447	0.8850420	0.3218777	0.6358231	0.2012298	0.0665657	-0.1346641
	0.3852521	0.7681010	0.1679198	0.6200211	0.0286245	0.1269667	0.6001813	0.0302481	-0.0989742	-0.1292223
	0.4450183	0.3448027	0.9580487	0.0334938	0.6223715	0.0373602	0.6132460	-0.3346527	-0.4637484	-0.1290957
	0.9626206	0.3323393	0.3615993	0.8971357	0.8947940	0.3577061	0.6302814	0.3618066	0.2327966	-0.1290100
	0.9579589	0.2856719	0.2557011	0.0294142	0.0312341	0.4495460	0.7022578	-0.1842660	-0.3066353	-0.1223693
	0.2722892	0.1030317	0.9532750	0.3335194	0.0179986	0.1046059	0.8502432	0.0914587	-0.0308574	-0.1223161
	0.2075435	0.6267518	0.9907035	0.0610969	0.8711902	0.5325762	0.7831600	0.3339092	0.2125552	-0.1213540
	0.1309917	0.9511009	0.6110001	0.0092469	0.1382892	0.3862037	0.8201092	0.1057264	-0.0118269	-0.1175533
	0.9469203	0.4771290	0.2975224	0.8483259	0.2756656	0.8366797	0.6493979	0.3148269	0.1973510	-0.1174758
	0.9141838	0.3947449	0.2582693	0.1776121	0.6284717	0.0485084	0.6559145	0.0149163	-0.1016151	-0.1165314
	0.2539480	0.3283935	0.9257231	0.5855638	0.1211694	0.0074839	0.6717752	-0.3135619	-0.4220422	-0.1084803
	0.7554315	0.0394385	0.8166883	0.9193390	0.1504442	0.4920783	0.7772497	0.5395735	0.4314412	-0.1081323
	0.5322302	0.8442719	0.1311744	0.7227207	0.1174348	0.2652317	0.7130975	-0.0700917	-0.1763950	-0.1063033

eTable 4: Marginal conditional probabilities resulting in bounds where the upper bound is smaller than the lower bound. (*continued*)

	P(X=1 Z=0)	P(X=1 Z=1)	P(X=1 Z=2)	P(Y=1 Z=0)	P(Y=1 Z=1)	P(Y=1 Z=2)	Strength	Lower Bound	Upper Bound	Width
	0.1022484	0.7850567	0.3114329	0.9983873	0.9750404	0.6040354	0.6828082	-0.0838413	-0.1882423	-0.1044009
	0.8859779	0.1854690	0.2675919	0.9352886	0.8113619	0.3954484	0.7005089	0.2470847	0.1436625	-0.1034222
	0.8858413	0.0577413	0.7457014	0.9231434	0.9814877	0.6837953	0.8281000	-0.0658260	-0.1636975	-0.0978715
	0.5688937	0.0533840	0.9092544	0.4161218	0.0847550	0.1385937	0.8558704	0.1398438	0.0425567	-0.0972870
	0.0111502	0.5785773	0.7360408	0.9491940	0.9715842	0.4417906	0.7248905	-0.3414676	-0.4342969	-0.0928294
	0.8016434	0.0919814	0.6269118	0.0598012	0.0080604	0.4024806	0.7096620	0.2023970	0.1138349	-0.0885621
	0.5613155	0.3343263	0.9641096	0.1739435	0.9413168	0.6466249	0.6297833	0.0475254	-0.0400375	-0.0875629
	0.9421035	0.7800406	0.0170238	0.6536674	0.8584000	0.0860958	0.9250797	0.6521608	0.5647278	-0.0874330
	0.4856718	0.1412137	0.8327200	0.2353279	0.7698770	0.8171080	0.6915064	0.0643282	-0.0219988	-0.0863269
E	0.7587967	0.2217142	0.4642144	0.1261614	0.0095185	0.6397095	0.5370825	0.1772441	0.0950201	-0.0822241
	0.8476325	0.0321449	0.5761561	0.7137147	0.9222930	0.4156565	0.8154876	-0.2929622	-0.3646398	-0.0716776
	0.8443266	0.0231323	0.6135112	0.5114541	0.9662261	0.9901356	0.8211943	-0.3041605	-0.3747334	-0.0705729
	0.7090756	0.0306938	0.8591612	0.8275547	0.1987801	0.4221209	0.8284674	0.3686070	0.2983647	-0.0702424
	0.5210445	0.6877412	0.1936365	0.2077578	0.8583608	0.8895555	0.4941047	-0.1155538	-0.1840802	-0.0685264
	0.7325333	0.0360979	0.7452189	0.9243027	0.1841382	0.4150783	0.7091209	0.4838304	0.4154162	-0.0684143
	0.3112649	0.5408216	0.7700621	0.0719339	0.8911155	0.9844600	0.4587973	0.4371103	0.3713461	-0.0657642
	0.6839198	0.0601158	0.7429099	0.3546209	0.0832522	0.8458772	0.6827941	0.5591411	0.4955250	-0.0636161
	0.4925476	0.1475428	0.6432137	0.1357593	0.7295215	0.9418075	0.4956709	0.0342830	-0.0281982	-0.0624812
	0.0567614	0.4716677	0.8412115	0.9781020	0.6182925	0.8866750	0.7844501	-0.1625195	-0.2243887	-0.0618691
	0.1902110	0.3836209	0.9071890	0.8456573	0.3088491	0.0296753	0.7169780	-0.5392827	-0.6006846	-0.0614020
	0.3772296	0.8822068	0.2883994	0.2173902	0.9350335	0.7191264	0.5938073	0.4170904	0.3559363	-0.0611541

eTable 4: Marginal conditional probabilities resulting in bounds where the upper bound is smaller than the lower bound. (*continued*)

P(X=1 Z=0)	P(X=1 Z=1)	P(X=1 Z=2)	P(Y=1 Z=0)	P(Y=1 Z=1)	P(Y=1 Z=2)	Strength	Lower Bound	Upper Bound	Width
0.5973862	0.8450983	0.2624347	0.1392309	0.6156584	0.9712264	0.5826636	-0.2177176	-0.2783525	-0.0606348
0.6339672	0.0297922	0.8123455	0.7376053	0.9506195	0.2630108	0.7825533	-0.5198657	-0.5786439	-0.0587783
0.0823461	0.5840173	0.6679903	0.9677474	0.8284869	0.2712011	0.5856442	-0.4461926	-0.4996015	-0.0534089
0.6535119	0.8883952	0.1073055	0.2820041	0.7154519	0.8117950	0.7810897	-0.0743099	-0.1269749	-0.0526651
0.7404535	0.1312750	0.4474163	0.1314948	0.9068344	0.9347602	0.6091785	-0.3671417	-0.4196239	-0.0524822
0.0820021	0.8994346	0.3178099	0.4734612	0.1446546	0.8253918	0.8174325	-0.2855348	-0.3349518	-0.0494170
0.0143154	0.1408971	0.9883829	0.5259441	0.4011591	0.9257180	0.9740675	0.4270428	0.3779018	-0.0491410
0.5142074	0.8446779	0.0753746	0.5067568	0.0715657	0.1808748	0.7693032	-0.0057421	-0.0529810	-0.0472389
0.1391137	0.4452852	0.7319911	0.0201224	0.4730480	0.0227584	0.5928773	0.1545757	0.1084867	-0.0460890
0.7671998	0.0911903	0.9424491	0.7190755	0.0257481	0.5228183	0.8512587	0.4851985	0.4416630	-0.0435356
0.2249334	0.9771968	0.6502243	0.9434316	0.7995282	0.4743734	0.7522634	0.0790767	0.0373769	-0.0416998
0.9124694	0.5503730	0.0400667	0.7951134	0.6099932	0.9632078	0.8724027	-0.1948275	-0.2362891	-0.0414616
0.1645046	0.8060324	0.5635964	0.9246119	0.7605022	0.3061245	0.6415279	-0.1730552	-0.2140902	-0.0410350
0.7079565	0.5723802	0.2806847	0.8839699	0.2430289	0.9515723	0.4272719	-0.0591760	-0.0987463	-0.0395703
0.2097282	0.9124687	0.2747676	0.2570863	0.1285457	0.7024909	0.7027405	-0.2311382	-0.2703369	-0.0391987
0.9736240	0.0208031	0.3737885	0.9045140	0.4334044	0.2716260	0.9528209	0.4846500	0.4464234	-0.0382266
0.1845828	0.1851770	0.8937890	0.8433725	0.4857333	0.9516657	0.7092062	0.2051761	0.1681541	-0.0370221
0.1904095	0.9898458	0.0778574	0.3241436	0.0396418	0.5826816	0.9119883	-0.4464247	-0.4830894	-0.0366648
0.3058563	0.8758829	0.3221585	0.8338573	0.0715108	0.2981029	0.5700266	-0.4066656	-0.4426015	-0.0359359
0.5517228	0.8850872	0.1379439	0.7797196	0.3208303	0.1888349	0.7471432	0.1261619	0.0917667	-0.0343952
0.0614376	0.2965834	0.9979328	0.0027831	0.1401460	0.0597136	0.9364952	0.0117046	-0.0165844	-0.0282890

eTable 4: Marginal conditional probabilities resulting in bounds where the upper bound is smaller than the lower bound. (*continued*)

	P(X=1 Z=0)	P(X=1 Z=1)	P(X=1 Z=2)	P(Y=1 Z=0)	P(Y=1 Z=1)	P(Y=1 Z=2)	Strength	Lower Bound	Upper Bound	Width
	0.8779495	0.4096741	0.2304406	0.7998226	0.4274697	0.9938156	0.6475089	-0.0719255	-0.0992804	-0.0273549
	0.6979215	0.7737010	0.0234315	0.9852010	0.4651610	0.8182570	0.7502694	-0.0989160	-0.1244899	-0.0255739
	0.6623782	0.7107869	0.1608789	0.9024376	0.2805005	0.8890312	0.5499081	-0.1508689	-0.1758042	-0.0249354
	0.4107040	0.6300393	0.0755462	0.7135503	0.0247311	0.2318819	0.5544931	0.0986941	0.0758333	-0.0228608
	0.2389620	0.9996788	0.3607017	0.1224239	0.2775328	0.6499732	0.7607167	-0.0727986	-0.0942652	-0.0214665
	0.2466505	0.3150522	0.9973913	0.7941729	0.4943148	0.9589104	0.7507408	0.4182885	0.3992699	-0.0190186
	0.1047963	0.5872602	0.6265764	0.1702907	0.0689137	0.7661262	0.5217801	0.2159521	0.1971807	-0.0187714
	0.6454304	0.5477765	0.0021959	0.8270074	0.1628806	0.2007895	0.6432345	0.4210367	0.4032008	-0.0178359
	0.0147348	0.9403617	0.7719393	0.1339251	0.5201033	0.7372833	0.9256270	0.4399636	0.4221999	-0.0177637
L	0.6149141	0.1287129	0.8052456	0.3774013	0.9281094	0.7809966	0.6765327	-0.2049168	-0.2213916	-0.0164747
	0.6318831	0.8417779	0.1046526	0.1803197	0.6822984	0.0227946	0.7371254	0.4274041	0.4145748	-0.0128292
	0.4658334	0.1177519	0.8202813	0.3008471	0.8740505	0.7295855	0.7025294	-0.2011135	-0.2117500	-0.0106365
	0.4692894	0.9793264	0.2505315	0.6858286	0.3586177	0.0507586	0.7287948	0.0832484	0.0727541	-0.0104943
	0.9053262	0.4920161	0.2908324	0.8237065	0.8801458	0.1128271	0.6144939	0.3452384	0.3365678	-0.0086706
	0.8400507	0.6066834	0.0207922	0.8392446	0.3014262	0.1199182	0.8192585	0.5578239	0.5502410	-0.0075829
	0.2986999	0.3574011	0.7508847	0.7003727	0.1246649	0.9739429	0.4521849	0.3249903	0.3213192	-0.0036711
	0.0463115	0.4417234	0.7452841	0.1110238	0.4748895	0.0612693	0.6989726	0.1602189	0.1570808	-0.0031381
	0.8543023	0.0104242	0.1896705	0.9925313	0.2311163	0.0674310	0.8438782	0.6262363	0.6260467	-0.0001896

eTable 5: Lower and Upper limits of bounds where the upper limit is less than the lower limit for trivariate distributions with four category instruments.

Lower	Upper	Strength	Width
0.1796920	0.0395535	0.0853119	-0.1401385
-0.0038326	-0.1264492	0.1539099	-0.1226166
-0.0169573	-0.1304422	0.2235469	-0.1134849
-0.0620851	-0.1743916	0.0805434	-0.1123066
0.0996764	-0.0065497	0.2112420	-0.1062260
-0.0348047	-0.1393748	0.1884223	-0.1045701
-0.0097177	-0.1102060	0.0874967	-0.1004882
-0.0470850	-0.1435686	0.1458296	-0.0964835
-0.1052398	-0.1993785	0.2667633	-0.0941387
0.1097975	0.0268471	0.1774704	-0.0829504
0.1884781	0.1110487	0.3297432	-0.0774293
0.0174359	-0.0580424	0.2058740	-0.0754784
-0.0530855	-0.1187770	0.2521754	-0.0656915
0.0534080	-0.0107149	0.1509847	-0.0641230
-0.0660707	-0.1258819	0.2831483	-0.0598112
0.3495840	0.2945716	0.3633999	-0.0550124
0.1665198	0.1136389	0.2131245	-0.0528809
-0.0356540	-0.0879713	0.2476628	-0.0523173
0.1089847	0.0575836	0.1941017	-0.0514012
0.0086756	-0.0338341	0.2340061	-0.0425097
0.1335166	0.0930974	0.4555966	-0.0404192
0.1163970	0.0761754	0.1573917	-0.0402216
-0.1249197	-0.1611461	0.1712798	-0.0362264
-0.1252239	-0.1581375	0.1035529	-0.0329136
-0.2954311	-0.3273509	0.3077593	-0.0319199
0.0274287	-0.0007244	0.0813449	-0.0281530
-0.1317444	-0.1586467	0.3469784	-0.0269023

eTable 5: Lower and Upper limits of bounds where the upper limit is less than the lower limit for trivariate distributions with four category instruments. (*continued*)

Lower	Upper	Strength	Width
0.1050533	0.0818064	0.2388595	-0.0232469
-0.1980031	-0.2156885	0.2205149	-0.0176854
0.0408272	0.0265662	0.1314643	-0.0142609
0.1255375	0.1131666	0.0426523	-0.0123709
-0.1421790	-0.1523644	0.1409053	-0.0101854
-0.0997312	-0.1083943	0.3816466	-0.0086630
-0.0304169	-0.0353880	0.1323408	-0.0049711
0.0094786	0.0046709	0.2838685	-0.0048077
-0.0217285	-0.0245811	0.3531008	-0.0028526
-0.0563955	-0.0583218	0.4092683	-0.0019263

## A.2 Logistic Models

When a GWAS is run to find associations between genetic markers and a binary trait, the logistic regression model is often used. For this particular reason, we use the logistic model in our monte carlo integrations to characterize the behavior of the non-parametric bounds from two-sample data.

Specifically, we assume that  $P(Z = 0) = P(Z = 2) = 0.25$  and  $P(Z = 1) = 0.5$ , and a value of an unmeasured confounder  $U$  from the standard normal. We assume the exposure  $X$  is binary with  $\text{logit}(P(X = 1|Z_1 = z_1, \dots, Z_p = z_p, U = u)) = \gamma_0 + \sum_i \gamma_i z_i + \gamma_U u$ , where  $\text{logit}(a) = \frac{1}{1+\exp(a)}$  and  $\gamma_i$  corresponds to the estimand of the regression estimate one would obtain from GWAS studying the relationship between the genetic variant and the exposure. This model has been used in MR studies by Burgess [6] and Burgess and Thompson [9] so that every instrument estimates the same exposure effect. Similarly, we assume that the outcome  $Y$  is binary with  $P(Y = 1|X = x, U = u) = \text{logit}(\beta_0 + \beta_X \cdot x + \beta_U \cdot u)$ , which we use to compute the true ATE.

## A.3 Proof of Theorem 3.1

First of all, we note that the bounds found using the approach previously described when we impose (A5) and (A6) and the number of categories  $k$  of the IV  $Z$  is either 2, 3, or 4, are

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

This gives us a total of nine different expressions for the width of the bounds. We will show that each of these nine expressions are bounded by  $2 - 2 \cdot ST$ . Since we assume monotonicity of the effect of  $Z$  on  $X$ , the strength simplifies to  $ST = P(X = 1|Z = k) - P(X = 1|Z = 0)$ .

$$\text{Width} = U_1 - L_1$$

Since the lower bound is  $L1$ ,  $L1 \geq L2$ . Hence,  $P(X = 1|Z = k) \leq P(Y = 1|Z = k)$ . Therefore,

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

**Width = U2 - L1**

From  $U2 \leq U1$ ,  $1 - P(Y = 1|Z = k) \leq P(X = 1|Z = 0)$ , and from  $L2 \leq L1$ ,  $-P(Y = 1|Z = k) \leq -P(X = 1|Z = k)$ . So,

$$\begin{aligned}
U2 - L1 &= -2 \cdot P(Y = 1|Z = k) - P(X = 1|Z = k) + P(X = 1|Z = 0) + 3 \\
&= 3 - ST - 2 \cdot P(Y = 1|Z = k) \\
&< 2 - 2 \cdot ST
\end{aligned}$$

**Width = U3 - L1**

Again,  $L2 \leq L1$  and so  $-P(Y = 1|Z = k) \leq -P(X = 1|Z = k)$ . Therefore,

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

**Width = U1 - L2**

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

**Width = U2 - L2**

Since the upper bound is  $U2$ ,  $U2 \leq U1$  which leads us to  $1 - P(Y = 1|Z = k) \leq P(X = 1|Z = 0)$ . So,

$$\begin{aligned}
U2 - L2 &= 3 - P(Y = 1|Z = k) + P(X = 1|Z = 0) - 2 \cdot P(X = 1|Z = k) \\
&= 2 - ST + 1 - P(Y = 1|Z = k) - P(X = 1|Z = k) \\
&\leq 2 - 2 \cdot ST
\end{aligned}$$

**Width = U3 - L2**

From  $U3 \leq U2$ , we see that  $P(Y = 1|Z = 0) \leq 1 - P(X = 1|Z = k)$ . Therefore,

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

**Width = U1 - L3**

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

**Width = U2 - L3**

Since the upper bound is  $U2$ ,  $1 - P(Y = 1|Z = k) \leq P(X = 1|Z = 0)$ , we see that

$$\begin{aligned} U2 - L3 &= 3 - P(Y = 1|Z = k) - 2 \cdot P(X = 1|Z = k) \\ &\leq 2 - 2 \cdot P(X = 1|Z = k) + P(X = 1|Z = 0) \\ &\leq 2 - 2 \cdot ST \end{aligned}$$

### Width = $U3 - L3$

From  $U3 \leq U2$ , we see that  $P(Y = 1|Z = 0) \leq 1 - P(X = 1|Z = k)$ . Therefore,

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

As we see from the derivations above, regardless of which expression is the minimum and which is the maximum in the bounds, the width of the bounds is bounded from above by  $2 - 2 \cdot ST$ .

□

## A.4 Simulation Setup and Results for Section 3.1

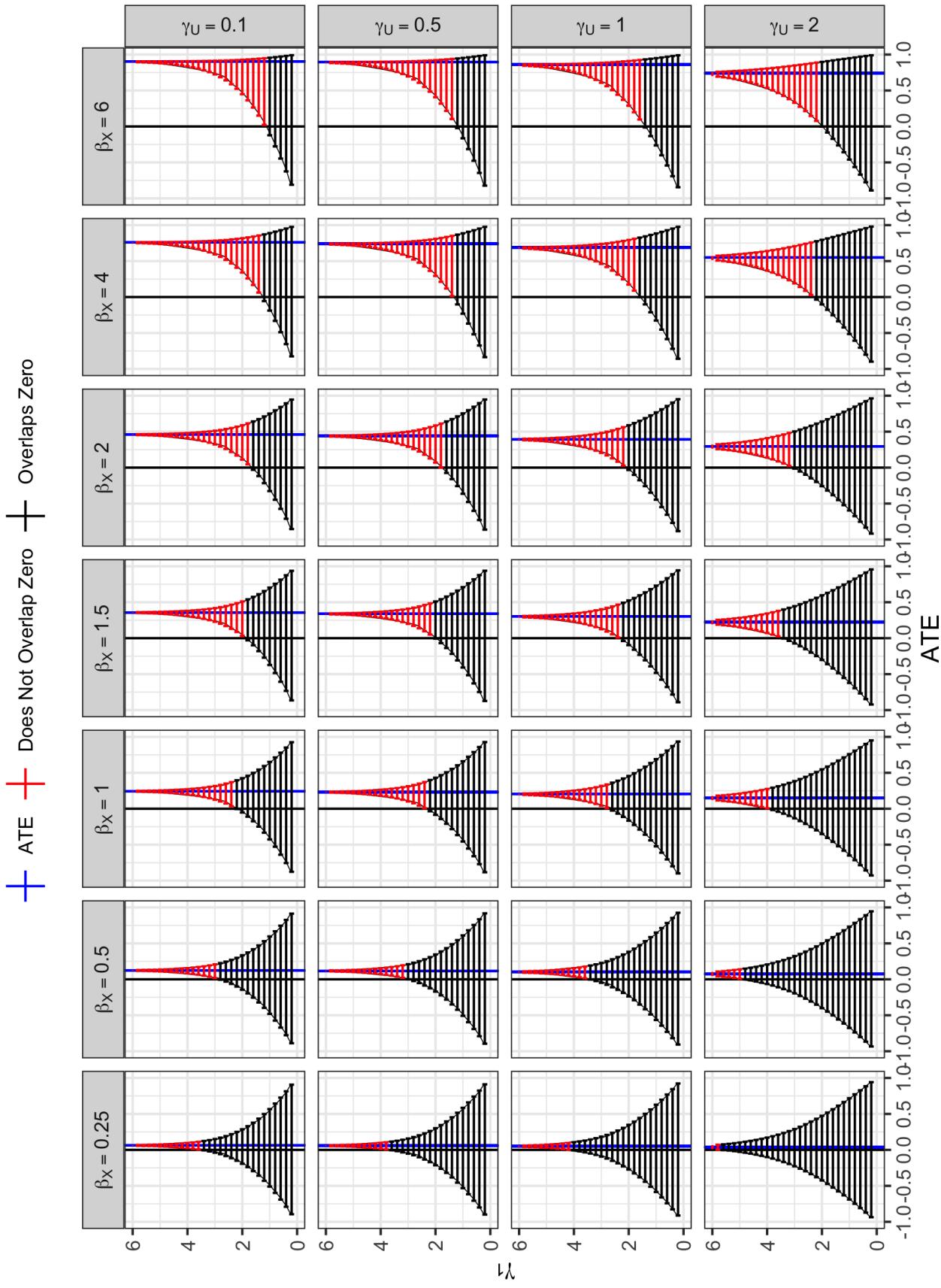
Since GWAS results are most often reported as summary statistics and coefficients from a logistic model, we use monte carlo integration to show the relationship between ST and coefficients in a logistic model. We use the model introduced in eAppendix A.2 with  $p = 1$ . Throughout, we set  $\gamma_0 = -\gamma_1$  and  $\beta_0 = -\beta_1/2$ . This is done to maximize the differences between probabilities  $P(X = 1|Z = z)$ ,  $z = 0, 1, 2$ , and  $P(Y = 1|Z = z)$ ,  $z = 0, 1, 2$ . For simplicity, we also keep  $\beta_U = \gamma_U$ .

For each combination of values of the coefficients  $\gamma_1, \gamma_U, \beta_1$  listed below, 10,000,000 realizations of the unmeasured confounder  $U$  are drawn from a standard normal distribution. For each realization, a value of  $Z$  is drawn such that  $P(Z = 0) = P(Z = 2) = 0.25$ , and  $P(Z = 1) = 0.5$ . Next, values of  $X$  and  $Y$  are generated using these values such that  $\text{logit}(P(X = 1|Z = z, U = u)) = \gamma_0 + \gamma_1 z + \gamma_U u$  and  $\text{logit}(P(Y = 1|X = x, U = u)) = \beta_0 + \beta_1 x + \beta_U u$ . This results in 10,000,000 realizations of  $(X, Y, Z, U)$ . From these, we find the marginal probabilities  $P(X = 1|Z = z)$  and  $P(Y = 1|Z = z)$ ,  $z = 0, 1, 2$ , the values of  $\text{ST} = \max_{z_1 \neq z_2} |P(X = 1|Z = z_1) - P(X = 1|Z = z_2)|$  and the  $\text{ATE} = P(Y = 1|X = 1) - P(Y = 1|X = 0)$ .

eTable 6: The monte carlo integration was performed for all combinations of values of the coefficients  $\gamma_1, \gamma_U$ , and  $\beta_1$  presented below.

$\beta_1$	$\gamma_1$	$\gamma_U$
0.25, 0.5, 1, 1.5, 2, 4, 6	0.2, 0.4, 0.6, 0.8, 1, 1.2, 1.4, 1.6, 1.8, 2, 2.2, 2.4, 2.6, 2.8, 3, 3.2, 3.4, 3.6, 3.8, 4, 4.2, 4.4, 4.6, 4.8, 5, 5.2, 5.4, 5.6, 5.8, 6	0.1, 0.5, 1, 2

Each set of marginal probabilities leads us to a set of non-parametric bounds from two-sample data. These are shown on eFigure 1 together with the ATE. Figure 1A shows the width of these bounds plotted against ST, while Figure 1B shows the values of  $\gamma_1$  plotted against ST.



eFigure 1: Bounds based on simulations as described. Upper and lower bounds are connected by a curve (dotted lines) based on a loess extrapolation. This curve is used to find the smallest coefficients needed to detect direction as plotted on Figure 2.

To find the smallest value of  $\gamma_1$  that results in bounds excluding 0, we fit a loess curve to the lower bounds in eFigure 1, and find the value where this curve crosses 0. This results in the values depicted on Figure 2.

## A.5 Bounds From Two Sample Data With Multiple IVs

Here, we will describe how to expand the monte carlo integration to include multiple IVs. Consider the exposure and outcome models introduced in Appendix A.2.  $z_i \in \{0, 1, 2\}$  represents the  $i$ th instrument, and  $\gamma_i$  represents the  $i$ th instrument's effect on the exposure. Also, for each instrument  $i$ , we set  $P(Z_i = 0) = P(Z_i = 2) = 0.25$  and  $P(Z_i = 1) = 0.5$ . We set  $p = 10$  or  $p = 50$ , and draw  $U$  from a standard normal distribution. Again, for simplicity, we set  $\beta_U = \gamma_U$ , and  $\gamma_0 = -\sum_i \gamma_i$  and  $\beta_0 = -\beta_1/2$  to spread out the probabilities  $P(X = 1|Z = z)$  and  $P(Y = 1|X = x)$  as much as possible.  $\beta_1$  is set to be either 0.25, 0.5, 1, 1.5, or 2. We then consider four scenarios for setting the  $\gamma_i$ 's:

1. *Many weak instruments:*  $\gamma_i$  are spread out evenly on the interval 0 to 0.2.
2. *Many strong instruments:*  $\gamma_i$  are spread out evenly on the interval 1 to 4. This is the magnitude of  $\gamma$ s that detected the direction of the ATE in the previous section
3. *Many very weak instruments, one medium strength instrument:*  $\gamma_i$ ,  $i = 1, 2, \dots, p-1$ , are evenly spread out on the interval 0 to 0.01, and  $\gamma_p = 0.2$ .
4. *Many medium strong instruments, one strong instrument:*  $\gamma_i$ ,  $i = 1, 2, \dots, p-1$ , are evenly spread out on the interval 1 to 1.2, and  $\gamma_p = 4$ .

The first scenario mimics typical magnitudes of coefficients seen in MR studies, and is an example where many genetic traits weakly contribute to the expression of complex traits [25, 37, 28]. The third scenario represents a genetic architecture where only few genetic variants have strong effects on the exposure while others have weak effects [47]. Scenarios 2 and 4 are as scenarios 1 and 3, but with coefficients of larger magnitude. We don't expect to observe this in practice, but these are the magnitudes that our results in Section 3.1 suggests would result in informative bounds when  $p = 1$ .

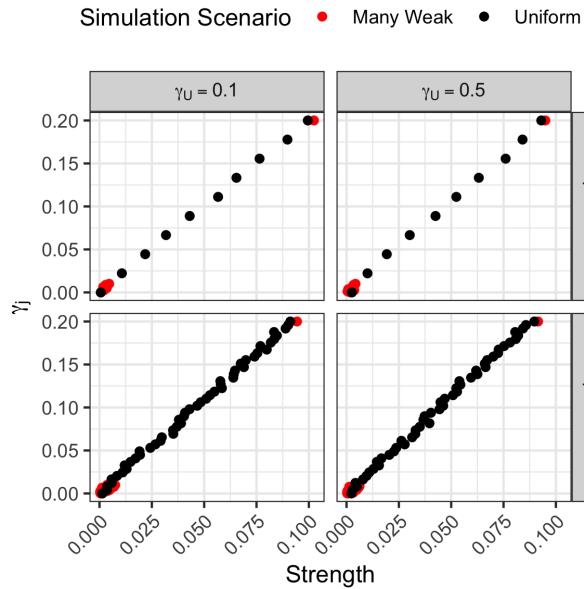
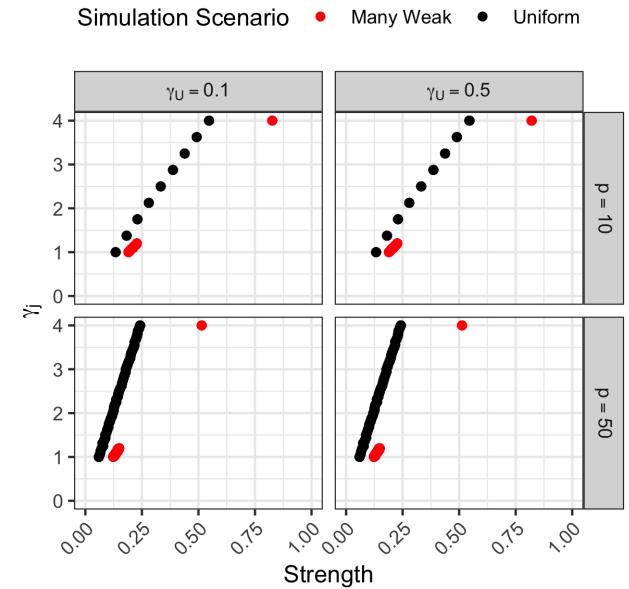
For each scenario, we use monte carlo integration with 1,000,000 re-samples to obtain  $P(X = 1|Z_j = z_j)$  and  $P(Y = 1|Z_j = z_j)$  – this procedure is as described in eAppendix A.4, but with multiple instruments. We then use these quantities to obtain two-sample IV bounds for each of the  $p$  instruments. eFigures 3, 4, 5, and 6 summarize the results. We see that in scenarios 1 and 2, every bound is non-informative, with widths close to or exceeding 1. Also, the bounds are nested within each other. Thus, if we were to aggregate

the bounds by taking intersections, the width of the intersection bounds will still be close to or exceed 1. In addition, the increase in magnitude of the  $\gamma_i$  coefficient did not improve the bounds. Scenarios 3 and 4 show similar results in that the bounds cover the null effect, but the strongest instrument in each scenario produces a much smaller bound than in scenarios 1 and 2. From eFigure 4 it is clear that on the scale that is often observed in MR studies, two-sample nonparametric bounds are generally non-informative. Also, the bounds in scenarios 3 and 4 are again nested leaving us with the conclusion that the intersection of bounds from multiple instruments will give no more information than the strongest of the instruments itself.

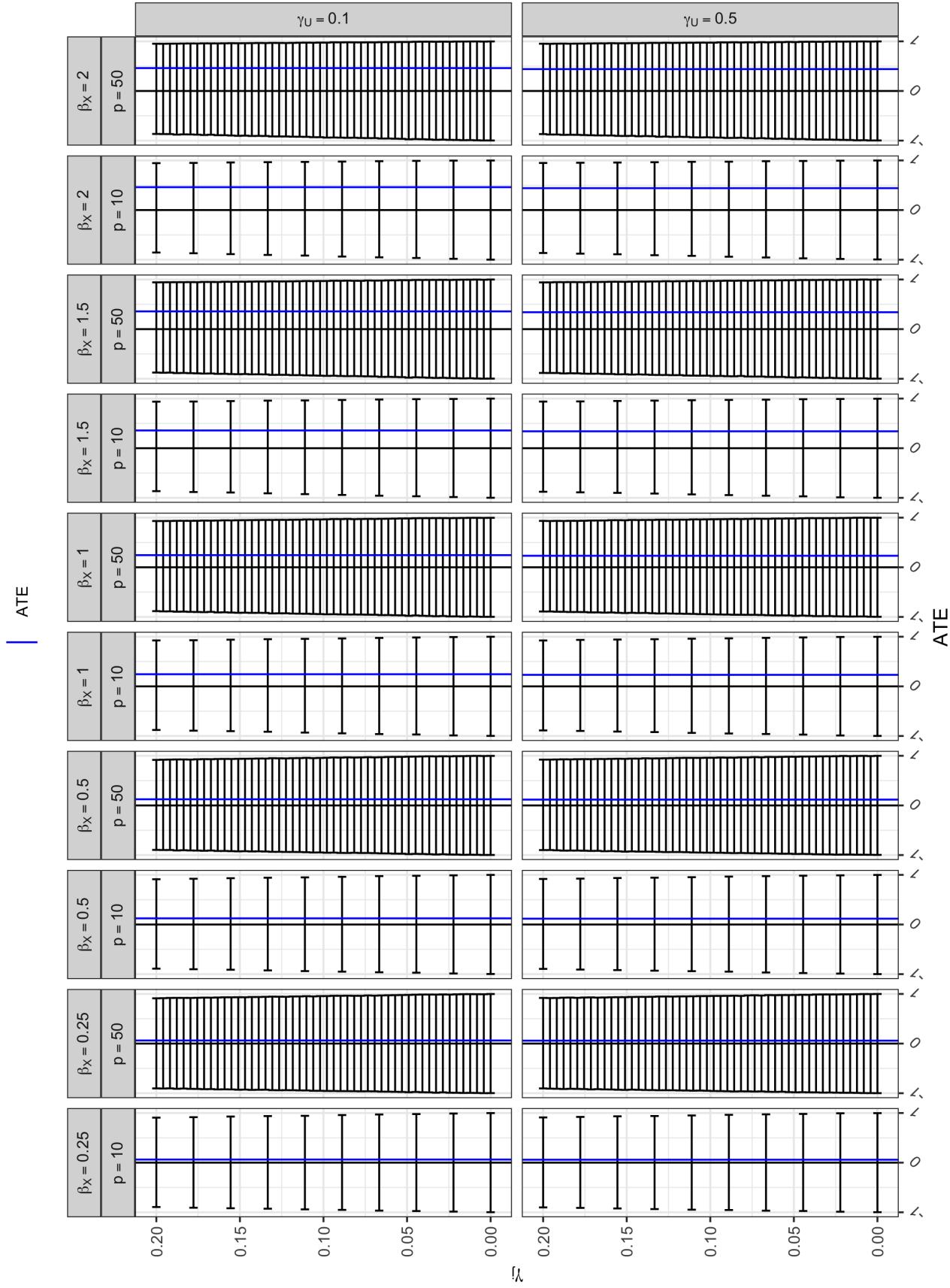
We take a moment to explain the differences between our result in Section 3.1 with a single instrument with  $\gamma_1 = 4$  and our results in this section where one of the instruments has  $\gamma_i = 4$ , but others have much smaller  $\gamma$ 's. We see that if the variation in the exposure model is determined by multiple independent instruments, the effect of one single instrument on producing an informative bound greatly diminishes. Specifically, eFigure 6 shows that in a setting where we would be able to detect the direction of the ATE from an instrument with  $\gamma_i = 4$  if only  $p = 10$  instruments are contributing to the exposure, that same coefficient would not be large enough if  $p = 50$  instruments were contributing. This suggests that for exposures that are determined by many instruments, the strongest among these instruments must be even stronger for a bound-based analysis to be useful. In other words, multiple instruments may not be helpful in a bound-based analysis when the exposure is polygenic in nature.

Our results also have dire implications when some instruments turn out to be invalid. If, as suggested by Swanson [41], we take the union of IV bounds so that the union bound is guaranteed to cover the true ATE so long as there is at least one valid instrument, the union bound will likely be non-informative because there was at least one IV bound in our scenario that was non-informative. Without making some assumptions about the nature of the invalid IVs, it would generally be infeasible to obtain useful information from a bound-based analysis.

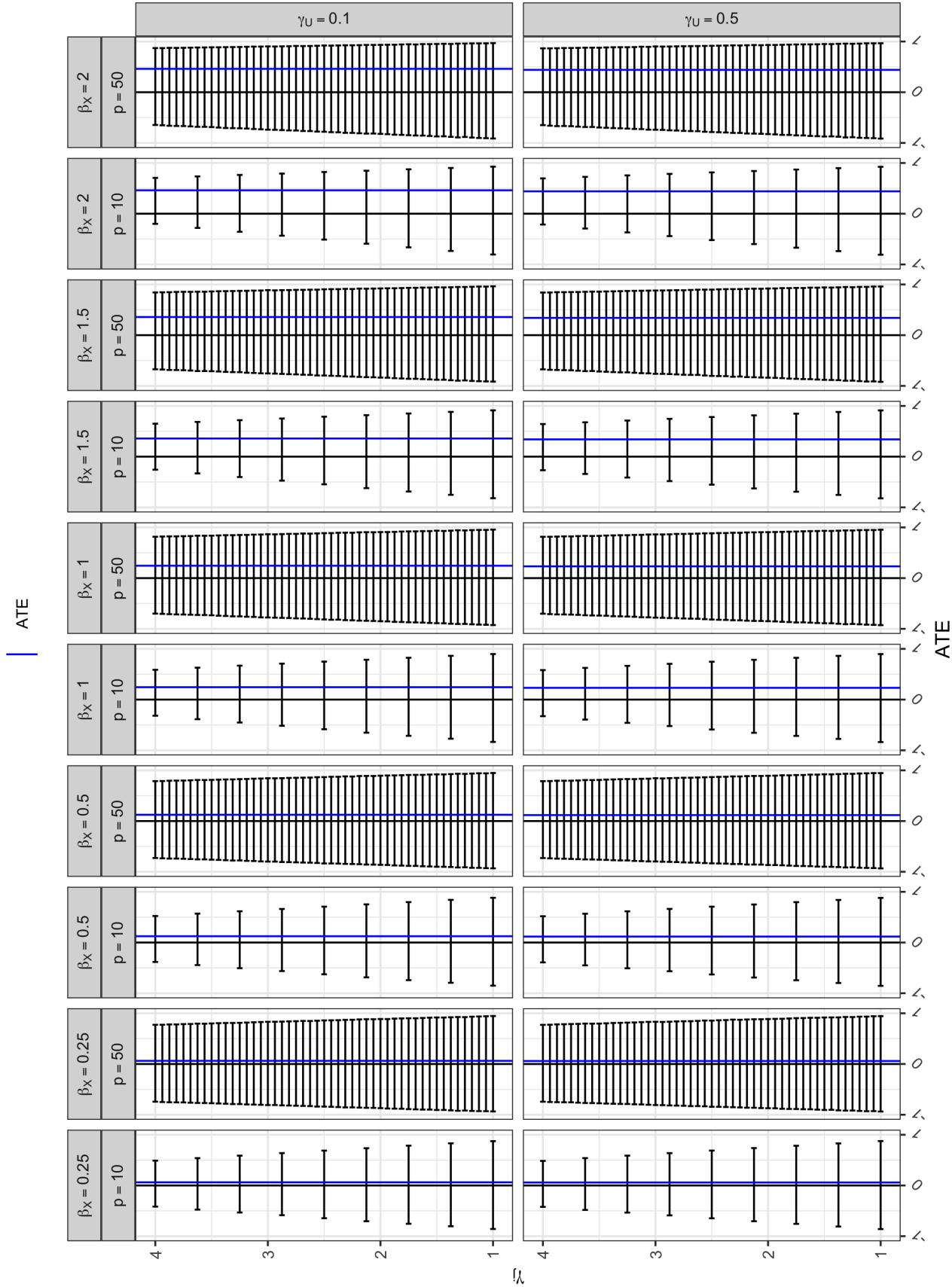
Overall, combining our results in Section 3.1, our conclusion about using nonparametric IV bounds in two-sample MR studies is grim. Such a nonparametric analysis would require very strong instruments and/or effect sizes, which are rare in MR studies, and even stronger than those in one-sample settings. Also, multiple instruments are no better than having a single, strong instrument.

**A****B**

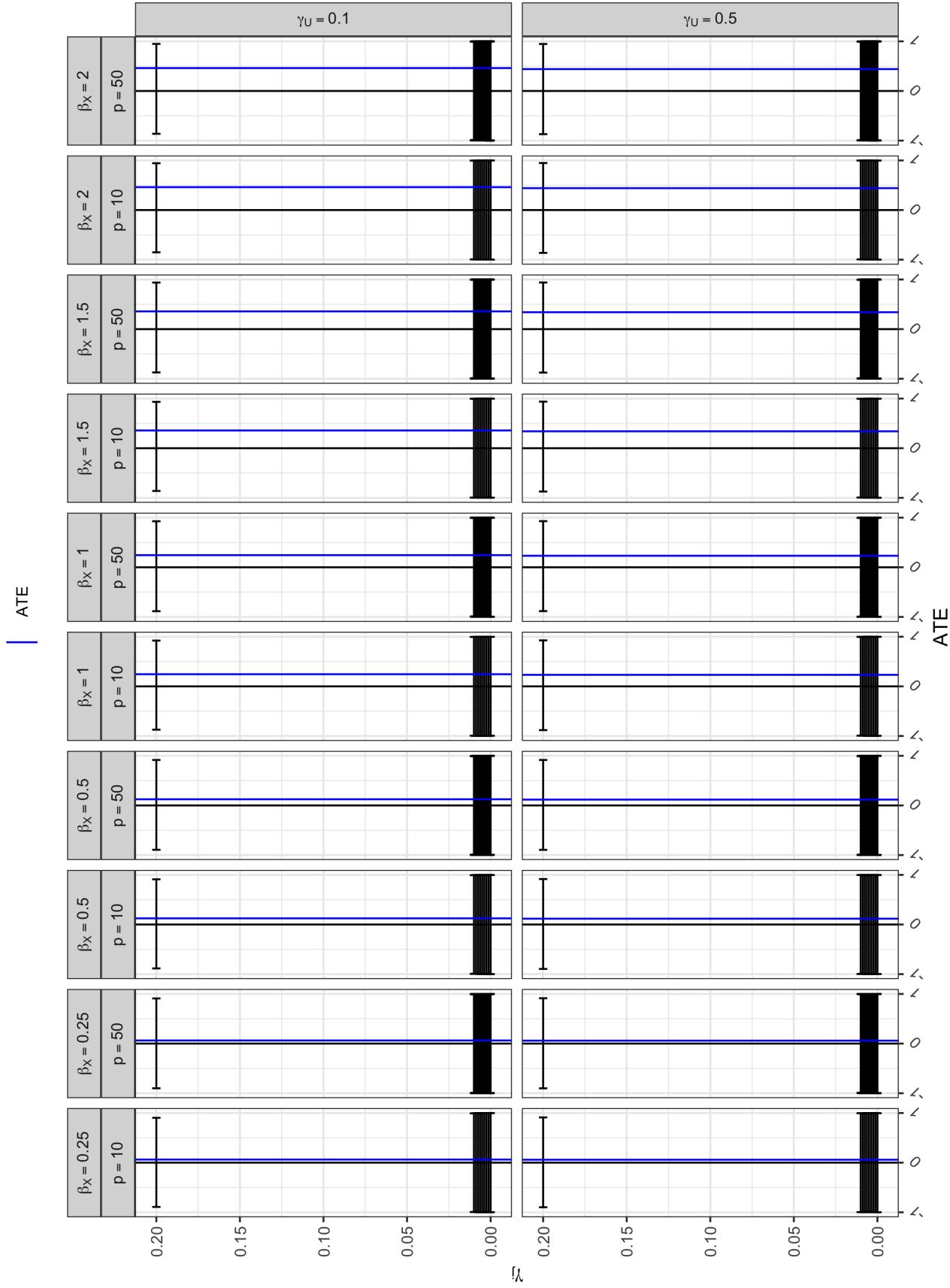
eFigure 2: Figure showing the dilution effect described in Section A.5 in each of the four scenarios. When  $p$  is larger, similar sized coefficients lead to lower strength. The effect is smaller when we are in a scenario where one coefficient is relatively much larger than the rest, rather than when the coefficients are evenly spread out. A: Scenarios 1 and 3. B: Scenarios 2 and 4.



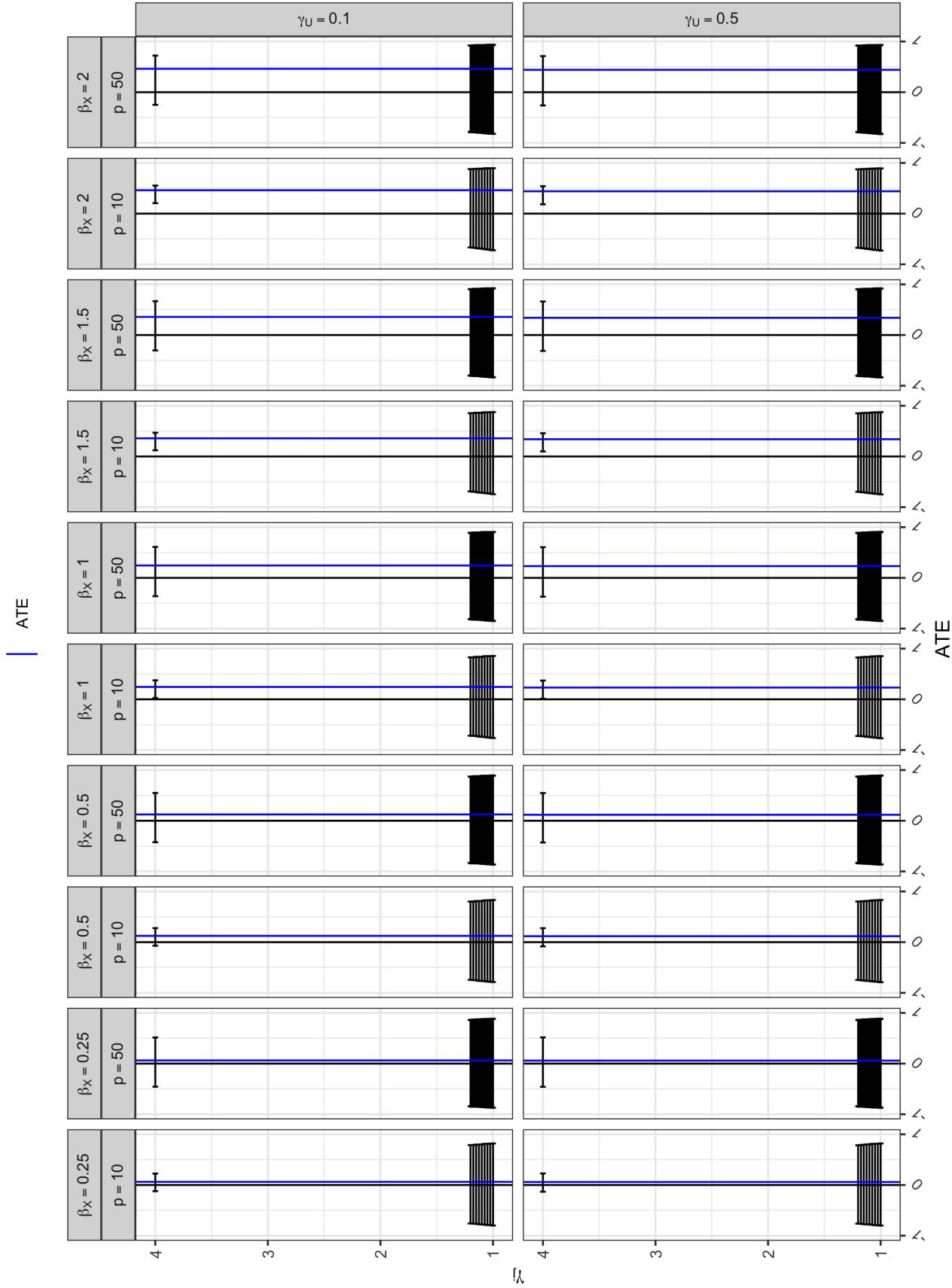
eFigure 3: Bounds based on monte carlo integration with 1,000,000 resamples in scenario 1.



eFigure 4: Bounds based on monte carlo integration with 1,000,000 resamples in scenario 2.



eFigure 5: Bounds based on monte carlo integration with 1,000,000 resamples in scenario 3.



eFigure 6: Bounds based on monte carlo integration with 1,000,000 resamples in scenario 4.

## A.6 Reconstructing the Joint Distribution $P(X, Y|Z)$

To draw a possible set of values for the joint conditional distribution  $P(X = x, Y = y|Z = z)$ , we start by writing the joint conditional distribution  $P(X = x, Y = y|Z = z)$  as a function of the marginal conditional distributions  $P(X = x|Z = z)$  and  $P(Y = y|Z = z)$  and the conditional covariance of the exposure  $X$  and  $Y$  given  $Z = z$ ,  $\text{Cov}(X, Y|Z = z)$ , for each  $z$

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

Because  $\text{Cov}(X, Y|Z = z)$  is impossible to estimate from two-sample MR studies, we instead propose to put a prior on this quantity. This prior must not only produce a proper probability distribution of  $(X, Y|Z)$ , but also satisfy the verifiable constraints from the IV assumptions  $\max_x \sum_y \max_z P(Y = y, X = x|Z = z) \leq 1$ . Specifically, by the definition of a proper probability distribution,  $\text{Cov}(X, Y|Z = z)$  must satisfy

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

Additionally, by the IV inequality constraints  $\max_x \sum_y \max_z P(X = x, Y = y|Z = z) \leq 1$ , for any pair of  $(z_1, z_2) \in \{0, 1, 2\} \times \{0, 1, 2\}$ , the values of  $\text{Cov}(X, Y|Z = z_1)$  and  $\text{Cov}(X, Y|Z = z_2)$  must satisfy

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

We sequentially sample values of  $\text{Cov}(X, Y|Z = 0)$ ,  $\text{Cov}(X, Y|Z = 1)$ ,  $\text{Cov}(X, Y|Z = 2)$ , such that the above inequalities are satisfied. Then, among samples of  $\text{Cov}(X, Y|Z = 0)$ ,  $\text{Cov}(X, Y|Z = 1)$ ,  $\text{Cov}(X, Y|Z = 2)$  that satisfy the constraints, we calculate the joint distribution of  $P(X = x, Y = y|Z = z)$  using (4), leading us to a plausible set of values for the joint distribution  $P(X = x, Y = y|Z = z)$ .

For each plausible joint distribution  $P(X = x, Y = y|Z = z)$ , we use the one-sample IV bounds by Balke and Pearl [3] and Richardson and Robins [31] to obtain a bound for the ATE. If a large number of the one-sample IV bounds do not cover zero, then there is some evidence for a non-zero exposure effect and the only reason we are not able to detect this effect is due to the limitations of the two-sample design. However, if a large number of the one-sample IV bounds do cover zero, there is less evidence for a non-zero causal effect or that utilizing bound-based approaches to obtain some information about the ATE may be a hopeless exercise even if we are under a one-sample design.

### A.6.1 Sampling of Intersection Bounds From Two Instruments

To extend our method for sampling plausible joint distributions of  $P(X = x, Y = y|Z = z)$  to the scenario where we have multiple instruments available, we simply repeat the one instrument sampling for each instrument. This is equivalent to assuming that the covariances of  $X$  and  $Y$  given  $Z_1$  are independent of the covariances of  $X$  and  $Y$  given  $Z_2$ . Once we have obtained bounds for each instrument, we take the intersection to get the intersection bounds.

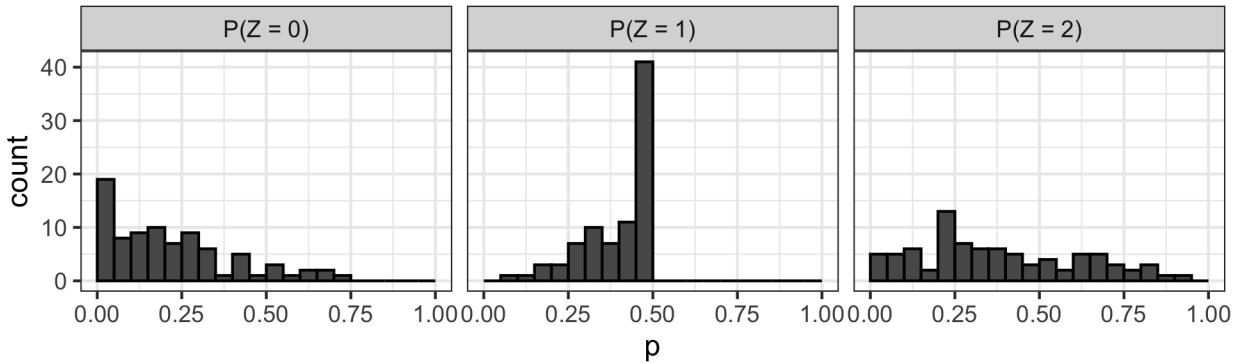
Specifically, say we get bounds  $(LB_{1i}, UB_{1i})$ ,  $i = 1, 2, \dots, m$  by sampling  $m$  trivariate distributions based

on the information we have on  $(X, Z_1)$  and  $(Y, Z_1)$ , and 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.

## A.7 Additional Summary Statistics and Figures for Analyses Presented in Section 5

We use the `TwoSampleMR` R package [21] to extract and preprocess the data for our analyses. For preprocessing, we followed the defaults of the R pacakge where linkage disequilibrium based clumping ( $r^2 \geq 0.001$  within a 10,000 kb window using  $p < 5 \times 10^{-8}$  as the level of significance) were performed such that only independent instruments with significant associations were used in the analysis. Afterwards, we obtain the estimated coefficients corresponding to the effects of the SNPs on the exposure and the outcome from a logistic model. Since estimates of the intercept are not included in these reported results, but the marginal proportions of the outcome, exposure, and allele frequencies are known, we find the intercepts by solving  $P(X = 1) = \sum_{z=0}^2 \text{logit}(\beta_0 + \hat{\beta}_1 \cdot z) \cdot P(Z_j = z)$  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. Overall, we have estimates of  $P(Y = 1|Z_j = z)$  and  $P(X = 1|Z_j = z)$  for every  $j$  and  $z = 0, 1, 2$ .

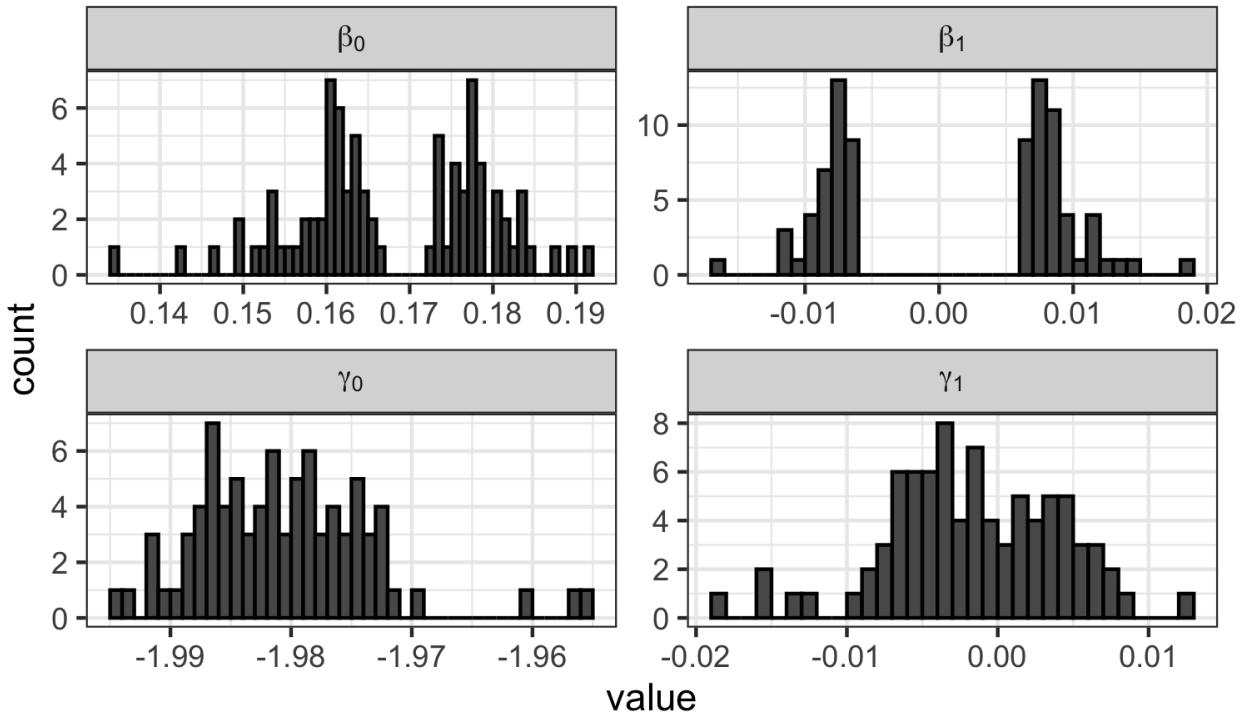
### A.7.1 Effect of Smoking on Lung Cancer



eFigure 7: Histograms of the marginal distribution of instruments,  $P(Z = z), z = 0, 1, 2$ , estimated after preprocessing.

eTable 7: Table of the marginal distribution of instruments,  $P(Z = z)$ ,  $z = 0, 1, 2$ , estimated after pre-processing for analysis.

SNP	P(Z = 2)	P(Z = 1)	P(Z = 0)	SNP	P(Z = 2)	P(Z = 1)	P(Z = 0)
rs10173733	0.3562119	0.4812460	0.1625421	rs2797116	0.5370791	0.3915554	0.0713655
rs10193706	0.2254196	0.4987283	0.2758521	rs2867749	0.4639468	0.4343792	0.1016740
rs10233018	0.2458307	0.4999649	0.2542044	rs299688	0.0806544	0.4066855	0.5126601
rs10274594	0.2540510	0.4999674	0.2459816	rs326341	0.2745833	0.4988473	0.2265693
rs1029986	0.1723980	0.4856208	0.3419813	rs35891966	0.8609698	0.1338295	0.0052006
rs10774625	0.2457332	0.4999633	0.2543035	rs379525	0.2690001	0.4993042	0.2316957
rs10813628	0.2349574	0.4995333	0.2655093	rs42417	0.0959979	0.4276747	0.4763274
rs10897561	0.4140371	0.4588401	0.1271228	rs4566215	0.2184561	0.4978736	0.2836703
rs10905461	0.0654474	0.3807590	0.5537936	rs4910656	0.4334112	0.4498570	0.1167317
rs10914684	0.4570550	0.4380069	0.1049382	rs4957528	0.0432505	0.3294341	0.6273153
rs10956808	0.3337643	0.4879181	0.1783175	rs523528	0.1717181	0.4853414	0.3429405
rs11103667	0.6528207	0.3103050	0.0368743	rs528301	0.2006916	0.4945891	0.3047192
rs11127913	0.3717426	0.4759287	0.1523286	rs55921136	0.6351822	0.3236020	0.0412158
rs11429972	0.1128192	0.4461330	0.4410478	rs568599	0.2090011	0.4963306	0.2946684
rs11611651	0.8323808	0.1599365	0.0076827	rs5850689	0.1341980	0.4642649	0.4015371
rs11631530	0.7779345	0.2081429	0.0139226	rs60745548	0.0747101	0.3972427	0.5280472
rs11646575	0.3149600	0.4925059	0.1925340	rs6141314	0.5735637	0.3675524	0.0588839
rs11693702	0.2849095	0.4977193	0.2173712	rs6265	0.6582586	0.3061456	0.0355959
rs117435980	0.6998026	0.2734789	0.0267185	rs6433897	0.0693372	0.3879647	0.5426982
rs12042107	0.2025948	0.4950210	0.3023842	rs6676022	0.7713790	0.2138057	0.0148153
rs12244388	0.4404143	0.4464457	0.1131399	rs6690680	0.7094689	0.2656618	0.0248694
rs12450028	0.4293549	0.4517938	0.1188513	rs6828849	0.3395694	0.4863129	0.1741177
rs12479064	0.6268375	0.3297864	0.0433761	rs71550128	0.2008017	0.4946147	0.3045837
rs12487411	0.2788384	0.4984262	0.2227354	rs72505558	0.3617072	0.4794276	0.1588652
rs12608052	0.2306302	0.4992191	0.2701507	rs72678864	0.6825787	0.2872090	0.0302123
rs12725407	0.6546886	0.3088794	0.0364320	rs7333559	0.0439935	0.3315056	0.6245008
rs12886628	0.1124522	0.4457734	0.4417744	rs7451586	0.3541182	0.4819202	0.1639616
rs12910916	0.6206505	0.3343265	0.0450230	rs748828	0.5139770	0.4058898	0.0801332
rs13100688	0.3932914	0.4676762	0.1390324	rs7528604	0.3213716	0.4910497	0.1875787
rs1492546	0.2022894	0.4949531	0.3027575	rs7567570	0.0299625	0.2862686	0.6837689
rs1499982	0.0221071	0.2531548	0.7247382	rs763053	0.6013164	0.3482591	0.0504245
rs1549213	0.1285982	0.4600154	0.4113864	rs76608582	0.9070039	0.0907272	0.0022689
rs1561195	0.2279701	0.4989841	0.2730458	rs772921	0.4315416	0.4507533	0.1177051
rs1565735	0.6376078	0.3217914	0.0406009	rs77878475	0.8356836	0.1569474	0.0073690
rs16951001	0.3380123	0.4867519	0.1752358	rs7870475	0.2763346	0.4986816	0.2249839
rs17003752	0.7420669	0.2387323	0.0192008	rs7948789	0.3767706	0.4740916	0.1491378
rs17151637	0.5166809	0.4042486	0.0790705	rs883403	0.7156415	0.2606289	0.0237296
rs1899896	0.4934387	0.4180265	0.0885349	rs9375371	0.5345687	0.3931467	0.0722846
rs2240294	0.3093641	0.4936820	0.1969539	rs9381917	0.8063218	0.1832649	0.0104133
rs2416770	0.2199058	0.4980707	0.2820235	rs9423279	0.1179428	0.4509704	0.4310869
rs264974	0.2640248	0.4996173	0.2363579	rs9487626	0.0332246	0.2981030	0.6686724
rs2675609	0.1387352	0.4674731	0.3937917	rs9835772	0.5737177	0.3674477	0.0588346



eFigure 8: Histograms of the coefficients from GWAS results of logistic regression of the SNPs on smoking status and lung cancer status. Intercepts ( $\beta_0$  and  $\gamma_0$ ) are inferred, while slopes ( $\beta_1$  and  $\gamma_1$ ) are as reported.

eTable 8: Coefficients from GWAS results of logistic regression of the SNPs on smoking status and lung cancer status. Intercepts ( $\beta_0$  and  $\gamma_0$ ) are inferred, while slopes ( $\beta_1$  and  $\gamma_1$ ) are as reported.

SNP	$\beta_1$	$\beta_0$	$\gamma_1$	$\gamma_0$
rs10173733	-0.0065148	0.1773766	0.0033363	-1.987122
rs10193706	-0.0117667	0.1807753	-0.0015310	-1.981684
rs10233018	-0.0076551	0.1771914	0.0050495	-1.988150
rs10274594	0.0078326	0.1617046	-0.0015364	-1.981589
rs1029986	-0.0070208	0.1754303	0.0035498	-1.986088
rs10774625	0.0074868	0.1621777	-0.0084158	-1.974806
rs10813628	-0.0068761	0.1762662	0.0051706	-1.988156
rs10897561	-0.0066917	0.1782117	0.0066835	-1.991747
rs10905461	0.0072731	0.1658787	-0.0058844	-1.980131
rs10914684	0.0077356	0.1591408	-0.0026047	-1.979616
rs10956808	0.0076247	0.1607905	-0.0063546	-1.975802
rs11103667	-0.0086047	0.1835048	0.0063118	-1.993343

eTable 8: Coefficients from GWAS results of logistic regression of the SNPs on smoking status and lung cancer status. Intercepts ( $\beta_0$  and  $\gamma_0$ ) are inferred, while slopes ( $\beta_1$  and  $\gamma_1$ ) are as reported. *(continued)*

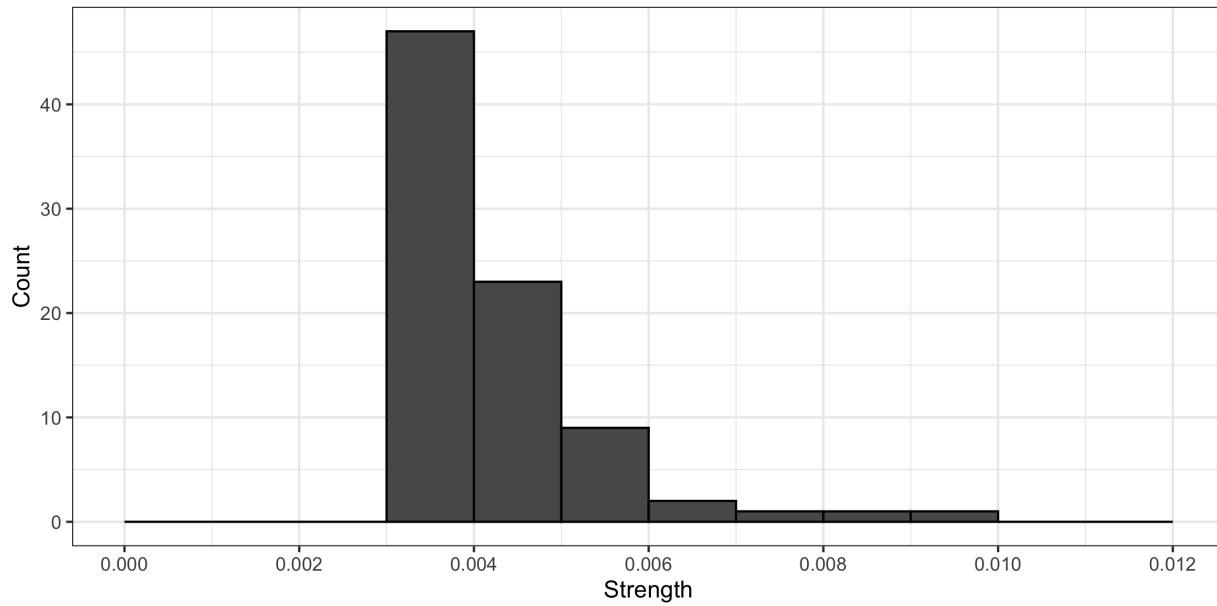
SNP	$\beta_1$	$\beta_0$	$\gamma_1$	$\gamma_0$
rs11127913	0.0081801	0.1596256	-0.0033969	-1.978997
rs11429972	0.0083148	0.1640148	-0.0096129	-1.976695
rs11611651	-0.0119868	0.1914724	0.0013059	-1.985521
rs11631530	-0.0099863	0.1872160	-0.0047887	-1.974691
rs11646575	-0.0082446	0.1788545	0.0012319	-1.984521
rs11693702	-0.0080254	0.1781679	0.0046224	-1.988077
rs117435980	-0.0092037	0.1849986	-0.0054804	-1.973970
rs12042107	0.0071759	0.1631404	-0.0020557	-1.981288
rs12244388	-0.0104344	0.1834505	0.0019355	-1.985707
rs12450028	-0.0070626	0.1788556	-0.0024536	-1.979923
rs12479064	-0.0080362	0.1823251	-0.0088600	-1.969116
rs12487411	0.0075048	0.1616745	-0.0077980	-1.974913
rs12608052	0.0067542	0.1631129	-0.0048100	-1.978521
rs12725407	0.0081386	0.1564297	-0.0067998	-1.972138
rs12886628	-0.0071010	0.1743626	-0.0018595	-1.981891
rs12910916	-0.0090138	0.1838027	0.0026458	-1.987308
rs13100688	0.0072663	0.1604864	-0.0055464	-1.976186
rs1492546	-0.0068801	0.1757890	0.0040638	-1.986797
rs1499982	-0.0114648	0.1730098	0.0024892	-1.983878
rs1549213	0.0085270	0.1634849	0.0056335	-1.987184
rs1561195	-0.0078947	0.1771393	0.0072232	-1.990046
rs1565735	0.0115901	0.1510915	-0.0072487	-1.971566
rs16951001	-0.0066035	0.1772784	0.0070226	-1.991313
rs17003752	0.0098606	0.1526117	-0.0055424	-1.973591
rs17151637	0.0075112	0.1588020	-0.0027771	-1.979146
rs1899896	-0.0079928	0.1808293	0.0047935	-1.989876
rs2240294	0.0069566	0.1618616	-0.0078381	-1.974429
rs2416770	-0.0064888	0.1756858	-0.0035668	-1.979794

eTable 8: Coefficients from GWAS results of logistic regression of the SNPs on smoking status and lung cancer status. Intercepts ( $\beta_0$  and  $\gamma_0$ ) are inferred, while slopes ( $\beta_1$  and  $\gamma_1$ ) are as reported. *(continued)*

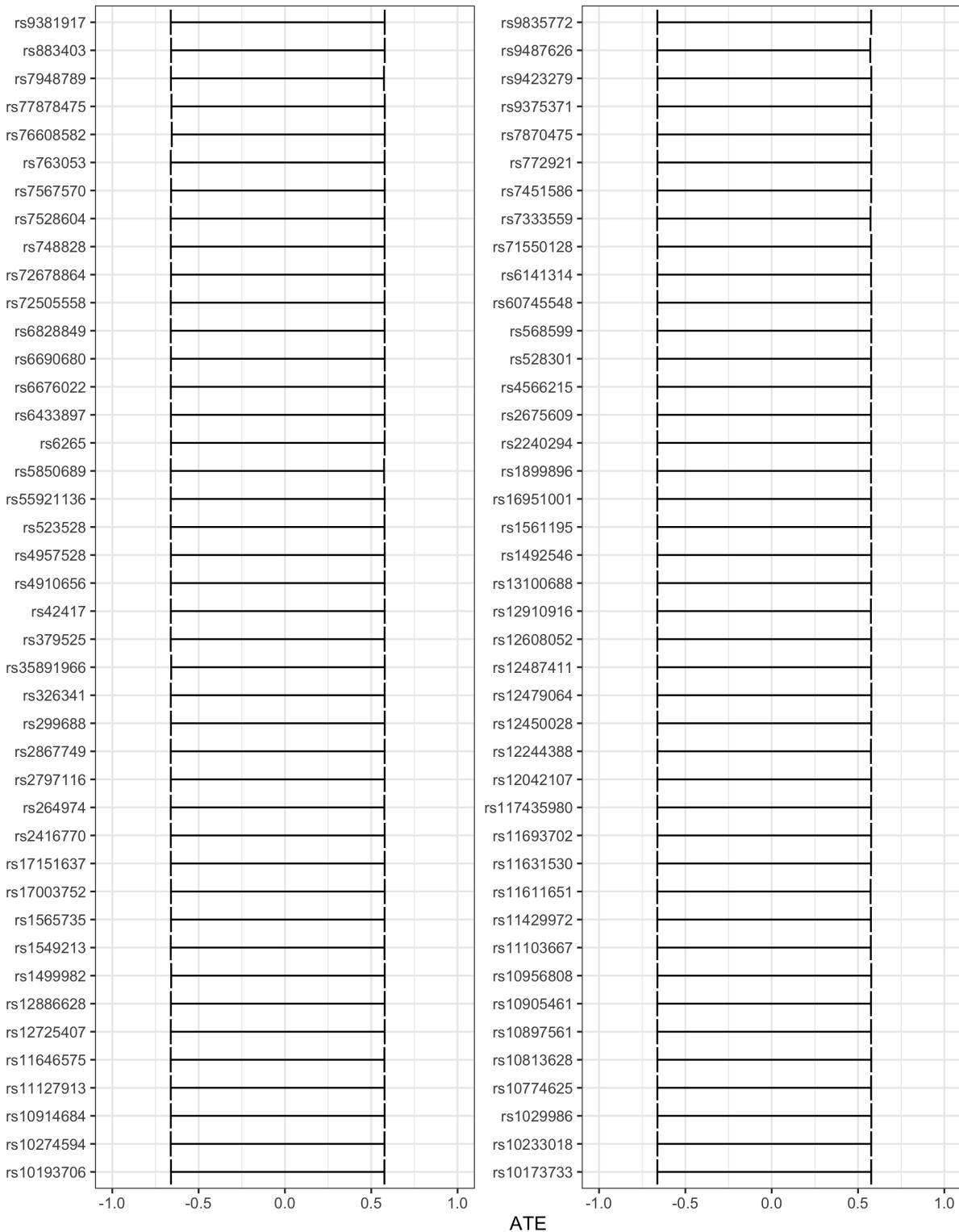
SNP	$\beta_1$	$\beta_0$	$\gamma_1$	$\gamma_0$
rs264974	0.0093111	0.1600323	-0.0047198	-1.978291
rs2675609	0.0081586	0.1635228	-0.0069708	-1.977953
rs2797116	0.0079136	0.1580011	-0.0039635	-1.977330
rs2867749	0.0069446	0.1601396	-0.0032894	-1.978658
rs299688	-0.0072721	0.1737306	-0.0019058	-1.982055
rs326341	0.0065809	0.1627032	0.0031753	-1.986468
rs35891966	0.0147752	0.1421811	-0.0122161	-1.960473
rs379525	-0.0064906	0.1763327	-0.0018594	-1.981209
rs42417	-0.0070331	0.1739582	0.0003829	-1.983375
rs4566215	0.0066219	0.1634100	-0.0035546	-1.979817
rs4910656	0.0068438	0.1605890	-0.0006962	-1.982221
rs4957528	-0.0084750	0.1731252	0.0036288	-1.984649
rs523528	0.0080708	0.1629116	0.0029251	-1.985564
rs528301	-0.0086008	0.1773068	0.0124616	-1.994333
rs55921136	0.0085950	0.1559000	-0.0069653	-1.972040
rs568599	-0.0067027	0.1757286	0.0043346	-1.987105
rs5850689	0.0119733	0.1608296	-0.0038879	-1.980291
rs60745548	0.0071946	0.1656670	0.0062353	-1.986552
rs6141314	-0.0080616	0.1818108	0.0010534	-1.984733
rs6265	0.0101598	0.1531146	-0.0043806	-1.976031
rs6433897	-0.0072353	0.1734104	-0.0011588	-1.982527
rs6676022	0.0115926	0.1492373	-0.0153059	-1.956268
rs6690680	0.0088409	0.1547067	-0.0050219	-1.974679
rs6828849	0.0067122	0.1617773	0.0008050	-1.984076
rs71550128	-0.0073950	0.1762278	0.0034139	-1.986200
rs72505558	0.0067437	0.1614885	-0.0009876	-1.981950
rs72678864	0.0097538	0.1534836	-0.0034394	-1.977455

eTable 8: Coefficients from GWAS results of logistic regression of the SNPs on smoking status and lung cancer status. Intercepts ( $\beta_0$  and  $\gamma_0$ ) are inferred, while slopes ( $\beta_1$  and  $\gamma_1$ ) are as reported. *(continued)*

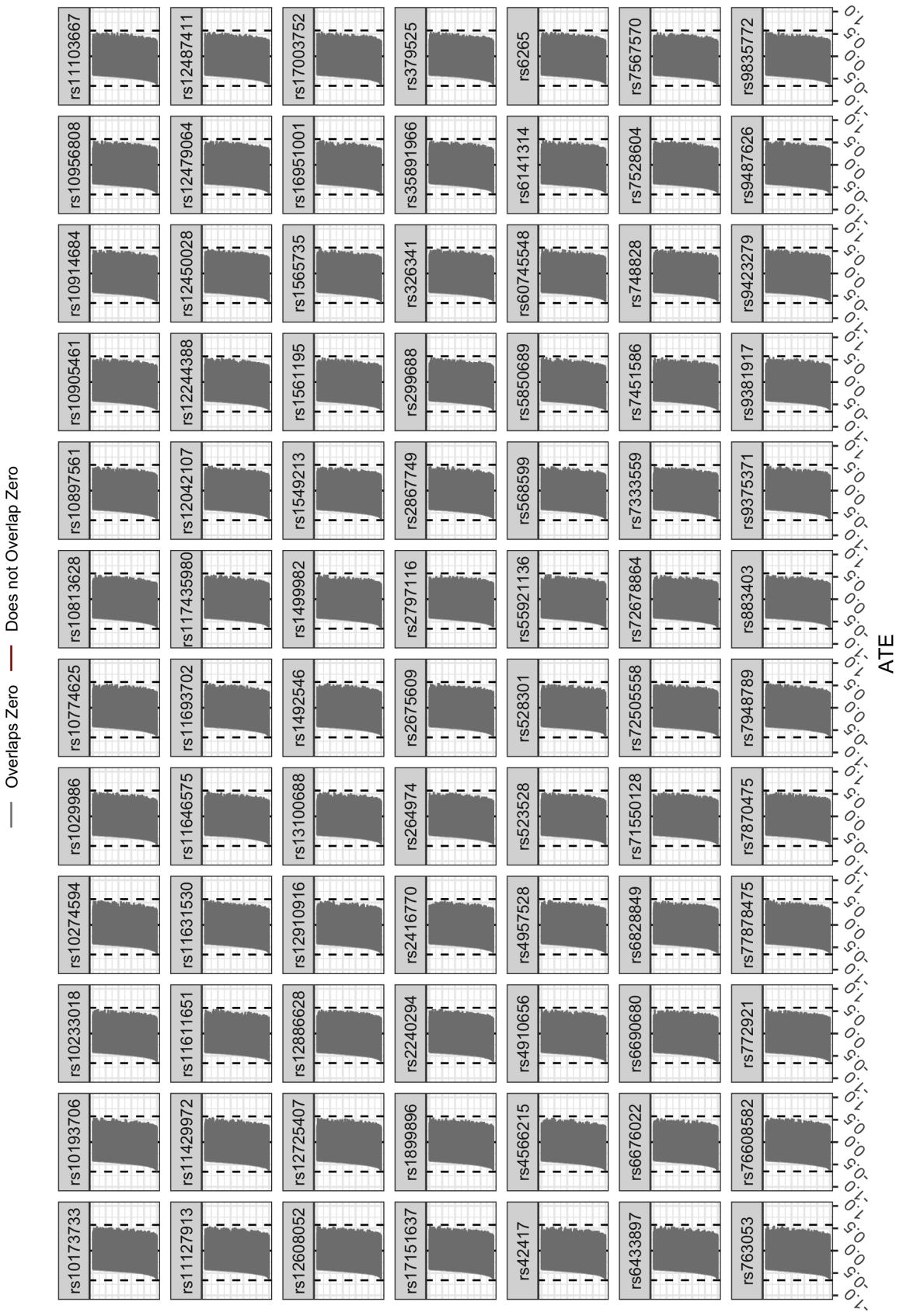
SNP	$\beta_1$	$\beta_0$	$\gamma_1$	$\gamma_0$
rs7333559	0.0080523	0.1662222	-0.0183846	-1.975467
rs7451586	-0.0066732	0.1775422	0.0027432	-1.986404
rs748828	0.0086213	0.1572389	-0.0047229	-1.976368
rs7528604	0.0068658	0.1618157	-0.0001820	-1.982931
rs7567570	-0.0091324	0.1727617	-0.0002451	-1.983053
rs763053	0.0080618	0.1570972	-0.0069210	-1.972409
rs76608582	0.0182891	0.1347646	-0.0048192	-1.973958
rs772921	0.0072725	0.1600453	-0.0054837	-1.975937
rs77878475	0.0125950	0.1465726	0.0010985	-1.985146
rs7870475	-0.0071900	0.1771594	0.0082598	-1.991835
rs7948789	-0.0161713	0.1894568	0.0009336	-1.984284
rs883403	0.0094240	0.1536556	-0.0014726	-1.980646
rs9375371	-0.0073963	0.1804155	-0.0069852	-1.972929
rs9381917	0.0112569	0.1493838	-0.0155636	-1.955201
rs9423279	0.0076695	0.1643324	0.0046716	-1.986350
rs9487626	0.0131029	0.1648247	-0.0136868	-1.978168
rs9835772	-0.0078024	0.1814198	-0.0031275	-1.978401



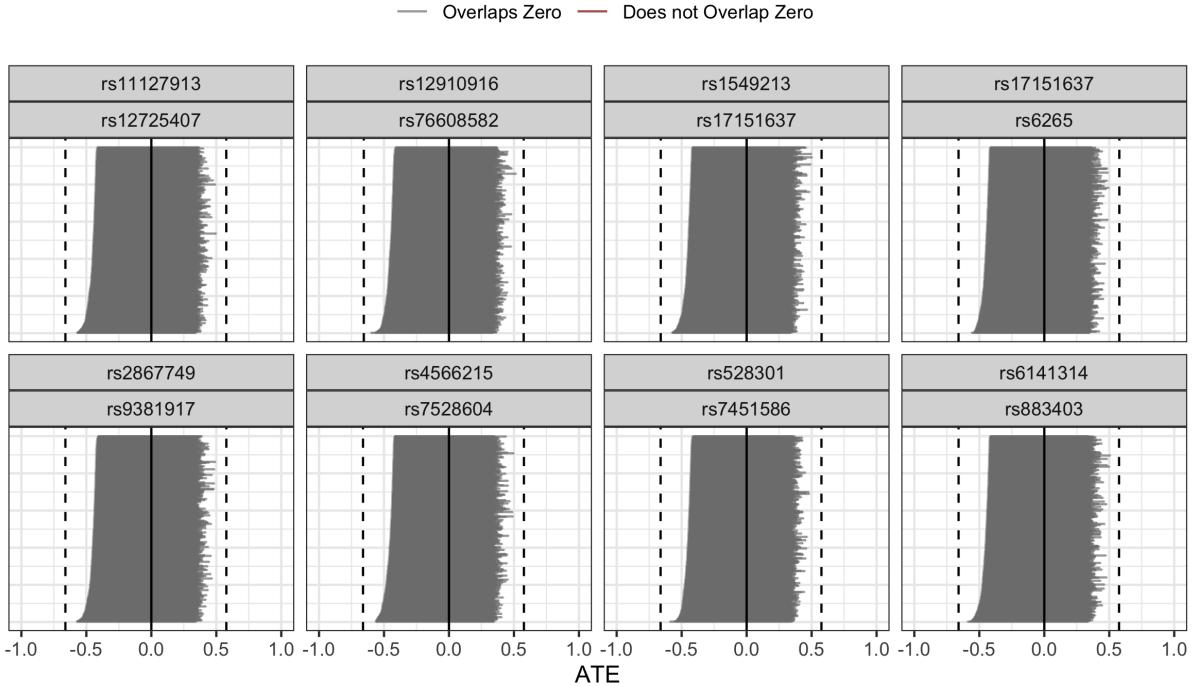
eFigure 9: Histogram of strengths of IVs on the exposure. Here, SNPs are IVs, and smoking status (ever/never) is exposure. We see that all IVs are very weak, with the largest value just below 0.01.



eFigure 10: Nonparametric two-sample IV bounds on the average treatment effect of smoking on the incidence of lung cancer.

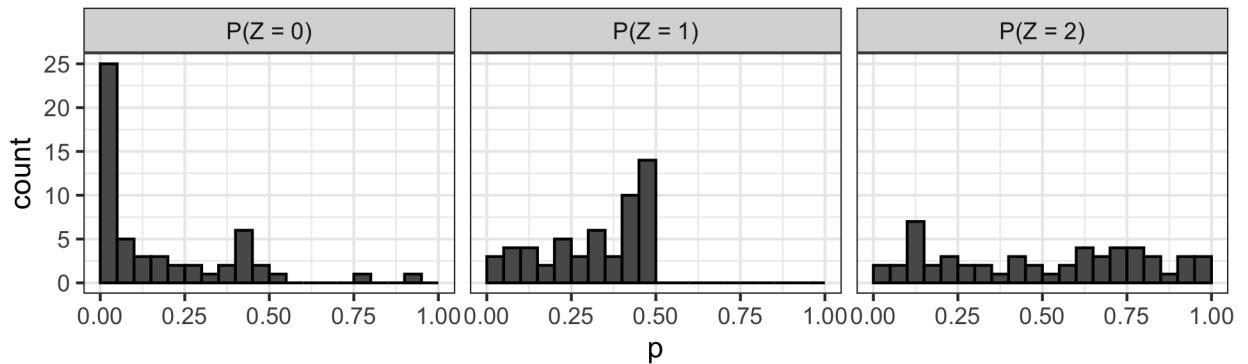


eFigure 11: 500 sets of bounds of the average treatment effect of smoking on lung cancer for each of the 84 SNPs. Each bound is based on a set of values for the trivariate distribution randomly sampled. Bounds are color coded to show if they overlap 0 (grey) or do not (red). All bounds overlap 0.



eFigure 12: Intersection bounds of the average treatment effect of smoking on lung cancer based on randomly sampled trivariate distributions from pairs of SNPs. These 8 pairs were randomly chosen from all possible pairs.

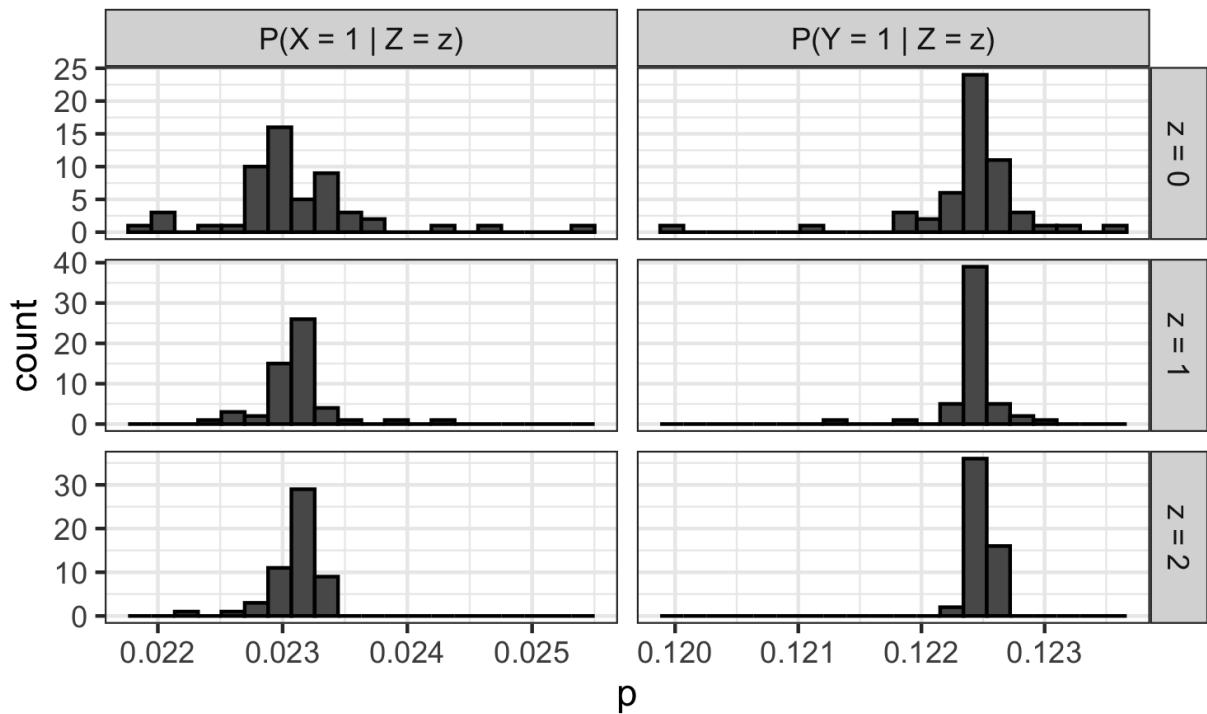
#### A.7.2 Effect of High Cholesterol on Heart Attack



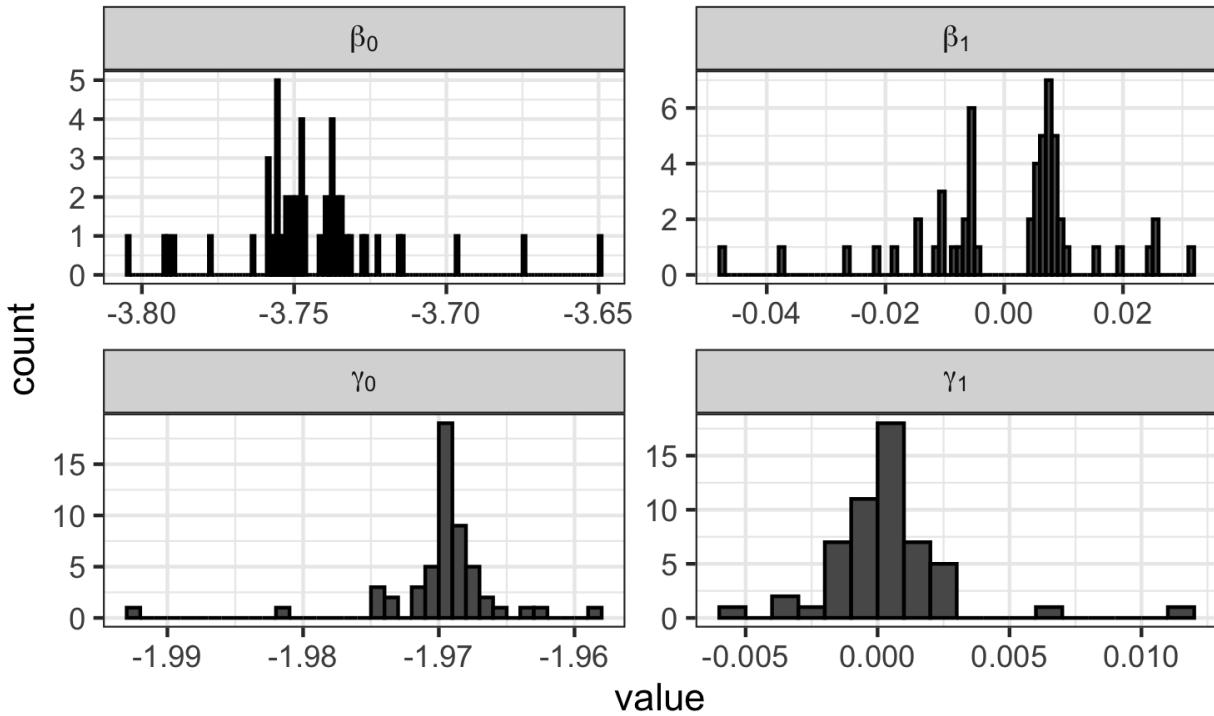
eFigure 13: Histograms of the marginal distribution of instruments,  $P(Z = z)$ ,  $z = 0, 1, 2$ , estimated after preprocessing.

eTable 9: Table of the marginal distribution of instruments,  $P(Z = z)$ ,  $z = 0, 1, 2$ , estimated after pre-processing for analysis.

SNP	P(Z = 2)	P(Z = 1)	P(Z = 0)	SNP	P(Z = 2)	P(Z = 1)	P(Z = 0)
rs10096633	0.7682873	0.2164654	0.0152473	rs3918226	0.8434773	0.1498658	0.0066569
rs10260606	0.6689457	0.2978906	0.0331637	rs4299376	0.1044835	0.4375111	0.4580055
rs10410835	0.2261041	0.4987999	0.2750961	rs4470903	0.6122421	0.3404338	0.0473241
rs10504255	0.1141345	0.4474070	0.4384585	rs456598	0.7353800	0.2443260	0.0202940
rs10804330	0.3246447	0.4902626	0.1850927	rs4704727	0.1153479	0.4485623	0.4360899
rs112019714	0.9445278	0.0546808	0.0007914	rs472495	0.1219232	0.4545036	0.4235732
rs11580878	0.2532012	0.4999796	0.2468192	rs56299331	0.6368870	0.3223300	0.0407830
rs11591147	0.9653935	0.0343018	0.0003047	rs57180587	0.7289642	0.2496596	0.0213762
rs117733303	0.9629825	0.0366685	0.0003491	rs58542926	0.8541959	0.1400626	0.0057415
rs12471811	0.7974669	0.1910863	0.0114469	rs58691354	0.7129641	0.2628159	0.0242201
rs1260326	0.1542518	0.4769944	0.3687538	rs59950280	0.4469685	0.4431771	0.1098545
rs12740374	0.6060342	0.3448956	0.0490702	rs6090040	0.2300488	0.4991705	0.2707808
rs12916	0.3593703	0.4802094	0.1604203	rs622871	0.0988228	0.4310763	0.4701008
rs1367117	0.4370916	0.4480749	0.1148336	rs635634	0.6627002	0.3027276	0.0345722
rs1601935	0.1186871	0.4516457	0.4296671	rs6458349	0.0768498	0.4007364	0.5224138
rs1883025	0.5579089	0.3780482	0.0640429	rs6511720	0.7764852	0.2093975	0.0141172
rs1883711	0.9385769	0.0604497	0.0009733	rs7012637	0.2755284	0.4987592	0.2257124
rs2125345	0.4990744	0.4147551	0.0861704	rs7213086	0.2001050	0.4944520	0.3054430
rs2237107	0.6333104	0.3249953	0.0416944	rs73534263	0.7971401	0.1913739	0.0114861
rs2244608	0.4686429	0.4318641	0.0994929	rs7412	0.8445834	0.1488576	0.0065590
rs2618567	0.1161249	0.4492923	0.4345829	rs74617384	0.8447171	0.1487357	0.0065473
rs2738447	0.1661712	0.4829396	0.3508892	rs7534572	0.1255675	0.4575751	0.4168575
rs28601761	0.3342690	0.4877820	0.1779490	rs7707394	0.4169078	0.4575523	0.1255398
rs28807203	0.9046336	0.0929773	0.0023890	rs77542162	0.9546715	0.0448029	0.0005257
rs3127580	0.7081492	0.2667336	0.0251172	rs799157	0.0018869	0.0831041	0.9150089
rs34042070	0.6625016	0.3028808	0.0346176	rs9376091	0.5451282	0.3863995	0.0684722
rs34707604	0.5518930	0.3820040	0.0661030	rs964184	0.0174433	0.2292594	0.7532973



eFigure 14: Histograms of the marginal conditional probabilities  $P(X = 1 | Z = z), z = 0, 1, 2$  and  $P(Y = 1 | Z = z), z = 0, 1, 2$ .



eFigure 15: Histograms of the coefficients from GWAS results of logistic regression of the SNPs on high cholesterol and heart attack, respectively. Intercepts ( $\beta_0$  and  $\gamma_0$ ) are inferred, while slopes ( $\beta_1$  and  $\gamma_1$ ) are as reported.

eTable 10: Coefficients from GWAS results of logistic regression of the SNPs on high cholesterol and heart attack status. Intercepts ( $\beta_0$  and  $\gamma_0$ ) are inferred, while slopes ( $\beta_1$  and  $\gamma_1$ ) are as reported.

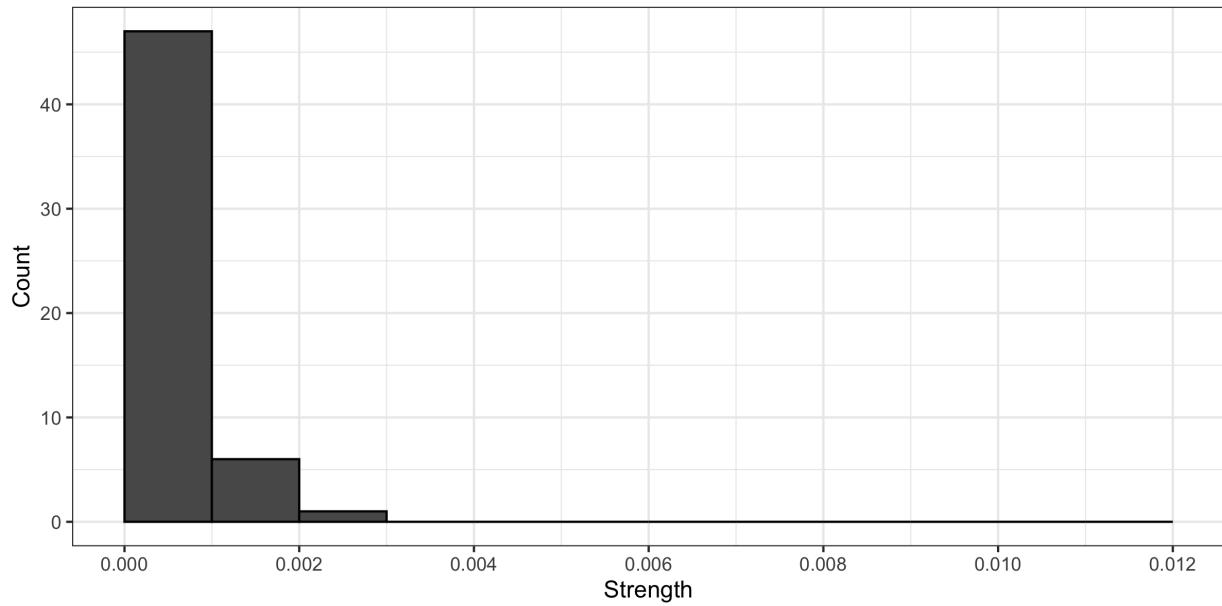
SNP	$\beta_1$	$\beta_0$	$\gamma_1$	$\gamma_0$
rs10096633	-0.0089830	-3.727152	-0.0012995	-1.966860
rs10260606	0.0076950	-3.755485	0.0007029	-1.970288
rs10410835	0.0071078	-3.749661	0.0007948	-1.969894
rs10504255	-0.0056764	-3.739063	-0.0000742	-1.969088
rs10804330	-0.0050169	-3.737181	-0.0012539	-1.967709
rs112019714	0.0251675	-3.791824	0.0025525	-1.974100
rs11580878	-0.0051399	-3.737725	-0.0006621	-1.968472
rs11591147	-0.0476105	-3.649365	-0.0054389	-1.958449
rs117733303	0.0311528	-3.804047	0.0116909	-1.992088
rs12471811	0.0084776	-3.758037	0.0000048	-1.969147
rs1260326	-0.0102312	-3.734879	-0.0003941	-1.968828

eTable 10: Coefficients from GWAS results of logistic regression of the SNPs on high cholesterol and heart attack status. Intercepts ( $\beta_0$  and  $\gamma_0$ ) are inferred, while slopes ( $\beta_1$  and  $\gamma_1$ ) are as reported. *(continued)*

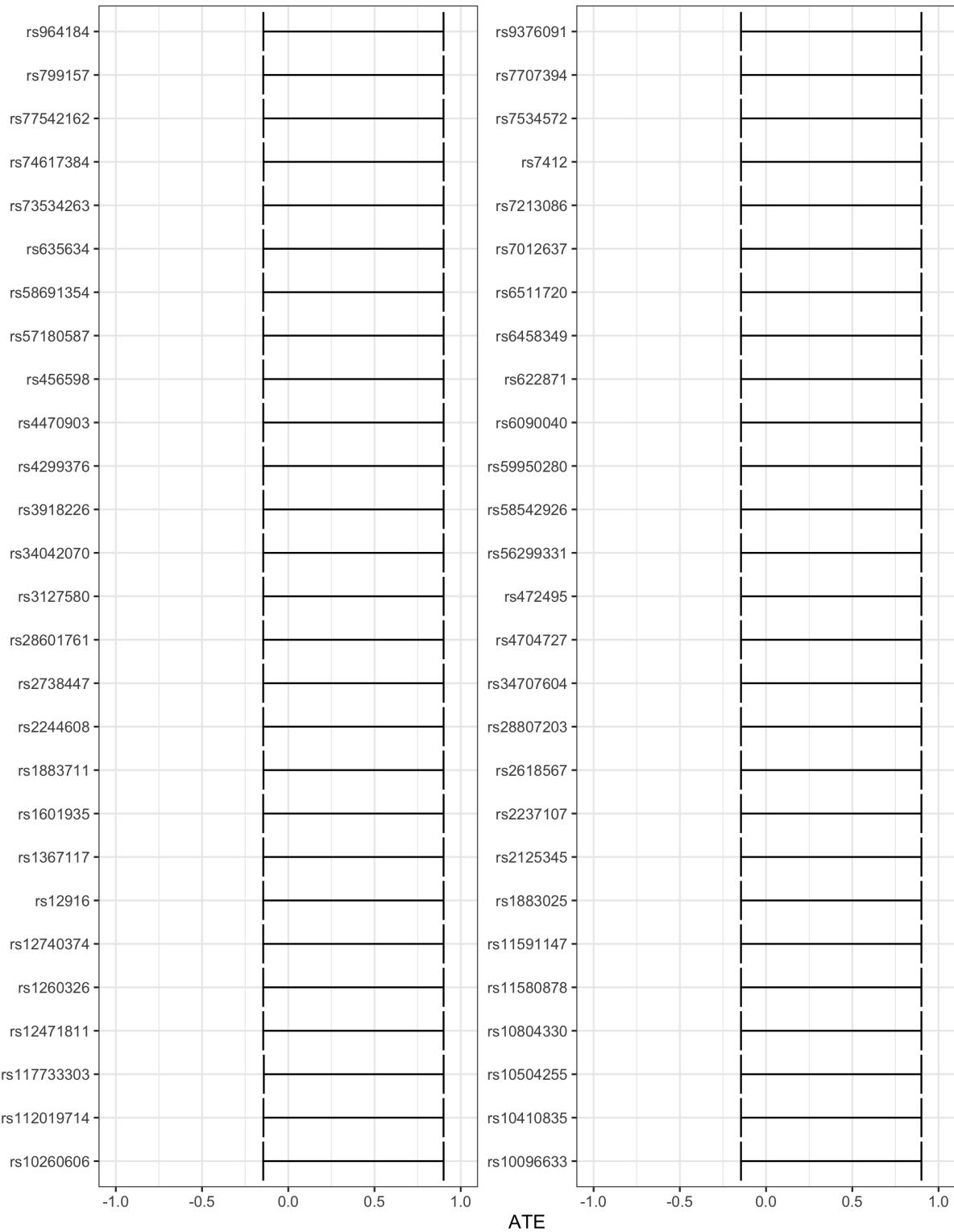
SNP	$\beta_1$	$\beta_0$	$\gamma_1$	$\gamma_0$
rs12740374	-0.0183231	-3.714419	-0.0025251	-1.965207
rs12916	0.0104793	-3.755479	0.0006700	-1.969941
rs1367117	0.0155585	-3.763513	0.0011495	-1.970658
rs1601935	-0.0061378	-3.738671	-0.0007014	-1.968655
rs1883025	-0.0069826	-3.732469	-0.0013153	-1.967173
rs1883711	0.0241076	-3.789616	0.0026734	-1.974319
rs2125345	-0.0056374	-3.734933	-0.0009408	-1.967809
rs2237107	-0.0070166	-3.731732	-0.0007194	-1.967993
rs2244608	0.0070205	-3.752512	0.0010406	-1.970563
rs2618567	-0.0047485	-3.739660	-0.0007455	-1.968630
rs2738447	0.0081671	-3.749563	0.0016947	-1.970520
rs28601761	-0.0140739	-3.726664	-0.0011169	-1.967847
rs28807203	-0.0106943	-3.722554	-0.0002164	-1.968726
rs3127580	0.0076693	-3.755804	0.0022978	-1.973006
rs34042070	0.0094413	-3.758272	0.0002698	-1.969577
rs34707604	0.0058521	-3.751591	0.0002016	-1.969438
rs3918226	0.0081783	-3.757916	0.0028105	-1.974301
rs4299376	-0.0111342	-3.735719	-0.0012431	-1.968335
rs4470903	0.0067035	-3.753387	0.0014579	-1.971420
rs456598	0.0065720	-3.754166	0.0005768	-1.970127
rs4704727	0.0074887	-3.747988	0.0007432	-1.969643
rs472495	0.0064154	-3.747379	0.0004743	-1.969469
rs56299331	0.0057258	-3.752033	0.0001068	-1.969308
rs57180587	0.0081592	-3.756830	0.0013685	-1.971475
rs58542926	-0.0146353	-3.715853	-0.0013536	-1.966636
rs58691354	0.0074756	-3.755521	0.0000196	-1.969171
rs59950280	0.0058286	-3.750690	0.0004805	-1.969780
rs6090040	-0.0055812	-3.737545	-0.0007168	-1.968450

eTable 10: Coefficients from GWAS results of logistic regression of the SNPs on high cholesterol and heart attack status. Intercepts ( $\beta_0$  and  $\gamma_0$ ) are inferred, while slopes ( $\beta_1$  and  $\gamma_1$ ) are as reported. *(continued)*

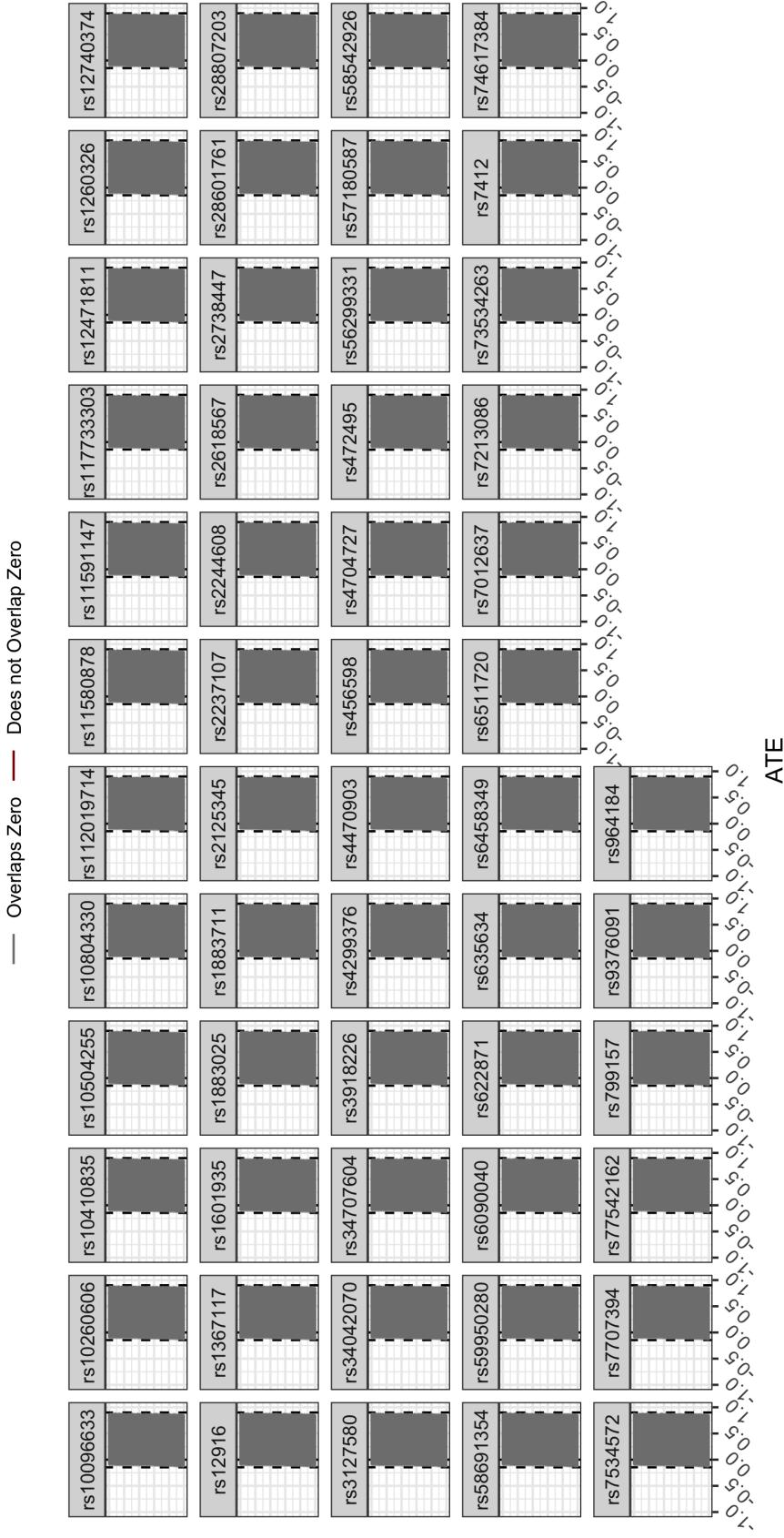
SNP	$\beta_1$	$\beta_0$	$\gamma_1$	$\gamma_0$
rs622871	0.0065093	-3.746991	0.0013161	-1.969966
rs635634	0.0098788	-3.758987	0.0014151	-1.971442
rs6458349	0.0056558	-3.746031	0.0007529	-1.969556
rs6511720	-0.0261322	-3.696906	-0.0030216	-1.963813
rs7012637	0.0047984	-3.747932	0.0002456	-1.969396
rs7213086	0.0047773	-3.747169	0.0007846	-1.969840
rs73534263	0.0071810	-3.755717	0.0000767	-1.969275
rs7412	-0.0374088	-3.674234	-0.0038000	-1.962153
rs74617384	0.0190473	-3.777927	0.0069894	-1.981990
rs7534572	0.0081187	-3.748658	0.0005830	-1.969551
rs7707394	0.0061511	-3.750841	0.0000817	-1.969243
rs77542162	0.0253674	-3.792474	0.0020548	-1.973154
rs799157	-0.0108031	-3.741956	-0.0003979	-1.969103
rs9376091	-0.0053004	-3.735070	-0.0005561	-1.968317
rs964184	-0.0215630	-3.737246	-0.0013629	-1.968778



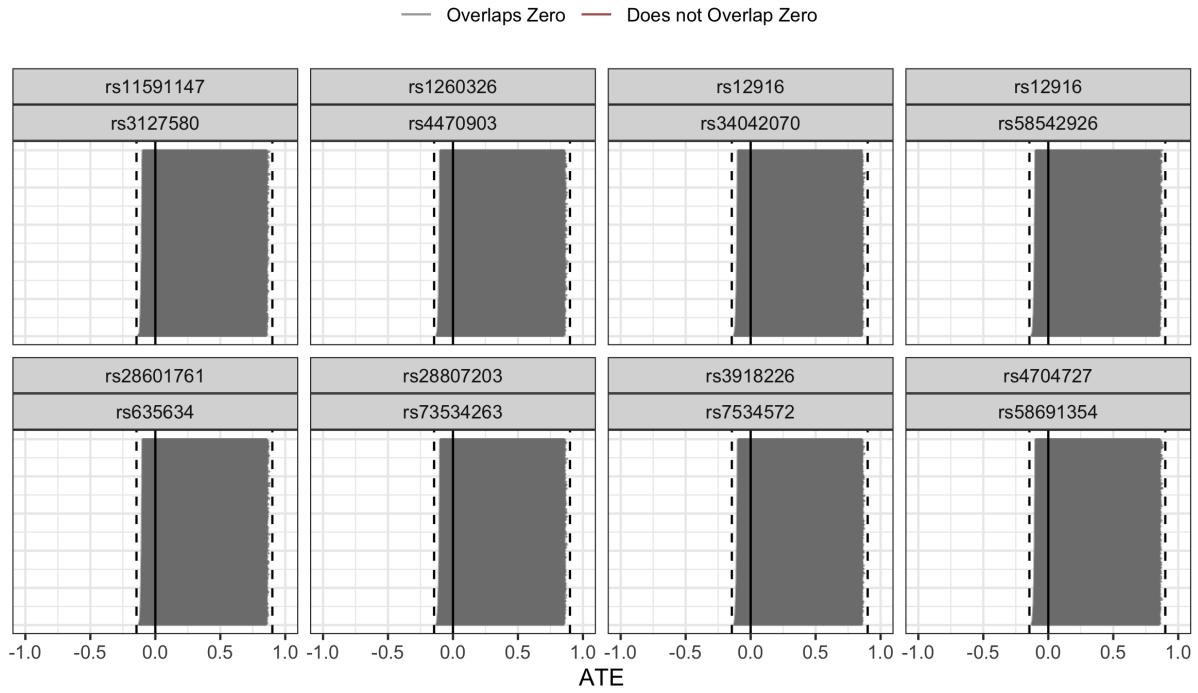
eFigure 16: Histogram of strengths of IVs on the exposure. Here, SNPs are IVs, and high cholesterol is the exposure. We see that all IVs are very weak, with the largest value below 0.003.



eFigure 17: Nonparametric two-sample IV bounds on the average treatment effect of high cholesterol on the incidence of heart attack.



eFigure 18: 500 sets of bounds of the average treatment effect of high cholesterol on heart attack for each of the 54 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.



eFigure 19: Intersection bounds of the average treatment effect of high cholesterol on heart attack based on randomly sampled trivariate distributions from pairs of SNPs. These 8 pairs were randomly chosen from all possible pairs.

## References

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