

Bounds in Two-Sample Mendelian Randomization With Summary Statistics

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 one of several parametric models for estimation. However, little is understood about using a nonparametric bound-based analysis, a popular approach in instrumental variables frameworks, to estimate causal effects in MR. In this work, we explore different properties about using a bound-based analysis to estimate causal effects in two-sample MR studies. We also propose a method to assess how likely one can obtain a more informative analysis had we had a one-sample MR study compared to a two-sample MR study. We replicate 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 nonparametric bounds are rarely suitable to analyze causal effects in two-sample MR studies unless strong assumptions are met.

1 Introduction

In recent years, the use of genetic variants as instrumental variables (IV) in analyses estimating causal effects in epidemiological studies have gained popularity [18, 27]. Such analyses, often referred to as Mendelian randomization (MR) studies, are often based on 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. This setup is often referred to as a two-sample study design [8, 12, 19]. With summary statistics from the two GWAS, investigators often use parametric methods to arrive at estimates and tests for the exposure effect. Examples of such are the IVW estimator [8], MR-Egger regression [5], weighted median [6], weighted modes [22], MR-PRESSO [45] and MRRAPs [49], to name a few; see Burgess and Thompson [11], Burgess, Small, and Thompson [9] and Slob and Burgess [40] for recent reviews.

An alternative approach to study the exposure effect without parametric assumptions is through nonparametric IV bounds [3, 13, 29, 34, 36]. 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 common in MR studies. The most well-known bounds are the Balke-Pearl bounds [3] for the average treatment effect. Since then, Cheng and Small [13] and Richardson and Robins [34] extended the Balke-Pearl bounds to allow for a non-binary instrument. Ramsahai [33] derived bounds of the exposure effect under the two-sample setting. Palmer et al. [32] provides software to compute IV bounds for two-sample MR studies using only summary statistics.

Due to their nonparametric nature, IV bounds have been attractive alternatives to study exposure effects in non-MR, one-sample settings, especially when some parametric assumptions are difficult to justify. Despite their attractive properties, there is little work on using IV bounds in MR settings with summary statistics from GWAS.

The goal of the paper is to characterize the behavior of IV bounds in two-sample settings, specifically addressing what can be learned from two-sample MR studies that choose to use nonparametric IV bounds to analyze the exposure effect using summary statistics from GWAS.

2 Methods

2.1 Review: Notation and Definitions

Let X and Y be binary exposure and outcome, 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 [37, 41] had the subject received exposure value $X = x$ and instrument value $Z = z$. We assume the stable unit treatment value assumption (SUTVA) [17, 38], 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 the instrument, the exposure, the outcome, and the unmeasured confounder that are typical in MR studies; see Didelez and Sheehan [20] and Wang and Tchetgen Tchetgen [47] 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 assessed by finding SNPs that have been consistently associated with the exposure. (A2) is usually checked based on scientific theory surrounding how the genetic instrument was inherited. (A3) states that there is no direct effect of the instrument Z on the outcome Y and like (A2), is assessed by scientific theory. Both (A2) and (A3) can be violated if the SNP is (i) in linkage disequilibrium with an unmeasured SNP that affects the exposure and outcome, (ii) pleiotropic and has multiple functions beyond affecting the exposure, or (iii) under population stratification, to name a few. Finally, (A4) states that if U is observed, then it is sufficient to unconfound the relationship between X and Y .

We make a few additional remarks about assumptions (A1)-(A4). Most MR studies only make assumptions (A1)-(A3) along with some modeling assumptions [11]. Second, the role of assumption (A4) is to show the role that an unmeasured confounder U plays in identification of causal effects; Richardson and Robins [34] 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 assumption in MR studies [20]. Fourth, for simplicity, we do not assume the existence of a potential treatment X^z ; the existence of X^z does not change the IV bounds [44, 34], and its primary purpose is to define a “causal” instrument [24].

We conclude by introducing two assumptions and defining instrument strength; the assumptions are not necessary to construct bounds, but will help us explain the behavior of the IV bounds in two-sample studies. First, we state the assumptions restricting the direction of the instrument's effect on the exposure and the outcome.

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

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

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 effect of the genetic instrument on the exposure or the outcome is well-established from scientific theory and/or has been replicated in many observational studies.

Second, we define instrument strength as the maximum possible contrast of the exposure when instruments take on different values

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

The formula for ST reduces to the definition of instrument strength used in Balke and Pearl [3] when the instrument is binary; Balke and Pearl [3] used ST to characterize the width of the IV bounds. We remark that (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 [42] for an overview.

Another popular summary statistic measuring instrument strength in MR studies is the coefficient from a logistic model [27, 7, 46, 30, 26]. We will utilize a logistic model for the exposure, where the log-odds is given as a linear combination of an intercept, the instruments, and an unmeasured confounder U from the standard normal, and a logistic model for the outcome, where the log-odds is given as a linear combination of an intercept, the exposure, and the unmeasured confounder U ; see Appendix A for details.

2.2 Review: Study Designs and Target Estimand

For the purposes of studying IV bounds, we divide IV studies into two designs, the two-sample design and the one-sample design. The two-sample design has two separate data sources, one providing information about (X, Z) and one providing information about (Y, Z) , and is the most popular design in MR studies.

The one-sample design has a single data source providing information on all observed variables (X, Y, Z) and is more common in traditional IV studies involving non-genetic instruments. The behavior of bounds under a one-sample design has been well-studied [3, 34, 44].

However, not much is known about the behavior of bounds under the two-sample design often used in MR studies. If both the outcome and the exposure are binary as is the case for case-control studies, GWAS summary statistics are computed by running a logistic regression between the exposure X and the outcome Y for each genetic instrument Z and extracting the estimated slope coefficients associated with Z ; it's also common for the logistic regression to adjust for age, sex, and principal components. To focus our paper on studying behavior of bounds not due to sampling errors, we will assume that we have population-level quantities $P(Y = 1|Z = z)$ for different values of z from one data source and $P(X = 1|Z = z)$ for different values of z from another data source.

Given $P(Y = 1|Z = z)$ and $P(X = 1|Z = z)$ for each $z = 0, 1, 2$ from a two-sample design, the goal is to study the average treatment effect (ATE)

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

Here, the second equality follows from SUTVA and assumptions (A3) and (A4). Since U is unobserved, additional assumptions are needed to point-identify the ATE. In particular, even with the remaining assumptions (A1), (A2), and (A5), the ATE cannot be point-identified; see Robins [36], Manski [29], and Balke and Pearl [4].

In two-sample designs, Ramsahai [33] showed that under assumptions (A1)-(A4), the bounds for the ATE are

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

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

Additionally, the data from two-sample designs can be used to check the validity of the IV assumptions

$$\min \left\{ \begin{array}{ll} \min_{z_1 \neq z_2} & P(Y = 1|Z = z_1) - P(X = 1|Z = z_1) - P(Y = 1|Z = z_2) - P(X = 1|Z = z_2) + 2 \\ \min_{z_1 \neq z_2} & P(Y = 1|Z = z_1) + P(X = 1|Z = z_1) - P(Y = 1|Z = z_2) + P(X = 1|Z = z_2) \\ \min_z & P(X = 1|Z = z) \\ \min_z & P(Y = 1|Z = z) \\ \min_z & 1 - P(X = 1|Z = z) \\ \min_z & 1 - P(Y = 1|Z = z) \end{array} \right\} \geq 0 \quad (3)$$

The inequalities in equation (3) are extensions of the “IV inequalities” of Balke and Pearl [3] used to check the validity of the IV assumptions. Versions of these inequalities have been used in MR studies [21] to check whether the genetic variants satisfy the IV assumptions. See Appendix B for details on the derivation of equations (2) and (3).

The rest of the sections is devoted to studying the behavior of the two-sample IV bound in (2) under a variety of settings.

2.3 Properties of Bounds from Summary-Level Data

Our investigation into the behavior of the bounds in equation (2) is focused on two characteristics: (1) the length of the bounds and (2) the ability to obtain bounds not covering the null effect allowing us to make conclusions about the direction of the ATE.

Theorem 2.1 shows the width of the ATE bound in equation (2) when all the assumptions (A1)-(A6) hold. The extra assumptions (A5)-(A6) simplify the bound formula in equation (2) and allow us to algebraically characterize its width by instrument strength ST.

Theorem 2.1. *Under assumptions (A1)-(A6), the bounds for the ATE in (2) become*

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

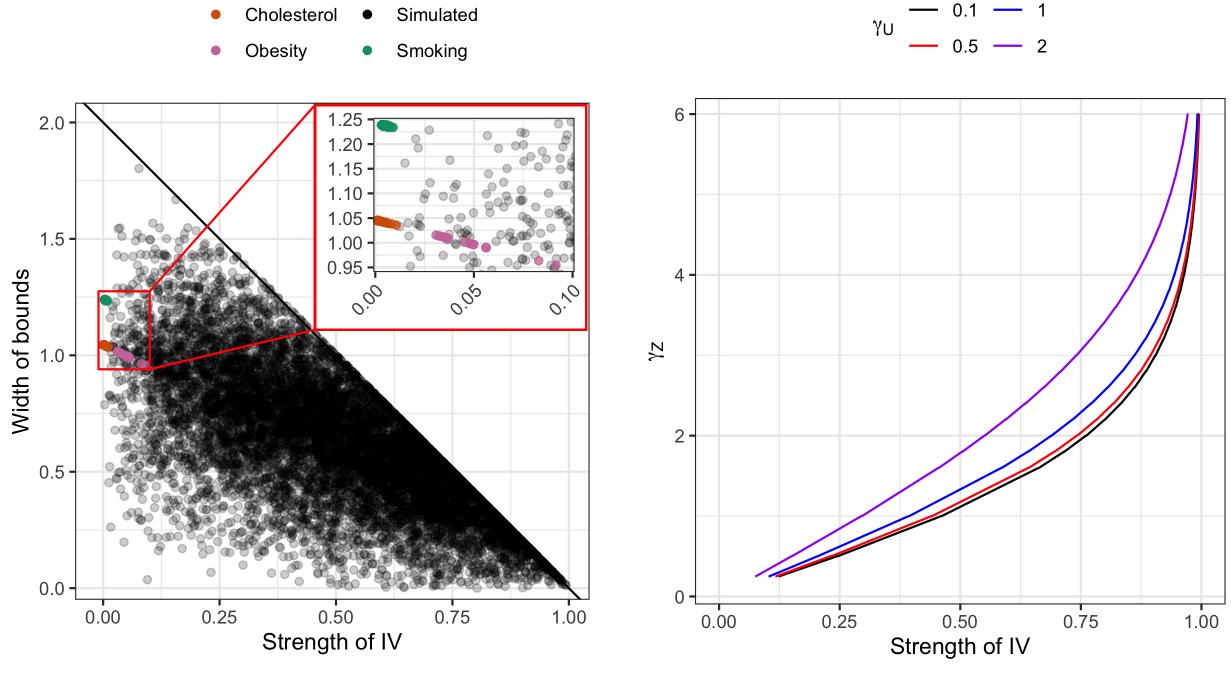
and a sharp upper bound on the width of the bounds is $2 - 2 \cdot ST$, i.e. there exists a data generating process satisfying (A1)-(A6) and has width equal to $2 - 2 \cdot ST$.

The proof is presented in Appendix D. The width of the two-sample bounds is up to twice as large as the Balke-Pearl bounds with a binary IV in single-sample designs where the width is $1 - ST$ [3]. This potential doubling of the width is the “cost” of using a two-sample instead of a one-sample design – the loss of information about the joint distribution $P(Y, X|Z)$ leads to wider bounds.

Based on Theorem 2.1, the width of the IV bounds in two-sample settings is only guaranteed to be less than 1 when ST is greater than 0.5; we remark that a bound with length greater than 1 provides no information about the existence of the exposure effect. In contrast, in one-sample settings, the IV bounds are always less than 1 unless instrument strength is zero. We remark that instruments with strength less than 0.5 could still generate a bound with width less than 1 (see Figure 1).

To numerically illustrate our theorem, we randomly generate 10,000 sets of values of $P(X = 1|Z = z)$ and $P(Y = 1|Z = z)$ that satisfy the IV inequalities, and calculate the corresponding bounds from equation

(2). Note we do not impose assumptions (A5) or (A6). This mimics a scenario with a flat prior over the possible summary statistics that can arise from two-sample MR studies satisfying assumptions (A1)-(A4) and illustrates the large variety of bounds two-sample MR studies can generate.



(a) Relationship between strength of an instrument (ST) and width of the IV bounds. Black line is the upper bound on the bound's width based on Theorem 1. Black dots indicate one of the 10,000 IV bounds. Colored dots indicate bounds from real data; see Section 3 for details.

(b) Coefficients from simple logistic regression model used to derive summary statistics and strength of instrument (ST).

Figure 1: Illustration of the relationship between instrument strength, and width of bounds obtained from two-sample design and coefficients from logistic regression model.

Figure 1a shows the widths of the 10,000 bounds plotted against the strength of the instruments. The black line is the upper bound for the width of the bounds in Theorem 2.1. We have included instruments from three real-world data examples: instruments for the effect of high cholesterol on the incidence of heart attack, instruments for the effect of smoking on the incidence of developing lung cancer, and instruments for the effect of obesity on the incidence of heart attack. The two former are presented in full in Section 3. We see that the width of the bounds often exceed 1 as the instrument strength decreases. Table 1 shows the proportion of bounds presented in Figure 1a with widths greater than 1, 0.75, and 0.5, stratified by instrument strength. The table shows that it is possible to observe bounds with width less than 1 for weak IVs, but it is far from guaranteed.

Table 1: Proportion of bounds where the width is greater than 1, 0.75, and 0.5, stratified by strength of the instrument (ST).

Strength	Proportion of bounds with width greater than...		
	1	0.75	0.5
[0, 0.05]	0.470	0.783	0.892
(0.05, 0.1]	0.464	0.724	0.895
(0.1, 0.25]	0.326	0.705	0.923
(0.25, 0.5]	0.136	0.497	0.838
(0.5, 1]	0.000	0.076	0.380

To better understand the implications of Theorem 2.1 in practice, Figure 1b characterizes the relationship between instrument strength ST and the corresponding coefficient from the logistic model with a single IV; see Appendix E for details. We see that instrument strength ST of 0.5 corresponds to a regression coefficient γ_1 of approximately 1.1, 1.16, 1.4 and 1.8 if γ_U is 0.1, 0.5, 1 and 2, respectively. Coefficients with such magnitudes are rarely encountered in GWAS summary statistics.

For bounds that have width less than 1 and has the potential to be informative, we study whether they can tell investigators about the direction of the exposure effect. For an anticipated effect size, we ask what kind of coefficient γ_1 is needed in order for the two-sample IV bounds to exclude 0. This question is akin to computing the power of bounds where instrument strength roughly stands for sample size; a major difference, though, is that we are using population-level estimates of the probability distributions. We reuse the exposure model from above, and introduce a logistic model for the outcome; see Appendix E for details.

Figure 2 shows the smallest coefficient needed to detect direction of the ATE for different effect sizes. We see that to detect even moderate effect sizes of 0.4, the corresponding γ_1 must be around 2, a tall order for most GWAS summary statistics.

Overall, in the context of two-sample MR studies where most genetic instruments are weak, an MR analysis based on bounds is unlikely to be informative. The bounds will often have width greater than 1 for most genetic instruments and detecting even moderate effect sizes require uncharacteristically strong genetic variants. This is illustrated by all three real data examples included in Figure 1a; all instruments have ST less than 0.1, all have width greater than 0.95, and most have width greater than 1.

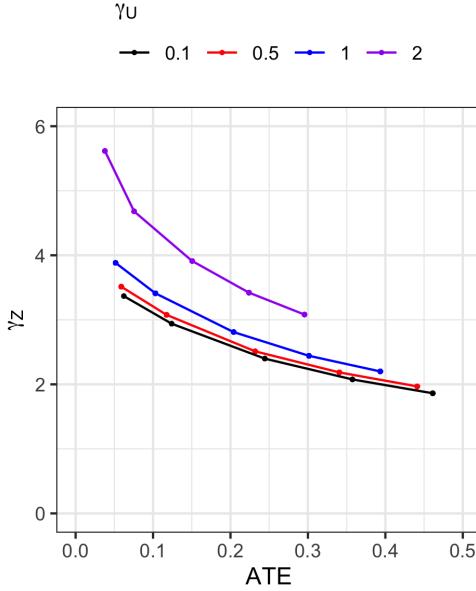


Figure 2: The smallest γ_1 needed for a two-sample IV bound to exclude 0.

2.3.1 Using Multiple IVs

Prior section revealed that two-sample bounds from MR studies require a strong instrument to be informative. However, it did not address whether the bounds can become more informative if multiple valid instruments are available. We use the simplest and most naive approach to aggregate two-sample IV bounds across multiple instruments by taking intersections of separate IV bounds. This may be inferior to another alternative where we expand the levels of Z from 0, 1, 2 to accommodate multiple instruments [43], but has the benefit of being applicable to two-sample MR studies. We consider the exposure and outcome models presented in Appendix A, and use monte carlo integration with 1,000,000 re-samples to obtain the probabilities needed to find bivariate bounds for multiple IVs in four different scenarios. These are characterized by the domain of the coefficients γ_i , and whether these are spread out across the domain, or if $p - 1$ are located at the low end and 1 at the high end of the range. See Appendix F for details. Results are shown in Figure 3.

A few important things to note from Figure 3. First, we note that all bounds are nested in all scenarios. This means that taking intersections of bounds simply returns the bounds obtained from the strongest instrument. Second, as the number of instruments is increased, the width of the bounds increase. Coefficients of similar magnitude lead to different widths in scenarios where different number of IVs are included. Third, the width of bounds obtained from the strongest IV decreases if the coefficients of the other instruments are spread out across the domain rather than concentrated at the lower end of the scale. These observations suggest

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.

2.4 Obtaining More Informative Bounds: Reconstructing the Joint Distribution $P(X, Y|Z)$

2.4.1 Method

Our method to creating more informative bounds from two-sample MR rests on creating a plausible range of the joint distribution of the outcome and the exposure given the instrument Z , $P(X = x, Y = y|Z = z)$. The plausible range of the joint distribution is informed by quantities available from two-sample MR studies, specifically $P(X = x|Z = z)$ and $P(Y = y|Z = z)$, and a uniform prior on unknown quantities subject to IV assumptions. For each plausible joint distribution $P(X = x, Y = y|Z = z)$, we compute the one-sample IV bounds of Balke and Pearl [3] and Richardson and Robins [34]. By doing this, we address the question “had we observed one-sample data that satisfies the constraints of the two-sample data we currently have, could we have detected the presence of an exposure effect?”

We use that the conditional distribution $P(X = x, Y = y|Z = z)$ can be written as a function of $P(X = x|Z = z)$ and $P(Y = y|Z = z)$, and the conditional covariance $\text{Cov}(X, Y|Z = z)$. The only unknown in a two-sample MR study is the covariance. This value is bound by -1 and 1 by definition, but stricter bounds can be found when we only allow values that result in a proper probability distribution of $(X, Y|Z)$ that also satisfy the verifiable constraints (3) from the IV assumptions; see Appendix G.

We sample values of $\text{Cov}(X, Y|Z = 0)$, $\text{Cov}(X, Y|Z = 1)$, $\text{Cov}(X, Y|Z = 2)$, such that the existing constraints in (3) are satisfied, leading us to a plausible joint distribution $P(X = x, Y = y|Z = z)$. This is used to calculate one-sample IV bounds for the ATE [3, 34]. If, when repeated, a large number of the one-sample IV bounds obtained do not cover zero, then there is some evidence for a non-zero exposure effect that our two-sample IV bounds do not detect due to the limitations of the two-sample design. 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 are under a one-sample design.

This analysis can be extended to handle multiple IVs by simply repeating the above procedure for each proposed instrument and taking intersections of the one-sample IV bounds. For additional details, see Appendices H and I.

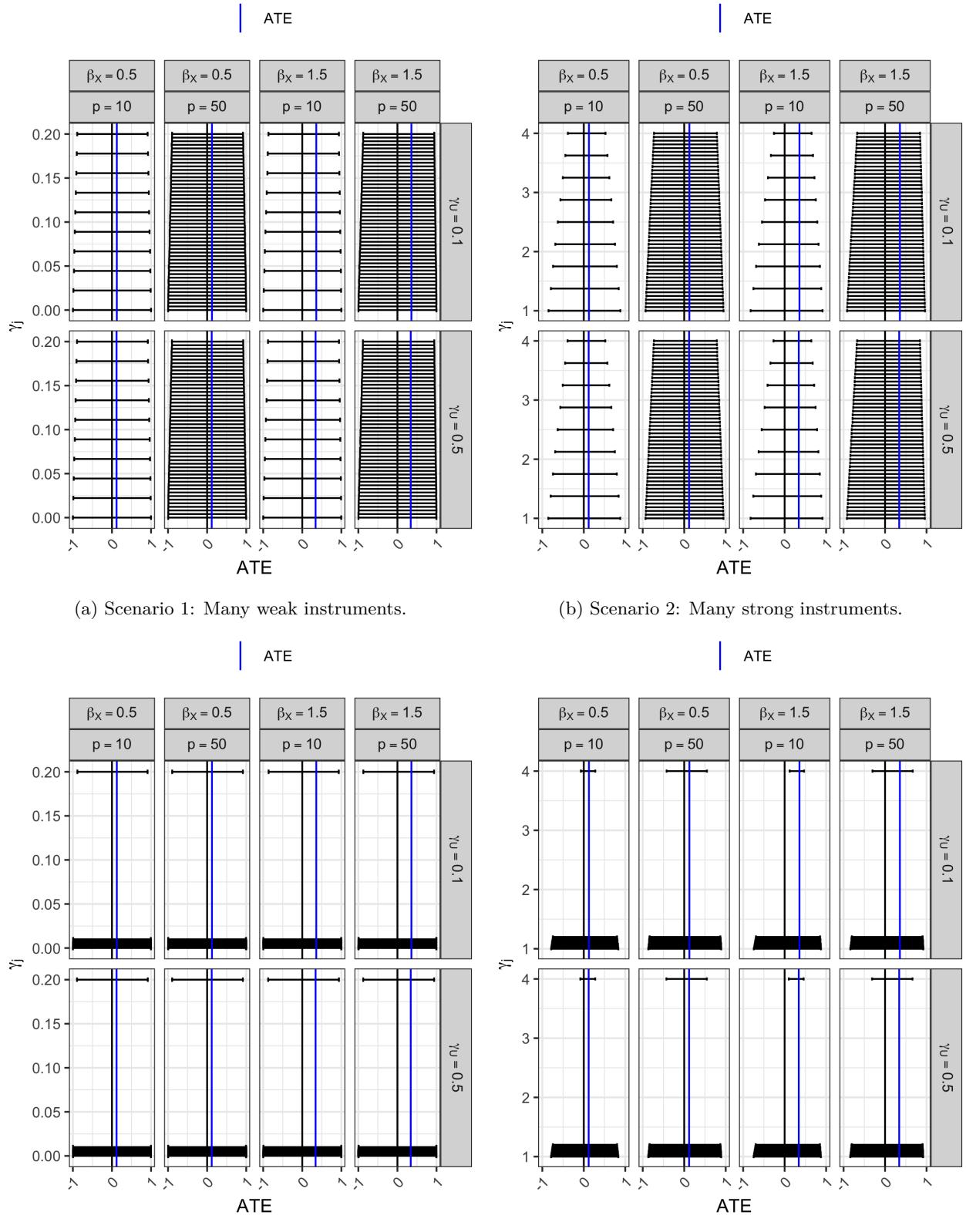


Figure 3: Two-sample IV bounds with 10 or 50 instruments. Blue line represents the true ATE and each black segment represents a bound from one of the p instruments.

Finally, we remark that the proposed method can be thought of as using an empirically bayesian framework for partially identified sets. Specifically, our procedure generates a posterior distribution of one-sample IV bounds given the marginalized probabilities from two-sample data (i.e. the likelihood) and a uniform, flat prior on the unknown quantities $\text{Cov}(X, Y|Z = z)$. The constraints that we impose on $\text{Cov}(X, Y|Z = z)$ are almost empirically Bayesian in that they are informed by data from two-sample MR studies.

2.4.2 Results

We illustrate our proposed method by considering nine hypothetical MR studies, each using one instrument. Table 2 presents nine different sets of values of the marginal distributions $P(Y|Z)$ and $P(X|Z)$ and Figure 4 shows the sampled one-sample IV bounds from our method.

Table 2: 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	$\{0.175, 0.079, 0.365\}$	$\{0.493, 0.911, 0.085\}$	$\{0.434, 0.045, 0.733\}$
	$\{0.599, 0.358, 0.087\}$	$\{0.360, 0.480, 0.441\}$	$\{0.747, 0.370, 0.169\}$

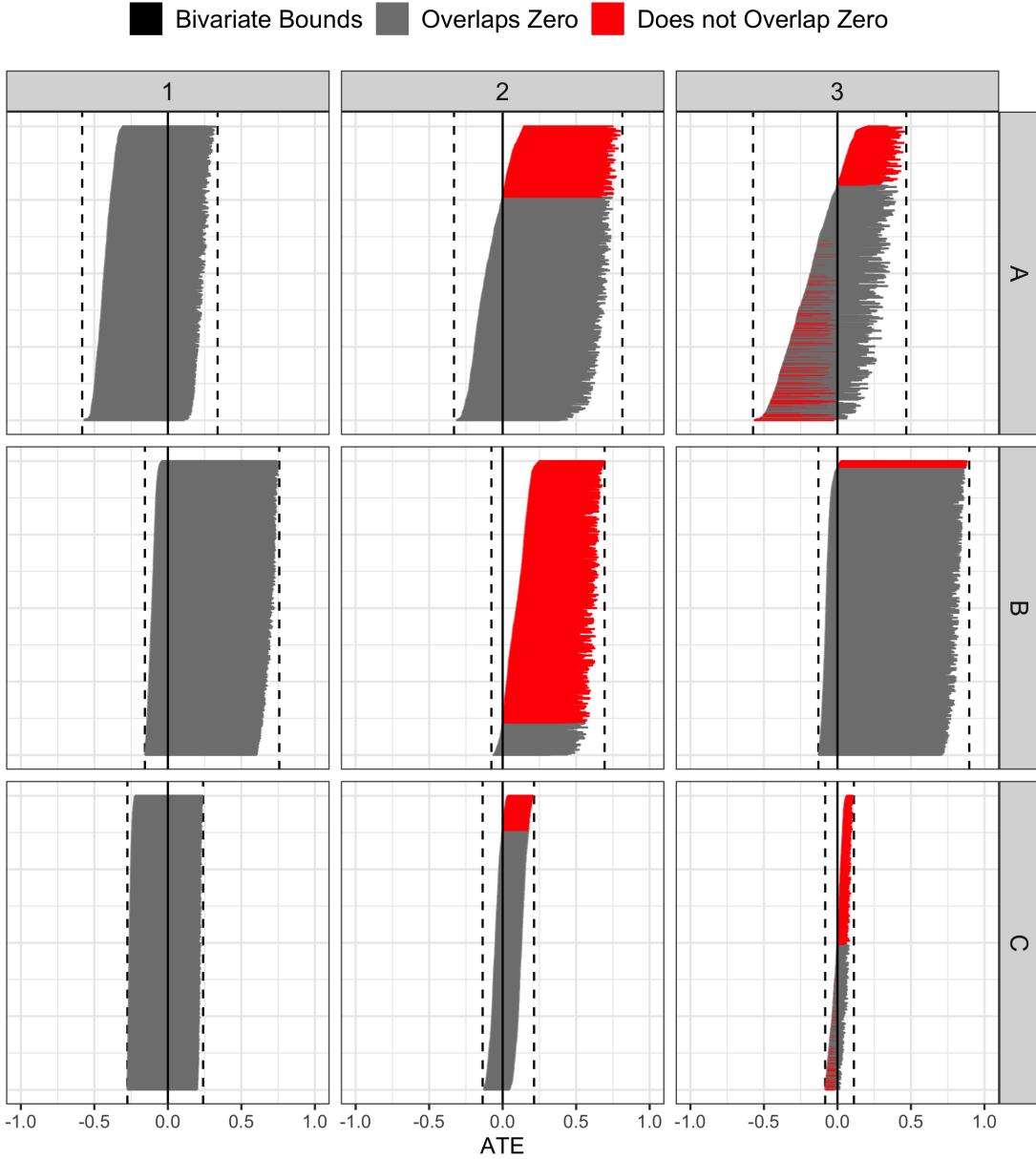


Figure 4: One-sample bounds (solid lines) and two-sample bounds (dotted lines). Red color represents one-sample bounds that do not cover zero and gray color represents one-sample bounds that do cover zero.

Row A of Figure 4 shows three scenarios where the two-sample bounds are all centered close to zero with similar widths. However, the conclusions are rather different. Column 1 shows no one-sample bounds would allow us to determine the presence of a non-zero causal effect. Column 2 indicates that about 24% of the one-sample IV bounds does not contain 0 while for column 3 that number is approximately 36.8%. However, while the direction of the effect is always the same for column 2 (positive), it varies for column 3.

Row B illustrates three scenarios where the two-sample bounds are centered well above zero and have larger

widths. We see one case where we have no hope of determining direction from the one-sample bounds (column 1), one case where we are most likely to determine the direction of the ATE (column 2), and one case where we are unlikely to determine the direction of the ATE (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.

Despite showing promise about studying the ATE, some caution should be exercised when interpreting the proportion of one-sample bounds not containing 0 from our method. In particular, 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. Under this prior, it tells us that it is much more likely that the ATE is positive. 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. Overall, with these limitations in mind, the method presented above can reveal some information about the ATE from two-sample bounds as well as the potential loss of information from using two-sample designs over one-sample designs.

3 Results

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 lung cancer and our second study examines the effect of self-reported high cholesterol on incidence of heart attack. The causal effects underlying both analyses are well-established. Specifically, the effect of smoking on lung cancer is known to be strong and positive. Also, while the exact mechanism between high cholesterol and heart disease is still being discussed [25, 35], some meta-analyses of randomized clinical trials of the effect of cholesterol-lowering medication suggest a strong causal relationship [14, 15]. In both cases, we assess what conclusions are attainable based on bound-based approaches in settings where the causal effects are known to be strong and positive.

The data to study these causal effects were obtained from the UK Biobank data stored in the Integrative Epidemiology Unit (IEU) GWAS database. We use the `TwoSampleMR` R package [23] to extract and preprocess the data for our analyses. 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 followed the defaults of the R package.

For the effect of smoking on lung cancer, we found and used 84 genetic instruments, and for the effect of cholesterol on heart attack, we found and used 54 genetic instruments. The average instrument strengths were 0.0042 (range: 0.0032 to 0.0091) and 0.0005 (range: 0.0002 to 0.0022) for instruments on smoking and cholesterol, respectively; these values are much smaller than the $ST = 0.5$ needed to guarantee narrow bounds. As such, the two-sample bounds in Figure ?? are rather wide; all of them have width greater than 1 and they convey no information about the causal effects of interest. Additionally, even after applying our method from Section 2.4 to get more informative bounds, we find that we are unable to determine the direction of either of the ATEs; see Figure ??. See Appendix I for more details, where we also show that aggregating bounds through intersections show similar results.

Overall, while nonparametric bounds allow us to make little assumptions about the data and as such, is robust to some common modeling assumptions in MR analyses, they are often too conservative and provide little, if any, information about the exposure effect, even if the exposure effect is known to be positive and strong, as is the case for the effect of smoking on lung cancer [16]. Because many MR studies are often two-sampled and involve weak instruments, we believe bound-based approaches will likely have limited practical value to uncover causal effects.

4 Discussion

Nonparametric bounds are without a doubt an attractive concept. With a minimal set of assumptions they let us obtain bounds on the average treatment effect. However, as we have seen here, in typical MR studies with two-sample summary data and many instruments, a bound-based analysis may be too uninformative to make meaningful conclusions about the ATE. Specifically, nonparametric bounds in usual one-sample settings data come with very nice guarantees, such as the width always being less than 1. But, in Mendelian randomization analyses with two-sample data, we lose the strong guarantees on the maximum width of the bounds and strong assumptions about the strength of the IV are often required to make sure that the width is less than 1. Even aggregating information from many instruments through simple intersections will only be as good as using a single strong instrument.

To make two-sample IV bounds more informative, we outline an approach to generate a plausible range of one-sample bounds that are in agreement with the two-sample data at hand. This gives us the opportunity 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 conclusions about the ATE that can be drawn from our method. This exercise also highlighted a significant loss of information in two-sample designs compared to one-sample designs. Finally, our two real data examples showed that despite having strong causal effects, a bound-based analysis was unable to detect this effect.

What does this mean for bound-based analysis in two-sample MR settings in practice? Broadly speaking, not much. The nonparametric nature and the two-sample design can make these bounds often meaningless in practice. Nevertheless, we believe there are still a few potential use cases of nonparametric 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 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 propensity of lung cancer. Second, two-sample IV bounds can be used to check estimates from parametric models to see if they are inside of the nonparametric IV bounds; if the estimates lie outside of the bounds, then most likely the models underlying the estimates are mis-specified.

A Logistic Models

When a GWAS is run to find associations between genetic markers and a binary trait, the logitisc 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 γ_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 [7] and Burgess and Thompson [10] 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.

B Bounds on Average Treatment Effect

We briefly review the method presented by Ramsahai [33] to bound the average treatment effect using two-sample summary data. Let $\vec{\tau}^* = (P(Y = 1|X = 0, U), P(Y = 1|X = 1, U), P(X = 1|Z = 0, U), \dots, P(X = 1|Z = k - 1, U)) \in [0, 1]^{2+k}$ and $\vec{v}^* = (P(Y = 0|Z = 0, U), \dots, P(Y = 1|Z = k - 1, U), P(X = 0|Z = 0, U), \dots, P(X = 1|Z = k - 1, U), \alpha^*)$ 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 $\vec{v} = E_U[\vec{v}^*] = (P(Y = 0|Z = 0), \dots, P(Y = 1|Z = k - 1), P(X = 0|Z = 0), \dots, P(X = 1|Z = k - 1), \alpha)$, 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 [33], $\mathcal{H} = \hat{\mathcal{H}}$. 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 α . Others will not be verifiable, but will allow us to obtain bounds on the unobservable quantity α 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.

Table 3: 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 , as presented in (B), to each row, we get the most extreme vertices of $P(X = x|Z = z, U)$ and $P(Y = y|Z = z, U)$ for all $x = 0, 1$, $y = 0, 1$ and $z = 0, 1, 2$.

Table 4: 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	α
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	α
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 Table 4. 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 α 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 $\sum_{z=0}^2 c_{X1Zz} \cdot P(X = 1|Z = z) + \sum_{z=0}^2 c_{Y0Zz} \cdot P(Y = 0|Z = z) + c_{Y1Z0} \cdot P(Y = 1|Z = 0) + c_\alpha \alpha \geq 0$.

Table 5: Results from polymake. Columns with all zeroes have been removed.

PY0Z0	PY0Z1	PY0Z2	PY1Z0	PX1Z0	PX1Z1	PX1Z2	c_α
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

PY0Z0	PY0Z1	PY0Z2	PY1Z0	PX1Z0	PX1Z1	PX1Z2	c_α
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

PY0Z0	PY0Z1	PY0Z2	PY1Z0	PX1Z0	PX1Z1	PX1Z2	c_α
-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

PY0Z0	PY0Z1	PY0Z2	PY1Z0	PX1Z0	PX1Z1	PX1Z2	c_α
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 $\alpha = 0$:

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

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.

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

$$\leq ATE \leq$$

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

C Exploration of Scenarios Where Bounds are Flipped

Of 10,000 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). Table 6 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 trivariate to bivariate bounds, but later realized similar scenarios arise when dealing with trivariate 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 trivariate 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. Table 7 show the bounds from these trivariate 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.

Table 6: 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	
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	
62	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	

Table 6: 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
30	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

Table 6: 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
0.9294752	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

Table 6: 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
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

Table 6: 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

Table 6: 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
34	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

Table 7: 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

Table 7: 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

D Proof of Theorem 2.1

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

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

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

Width = U1 - L1

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

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

Width = U2 - L1

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

Width = U3 - L1

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

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

Width = U1 - L2

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

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

Width = U2 - L2

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

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

Width = U3 - L2

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

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

Width = U1 - L3

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

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

Width = U2 - L3

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

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

Width = U3 - L3

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

$1 - P(X = 0|Z = 0) \geq P(Y = 1|Z = 0)$. Therefore,

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

E Simulation Setup and Results for Section 2.3

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 Appendix A 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) . 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 $\text{ATE} = P(Y = 1|X = 1) - P(Y = 1|X = 0)$.

Table 8: The monte carlo integration was performed for all combinations of values of the coefficients γ_1, γ_U , and β_1 presented below.

β_1	γ_1	γ_U
0.25, 0.5, 1, 1.5, 2	0.25, 0.5, 1, 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 Figure 5 together with the ATE. Figure 1a shows the width of these bounds plotted against ST, while Figure 1b shows the values of γ_1 plotted against ST.

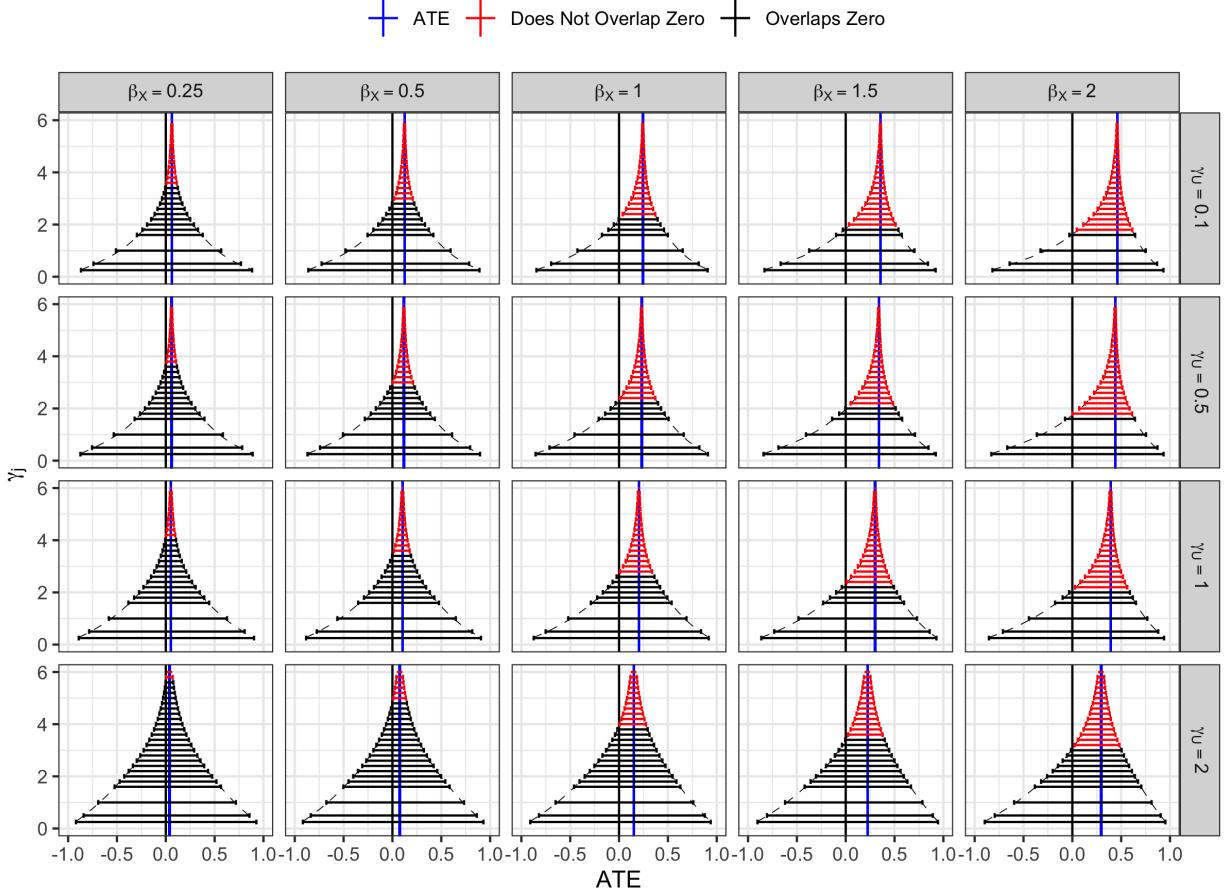


Figure 5: Bounds based on simulations as described in Section 2.3. Upper and lower bounds are connected a curve based on a loess extrapolation. This curve is used to find the smallest coefficients needed to detect direction as plotted on Figure 2.

To find the smallest value of γ_1 that results in bounds excluding 0, we fit a loess curve to the lower bounds in Figure 5, and find the value where this curve crosses 0. This results in the values depicted on Figure 2.

F 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. $z_i \in \{0, 1, 2\}$ represents the i th instrument, and γ_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. β_1 is set to be either 0.25, 0.5, 1,

1.5, or 2. We then consider four scenarios for setting the γ_i 's:

1. *Many weak instruments:* γ_i are spread out evenly on the interval 0 to 0.2.
2. *Many strong instruments:* γ_i are spread out evenly on the interval 1 to 4. This is the magnitude of γ s that detected the direction of the ATE in the previous section
3. *Many very weak instruments, one medium strength instrument:* γ_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:* γ_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 [28, 39, 31]. The third scenario represents a genetic architecture where only few genetic variants have strong effects on the exposure while others have weak effects [48]. 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 2.3 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 Appendix E. We then use these quantities to obtain two-sample IV bounds for each of the p instruments. Figures 7, 8, 9, and 10 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 γ_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 Figure 3c 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 2.3 with a single instrument with $\gamma_i = 4$ and our results in this section where one of the instruments has $\gamma_i = 4$, but others have much smaller γ 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, Figure

3d 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 included. 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 [43], 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 2.3, 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. As discussed in Section 2.3, a primary reason for the non-informative nature of the IV bounds in two-sample settings is that we don't have information about the joint distribution of X, Y given Z . While obtaining this joint distribution is generally difficult in many MR studies, in the next section, we discuss how to obtain a plausible range of the joint distribution $P(Y, X|Z)$ given two sample MR data $P(Y|Z)$ and $P(X|Z)$ in order to create more informative bounds from two-sample MR studies.

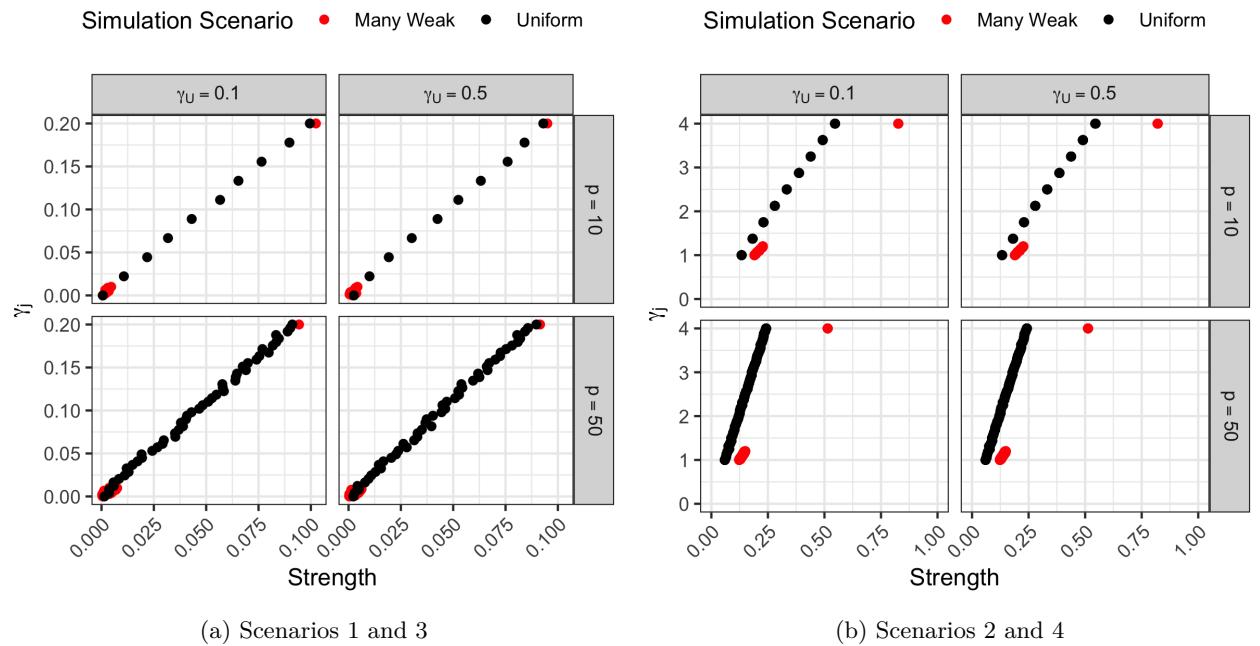


Figure 6: Figure showing the dilution effect described in Section F in each of the four scenarios. When p is larger, similar sized coefficients lead to lower strength. The effect is smaller when we are in a scenario where one coefficient is relatively much larger than the rest, rather than when the coefficients are evenly spread out.

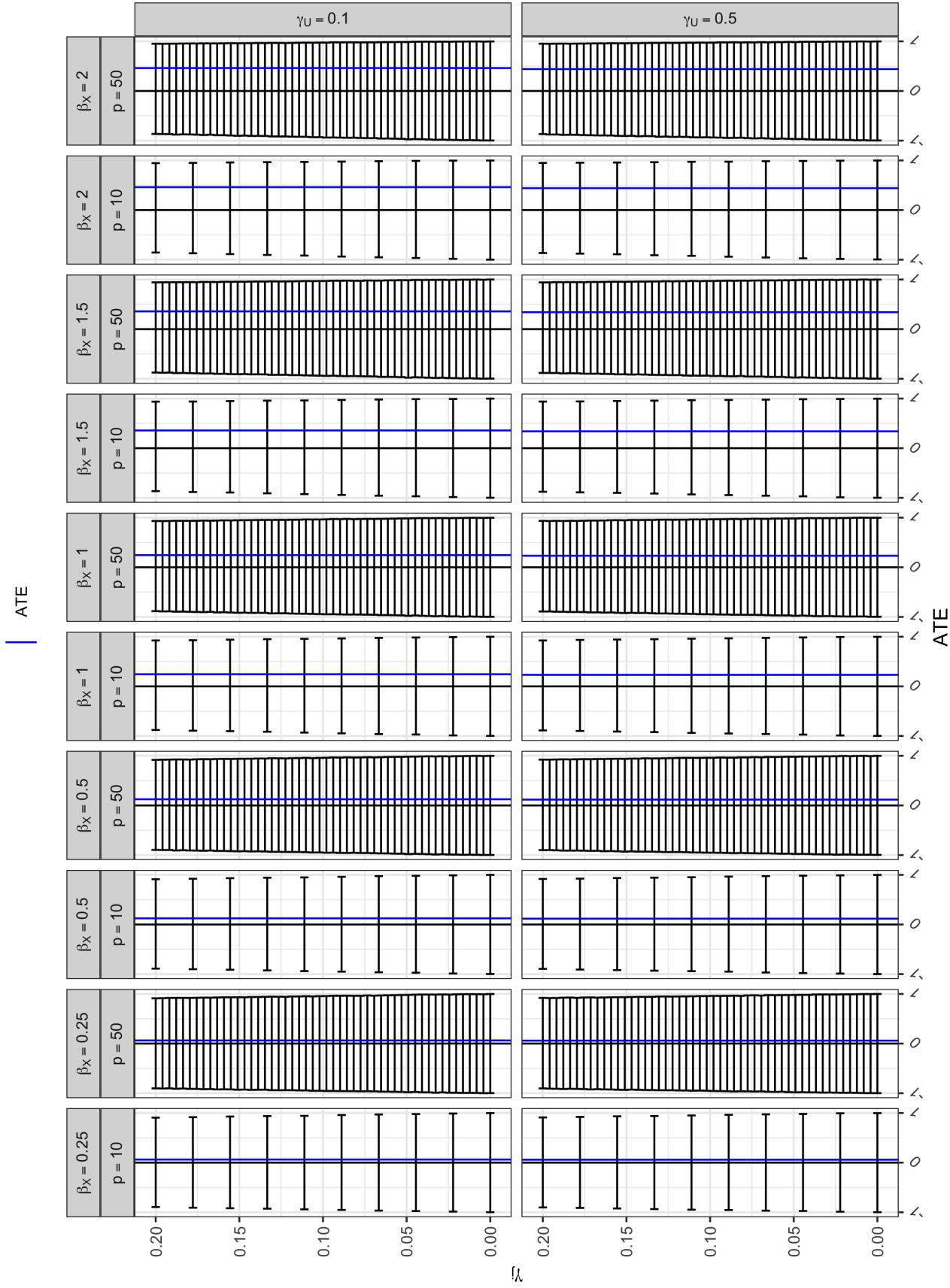


Figure 7: Bounds based on monte carlo integration with 1,000,000 resamples in scenario 1.

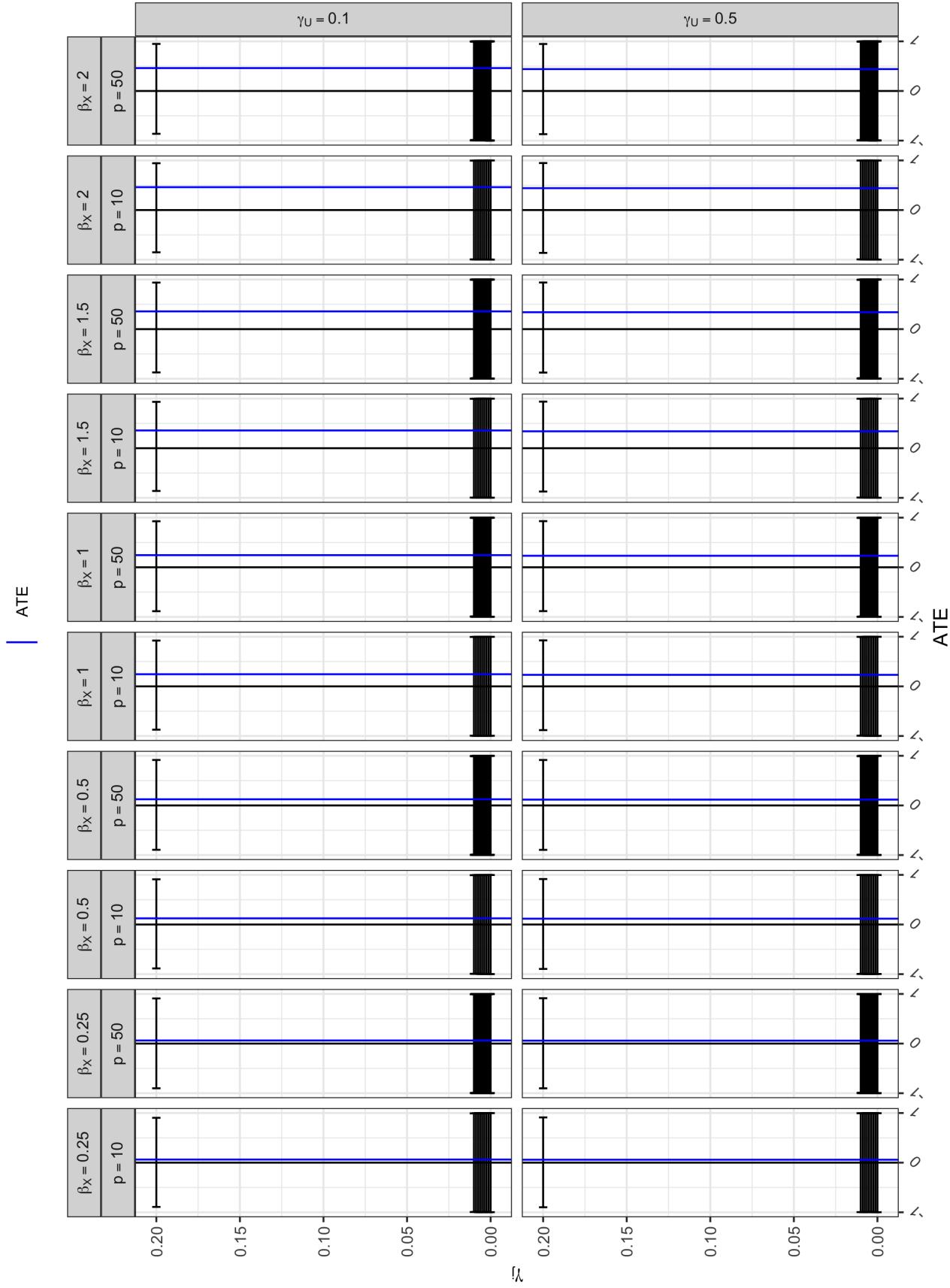


Figure 8: Bounds based on monte carlo integration with 1,000,000 resamples in scenario 3.

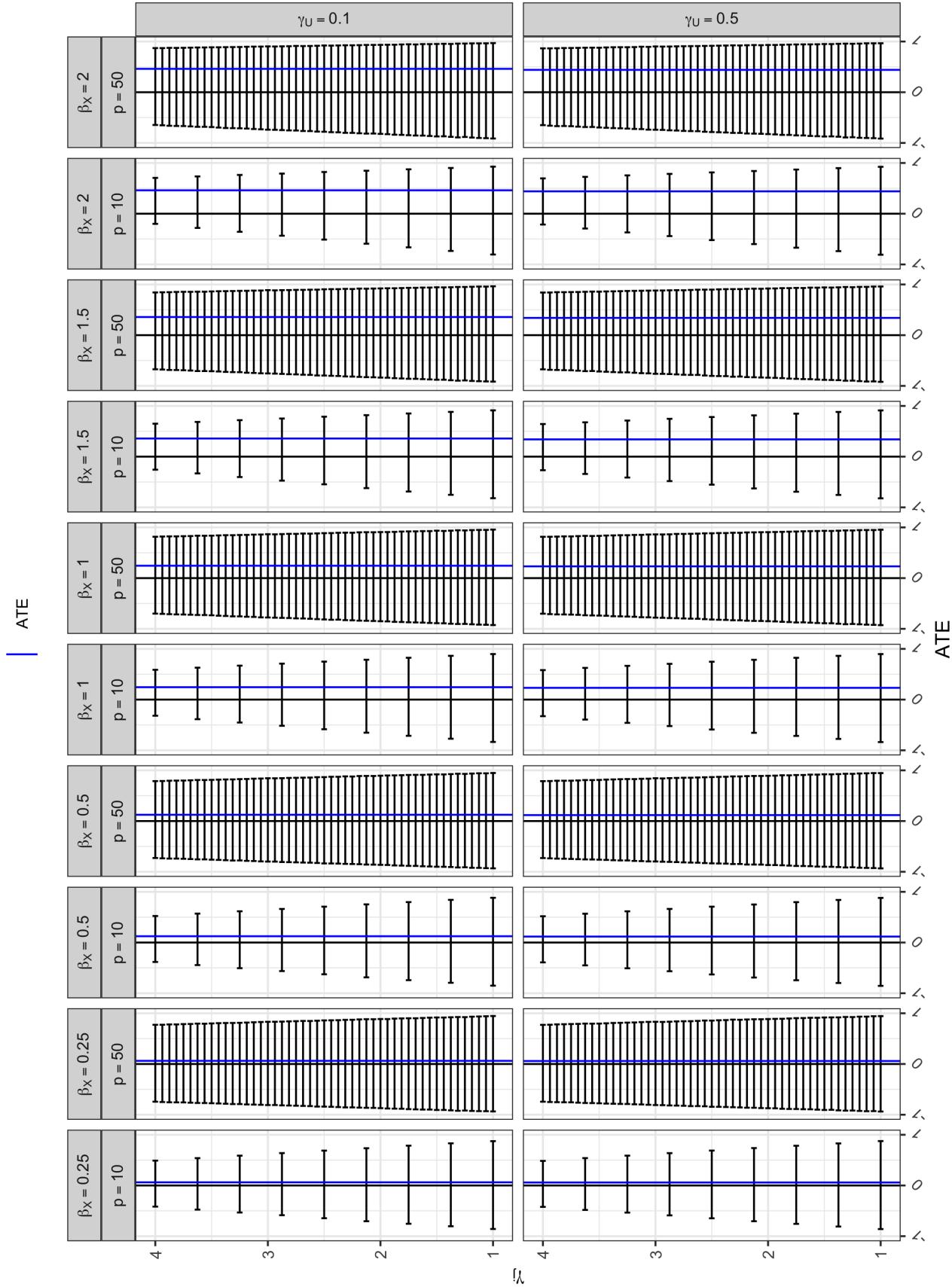


Figure 9: Bounds based on monte carlo integration with 1,000,000 resamples in scenario 2.

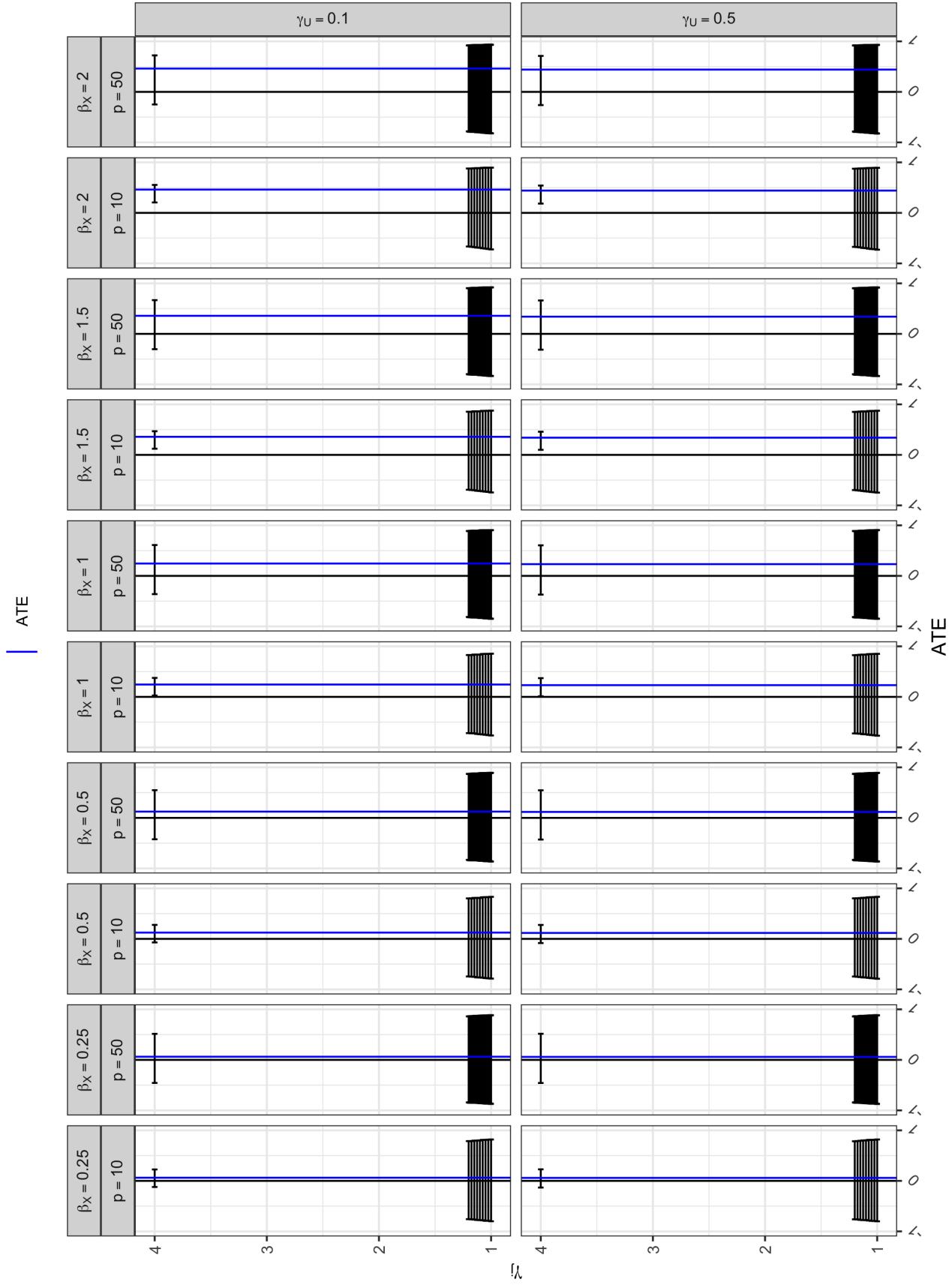


Figure 10: Bounds based on monte carlo integration with 1,000,000 resamples in scenario 4.

G 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 (3) from the IV assumptions. 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 $\max_x \sum_y \max_z P(X = x, Y = y|Z = z)$, 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

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

$$\leq \text{Cov}(X, Y|Z = z_1) - \text{Cov}(X, Y|Z = z_2) \leq$$

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

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 plus the existing constraints in (3) 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 [34] 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.

H 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.

I Additional Summary Statistics and Figures for Analyses Presented in Section 3

We use the `TwoSampleMR` R package [23] 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 β_0 and γ_0 , respectively. Overall, we have estimates of $P(Y = 1|Z_j = z)$ and $P(X = 1|Z_j = z)$ for every j and $z = 0, 1, 2$.

I.1 Effect of Smoking on Lung Cancer

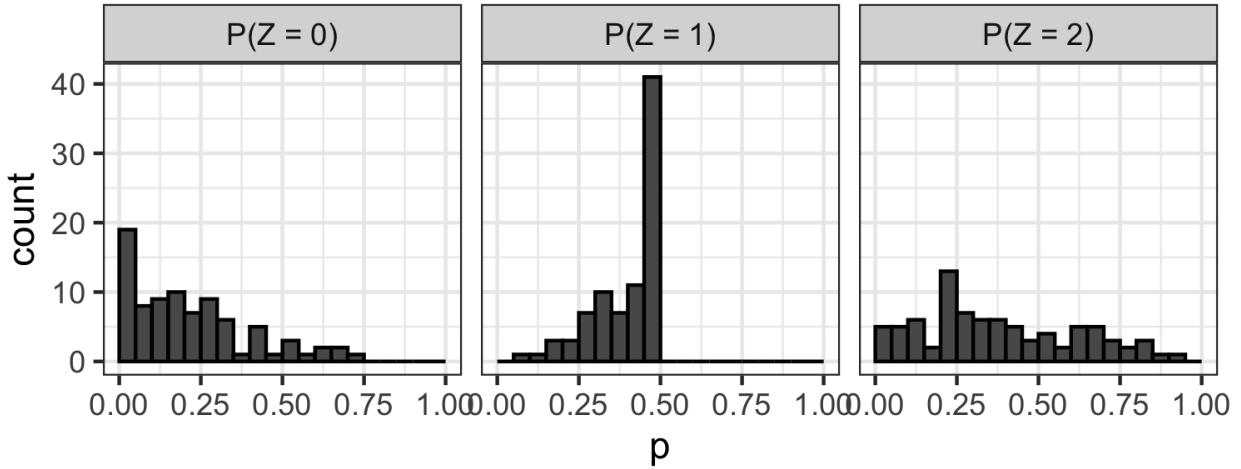


Figure 11: Histograms of the marginal distribution of instruments, $P(Z = z), z = 0, 1, 2$, estimated after preprocessing for analysis in Section ??.

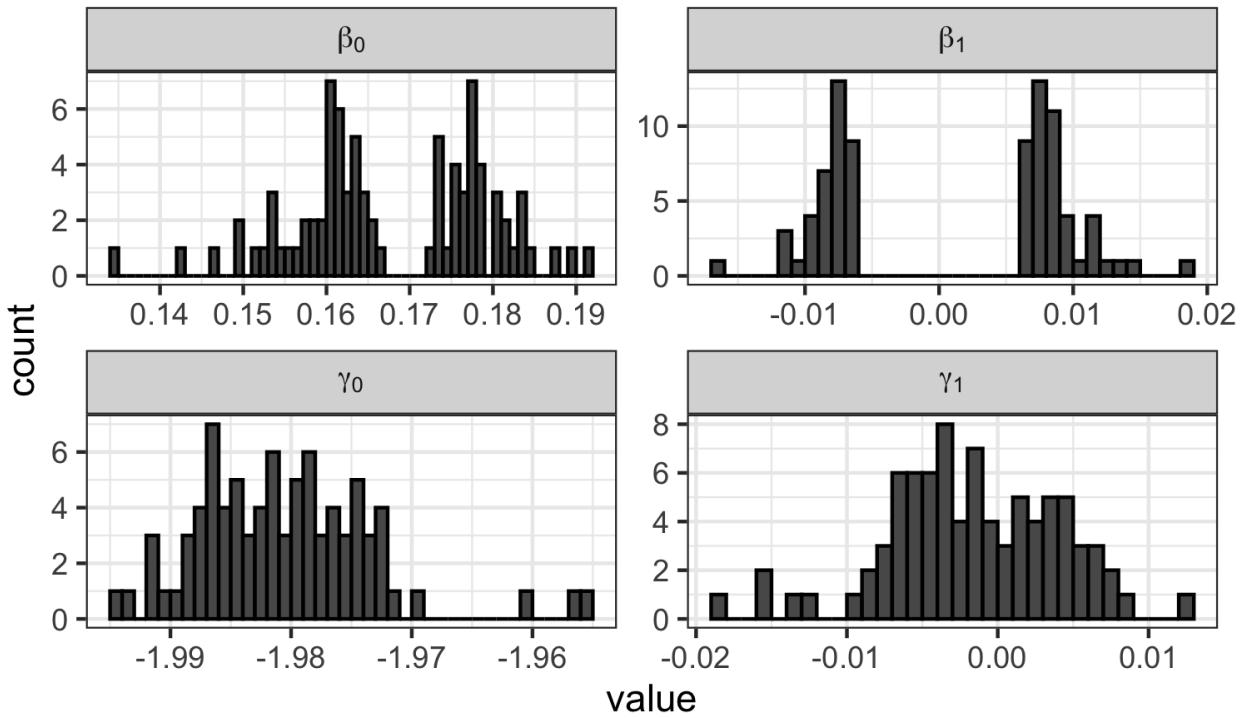


Figure 12: Histograms of the coefficients from GWAS results of logistic regression of the SNPs on smoking status and lung cancer status. Intercepts (β_0 and γ_0) are inferred, while slopes (β_1 and γ_1) are as reported.

Table 9: Coefficients from GWAS results of logistic regression of the SNPs on smoking status and lung cancer status. Intercepts (β_0 and γ_0) are inferred, while slopes (β_1 and γ_1) are as reported.

SNP	β_1	β_0	γ_1	γ_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
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

Table 9: Coefficients from GWAS results of logistic regression of the SNPs on smoking status and lung cancer status. Intercepts (β_0 and γ_0) are inferred, while slopes (β_1 and γ_1) are as reported. *(continued)*

SNP	β_1	β_0	γ_1	γ_0
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
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

Table 9: Coefficients from GWAS results of logistic regression of the SNPs on smoking status and lung cancer status. Intercepts (β_0 and γ_0) are inferred, while slopes (β_1 and γ_1) are as reported. *(continued)*

SNP	β_1	β_0	γ_1	γ_0
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
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

Table 9: Coefficients from GWAS results of logistic regression of the SNPs on smoking status and lung cancer status. Intercepts (β_0 and γ_0) are inferred, while slopes (β_1 and γ_1) are as reported. *(continued)*

SNP	β_1	β_0	γ_1	γ_0
rs9487626	0.0131029	0.1648247	-0.0136868	-1.978168
rs9835772	-0.0078024	0.1814198	-0.0031275	-1.978401

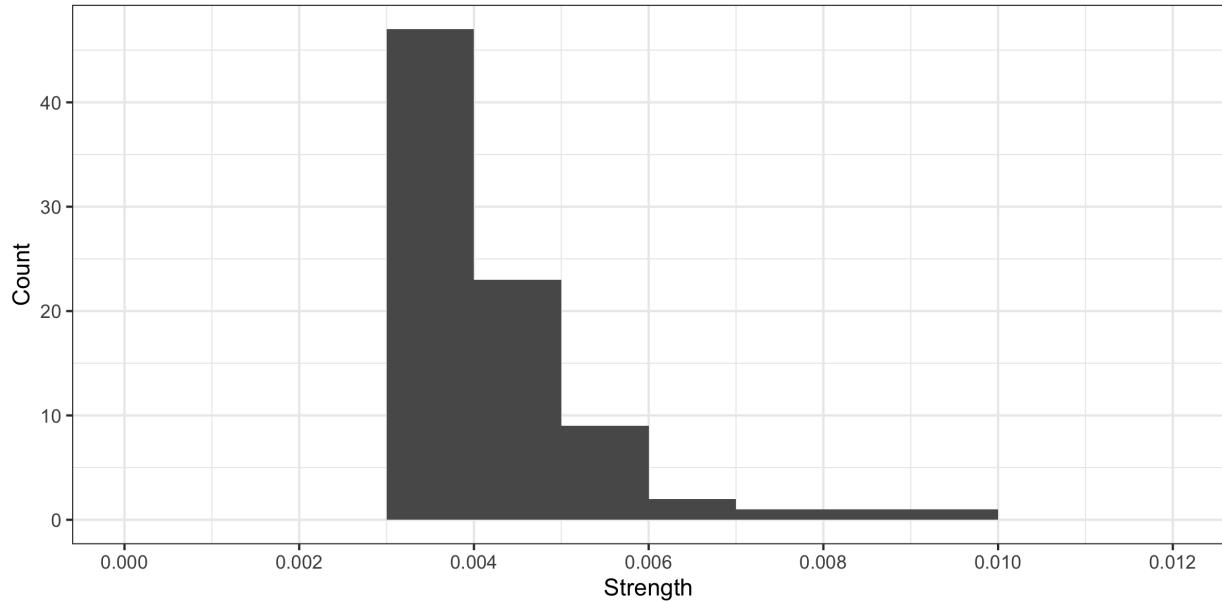


Figure 13: Histogram of strengths of IVs on the exposure. Here, SNPs are IVs, and smoking status (ever/never) is exposure. We see that all IVs are very weak, with the largest value just below 0.01.

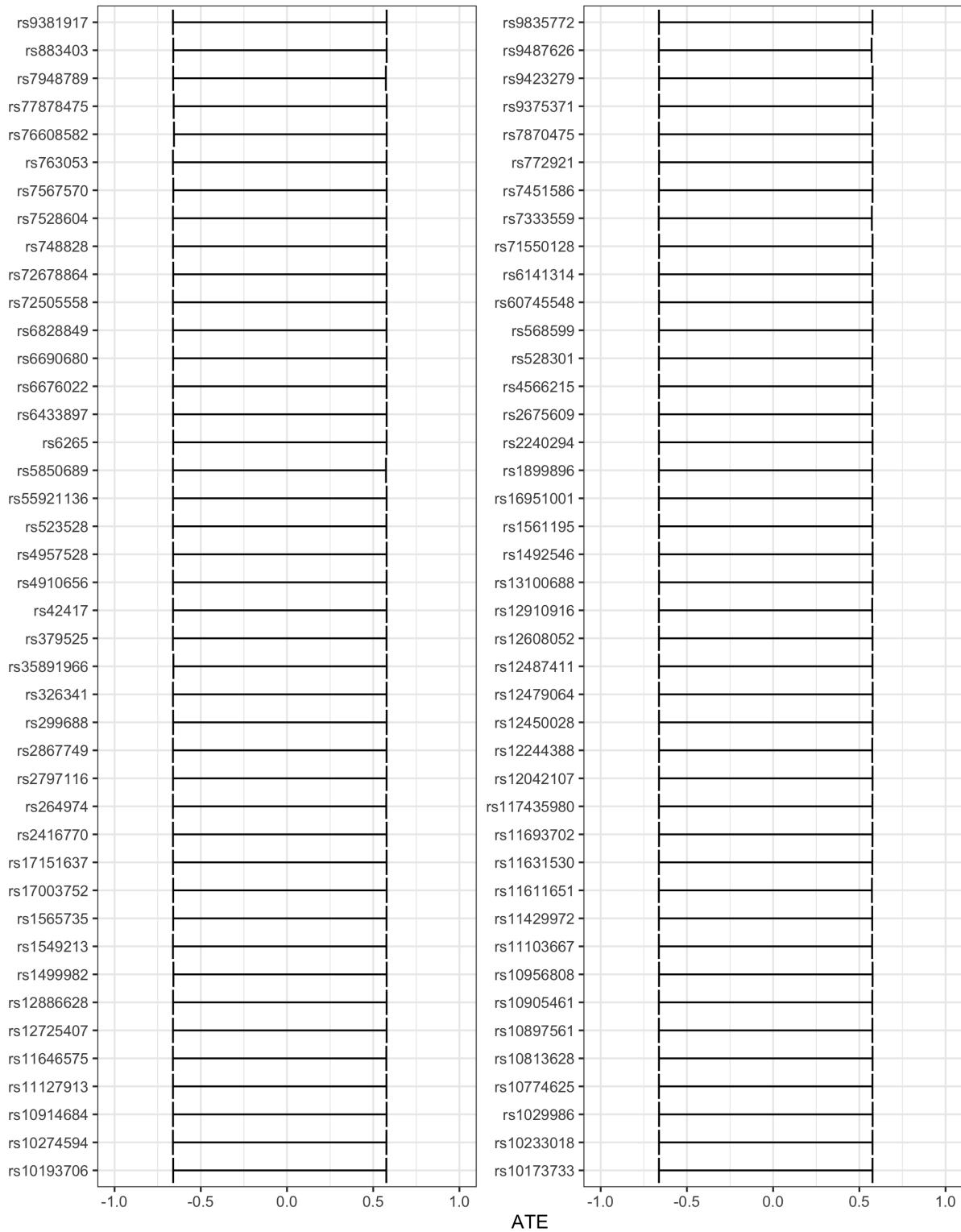


Figure 14: Nonparametric two-sample IV bounds on the average treatment effect of smoking on the incidence of lung cancer.

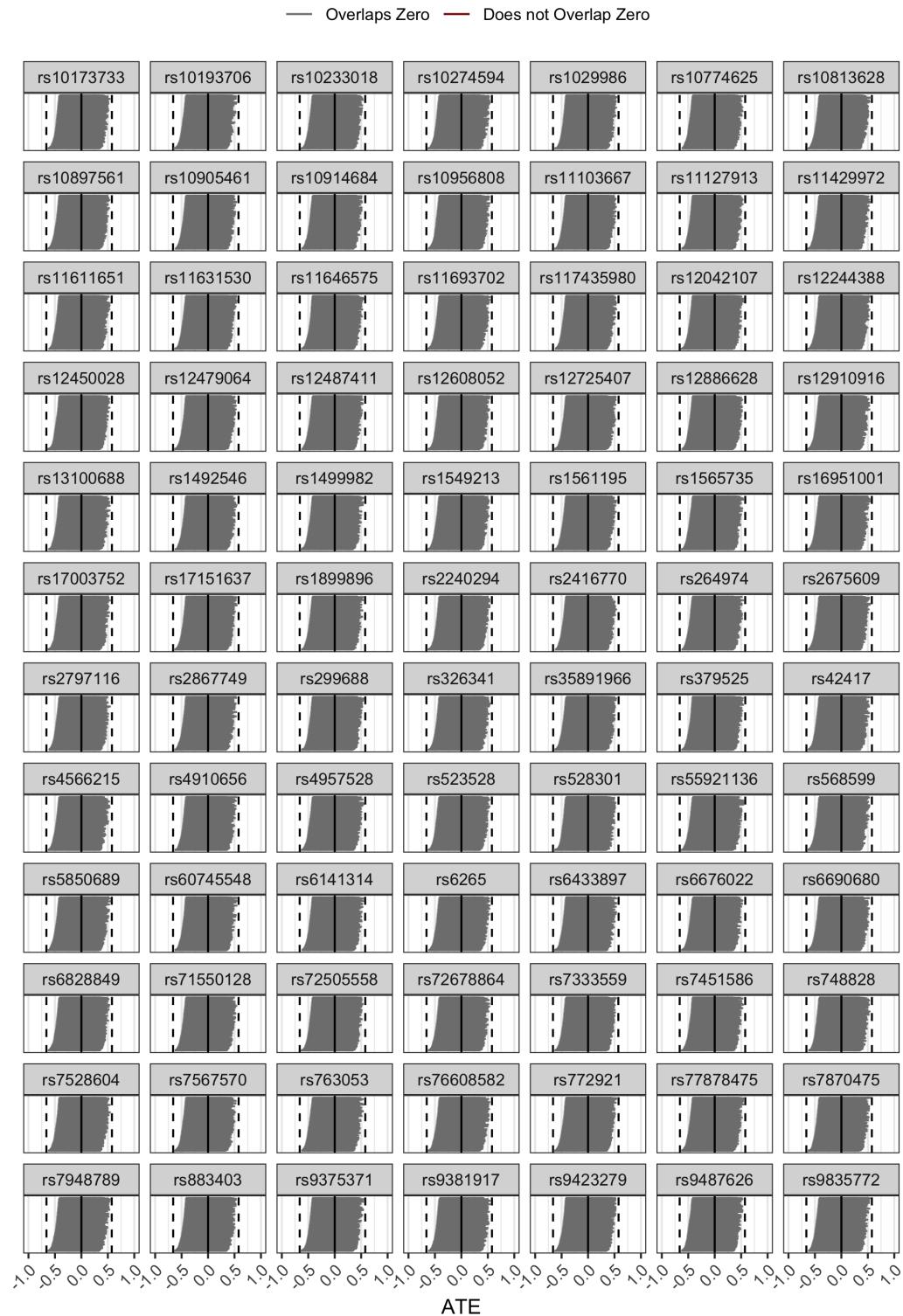


Figure 15: 500 sets of bounds of the average treatment effect of smoking on lung cancer for each of the 84 SNPs. Each bound is based on a set of values for the trivariate distribution randomly sampled. Bounds are color coded to show if they overlap 0 (grey) or do not (red). All bounds overlap 0.

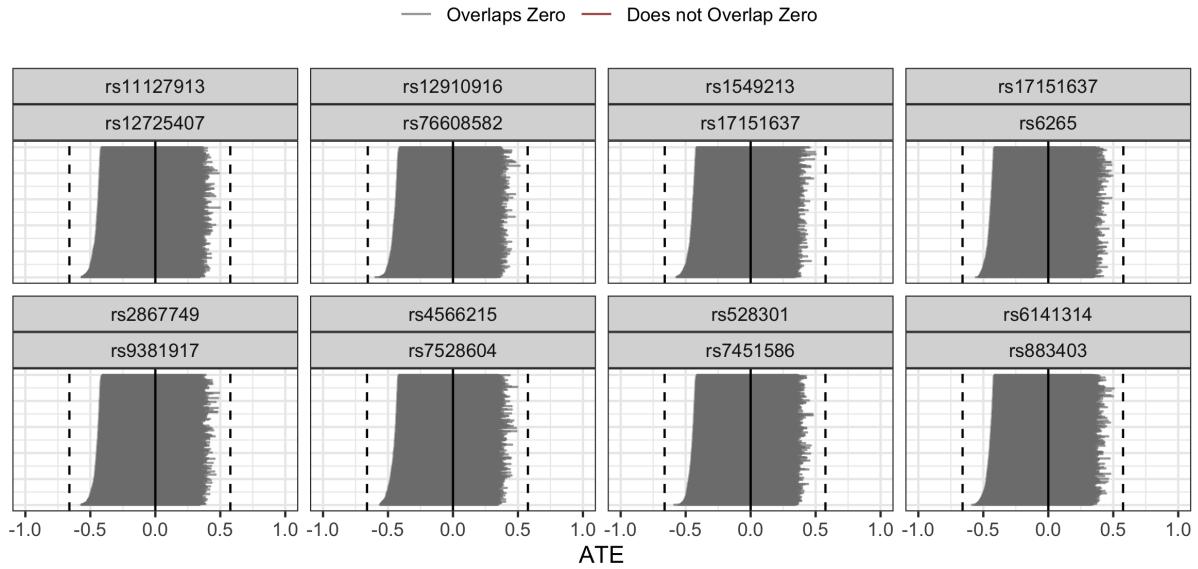


Figure 16: Intersection bounds of the average treatment effect of smoking on lung cancer based on randomly sampled trivariate distributions from pairs of SNPs. These 8 pairs were randomly chosen from all possible pairs.

I.2 Effect of High Cholesterol on Heart Attack

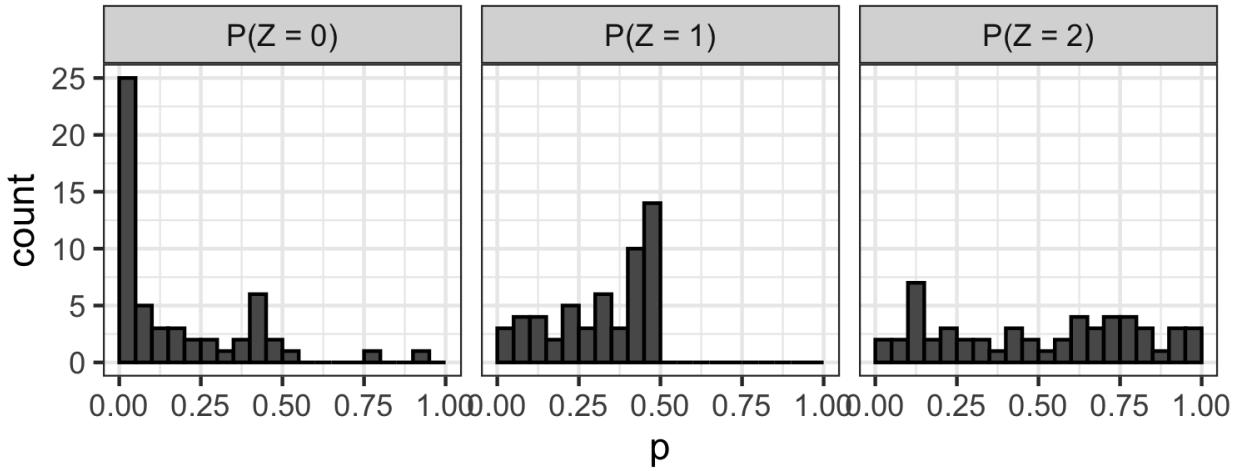


Figure 17: Histograms of the marginal distribution of instruments, $P(Z = z)$, $z = 0, 1, 2$, estimated after preprocessing for analysis in Section ??

Table 10: Table of the marginal distribution of instruments, $P(Z = z), z = 0, 1, 2$, estimated after pre-processing for analysis in Section ??

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

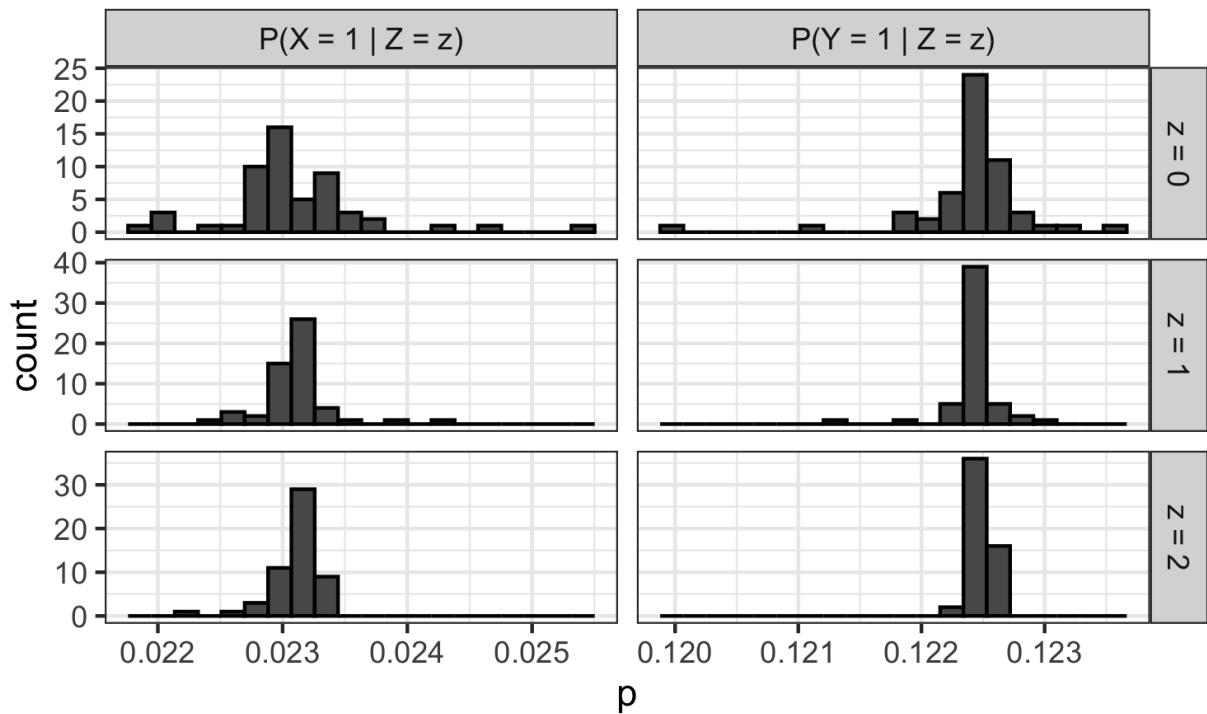


Figure 18: Histograms of the marginal conditional probabilities $P(X = 1 | Z = z), z = 0, 1, 2$ and $P(Y = 1 | Z = z), z = 0, 1, 2$.

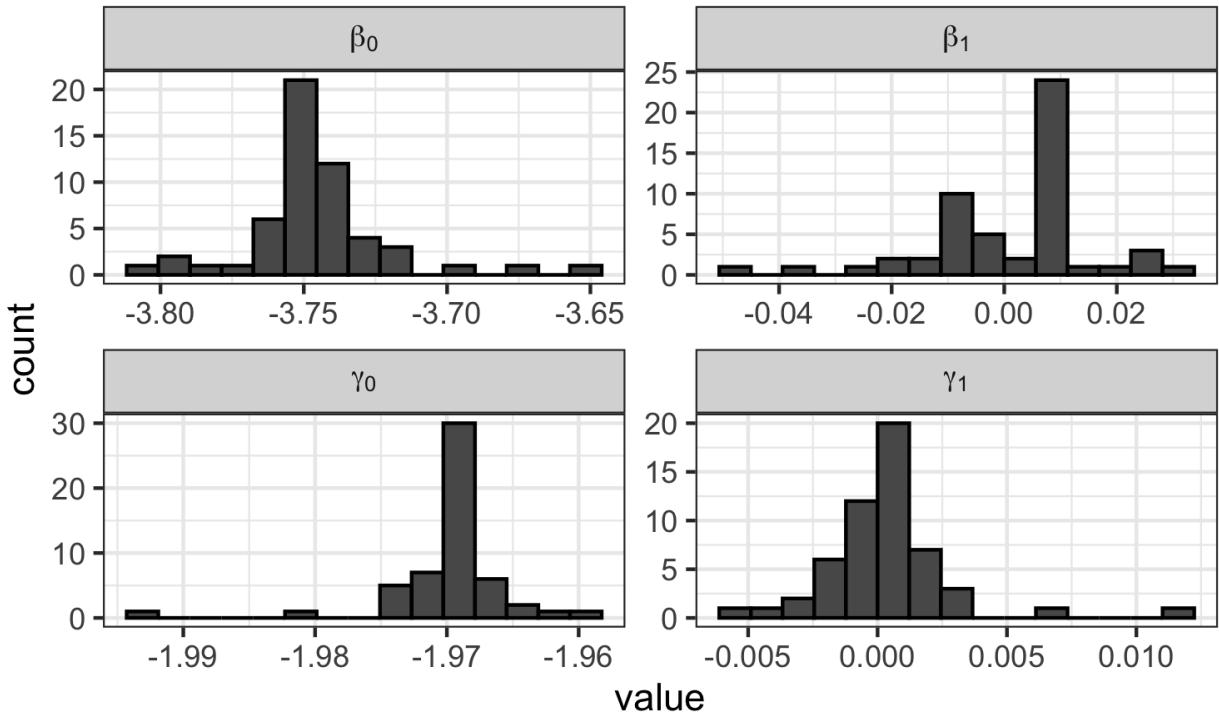


Figure 19: Histograms of the coefficients from GWAS results of logistic regression of the SNPs on high cholesterol and heart attack, respectively. Intercepts (β_0 and γ_0) are inferred, while slopes (β_1 and γ_1) are as reported.

Table 11: Coefficients from GWAS results of logistic regression of the SNPs on high cholesterol and heart attack status. Intercepts (β_0 and γ_0) are inferred, while slopes (β_1 and γ_1) are as reported.

SNP	β_1	β_0	γ_1	γ_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

Table 11: Coefficients from GWAS results of logistic regression of the SNPs on high cholesterol and heart attack status. Intercepts (β_0 and γ_0) are inferred, while slopes (β_1 and γ_1) are as reported. *(continued)*

SNP	β_1	β_0	γ_1	γ_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

Table 11: Coefficients from GWAS results of logistic regression of the SNPs on high cholesterol and heart attack status. Intercepts (β_0 and γ_0) are inferred, while slopes (β_1 and γ_1) are as reported. *(continued)*

SNP	β_1	β_0	γ_1	γ_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

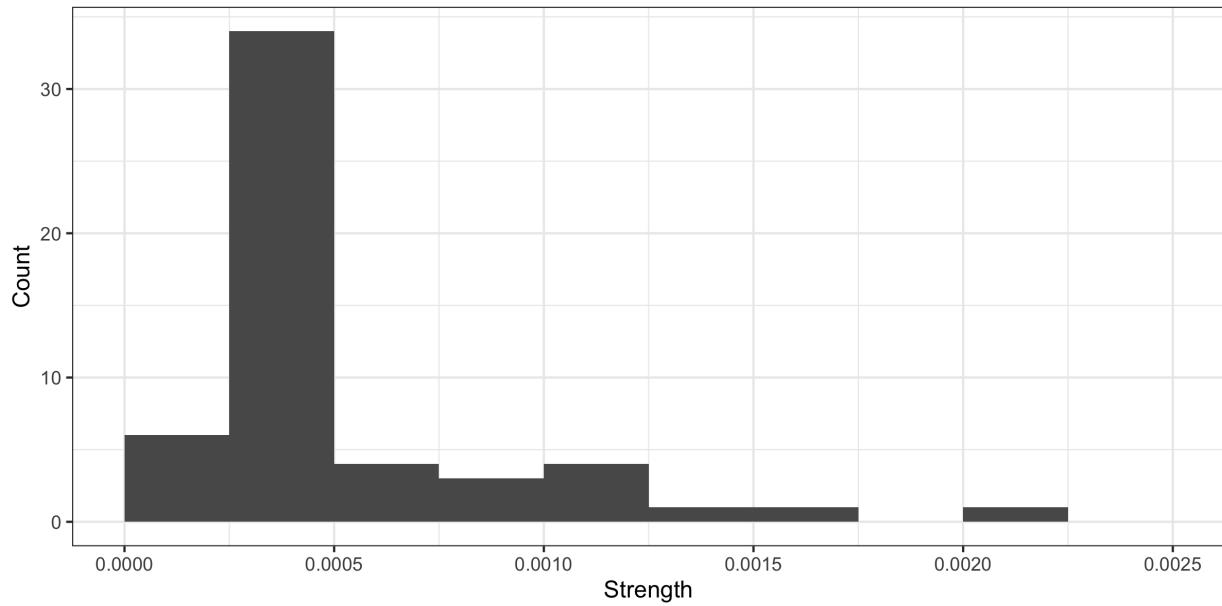


Figure 20: Histogram of strengths of IVs on the exposure. Here, SNPs are IVs, and high cholesterol is the exposure. We see that all IVs are very weak, with the largest value below 0.00225.

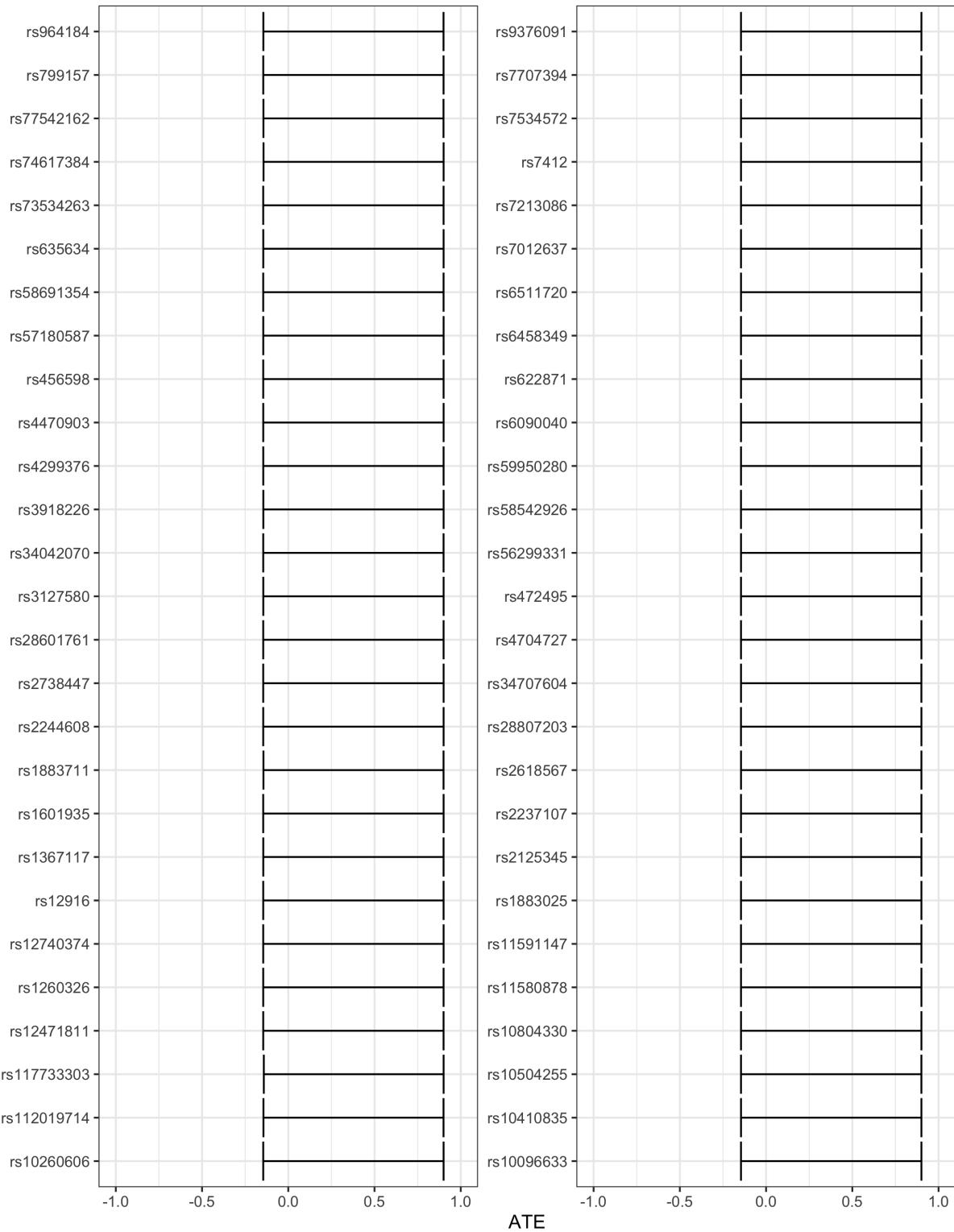


Figure 21: Nonparametric two-sample IV bounds on the average treatment effect of high cholesterol on the incidence of heart attack.

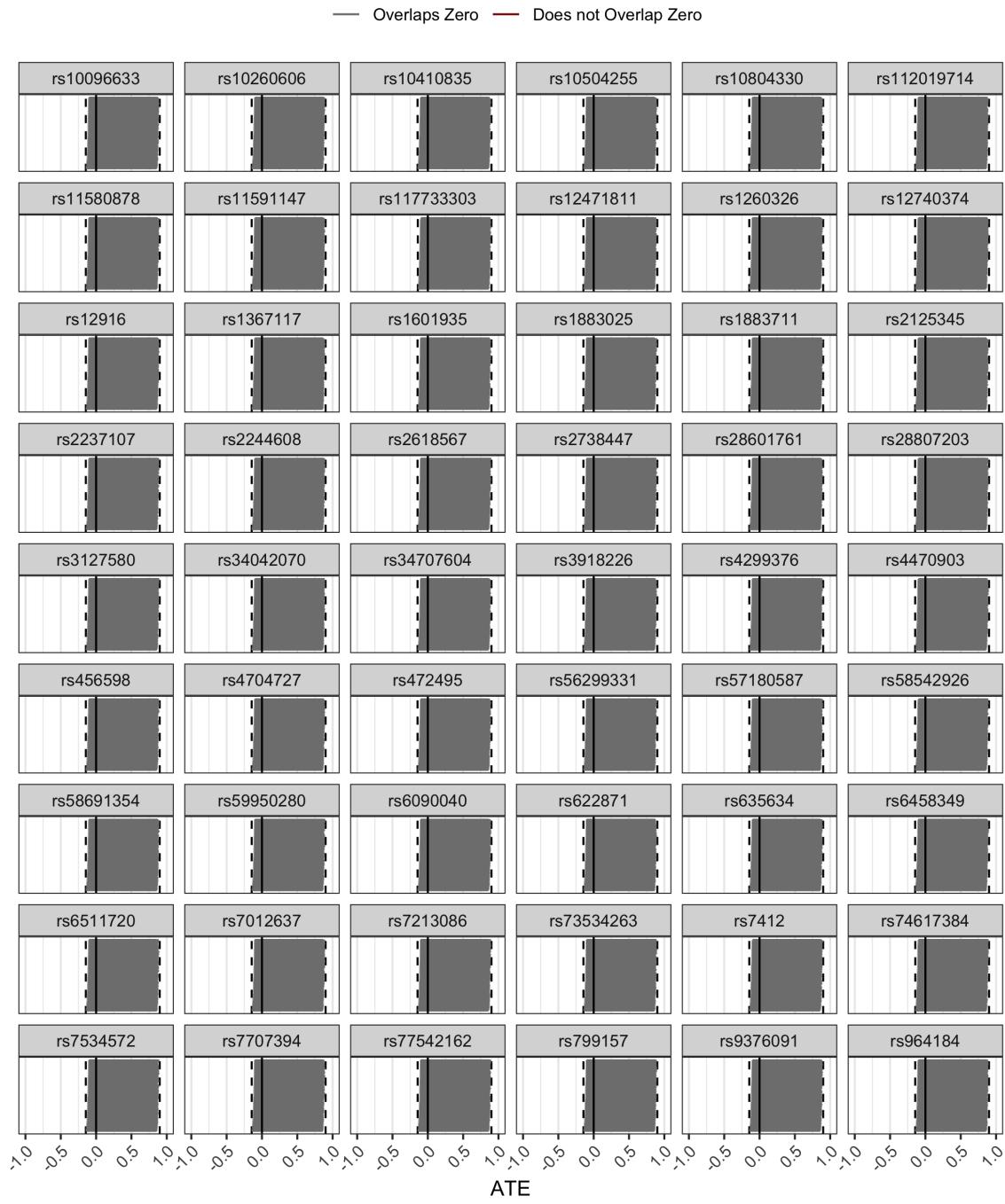


Figure 22: 500 sets of bounds of the average treatment effect of high cholesterol on heart attack for each of the 54 SNPs. Each bound is based on a set of values for the trivariate distribution randomly sampled. Bounds are color coded to show if they overlap 0 (grey) or do not (red). All bounds overlap 0.

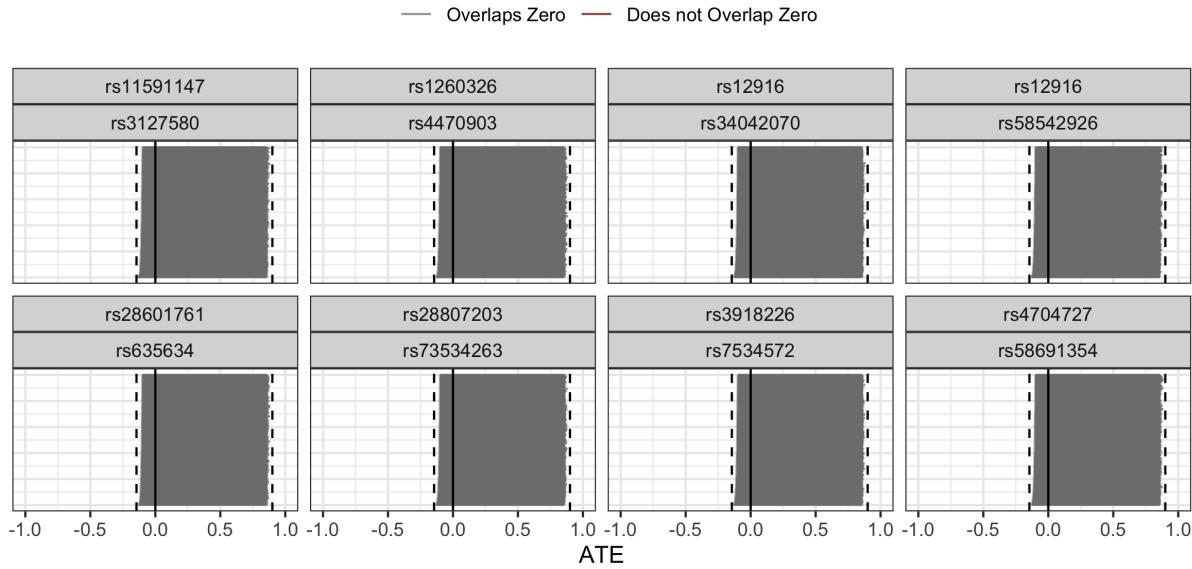


Figure 23: Intersection bounds of the average treatment effect of high cholesterol on heart attack based on randomly sampled trivariate distributions from pairs of SNPs. These 8 pairs were randomly chosen from all possible pairs.

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