Bounds in Two-Sample Mendelian Randomization With Summary Statistics

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1 Introduction

The gold standard to estimate the causal effect of a treatment or an exposure on an outcome is a randomized experiment. However, in many epidemiological studies, randomized experiments are not feasible. For example, a study estimating the negative effects of smoking on depression [Wootton et al., 2019] with a randomized experiment would not be feasible due to ethical concerns. As an alternative to randomized experiments, recently, there has been an increase in using instrumental variable (IV) in the form of Mendelian randomization (MR) to deduce causal effects [Davey Smith and Ebrahim, 2003, Lawlor et al., 2008]. Briefly, IV is a variable that is (A1) associated with the exposure, (A2) is independent from unmeasured confounders affecting the exposure and the outcome, and (A3) affects the outcome only through its effect on the exposure; see **??** for details. MR uses genetic variants, usually single nucleotide polymorphisms and encoded as 0, 1, or 2, as instruments due to an idea that genotypes are randomly assigned when passed on from parents to offspring by meiosis and thus, possibly satisfying (A2). For additional discussions on the plausibility of assumptions (A1)-(A3) in MR, see Lawlor et al. [2008], Didelez and Sheehan [2007], cite https://pubmed.ncbi.nlm.nih.gov/28114746/, and references within.

Data from MR studies often consist of published summary statistics from two independent genome wide association studies (GWAS), often referred to as the two-sample setting [Burgess et al., 2013, 2015, Davies et al., 2018]. Typically, the first GWAS provides information about the exposure and instrument and the second GWAS provides information about the outcome and instrument. With the summary statistics from two studies, investigators often use parametric methods to arrive at estimates and tests for the exposure effect. Examples of such estimators and test are the IVW estimator [Burgess et al., 2013], MR-Egger regression [Bowden et al., 2016b], weighted median [Bowden et al., 2016a] and modes [Hartwig et al., 2017], and MRRAPs [Zhao et al., 2020], to name a few; see Burgess and Thompson [2015] and Burgess et al. [2017] for recent reviews.

An alternative approach to study the exposure effect without parametric assumptions is through non-parametric IV bounds [Balke and Pearl, Cheng and Small, 2006, Manski, 1990, Richardson and Robins, 2014, Robins, 1989]. Briefly, nonparametric IV bounds only use a minimum set of amount of assumptions, usually (A1)-(A3), 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 in MR. The most well-known are the Balke-Pearl bounds [Balke and Pearl] for the average treatment effect under slight variants of assumptions (A1)-(A3). Also, the conditions underlying these bounds lead to a set of instrumental inequalities to falsify the IV assumptions. Since then, Cheng and Small [2006] and Richardson and Robins [2014] extended the Balke-Pearl bounds to allow for a non-binary instrument. Ramsahai [2012] derived bounds for the two-sample setting. Palmer et al. [2018] provides software to compute IV bounds for two-sample MR studies using only summary statistics. For a recent overview, see Swanson et al. (2018). make sure to bibtex Swanson's reference.

Due to their nonparametric nature, IV bounds have been attractive alternatives in non-MR, one-sample settings to analyze treatment effects, especially in settings where some parametric assumptions are suspect or difficult to justify. More generally, if IV bounds using fewer assumptions arrive at similar conclusions about the treatment effect as those based on parametric approaches, the case for the treatment effect becomes stronger. But, there is little work on understanding about the behavior of IV bounds in MR settings where we have summary statistics from two samples. For example,

1. What kind of genetic instruments are needed in two-sample MR studies to provide useful conclusions about the exposure effect, say the bound does not contain the null effect?
2. Can combining multiple genetic instruments from GWAS lead to shorter and tighter bounds on the exposure effect?
3. How do the bounds change if many instruments have weak association with the exposure, which is typically in MR studies where genetic variants only explain a small amount of variation in the exposure?

In one sample setups where individual-level data are available, the Balke-Pearl bounds are known to be wide,

often containing the null effect; Balke and Pearl check this, I forget which pearl paper mentions this... showed that the width of the bound decrease linearly with the magnitude of the instrument's association to the exposure. However, it is not clear if the same principle holds for two-sample MR studies. The goal of the paper is to characterize the behavior of these bounds, specifically addressing what can be learned from MR studies that choose to use non-parametric IV bounds to analyze the exposure effect.

The paper is divided as follows. Section **??** Fill this after done.

2 Setup

2.1 Review: Notation and Definitions

Let X and Y be a binary exposure and outcome, respectively, Z be a categorical instrumental variable taking values in {0, 1, and 2}, and U an unmeasured confounder for the effect of X on Y. No assumptions about the structure of U are made. Let $Y^{z,x}$ be the potential outcome [Rubin, 1974, Splawa-Neyman et al., 1990] had the subject received exposure value $X = x$ and instrument value $Z = z$. Throughout the paper, we assume the stable unit treatment value assumption (SUTVA) [Cox, 1958, Rubin, 1980], formalized as $Y = \sum_{x,z} I[Z = z, X = x]Y^{x,z}$ and $I[\cdot]$ 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 [2007], Lawlor et al. [2008], and Wang and Tchetgen [2018] 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, assumption (A1) states that the SNP must be associated with the exposure and can be assessed by finding a SNP that has been consistently associated with the exposure through multiple GWAS convert to bibtex (Marigorta et al. 2018). Assumption (A2) states that the SNP is randomly assigned and is usually checked based on scientific theory surrounding how the genetic variant was inherited to the offspring. Assumption (A3) states that there is no direct effect of the instrument Z on the outcome Y other than that through the exposure X and like assumption (A2), is assessed by scientific theory. Both assumptions (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 the unmeasured confounder U, if observed, is sufficient to unconfound the relationship between X and Y.

We make a few additional remarks about assumptions (A1)-(A4). First, most MR studies only make assumptions (A1)-(A3) and some parametric modeling assumptions [Burgess and Thompson, 2015]. 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 [2014] 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 [Didelez and Sheehan, 2007]. Fourth, for simplicity, we do not assume the the existence of a potential treatment X^z; the existence of X^z does not change the IV bounds [Swanson et al., 2018, Richardson and Robins, 2014], and its primarily purpose is to define a "causal" instrument [Hern??n and Robins, 2006]. fix Hernan's name

We conclude by introducing two assumptions and defining instrument strength; the assumptions are not necessarily to construct bounds, but will help us explain the behavior of the IV bounds. First, we present 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 assumption (A5) is common in the IV literature to study noncompliance [Angrist et al., 1996, Baiocchi et al., 2014]. Assumption (A6) is an extension of assumption (A5) to the outcome variable. Assumptions (A5) or (A6) is plausible in MR if the direction of the effects of the genetic instrument on the exposure or the outcome are well-established from scientific theory.

Second, we define instrument strength as the maximum possible contrast of the exposure

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

The formula for ST reduces to the definition of instrument strength used in Balke and Pearl when the instrument is binary. More importantly, in a binary IV setting, ST was used to characterize the width of the IV bounds. However, 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 et al. [2002] for an overview.

2.2 Review: MR/IV Study Designs and Target Estimand

For the purposes of studying IV bounds, we can 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 of (X, Z) and one providing information of (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. As mentioned in Section 1, the behavior of bounds under a one-sample design has been well-studied [Balke and Pearl, Richardson and Robins, 2014, Swanson et al., 2018]; we remark that these bounds can also be used when individual-level data are not available, but population summary statistics in the form of $P(Y = y, X = x|Z = z)$ for y, x, z are known.

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

Given the quantities $P(Y = 1|Z = z)$ 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)

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

Here, the second equality follows from SUTVA and assumptions (A3) and (A4). Since U is not observed, 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 [1989], Manski [1990], and Balke and Pearl [1995]. In two-sample designs, Ramsahai [2012] showed that under assumptions (A1)-(A4), the bounds for the ATE are

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

$$\leq ATE \leq$$

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

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

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

The inequalities in equation (2) are extensions of the "IV inequalities" of Balke and Pearl used to check the validity of the IV assumptions. Versions of these inequalities have been used in MR studies [Diemer et al., 2020] to check whether the genetic instruments satisfy the IV assumptions. In the Appendix, we provide some details on deriving equations (2.2) and (2) as well as numerically computing the bound using Polymake [Assarf et al., 2017]. We also discuss a minor, but important issue concerning ordering of the bounds in order to obtain "proper bounds", i.e. bounds where the lower bound is less than or equal to the upper bound. We believe this issue is pertinent among investigators who are using a linear-program based software to compute these bounds [Palmer et al., 2011], or investigators who are computing lower and upper bounds separately [Richardson and Robins, 2014].

The rest of the sections are devoted to studying the behavior of the bound in (2.2) under a variety of settings.

3 Properties of Bounds in Two-Sample Data

3.1 Bounds With One Instrument

We begin our investigation into the behavior of bounds in equation (2.2) when there is a single instrument. We are interested in whether we can gain any insights into the direction and magnitude of the ATE by examining the length of the bounds; wide bounds typically provide less information about the magnitude or the sign of the ATE compared to narrower bounds.

First, Theorem 3.1 shows the width of the ATE bound in equation (2.2) under a near-ideal MR study where all the assumptions (A1)-(A6) hold. That is, in addition to having some evidence in support of assumptions (A1)-(A4) that are needed to obtain the bound in equation (2.2), the investigator knows that the genetic instrument has a monotonic effect on the exposure and the outcome. The extra assumptions (A5)-(A6)

simplify the bound formula in equation (2.2) and allow us to characterize its width by instrument strength ST.

Theorem 3.1. *Under assumptions (A1)-(A6), the bounds for the ATE in* (2.2) *become*

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

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* $2 - 2 \cdot ST$*.*

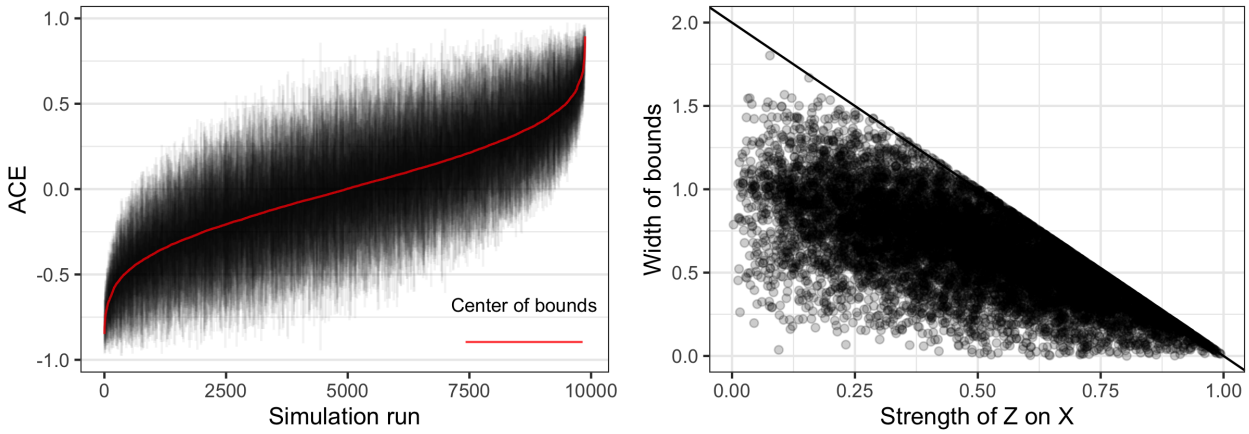
The proof is presented in Appendix A. The bounds under the near-ideal MR setting is up to twice as large as the Balke-Pearl bounds with a binary IV in one-sample designs where the width is $1 - \text{ST}$. An instrument with strength $\text{ST} = 0.6$ would lead to a smaller bound with width 0.4 under a binary IV, single-sample design setting compared to a length of up to 0.8 in the near-ideal MR study. The doubling of the bound is a "cost" of using two-samples instead of one-sample. In particular, two-sample designs do not provide any information about the joint distribution of $P(Y, X|Z)$, which can tighten the bounds; see Section 4 where we exploit this phenomena to obtain more informative bounds in MR studies.

Based on Theorem 3.1, the width of the IV bounds in two-sample settings is only guaranteed to be less than 1 when the instrument strength 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 since the bound will always cover zero. However, instruments with strength less than 0.5 could still generate a bound with width less than 1 (see Figure 1 for examples).

To 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 (2.2). This simulation mimics a scenario where there is a uniform/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 that can arise from MR studies. Figure 1 shows the bounds for 9,877; the remaining 123 were not proper bounds, meaning the lower bounds were greater than the upper bounds (see Appendix C). can we push this to simply 10,000 bounds by sampling a bit more?

I think Fig1a may not be as useful as I originally thought...I think Fig a could be perhaps replaced by a version of Fig 1b, but where we actually plot the smoking data example here? Or even find a GWAS in MR-Base where X and Y have strong causal link and there's a very strong genetic determinant (e.g. cholesterol/obesity to heart attack?) RMT: I have looked at a large number of pairs of studies from MR-Base. If we were to create a figure like Fig 1b, but based on real data, it would simply be a small cluster of points with width around 1.1 and strength around 0.01. Can we draw a box around this region? I actually think if we can extract some sample MR-Base results that relate to cholesterol-heart attack or other common MR relationships onto this plot, we can make a convincing case that most IV bounds in practice will live near this region and thus, we will rarely get any informative bounds. Perhaps use this paper to explore different exposure-outcome combinations https://www.biorxiv.org/content/10.1101/2020.05.06.077982v1.full.pdf (Section 2.3).

Figure 1b shows the widths of the same 9,877 bounds plotted against the strength of the instruments. The black line is the upper bound for the width of the bounds in Theorem 3.1. We see that the width of the bounds often exceed 1 as the instrument strength decreases. Table 1 makes this more precise by showing the proportion of bounds presented in Figure 1 with widths greater than 1, 0.75, and 0.5, stratified by instrument strength. The table reveals that while is possible to observe bounds with width less than 1, for IVs with strength less than 0.05, 47.0% of the bounds lead to widths greater than 1 and about 46.1% of bounds from



(a) Bounds ordered by the center of the bounds.

(b) Black line has intercept 2 and slope -2.

Figure 1: 10,000 values for bivariate distributions were randomly generated such that no constraints were violated. Of these, 123 resulted in bounds where the lower bound was greater than the upper bounds. These have been removed from these plots.

IVs with strength between 0.05 and 0.1 have width greater than 1. Also, only 62.9% of bounds with strength greater than 0.5 have widths less than 0.5.

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

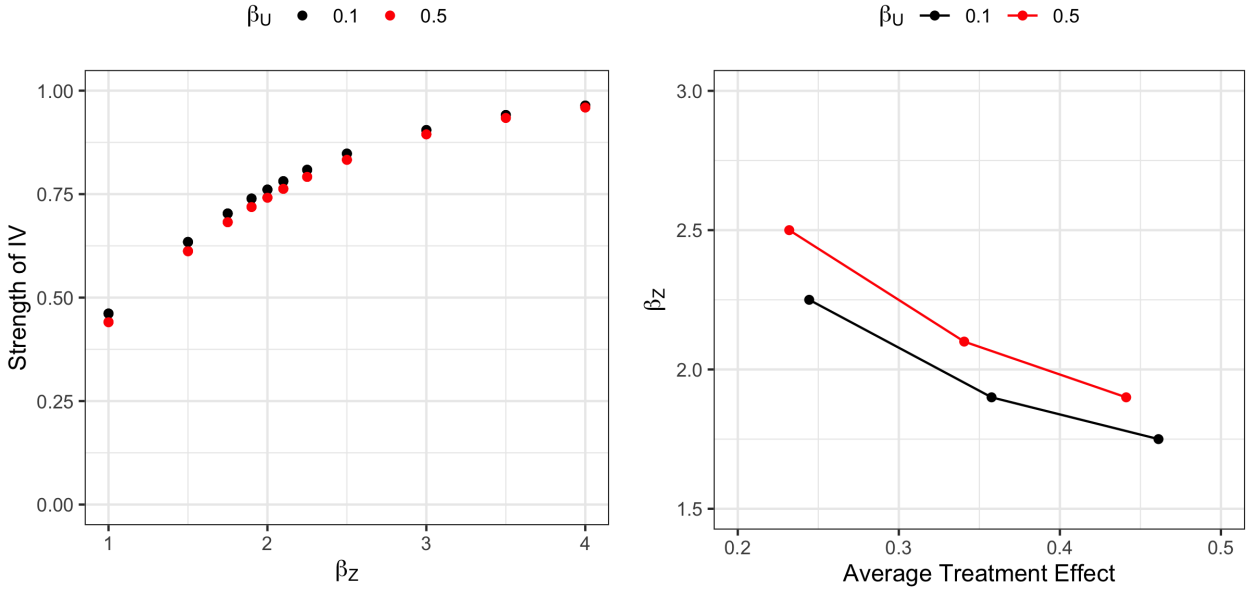
	Proportion of bounds with width greater than...		
Strength	1	0.75	0.5
$[0, 0.05]$	0.4698795	0.7831325	0.8915663
$(0.05, 0.1]$	0.4611111	0.7222222	0.8944444
$(0.1, 0.25]$	0.3227061	0.7029549	0.9222395
$(0.25, 0.5]$	0.1359280	0.4954981	0.8356085
$(0.5, 1]$	0.0000000	0.0738818	0.3708067

To better understand the implications of instrument strength on the width of bounds, Figure 2a characterizes the relationship between instrument strength ST and a popular summary statistic measuring instrument strength reported in MR methods [Lawlor et al., 2008, King et al., Millard et al., Burgess, Verma et al.]. make sure years show up to rest of citations. Specifically, suppose 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 follows $P(X = 1|Z = z, U = u) = \text{logit}(\gamma_0 + \gamma_Z \cdot z + \gamma_U \cdot u)$ where γ_Z corresponds to the regression estimate one would obtain from GWAS studying the relationship between the genetic variant and the exposure. For simplicity, we set $\gamma_0 = -\gamma_Z$; this corresponds to the scenario where difference in the probability $P(X = 1|Z = z, U)$ between zs is large. We then vary γ_z from 0 to 5 and set β_U to be either 0.1 or 0.5. For each combination of γ_z and β_U, we compute the corresponding ST through monte carlo integration involving $10,000,000$ samples. update x-axis with γ_Z. Also, can we draw a curve without the dots and extend this graph to 0 to 1? Also, rearrange x-y axis to be consistent with figure above? I'm also wondering if we should replace Fig1a with this one?. From Figure 2a, we see that instrument strength ST of 0.5 corresponds to a regression coefficient β_Z of 1.16 if $\beta_U = 0.5$ and 1.1 if $\beta_U = 0.1$. Such coefficients are rarely encountered in GWAS summary statistics meaning that we have little hope of guaranteeing narrow bounds from MR analyses.

Next, among bounds that have width less than 1, we study whether they can tell investigators about the direction of the exposure effect. More specifically, for an anticipated effect size, we ask what kind of genetic instrument in terms of instrument strength are needed in order for the IV bounds to not only contain this effect size, but also exclude 0. We remark that 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.

Formally, we again use the exposure model from the previous paragraph and suppose an outcome model $P(Y = 1|X = x, U = u) = \text{logit}(\beta_0 + \beta_X \cdot x + \beta_U \cdot u)$. For simplicity, we set $\beta_U = \gamma_U$ from the exposure model and $\beta_0 = -\beta_X/2$. We then vary β_X to be between 1 and 2 and for each β_X, we find the smallest γ_Z needed to produce an IV bound that contains the exposure effect, but does not contain 0. Figure 2b show the results. Similar to the story about instrument strength and width of bounds, we see that to detect even moderate effect sizes of 0.4, the corresponding γ_Z must be around 1.75, a tall order for most GWAS summary statistics.

Overall, in the context of two-sample MR studies where most genetic instruments are weak, the chances that the IV bounds are informative is unlikely. The bounds will often have width greater than 1 for most genetic instruments and detecting even moderate effect sizes require uncharacteristically strong genetic variants.



(a) Relationship between coefficients β_Z and strength of the IV. fix β_z to γ_z. change dots to smoothed curve.

(b) Size of coefficient β_Z needed to detect direction for different values of the average treatment effect. fix β_z to γ_z. Can we extend this range from 0 to 1? Also, what are your thoughts about reporting ST instead of γ_z? change segment to smoothed lines

Figure 2: For different values of β_Z, β_U, and γ_X.

3.2 Bounds With Multiple Instruments

Prior section revealed that bounds from two-sample MR studies require a strong instrument to obtain informative bounds. However, it did not address whether the bound can become more informative if multiple valid instruments are available. In this section, we consider an optimistic approach to aggregate bounds across multiple instruments by taking intersections of separate IV bounds. We say that this is optimistic compared to another alternative where we expand the levels of Z from $0, 1, 2$ to accommodate multiple instruments; this approach will require data that cannot be easily obtained from two-sample MR and more importantly,

will result in much wider bounds I forget if one of the Swanson papers actually mentioned this or not...can you look into citation?. We show that even with this optimistic aggregation strategy, bounds generally do not become more informative as the number of instruments increase.

Formally, consider the following outcome model when there are multiple instruments; this model has been used in MR studies by https://academic.oup.com/ije/article/43/3/922/761826 and https://onlinelibrary.wiley.com/doi/epdf/10.1002/ so that every instrument estimates the same exposure effect.

$$\text{logit}(P(X = 1|Z_1 = z_1, ..., Z_p = z_p, U = u)) = \gamma_0 + \sum_{j=1}^{p} \sum_{j} \gamma_j z_j + \gamma_U u$$
$$\text{logit}(P(Y = 1|X = x, U = u)) = \beta_0 + \beta_1 x + \beta_U u,$$

We allow either $p = 10$ or $p = 50$ instruments. For each of the p instruments, we set $P(Z_j = 0) = P(Z_j = 2) = 0.25$ and $P(Z_j = 1) = 0.5$, and draw U from a standard normal distribution. We also set $\beta_U = \gamma_U$, which is equal to either 0.1 or 0.5, and set β_1 to be either 1, 1.5, or 2. We then consider three scenarios for setting γ_j. Are these γ_j values fixed after you generate them? Or do they vary every time you draw one of the 1Mil sample? Just wanted to make sure we have this correct.

1. *Many weak instruments*: We draw γ_j i.i.d. from a uniform distribution with support 0 to 0.1.
2. *Many strong instruments*: We draw γ_j i.i.d. from a uniform distribution with support 1 to 4. This is the magnitude of γs that detected the ATE using bounds in the previous section
3. *One strong, many weak instruments*: fill

The first scenario mimics typical magnitudes of coefficients we see in MR studies, where most genetic variants have a weak effect on the exposure. The scenario is also an example of a genetic architecture where many genetic traits contribute to complex traits cite "Contrasting genetic architectures of schizophrenia and other complex diseases using fast variance-components analysis" and "Contrasting the genetic architecture of 30 complex traits from summary association data" and "Genetic architecture: the shape of the genetic contribution to human traits and disease", The second scenario is an extension of the first where we increase the magnitude of the genetic variants' effects on the exposure. We don't expect to observe this practice, but these are the magnitudes that our results in Section **??** fill suggests for an investigator to obtain informative bounds from a single instrument. Finally, the third scenario represents a genetic architecture where only few genetic variants have strong effects on the exposure while others have weak effects cite "Common SNPs explain a large proportion of the heritability for human height" Yang, Benyamin, McEvoy, ...Nature Genetics.

For each scenario, we use monte carlo integration with 1 million re-samples to obtain $P(X = 1|Z_j = z_j)$ and $P(Y = 1|Z_j = z_j)$ and obtain IV bounds for each instrument. Table add Table summarizes the results. We see that in scenarios 1 and 2, every bound is non-informative, with widths 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 greater than 1. In addition, the increase in magnitude of the γ_j coefficient did not improve the bounds and there was a dilution in the quality of the instruments when they are combined together. That is, where a single instrument with a γ_j of fill and explain.

Finally, for scenario 3, we see that the the intersection bounds explain and fill. Figure 3 examines this more closely explain and fill. In short, under scenario 3, aggregating information from multiple instruments through intersections will not result in more information than simply using a single, strongest individual bound.

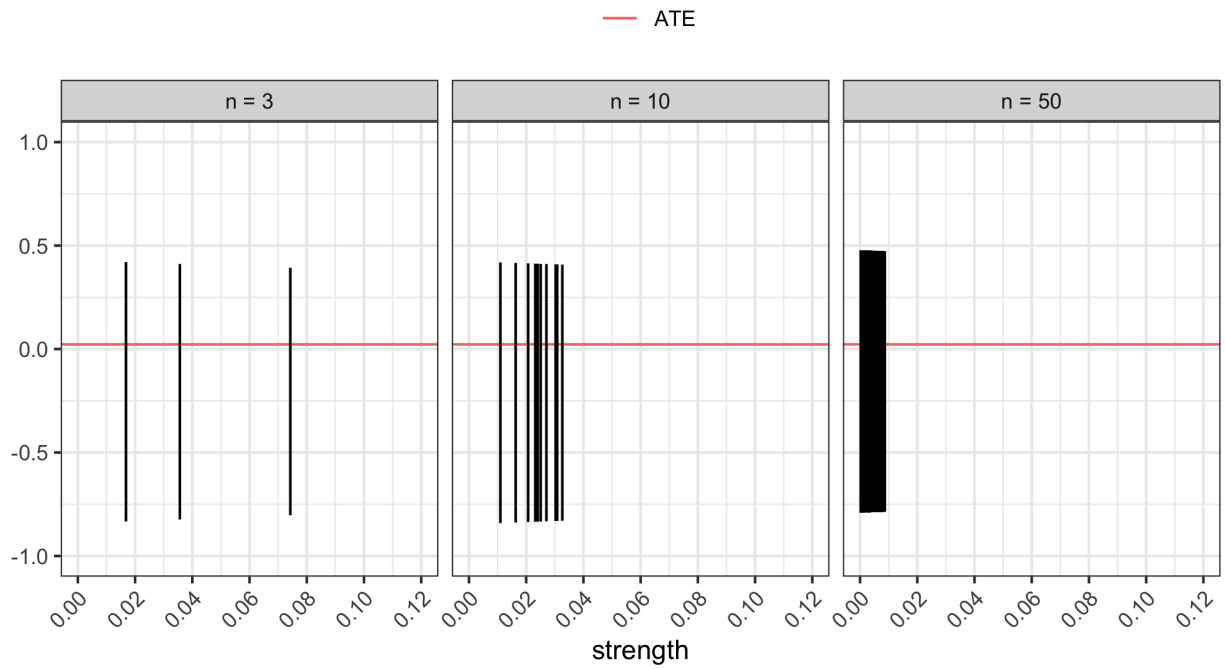


Figure 3: Bounds based on probabilities derived from the logistic model. Here, the coefficients are randomly chosen as Uniform$(0, 1/p)$ for different values of p. fix n to p

Our results above have dire implications when some instruments turn out to be invalid. If, as suggested by cite Swanson commentary paper that I shared awhile back on doing this approach, 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. More broadly, without making some assumptions about the nature of the invalid IVs, it would generally be infeasible to obtain useful information from using bound-based analysis.

Overall, combining our investigation into the behavior of bounds from Section 3.1, our conclusion about using nonparametric IV bounds in two-sample MR studies is grim. They generally require very strong instruments and/or effect sizes, which are are in MR studies, and multiple instruments are no better than having a single, strong instrument. Without having strong instruments in nature, this is generally difficult, if not impossible, to address with any statistical methodology. Also, as illustrated in our theory in Section 3.1, another primarily reason for the non-informative nature of the IV bounds is because of the two-sample setup. While this is also generally difficult to resolve in many studies, in the next section, we discuss how to obtain a plausible range of the joint distribution of the outcome and the exposure given the instrument $P(Y, X|Z)$ given two sample MR data $P(Y|Z)$ and $P(X|Z)$ in order to create more informative bounds from two-sample MR studies.

4 Towards a More Informative Bound by Bayesian Reconstruction of One-Sample Data From Two-Sample Data

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. We then compute an IV bound for each of the plausible sets of $P(X = x, Y = y|Z = z)$ by Balke and Pearl and Richardson and Robins [2014]. In short, the approach addresses 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?"

To formalize our method, 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

$$P(X = x, Y = y|Z = z) = P(X = x|Z = z)P(Y = y|Z = z) + (2 \cdot I[x = y] - 1)\text{Cov}(X, Y|Z = z). \quad (3)$$

Because $\text{Cov}(X, Y|Z = z)$ is impossible to estimate from two-sample data, 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 (2) from the IV assumptions. Specifically, by the definition of a proper probability distribution, $\text{Cov}(X, Y|Z = z)$ must satisfy

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

Additionally, by the IV inequality constraints, 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

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

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

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

Then, 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 (2) 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 (3), leading us to a plausible set of the joint distribution $P(X = x, Y = y|Z = z)$.

For each plausible set of the joint distribution of $P(X = x, Y = y|Z = z)$, we use theIV bounds by Balke and Pearl and Richardson and Robins [2014] from one-sample studies to obtain a one-sample IV bound for the ATE. If a large number of the 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 these 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.

We can also extend our method to handle multiple IVs by simply repeating the above method for each proposed instrument and taking intersections of the one-sample IV bounds. This builds on one assumption that the above sampling are done independently for each instrument; in other words, the assumption implicitly assumes that the covariances of X and Y given Z_1 are independent of the covariances of X and Y given Z_2. For additional details, see Section **??** fill of the Appendix. Move this to Appendix: Specifically, say we get bounds $(LB_{1i}, UB_{1i}), i = 1, 2, ..., m$ by sampling m trivariate distributions based on the information we have on (X, Z_1) and (Y, Z_1), and bounds $(LB_{2i}, UB_{2i}), i = 1, 2, ..., m$ 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 $(\max_{z\in 1,2} LB_{zi}, \min_{z\in 1,2} UB_{zi}), i = 1, 2, ..., m$. 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.

Finally, we remark that the proposed method above can be thought of as using an empirically bayesian framework for partially identified sets. Specifically, our procedure generates a posterior distribution of 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.

4.1 Illustration

We illustrate our proposed method from the previous section by considering nine hypothetical MR studies, each using one instrument; see Section **??** for the case with multiple instruments. Table 2 presents nine different sets of values of the marginal distributions $P(Y|Z)$ and $P(X|Z)$ and Figure 4 shows the resulting one-sample IV bounds from our method.

Table 2: Values of $P(X = 1|Z = z)$ and $P(Y = 1|Z = z)$ used in our illustration for one instrument. Each cell in the table presents $\{P(X = 1|Z = 0), P(X = 1|Z = 1), P(X = 1|Z = 2)\}$ 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}

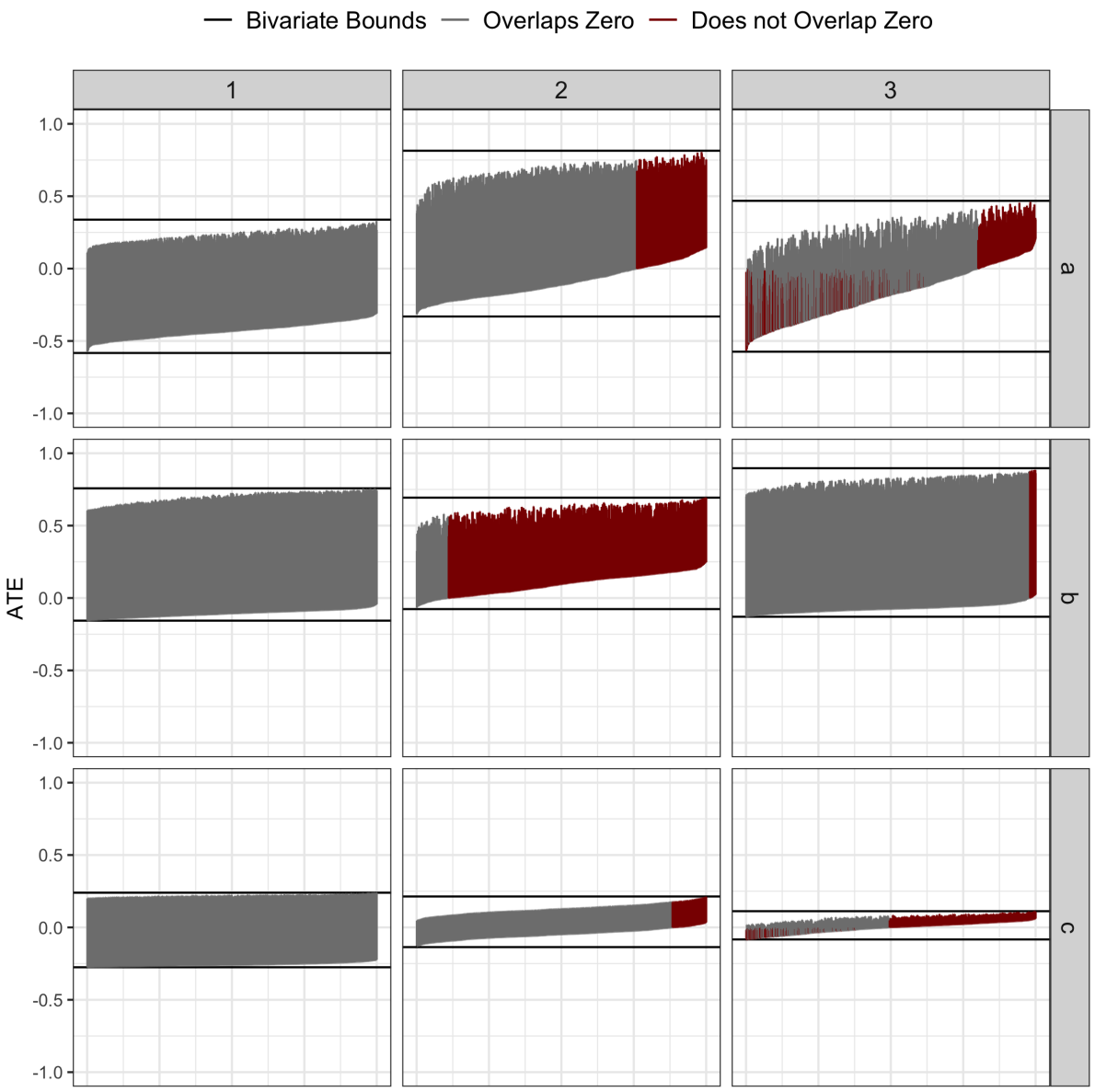


Figure 4: Plausible Range of One-sample Bounds From Our Method Base on Data from Table 2 Change a,b,c to A, B, and C

Row A of Figure 4 shows three scenarios where the two-sample bounds are all more or less centered around zero with similar widths. However, the conclusions are rather different. Column 1 shows no that one-sample bound 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 large widths. Here, 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 be able to determine the direction of the ATE to be positive from the one-sample bounds (column 2), and one case where we are rather unlikely to be able to determine the direction of the ATE from the one-sample bounds (column 3).

Row C is similar to row A in that all the two-sample bounds are centered around 0, but the width of the two-sample bounds are narrow. The three columns indicate similar conclusions as seen in row A. This shows that even with rather narrow two-sample bounds centered around 0, the one-sample bounds may still be have to 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 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, even in this case, if the ATE is in fact negative, our method does rule out the possibility of one-sample bounds being able to ascertain this because all one-sample bounds covering a negative ATE also covers 0.

5 Data Analysis

We present two example analyses to demonstrate our findings about the behavior of bounds and our proposed method to obtain more informative bounds. Our first analysis studies the effect of smoking on lung cancer and our second analysis studies the effect of self-reported high cholesterol on incidence of heart attack. The causal effects underlying both analyses are well-established and serve as positive controls. The effect of smoking on lung cancer is known to be strong and positive. add description on high cholesterol In both cases, we explore the non-parametric bounds obtained from two-sample designs and assess what conclusions are attainable based on bound-based approaches.

The data to study both effects was obtained from a curated the UK Biobank data available in the IEU GWAS database and we use the `TwoSampleMR` package [Hemani et al., 2018] to pre-process the data. Specifically, data on smoking was obtained from data entry with ID ukb-d-20116_0, data on depression from entry with ID ukb-d-20544_11, and data on lung cancer from entry with ID ukb-d-40001_C349. We followed the defaults of the package 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 are returned. The data was harmonized to make sure that the effects of the SNPs on exposure and outcome were measured with the same allele as reference. Afterwards, we obtain the estimated coefficients that correspond to the effects of the SNPs on the exposure, and the outcome from a simple logistic model. Since estimates of the intercept are not included in these reported results, but marginal proportions of the outcome, exposure, and allele frequencies are known, we estimate the intercepts by solving $P(X = 1) = \sum_{z=0}^{2} \text{logit}(\gamma_0 + \hat{\gamma}_1 \cdot z) \cdot P(Z = z)$ and $P(Y = 1) = \sum_{z=0}^{2} \text{logit}(\beta_0 + \hat{\beta}_1 \cdot z) \cdot P(Z_j = z)$ for β_0 and γ_0, respectively. The estimates of the intercept and slope coefficients allowed us to calculate $P(Y = 1|Z_j = z)$ and $P(X = 1|Z_j = z)$ for every j and $z = 0, 1, 2$; see [link to vignette showing analysis on pkgdown page] for the code.

We should stress test this intercept finding (and ultimately, recovering $P(Y|Z)$ and $P(X|Z)$) procedure? For example, I know the FTO-genetic marker is very strongly associated with obesity and hopefully, $P(X|Z = z) - P(X|Z = z')$ is large? Or, we can also simulate to verify this procedure...

5.1 Smoking effect on lung cancer

Our MR analysis of smoking's effect on lung cancer based on bounds uses 84 genetic variants as instruments; detailed information on the 84 instruments can be found in the Appendix D. On average, the instrument strength is around fill, with the strongest instrument having ST = 0.01; this is much smaller than the ST = 0.5 needed to guarantee narrow bounds. As such, the two-sample bounds in Figure 5 are rather wide; all of them have width greater than 1 and they convey no truly useful information about smoking's effect on lung cancer. Additionally, even after applying our method to get more informative bounds, we find that we are

unable to determine the direction of the ATE; see Figure 6. In the Appendix, we also show that aggregating bounds through intersections (Figure **??** move this to Appendix) show similar results.

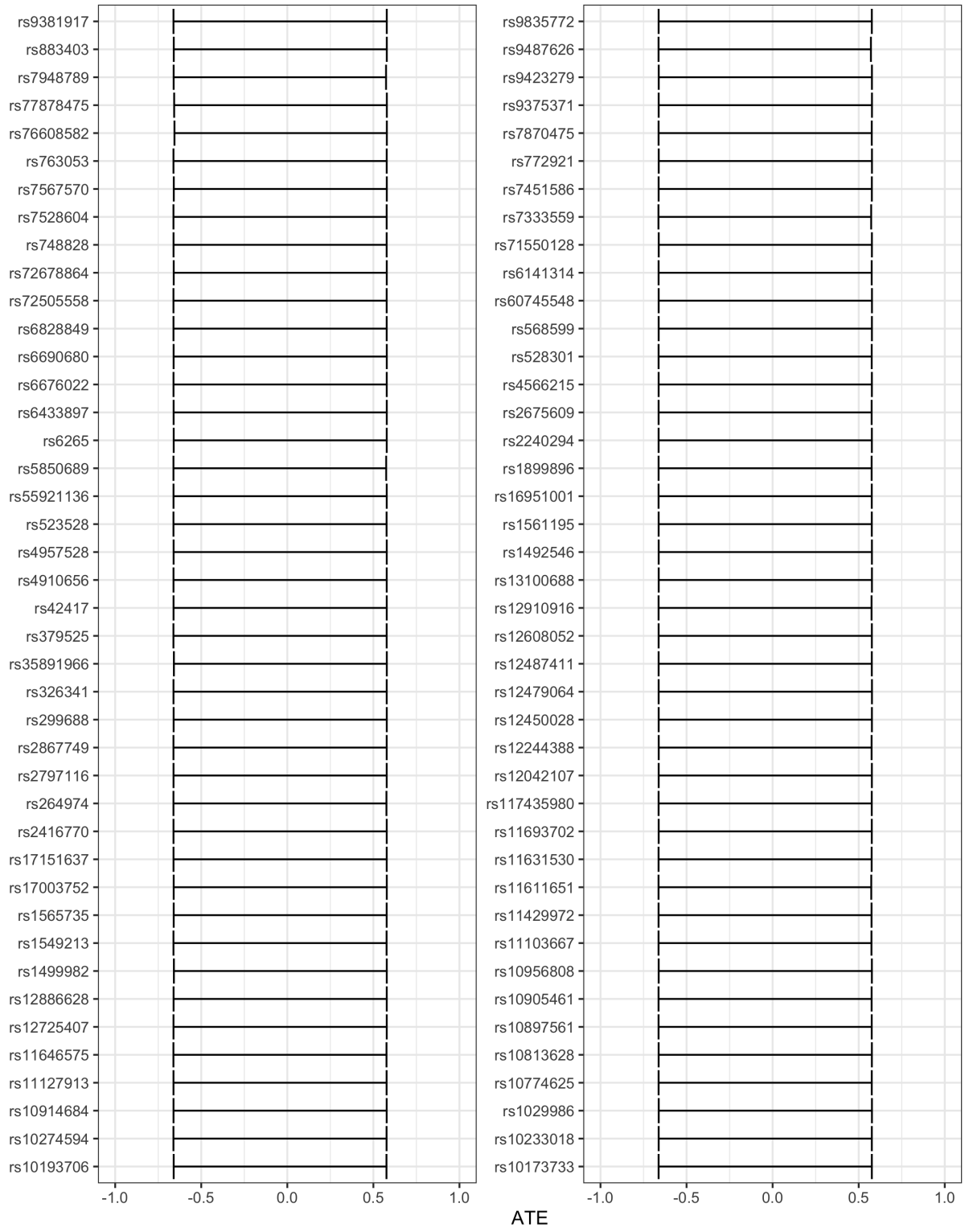


Figure 5: Non-parametric bounds on the average treatment effect of smoking on lung cancer.

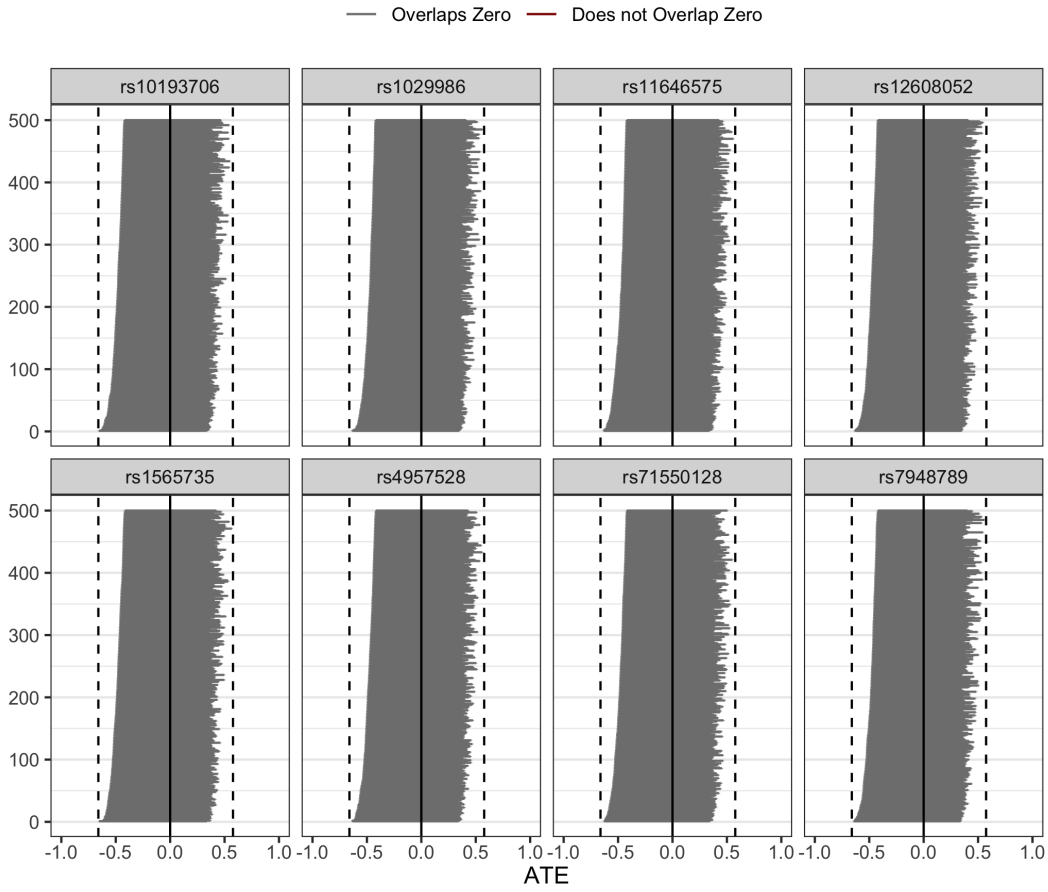


Figure 6: 500 sets of bounds of the average treatment effect of smoking on lung cancer for six of the 84 SNPs. Each bound is based on a set of values for the trivariate distribution randomly sampled. Bounds are color coded to show if they overlap 0 (grey) or do not (red). All bounds overlap 0.

The result is a cause for concern since is well established that smoking has a strong causal effect on the chances of developing lung cancer [Cornfield et al., 1959]. The fact that we are unable to say anything about the ATE in this case does not leave much hope in terms of future discoveries based on non-parametric IV bounds from two-sample MR studies. Even more concerning is the fact that our methodology reveals that had we obtained one-sample MR data, we would still be unsuccessful in determining the direction of the effect based on a bound-based analysis of the ATE. In short, while non-parametric bounds allow us to make little assumptions about the data and as such, is robust to some common modeling assumptions in MR, they are often too conservative and are not suited for MR studies with many weak instruments.

5.2 Cholesterol

fill: follow above example

6 Conclusion and Practical Considerations

Non-parametric bounds are without a doubt an attractive concept. With a minimal set of assumptions they let us obtain bounds on the average treatment effect. However, as we have seen here, in typical MR studies with two-sample summary data and many weak instruments, bounds may be too uninformative to make meaningful conclusions about the ATE. Specifically, non-parametric 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 address the limitations that the two-sample design has in terms of producing informative bounds, we outline a method to generate a plausible range of one-sample IV 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 had we had one-sample data. We applied our method to a few different settings of two-sample data and showed the range conclusions about the ATE that can be drawn from it. This exercise also highlighted a significant loss of information in two-sample designs compared to one-sample designs.

need a better way to tie these two paragraphs to rest To demonstrate the use of non-parametric bounds in Mendelian randomization analyses, we considered two examples. In the first example, we aimed at finding bounds on the effect of smoking on the chances of developing depression. Unfortunately, all instruments available were very weak with the strongest instrument having a strength of less than 0.01. This result in bounds that provide very little information. Our approach suggests that even one-sample bounds would not be able to provide much extra information.

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

Using non-parametric bounds in two-sample MR studies seem a promising idea since many MR analysis rely on a host of potentially unjustifiable modeling assumptions. But, as we seen above, the non-parametric nature of these bounds as well as the two-sample design can make these bounds often meaningless in practice. Nevertheless, one potential use case of non-parametric bounds in two-sample MR studies could be when one has prior knowledge about the direction of the effect, but wish to get a better sense of the magnitude. By knowing the sign of the effect a priori, non-parametric 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.

A Proof of Theorem 3.1

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

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

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 $\text{ST} = P(X=1|Z=2) - P(X=1|Z=0)$.

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,

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

Width = U2 - L1

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

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,

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

Width = U1 - L2

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

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

Width = U2 - L2

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

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

Width = U3 - L2

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

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

Width = U1 - L3

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

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

Width = U2 - L3

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

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

Width = U3 - L3

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

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

B Bounds on Average Treatment Effect

We briefly review the method presented by Ramsahai [2012] to bound the average treatment effect using two-sample summary data. Let $\vec{\tau}^* = \Big(P(Y=1|X=0,U), P(Y=1|X=1,U), P(X=1|Z=0,U), ..., P(X=1|Z=k-1,U)\Big) \in [0,1]^{2+k}$ and $\vec{v}^* = \Big(P(Y=0|Z=0,U), ..., P(Y=1|Z=k-1,U), P(X=0|Z=0,U), ..., P(X=1|Z=k-1,U), \alpha^*\Big)$ 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 $\vec{v} = E_U[\vec{v}^*] = \Big(P(Y=0|Z=0), ..., P(Y=1|Z=k-1), P(X=0|Z=0), ..., P(X=1|Z=k-1), \alpha\Big)$, 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 unobervable, $\vec{v}$ 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

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

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

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

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

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

```
##
## -- Column specification --------------------------------------------------------
## cols(
##   PY0Z0 = col_double(),
##   PY0Z1 = col_double(),
##   PY0Z2 = col_double(),
##   PY1Z0 = col_double(),
##   PY1Z1 = col_double(),
##   PY1Z2 = col_double(),
##   PX0Z0 = col_double(),
##   PX0Z1 = col_double(),
##   PX0Z2 = col_double(),
##   PX1Z0 = col_double(),
```

```
##   PX1Z1 = col_double(),
##   PX1Z2 = col_double(),
##   `$\alpha$` = col_double()
## )
```

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
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	1	0	1	0	1	-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	1	1	1	0
1	1	1	0	0	0	0	0	0	1	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. This means that the vector of these values must be a convex combination of the rows in the matrix above. 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 $PYyZz, PXxZz$ such that $\sum_{z=0}^{2} PX1Zz \cdot P(X = 1|Z = z) + \sum_{z=0}^{2} PY0Zz \cdot P(Y = 0|Z = z) + PY1Z0 \cdot P(Y = 1|Z = 0) + c_\alpha \alpha \geq 0$.

```
##
## -- Column specification --------------------------------------------------------
## cols(
##   PY0Z0 = col_double(),
```

```
##   PY0Z1 = col_double(),
##   PY0Z2 = col_double(),
##   PY1Z0 = col_double(),
##   PX1Z0 = col_double(),
##   PX1Z1 = col_double(),
##   PX1Z2 = col_double(),
##   `$c_{\alpha}$` = col_double()
## )
```

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
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

PY0Z0	PY0Z1	PY0Z2	PY1Z0	PX1Z0	PX1Z1	PX1Z2	c_α
0	1	-1	0	0	1	1	0
0	1	0	1	-1	1	0	-1
0	0	1	0	0	0	0	0
-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
0	-1	2	0	0	0	2	-1
1	0	1	2	-1	0	-1	0
1	0	0	0	0	0	0	0

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

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

$$\leq \alpha \leq$$

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

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

$$\min \left\{ \begin{array}{ll} \min_{i \neq j} & P(Y=1|Z=i) - P(X=1|Z=i) - P(Y=1|Z=j) - P(X=1|Z=j) + 2 \\ \min_{i \neq j} & P(Y=1|Z=i) + P(X=1|Z=i) - P(Y=1|Z=j) + P(X=1|Z=j) \\ \min_{i} & P(X=1|Z=i) \\ \min_{i} & P(Y=1|Z=i) \\ \min_{i} & 1 - P(X=1|Z=i) \\ \min_{i} & 1 - P(Y=1|Z=i) \end{array} \right\} \geq 0 \quad (4)$$

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 (**??**) and (**??**), the bounds reduce to just three on the lower end and three on the upper end:

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

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 (2). 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
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
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

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
0.8824330	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
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
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

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
0.9421035	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
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
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
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 Additional Summary Statistics and Figures for Analyses Presented in Section 5

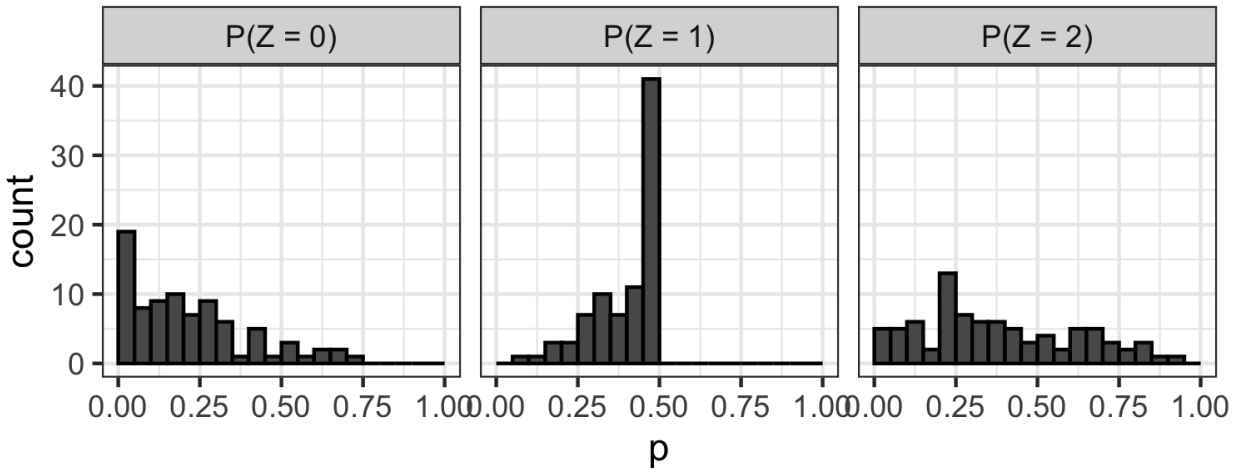


Figure 7: Histograms of the marginal distribution of instruments, $P(Z = z), z = 0, 1, 2$, estimated after preprocessing for analysis in Section **??**

Table 8: Table of the marginal distribution of instruments, $P(Z = z), z = 0, 1, 2$, estimated after preprocessing for analysis in Section **??**

SNP	P(Z = 2)	P(Z = 1)	P(Z = 0)
rs10173733	0.3567595	0.4810680	0.1621726
rs10193706	0.2250921	0.4986932	0.2762147
rs10233018	0.2456177	0.4999613	0.2544211
rs10274594	0.2534258	0.4999767	0.2465975
rs1029986	0.1723555	0.4856034	0.3420411
rs10774625	0.2452793	0.4999550	0.2547657
rs10813628	0.2353130	0.4995554	0.2651316
rs10897561	0.4145906	0.4585930	0.1268164
rs10905461	0.0653045	0.3804860	0.5542095
rs10914684	0.4568603	0.4381082	0.1050314
rs10956808	0.3341139	0.4878239	0.1780622
rs11103667	0.6529965	0.3101710	0.0368325
rs11127913	0.3714083	0.4760490	0.1525428
rs11429972	0.1121109	0.4454375	0.4424516
rs11611651	0.8320219	0.1602609	0.0077172
rs11631530	0.7776549	0.2083850	0.0139600
rs11646575	0.3152078	0.4924518	0.1923404
rs11693702	0.2857164	0.4976161	0.2166675
rs117435980	0.6997059	0.2735567	0.0267374
rs12042107	0.2018720	0.4948594	0.3032687
rs12244388	0.4406271	0.4463408	0.1130321
rs12450028	0.4295142	0.4517182	0.1187675
rs12479064	0.6269478	0.3297051	0.0433471
rs12487411	0.2787537	0.4984352	0.2228111
rs12608052	0.2309196	0.4992427	0.2698378
rs12725407	0.6539829	0.3094184	0.0365987
rs12886628	0.1122813	0.4456055	0.4421132
rs12910916	0.6211224	0.3339816	0.0448960
rs13100688	0.3932586	0.4676895	0.1390519
rs1492546	0.2020165	0.4948919	0.3030915
rs1499982	0.0222374	0.2537694	0.7239932
rs1549213	0.1277548	0.4593465	0.4128986
rs1561195	0.2282248	0.4990080	0.2727672
rs1565735	0.6370613	0.3221998	0.0407389
rs16951001	0.3381946	0.4867008	0.1751046
rs17003752	0.7422782	0.2385549	0.0191668
rs17151637	0.5169616	0.4040776	0.0789607
rs1899896	0.4936293	0.4179166	0.0884542
rs2240294	0.3090443	0.4937465	0.1972092
rs2416770	0.2198025	0.4980570	0.2821405
rs264974	0.2632013	0.4996604	0.2371383
rs2675609	0.1388997	0.4675856	0.3935147

SNP	P(Z = 2)	P(Z = 1)	P(Z = 0)
rs2797116	0.5378179	0.3910856	0.0710965
rs2867749	0.4635738	0.4345775	0.1018487
rs299688	0.0809490	0.4071328	0.5119182
rs326341	0.2744742	0.4988573	0.2266685
rs35891966	0.8606480	0.1341263	0.0052257
rs379525	0.2693148	0.4992814	0.2314038
rs42417	0.0958938	0.4275468	0.4765594
rs4566215	0.2180425	0.4978154	0.2841421
rs4910656	0.4335363	0.4497969	0.1166669
rs4957528	0.0432628	0.3294687	0.6272685
rs523528	0.1717489	0.4853542	0.3428969
rs528301	0.2008634	0.4946289	0.3045076
rs55921136	0.6345353	0.3240838	0.0413808
rs568599	0.2093354	0.4963929	0.2942717
rs5850689	0.1341769	0.4642495	0.4015736
rs60745548	0.0747215	0.3972616	0.5280169
rs6141314	0.5745378	0.3668899	0.0585724
rs6265	0.6582044	0.3061871	0.0356085
rs6433897	0.0693904	0.3880603	0.5425494
rs6676022	0.7719180	0.2133413	0.0147407
rs6690680	0.7092842	0.2658119	0.0249040
rs6828849	0.3390095	0.4864715	0.1745191
rs71550128	0.2006117	0.4945706	0.3048177
rs72505558	0.3617365	0.4794177	0.1588458
rs72678864	0.6820022	0.2876641	0.0303337
rs7333559	0.0438714	0.3311672	0.6249614
rs7451586	0.3546216	0.4817591	0.1636193
rs748828	0.5136337	0.4060975	0.0802688
rs7528604	0.3204723	0.4912608	0.1882668
rs7567570	0.0300586	0.2866312	0.6833102
rs763053	0.6007027	0.3486949	0.0506025
rs76608582	0.9065935	0.0911171	0.0022894
rs772921	0.4307261	0.4511423	0.1181316
rs77878475	0.8356274	0.1569984	0.0073742
rs7870475	0.2766026	0.4986552	0.2247422
rs7948789	0.3779911	0.4736374	0.1483715
rs883403	0.7155911	0.2606702	0.0237388
rs9375371	0.5339661	0.3935275	0.0725064
rs9381917	0.8061282	0.1834365	0.0104354
rs9423279	0.1176593	0.4507114	0.4316293
rs9487626	0.0333177	0.2984272	0.6682551
rs9835772	0.5732121	0.3677912	0.0589967

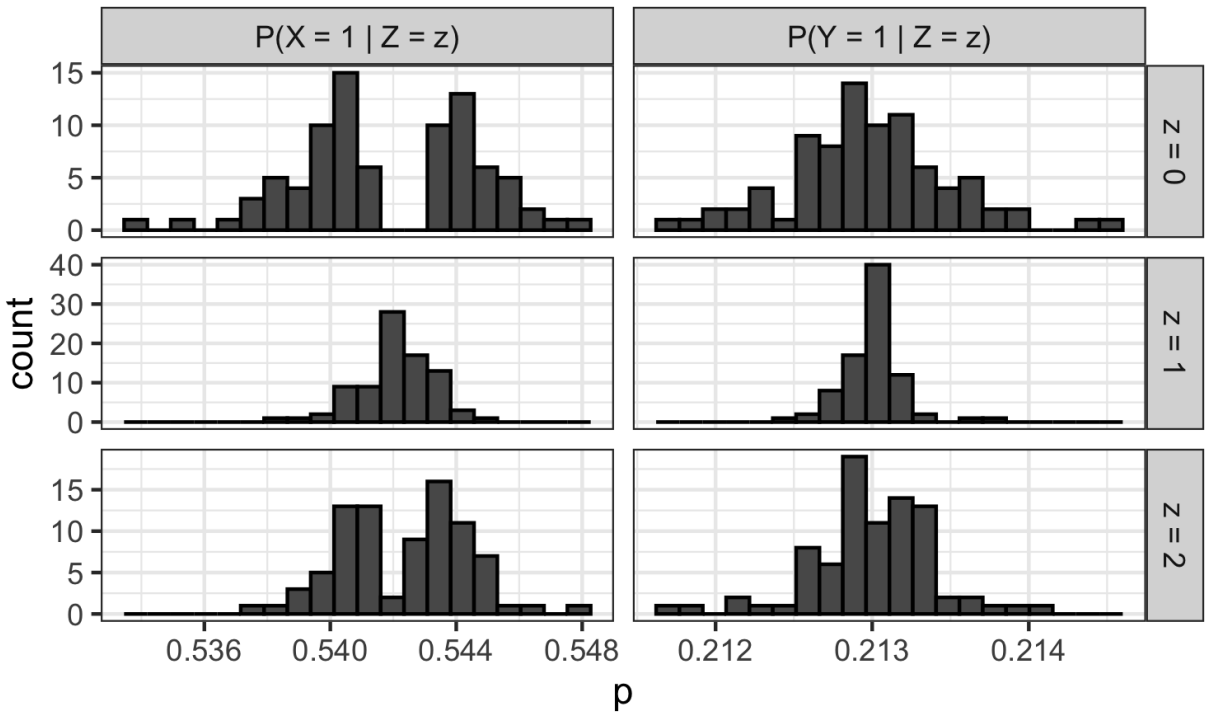


Figure 8: Histograms of the marginal conditional probabilities $P(X = 1|Z = z), z = 0, 1, 2$ and $P(Y = 1|Z = z), z = 0, 1, 2$.

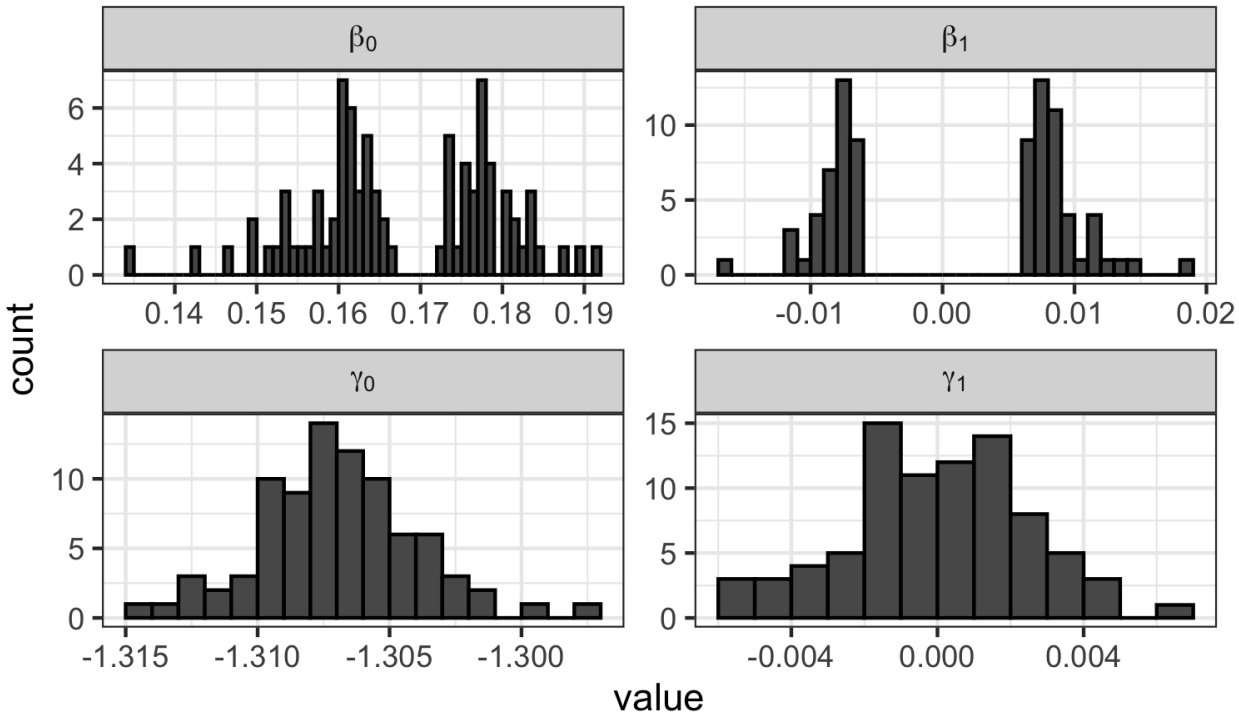


Figure 9: Histograms of the coefficients from GWAS results of logistic regression of the SNPs on smoking status and depression status, respectively. Intercepts (β_0 and γ_0) are inferred, while slopes (β_1 and γ_1) are as reported.

Table 9: Coefficients from GWAS results of logistic regression of the SNPs on smoking status and depression 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	0.1773825	-0.0005704	-1.306311
rs10193706	-0.0117667	0.1807672	0.0013967	-1.308318
rs10233018	-0.0076551	0.1771881	0.0067789	-1.313719
rs10274594	0.0078326	0.1617143	0.0012819	-1.308284
rs1029986	-0.0070208	0.1754296	0.0045713	-1.310792
rs10774625	0.0074868	0.1621846	-0.0006839	-1.306315
rs10813628	-0.0068761	0.1762712	0.0027284	-1.309641
rs10897561	-0.0066917	0.1782175	0.0016886	-1.309168
rs10905461	0.0072731	0.1658828	-0.0032370	-1.305339
rs10914684	0.0077356	0.1591430	-0.0011037	-1.305501
rs10956808	0.0076247	0.1607859	0.0000764	-1.307081
rs11103667	-0.0086047	0.1835067	0.0046866	-1.314570
rs11127913	0.0081801	0.1596300	0.0021709	-1.309640
rs11429972	0.0083148	0.1640324	-0.0016042	-1.305919
rs11611651	-0.0119868	0.1914677	0.0004842	-1.307876
rs11631530	-0.0099863	0.1872129	-0.0044324	-1.299176
rs11646575	-0.0082446	0.1788582	0.0009492	-1.308059
rs11693702	-0.0080254	0.1781801	0.0020852	-1.309223
rs117435980	-0.0092037	0.1849976	-0.0005583	-1.306059

Table 9: Coefficients from GWAS results of logistic regression of the SNPs on smoking status and depression 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
rs12042107	0.0071759	0.1631519	0.0017794	-1.308592
rs12244388	-0.0104344	0.1834539	-0.0006776	-1.306093
rs12450028	-0.0070626	0.1788573	-0.0010781	-1.305580
rs12479064	-0.0080362	0.1823262	0.0003346	-1.307523
rs12487411	0.0075048	0.1616757	-0.0035878	-1.303206
rs12608052	0.0067542	0.1631088	-0.0003997	-1.306609
rs12725407	0.0081386	0.1564368	-0.0012532	-1.304966
rs12886628	-0.0071010	0.1743590	0.0007171	-1.307473
rs12910916	-0.0090138	0.1838081	0.0029727	-1.311680
rs13100688	0.0072663	0.1604867	-0.0026558	-1.303662
rs1492546	-0.0068801	0.1757849	-0.0005566	-1.306493
rs1499982	-0.0114648	0.1730198	0.0012934	-1.307379
rs1549213	0.0085270	0.1635050	-0.0050107	-1.303414
rs1561195	-0.0078947	0.1771435	0.0015938	-1.308516
rs1565735	0.0115901	0.1510995	0.0017941	-1.309857
rs16951001	-0.0066035	0.1772805	0.0019827	-1.309300
rs17003752	0.0098606	0.1526093	0.0003979	-1.307678
rs17151637	0.0075112	0.1587990	0.0038108	-1.312475
rs1899896	-0.0079928	0.1808315	0.0040686	-1.312712
rs2240294	0.0069566	0.1618656	-0.0015763	-1.305240
rs2416770	-0.0064888	0.1756844	0.0016061	-1.308499
rs264974	0.0093111	0.1600472	-0.0048647	-1.302004
rs2675609	0.0081586	0.1635192	-0.0005645	-1.306572
rs2797116	0.0079136	0.1579931	-0.0039810	-1.301155
rs2867749	0.0069446	0.1601434	0.0030286	-1.311119
rs299688	-0.0072721	0.1737381	0.0008008	-1.307449
rs326341	0.0065809	0.1627046	-0.0024786	-1.304396
rs35891966	0.0147752	0.1421862	-0.0050131	-1.297691
rs379525	-0.0064906	0.1763367	0.0020069	-1.309077
rs42417	-0.0070331	0.1739558	0.0013904	-1.307854
rs4566215	0.0066219	0.1634159	-0.0011016	-1.305964
rs4910656	0.0068438	0.1605877	-0.0003634	-1.306514
rs4957528	-0.0084750	0.1731257	0.0023700	-1.307979
rs523528	0.0080708	0.1629110	-0.0015950	-1.305671
rs528301	-0.0086008	0.1773101	-0.0017745	-1.305403
rs55921136	0.0085950	0.1559070	-0.0002822	-1.306543
rs568599	-0.0067027	0.1757335	0.0008926	-1.307810
rs5850689	0.0119733	0.1608303	-0.0020322	-1.305504
rs60745548	0.0071946	0.1656667	-0.0050431	-1.304238
rs6141314	-0.0080616	0.1818212	0.0017309	-1.309617
rs6265	0.0101598	0.1531153	0.0034332	-1.312565
rs6433897	-0.0072353	0.1734119	0.0030499	-1.308601
rs6676022	0.0115926	0.1492301	0.0011867	-1.309078
rs6690680	0.0088409	0.1547086	-0.0012510	-1.304886
rs6828849	0.0067122	0.1617838	-0.0017619	-1.304941
rs71550128	-0.0073950	0.1762247	0.0013614	-1.308213

Table 9: Coefficients from GWAS results of logistic regression of the SNPs on smoking status and depression 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
rs72505558	0.0067437	0.1614881	0.0004530	-1.307538
rs72678864	0.0097538	0.1534904	-0.0012454	-1.304936
rs7333559	0.0080523	0.1662269	0.0023047	-1.307959
rs7451586	-0.0066732	0.1775479	-0.0000777	-1.306900
rs748828	0.0086213	0.1572430	-0.0006899	-1.306004
rs7528604	0.0068658	0.1618266	-0.0045708	-1.301820
rs7567570	-0.0091324	0.1727668	0.0007640	-1.307258
rs763053	0.0080618	0.1571035	-0.0026821	-1.302836
rs76608582	0.0182891	0.1347725	0.0020679	-1.310931
rs772921	0.0072725	0.1600543	0.0018384	-1.309406
rs77878475	0.0125950	0.1465734	-0.0021281	-1.303102
rs7870475	-0.0071900	0.1771631	0.0004378	-1.307453
rs7948789	-0.0161713	0.1894889	0.0032357	-1.310973
rs883403	0.0094240	0.1536561	-0.0018273	-1.303901
rs9375371	-0.0073963	0.1804094	-0.0032165	-1.302293
rs9381917	0.0112569	0.1493862	-0.0019346	-1.303519
rs9423279	0.0076695	0.1643388	-0.0015234	-1.305948
rs9487626	0.0131029	0.1648180	-0.0015171	-1.306439
rs9835772	-0.0078024	0.1814146	0.0006795	-1.308022

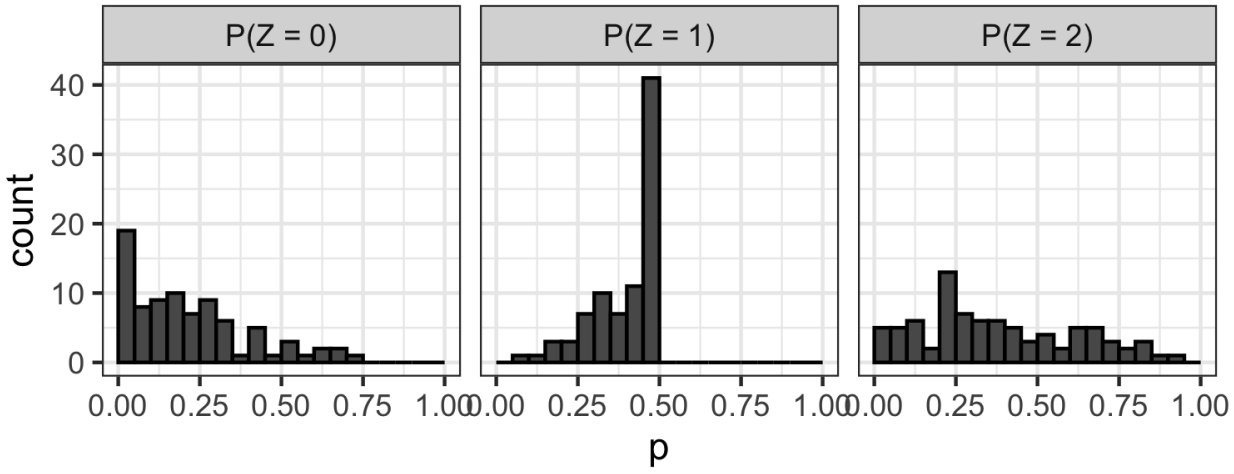


Figure 10: Histograms of the marginal distribution of instruments, $P(Z = z), z = 0, 1, 2$, estimated after preprocessing for analysis in Section 5.1.

Table 10: Table of the marginal distribution of instruments, $P(Z = z), z = 0, 1, 2$, estimated after preprocessing for analysis in Section 5.1

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

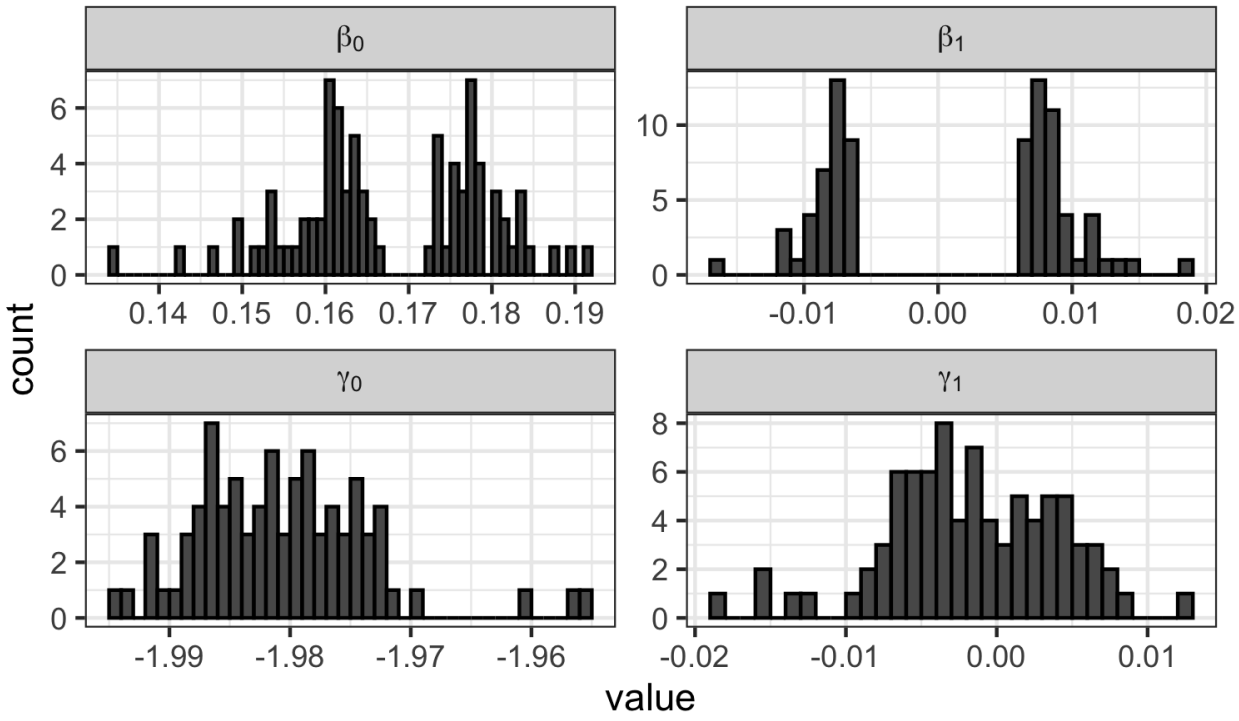


Figure 11: Histograms of the coefficients from GWAS results of logistic regression of the SNPs on smoking status and lung cancer status. Intercepts (β_0 and γ_0) are inferred, while slopes (β_1 and γ_1) are as reported.

Table 11: 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

Table 11: 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
rs12244388	-0.0104344	0.1834505	0.0019355	-1.985707
rs12450028	-0.0070626	0.1788556	-0.0024536	-1.979923
rs12479064	-0.0080362	0.1823251	-0.0088600	-1.969116
rs12487411	0.0075048	0.1616745	-0.0077980	-1.974913
rs12608052	0.0067542	0.1631129	-0.0048100	-1.978521
rs12725407	0.0081386	0.1564297	-0.0067998	-1.972138
rs12886628	-0.0071010	0.1743626	-0.0018595	-1.981891
rs12910916	-0.0090138	0.1838027	0.0026458	-1.987308
rs13100688	0.0072663	0.1604864	-0.0055464	-1.976186
rs1492546	-0.0068801	0.1757890	0.0040638	-1.986797
rs1499982	-0.0114648	0.1730098	0.0024892	-1.983878
rs1549213	0.0085270	0.1634849	0.0056335	-1.987184
rs1561195	-0.0078947	0.1771393	0.0072232	-1.990046
rs1565735	0.0115901	0.1510915	-0.0072487	-1.971566
rs16951001	-0.0066035	0.1772784	0.0070226	-1.991313
rs17003752	0.0098606	0.1526117	-0.0055424	-1.973591
rs17151637	0.0075112	0.1588020	-0.0027771	-1.979146
rs1899896	-0.0079928	0.1808293	0.0047935	-1.989876
rs2240294	0.0069566	0.1618616	-0.0078381	-1.974429
rs2416770	-0.0064888	0.1756858	-0.0035668	-1.979794
rs264974	0.0093111	0.1600323	-0.0047198	-1.978291
rs2675609	0.0081586	0.1635228	-0.0069708	-1.977953
rs2797116	0.0079136	0.1580011	-0.0039635	-1.977330
rs2867749	0.0069446	0.1601396	-0.0032894	-1.978658
rs299688	-0.0072721	0.1737306	-0.0019058	-1.982055
rs326341	0.0065809	0.1627032	0.0031753	-1.986468
rs35891966	0.0147752	0.1421811	-0.0122161	-1.960473
rs379525	-0.0064906	0.1763327	-0.0018594	-1.981209
rs42417	-0.0070331	0.1739582	0.0003829	-1.983375
rs4566215	0.0066219	0.1634100	-0.0035546	-1.979817
rs4910656	0.0068438	0.1605890	-0.0006962	-1.982221
rs4957528	-0.0084750	0.1731252	0.0036288	-1.984649
rs523528	0.0080708	0.1629116	0.0029251	-1.985564
rs528301	-0.0086008	0.1773068	0.0124616	-1.994333
rs55921136	0.0085950	0.1559000	-0.0069653	-1.972040
rs568599	-0.0067027	0.1757286	0.0043346	-1.987105
rs5850689	0.0119733	0.1608296	-0.0038879	-1.980291
rs60745548	0.0071946	0.1656670	0.0062353	-1.986552
rs6141314	-0.0080616	0.1818108	0.0010534	-1.984733
rs6265	0.0101598	0.1531146	-0.0043806	-1.976031
rs6433897	-0.0072353	0.1734104	-0.0011588	-1.982527
rs6676022	0.0115926	0.1492373	-0.0153059	-1.956268
rs6690680	0.0088409	0.1547067	-0.0050219	-1.974679
rs6828849	0.0067122	0.1617773	0.0008050	-1.984076
rs71550128	-0.0073950	0.1762278	0.0034139	-1.986200

Table 11: 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
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
rs9487626	0.0131029	0.1648247	-0.0136868	-1.978168
rs9835772	-0.0078024	0.1814198	-0.0031275	-1.978401

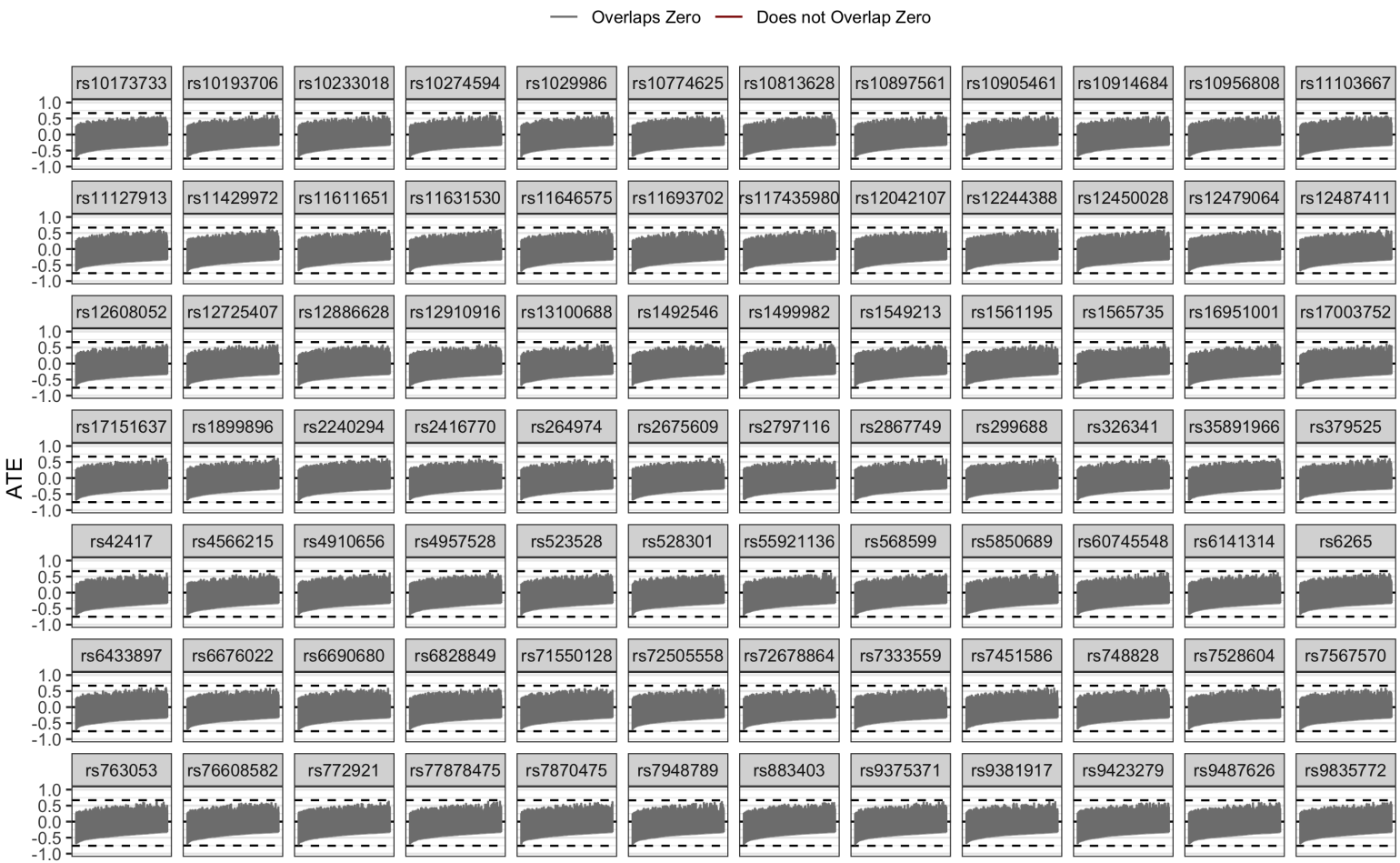


Figure 12: 500 sets of bounds of the average treatment effect of smoking on depression for each of the 84 SNPs. Each bound is based on a set of values for the trivariate distribution randomly sampled. Bounds are color coded to show if they overlap 0 (grey) or do not (red). All bounds overlap 0.

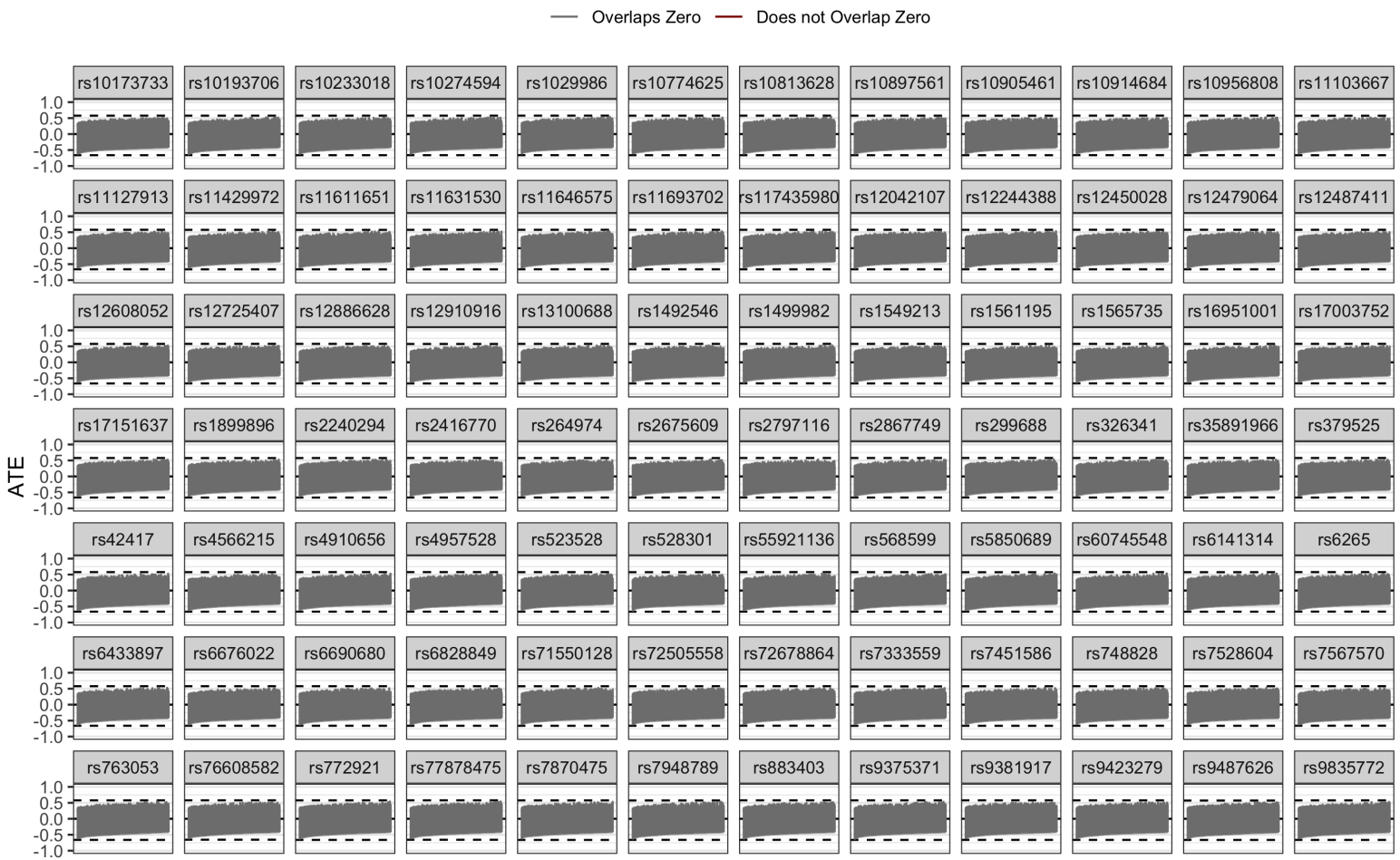


Figure 13: 500 sets of bounds of the average treatment effect of smoking on lung cancer for each of the 84 SNPs. Each bound is based on a set of values for the trivariate distribution randomly sampled. Bounds are color coded to show if they overlap 0 (grey) or do not (red). All bounds overlap 0.

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