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1 Introduction

Title: Bounds in Two-Sample Mendelian Randomization With Summary Statistics: A Guide to Practice? or Promises and Pitfalls?

I would use Bibtex to manage your references. This is almost always required for most journals.

The gold standard to estimate the causal effect of a treatment or an exposure on an outcome is a randomized trial where the treatment assignment is randomized. 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) would not be feasible with a randomized trial due to ethical concerns. In such settings, epidemiologists rely on different types of observational studies, which introduces potential biases from unmeasured confounders. In recent years, there has been an increase in using instrumental variable (IV) in the form of Mendelian randomization (MR) Cite <https://academic.oup.com/ije/article/32/1/1/642797> and 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, as instruments to estimate the causal effect of an exposure on an outcome. This is based on the idea being that genotypes are randomly assigned when passed on from parents to offspring at meiosis (Lawlor et al. 2008) and thus, they make excellent candidates for satisfying (A2), especially when the exposure of interest is environmental.

MR analyses often use published summary statistics from two independent genome wide association studies Cite Burgess, Butterworth, and Thompson's Mendelian randomization analysis...; Pierce and Burgess' efficient design for mendelian...; and Burgess et al's Using published data in mendelian randomization...;(Davies, Holmes, and Smith 2018) Not sure about these citations...we can discuss(Erich and Narayanan 2014; Fuller et al. 1999; Wang et al. 2017). Typically, the first study provides information about the exposure and instrument and the second study provides information about the outcome and instrument. Once investigator have summary statistics from two studies, they use methods based on parametric modeling assumptions Cite <https://www.amazon.com/Mendelian-Randomization-Estimation-Interdisciplinary-Statistics/dp/1466573171> and <https://journals.sagepub.com/doi/full/10.1177/0962280215597579> to arrive at point estimates and tests for the exposure effect.

An alternative approach to study the casual effect of the exposure without parametric assumptions is through non-parametric IV bounds (Robins (1989), Manski (1990), Balke and Pearl (1997), Richardson and Robins (2014), Cheng and Small (2006)) cite cheng and small Briefly, nonparametric IV bounds only use the bare minimum 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. The most well-known are the Balke-Pearl bounds for the average treatment effect under slight variants of assumptions (A1)-(A3), and 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 where the exposure and instrument are observed from one study and the outcome and instrument are observed from another study. For a recent overview, see Swanson et al. (2018).

Due to their nonparametric nature, the IV bounds are attractive approaches to analyze exposure effects especially if some modeling assumptions are suspect or difficult to justify. In MR, the minimal set of assumptions needed for non-parametric bounds is a stark contrast to many other MR approaches, such as the IVW estimator Cite Burgess, S., Butterworth, A., and Thompson, S. G. (2013). Mendelian randomization analysis..., MR-Egger regression Cite Bowden paper in Int Journal of Epi, weighted median Cite Bowden's paper in genetic epi and modes Hartwig's paper in Int Journal of Epi, MRRAPs cite recent AoS paper by Zhao et al. on RAPs, and others, that make parametric assumptions about the exposure effect. More generally, if IV bounds using fewer assumptions arrive at similar conclusions about the exposure effect as those based on parametric approaches, the case for the causal effect on the exposure becomes stronger.

Despite their attractive properties, there is a poor understanding about the behavior of IV bounds in two-sample MR studies using only summary statistics. The specific questions we will tackle in our work are

1. What kind of genetic instruments are needed to provide useful conclusions about the exposure effect, say the bound does not contain the null effect?
2. Can combining multiple instruments lead to shorter and tighter bounds on the exposure effect?
3. How do the bounds change if many instruments are weak, which is typically the case in MR studies based on genetic instruments?

In traditional setups for IV bounds where individual-level data consisting jointly of the outcome, the exposure, and a single instrument are available, the Balke-Pearl bounds are usually conservative and contain the null effect. However, it is not clear if the same principle holds for two-sample MR studies, especially if multiple candidate IVs are available. The goal of the paper is to address these questions and provide a more in-depth exploration of these bounds, specifically addressing what we can expect to learn and what information can be gained by utilizing multiple IVs under assumptions similar to Balke-Pearl bounds

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

2 Setup

2.1 Review: Notation and Assumptions

In the following, let X and Y be binary exposure and outcome, respectively, Z be a categorical instrumental variable taking values in $\{0, 1, \text{ and } 2\}$, 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 **Cite Neyman 1923 and Rubin’s Estimating Causal Effects of Treatment in Randomized... (1974)** 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) **Cite Cox (1958), Rubin’s original 1980 work on this**, 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 **cite <https://journals-sagepub-com.ezproxy.library.wisc.edu/doi/pdf/10.1177/0962280206077743> and <https://arxiv.org/pdf/1611.09925.pdf>** 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) can be assessed by finding SNPs that have been consistently associated with the exposure through multiple GWAS (Marigorta et al. 2018). Assumption (A2) is usually checked based on scientific theory surrounding how the genetic instrument was inherited from the parents 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. For a more in-depth discussion of (A1)-(A3) in MR studies, see Lawlor et al. (2008). Finally (A4) states that if U is observed, then it is sufficient to unconfound the relationship between X and Y .

We make a few additional remarks about assumptions (A1)-(A4). First, most MR studies only make assumptions (A1)-(A3) along with some modeling assumptions **Cite MR book**. Second, the role of assumption (A4) is to mainly show the role that an unmeasured confounder U plays in potentially allowing identification of the causal effect of the treatment if it were measured; **Richardson and Robins** showed that one can remove (A4) and strengthen (A2) with $Z \perp U, Y^{z,x}$ and arrive at the same IV bounds of Balke and Pearl. Third, under SUTVA and assumptions (A3)-(A4), we have $Y \perp Z | X, U$, which is another common way to express the exclusion restriction in MR studies **cite <https://journals-sagepub-com.ezproxy.library.wisc.edu/doi/pdf/10.1177/0962280206077743>**

1177/0962280206077743. 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 boundsSwanson’s paper cite, Richardson and Robin’s bounds paperand its primarily purpose is to define a “causal” instrument Cite Hernan and Robins’s review paper of IV.

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 state the assumptions restricting the direction of the instrument’s effect on the exposure and the outcome.

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

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

A variant of assumption (A5) is common in the IV literature to study noncompliance Cite Angrist, Imbens, Rubin 1996 and Baiocchi, Cheng, and Small review paper in stat med. 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 and replication of findings from many observational studies.

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

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

ST matches the definition of instrument strength used in Balke and Pearl cite year when the instrument is binary; in that work, it was used to justify how the width of the IV bounds changed as a function of ST. However, (1) differs from other definitions of strength based on a parametric model between the exposure and the outcome, say the concentration parameter; see Stock et al. (review paper on weak IV, in JBES, early 2000, highly cited) for an overview.

2.2 Review: Study Designs and Target Estimand

There are roughly two designs of IV studies, 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. Also, the behavior of bounds under a one-sample design has been well-studied more extensively than in two-sample design Swanson’s paper cite.

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

The focus of the paper is on the average treatment effect (ATE)

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

where the second equality follows from SUTVA and assumptions (A3)-(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 cite Robins 1989 “The analysis of randomized and nonrandomized AIDS treatment trials using a new approach to causal inference in longitudinal studies”, Manski 1990, Balke and Pearl 1995.

In one-sample designs, sharp bounds on the ATE are well-established under assumptions (A1)-(A4) [Cite Balke and Pearl JASA, Ricahrdson and Robins, and Swanson](#); these bounds can also be used when individual-level data are not available, but population summary statistics in the form of $P(Y = y, X = x|Z = x)$ for y, x, z are known. In two-sample designs, Ramsahai (2012) showed that under assumptions (A1)-(A4), the bounds for the ATE are [Unify using \$Z = i\$ or \$Z = z_1\$ as we did with IV strength above. I'm fine with either one.](#)

$$\begin{aligned} \max \left\{ \begin{array}{l} \max_{i \neq j} P(Y = 1|Z = i) - 2 \cdot P(Y = 1|Z = j) - 2 \cdot P(X = 1|Z = j) \\ \max_{i \neq j} P(Y = 1|Z = i) + P(X = 1|Z = i) - P(Y = 1|Z = j) - P(X = 1|Z = j) - 1 \\ \max_{i \neq j} 2 \cdot P(Y = 1|Z = i) + 2 \cdot P(X = 1|Z = i) - P(Y = 1|Z = j) - 3 \\ \max_i -P(Y = 1|Z = i) - P(X = 1|Z = i) \\ \max_i P(Y = 1|Z = i) + P(X = 1|Z = i) - 2 \end{array} \right\} \\ \leq ATE \leq \\ \min \left\{ \begin{array}{l} \min_{i \neq j} P(Y = 1|Z = i) - 2 \cdot P(Y = 1|Z = j) + 2 \cdot P(X = 1|Z = j) + 1 \\ \min_{i \neq j} P(Y = 1|Z = i) + 2 \cdot P(Y = 1|Z = j) - 2 \cdot P(X = 1|Z = j) + 1 \\ \min_{i \neq j} P(Y = 1|Z = i) - P(X = 1|Z = i) + P(X = 1|Z = j) - P(Y = 1|Z = j) + 1 \\ \min_i P(X = 1|Z = i) - P(Y = 1|Z = i) + 1 \\ \min_i P(Y = 1|Z = i) - P(X = 1|Z = i) + 1 \end{array} \right\} \end{aligned}$$

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

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

The inequalities in equation (4) are extensions of the “IV inequalities” of Balke and Pearl [cite](#) used to check the validity of the IV assumptions. Versions of these inequalities have been used in MR studies [Cite swanson papers that used IV falsification inequalities](#) to check whether the genetic variants satisfy the IV assumptions. In the Appendix, we provide some details on deriving equations (2.2) and (4) as well as implementing the procedure using Polymake (Assarf et al. 2017), a linear program solver in R. We also discuss a minor, but important numerical issue concerning ordering of the bounds; we believe this issue is pertinent among investigators who are using a linear-program based software to compute these bounds [Cite R package from Vanessa](#).

3 Properties of Bounds from Two-Sample MR Studies With Summary Data

3.1 Bound From Single Instrument

We begin our investigation of bounds in equation (2.2) under two-sample MR studies with summary data 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 provide less information about the magnitude of the ATE, and are much less likely to provide any information regarding direction as compared to narrower bounds.

Theorem ?? shows the width of the ATE bound in equation (2.2) under a near-ideal MR study where all the assumptions (A1)-(A6) hold; 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 for every value of the unmeasured value. Theoretically, the extra assumptions (A5)-(A6) simplify the bound formula in equation (2.2), allowing us to precisely characterize the width of the min/max inequalities.

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

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

and the width of the above bounds is bounded from above by $2 - 2 \cdot ST$. *is this upper bound sharp when (A1)-(A6) hold? That is, there exists a DGP that satisfy (A1)-(A6) and the width of the bound from it is equal to the upper bound?*

The proof is presented in Appendix A. The bounds under the near-ideal MR setting is twice as large as the Balke-Pearl bounds with a binary IV in single-sample designs where the width is $1 - ST$. An instrument with strength $ST = 0.6$ would lead to a smaller bound with width 0.4 under a binary IV, single-sample design setting compared to a length of 0.8 in the near-ideal MR study. The doubling of the bound length under two-sample MR with summary data is a “cost” of using both non-binary instruments and two-sample designs. 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 ?? *cite section* where we exploit this phenomena to obtain more informative bounds in MR studies. Also, the width of the bounds in Theorem 3.1 is only guaranteed to be less than 1 when the instrument strength ST is greater than 0.5; a bound with length greater than 1 provides no information about the existence of the exposure effect since it will always cover zero. However, this does not imply that instruments with strength less than 0.5 have length less than 1 (see Figure 1 for an example).

We’ve been mostly focusing on width, but is it possible to derive sufficient condition about when $0 < \text{lower bound}$ OR when $0 > \text{UB}$? Th is would help us justify the centering plot in Fig 1a.

Contrary to what we discussed before, the more I think about this, the more I feel like we should avoid discussing this result since we don’t exactly know what’s going on with the bounds with $LB > UB$ and simply simulate until we have bounds that not only satisfy the IV inequalities above but pass basic sanity checks? It also distracts from the main message of the paper, I think. I did mention the $LB > UB$ issue above, just in case. 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 distribution of possible summary statistics that can arise from two-sample MR studies satisfying assumptions (A1)-(A4) and *fix this later?: provides a benchmark to compare with real data*. Figure 1 shows the bounds for 9,877; the remaining 123 did not satisfy the constraints *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?)*

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 frequently exceed 1. In particular, Table 1 shows that the proportion of the intervals presented on Figure 1 with width greater than 1, 0.75, and 0.5, stratified by 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% of the bounds lead to widths greater than 1 and about 46% of bounds from IVs with strength between 0.05 and 0.1 have width greater than 1. Also, only 63% of bounds with strength greater than 0.5 have widths less than 0.5.

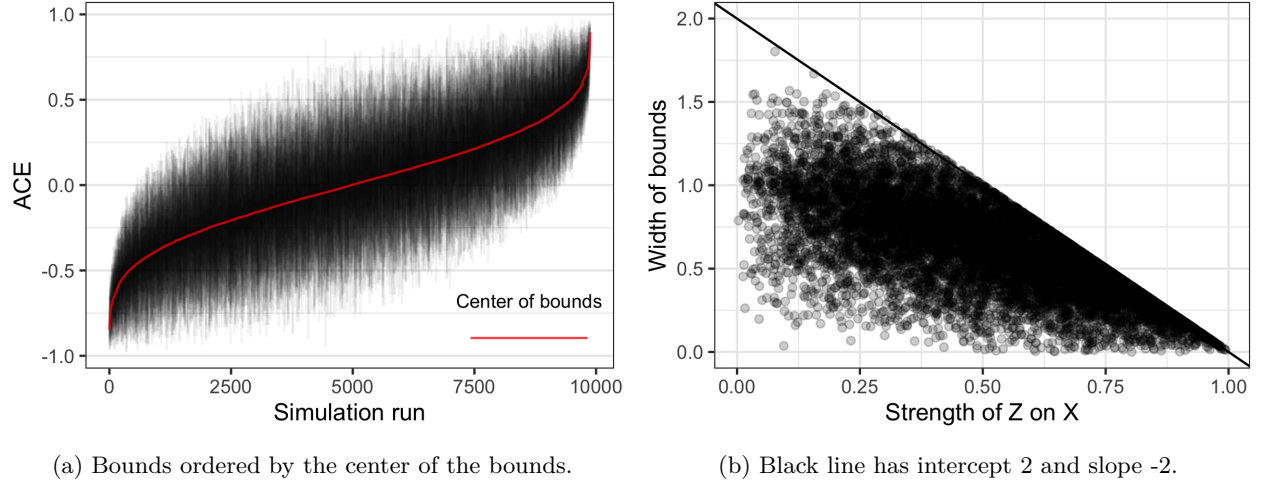


Figure 1: 10,000 values for bivariate distributions were randomly generated such that no constraints were violated. Of these, 123 resulted in bounds where the lower bound was greater than the upper bounds. These have been removed from these plots.

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 .

Strength	Proportion of bounds with width greater than...		
	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

Overall, in the context of two-sample MR studies with summary statistics, most genetic instruments are weak, which means that the chances that bivariate bounds from MR analyses are informative with width less than 1 are very slim. In particular, a strength requirement of $ST > 0.5$ to guarantee a bound with length less than 1 is a tall order in many MR studies. Perhaps, convert the difference in probability to roughly what it would correspond to in a logistic model, either as an odds ratio or beta coef? Even tying it to the smoking example by saying that one must find a genetic variant that can change the odds of smoking by a factor of BLANK would be helpful to understand for MR/GWAS practitioners looking at odds ratios/z-stats/p-val all day. Additionally, as our numerical results revealed, a set of bounds with width just below 1 does not provide much more information; a bound of $[-0.1, 0.8]$ for the ATE does not indicate that the average treatment effect is more likely to be positive than a bound of $[-0.7, 0.2]$ for the ATE.

Another good thing that we can perhaps include is a power curve of sorts? That is, given that the effect size to detect is equal to $0.2 = E[P(Y|X = 1, U) - P(Y|X = 0, U)]$, what kind of instrument do we need to detect this?

3.2 Bound With Multiple Instruments

Prior section revealed that bounds from two-sample MR studies with summary data require a strong instrument to guarantee meaningful widths. However, it did not address whether the bound can be used

improved upon by using multiple instruments. In this section, we consider one approach a few approaches to aggregate bounds across multiple instruments.

Formally, consider the following logistic model for the outcome when there are multiple instruments

$$\begin{aligned}\text{logit}(P(X = 1|Z_1 = z_1, \dots, Z_n = z_n)) &= \beta_0 + \sum_i \beta_i z_i \\ \text{logit}(P(Y = 1|X = x)) &= \gamma_0 + \gamma_1 x,\end{aligned}$$

where $\text{logit}(a) = \frac{1}{1+\exp(-a)}$, $y \in \{0, 1\}$, $x \in \{0, 1\}$, $z_i \in \{0, 1, 2\}$, and $\beta_i, \gamma_j \in \mathbb{R}$. This particular model is popular in MR I would actually use MR methods/studies to justify this model; I think some of the parametric approaches that I mentioned above use this model. I should have caught this earlier, but are we simulating unmeasured U ? Otherwise, the effect of X on Y is not confounded at all and you would be able to estimate without needing IVs We set $P(Z_j = 0) = P(Z_j = 2) = 0.25$ and $P(Z_j = 1) = 0.5$ and $\gamma_0 = -2, \gamma_1 = 0.2$. We also generate β_i from an i.i.d. uniform distribution with support 0 to $1/n$ Ralph, can we actually draw this from our smoking data's distribution? This way, it doesn't seem like the simulation is highly contrived?. I just realized that perhaps we should use p instead of n to denote number of IVs since n is typically used for sample size?. We then obtain summary-level statistics $P(Y = 1|Z_j = z_j)$ and $P(X = 1|Z_j = z_j)$ by numerically integration the above model.

Figure 2 shows the resulting bounds for the three different values of n plotted against the strengths of the IVs.

Thinking about this figure more closely and what this section represents, I actually think we need a bit more in-depth discussion about the behavior of multi-IV bounds when IV may be invalid, specifically discussing (1) union bounds and (2) finding a region of $[-1, 1]$, say \mathcal{S} where more than 50% of bounds contain \mathcal{S} ; the latter idea is inspired by the fact that if majority of the IVs are valid, then all these valid IV bounds will contain the ATE and thus, we only need to find the region of $[-1, 1]$ where majority of the IV bounds agree on.

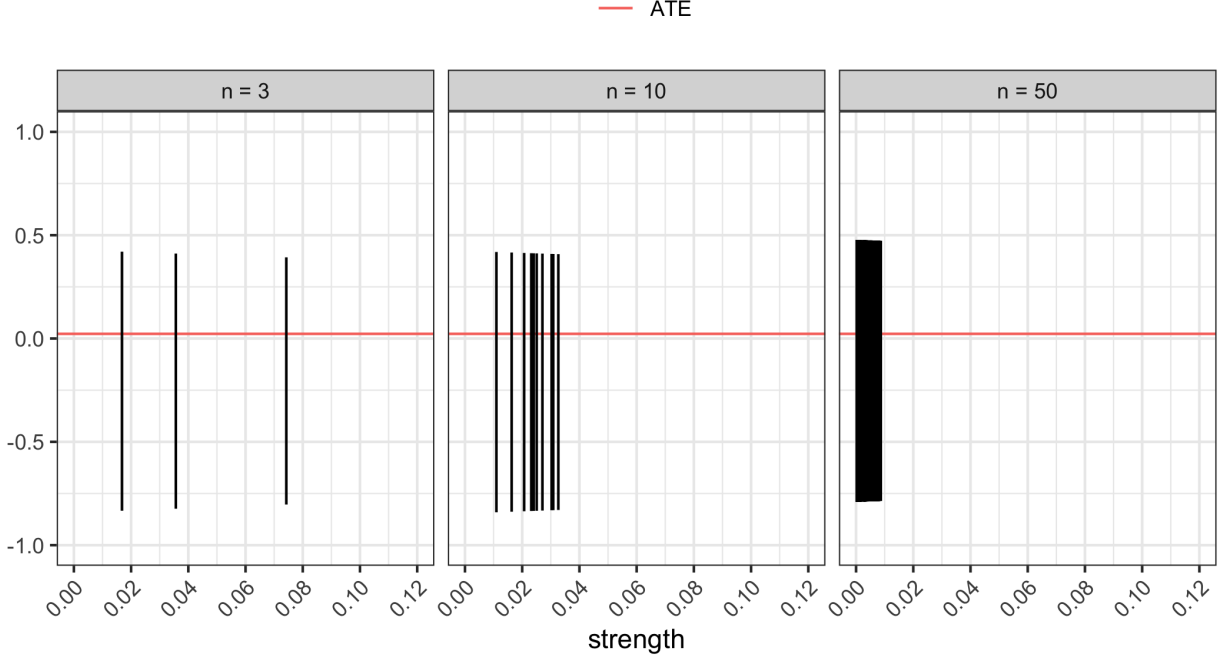


Figure 2: Bounds based on probabilities derived from the logistic model. Here, the coefficients are randomly chosen as $\text{Uniform}(0, 1/n)$ for different values of n .

Our results suggest that if all the instruments are valid, aggregating information from multiple instruments through intersections will not result in more information than simply using a single, strongest individual

bound. If, on the other hand, some instruments do not satisfy the IV assumptions and one takes a conservative approach by taking unions of bounds, the resulting bound would be valid in the sense that it will cover the true ATE. But, the union bound would be extremely conservative and ultimately provide even less information about the ATE. While other approaches to aggregation are possible, **work on later**

Combining our investigation into the behavior of bounds from Section 3.1, our general conclusion is that constructing bounds for two-sample MR studies with summary data rely on few assumptions, but are rarely informative. The two primary reasons for this is that (1) genetic instruments in MR are generally weak, leading to wide bounds and (2) only two-sample data is available to construct bounds. Without having strong instruments in the study, reason (1) is generally difficult, if not impossible, to address with any statistical methodology. Also, unless we change how MR data is collected, going from one-sample to two-sample studies, reason (2) is challenging, but not necessarily impossible, to address. In particular, 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 A More Informative Bound Through Construction of Plausible One-Sample Bounds

4.1 Approach

Our approach 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 $P(Y = y|Z = z)$, as well as the constraints imposed by the IV assumptions.

Formally, the joint conditional distribution $P(X = x, Y = y|Z = z)$ is a function of the marginal conditional distributions $P(X = x|Z = z)$ and $P(Y = y|Z = z)$ and the conditional covariate of the exposure X and Y given $Z = z$ $\text{Cov}(X, Y|Z = z)$ for each z

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

Since $\text{Cov}(X, Y|Z = z)$ is impossible to estimate, we instead propose to put a, uniform flat prior on this quantity that also results in the joint conditional distribution of $(X, Y|Z)$ being an actual probability distribution and satisfying the verifiable constraints from (4) from IV assumptions. Specifically, by the definition of a proper probability distribution, $\text{Cov}(X, Y|Z = z)$ must satisfy **If you want, I think we can make a lemma out of this?**

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

Additionally, by the IV inequality constraints, for any pair of $(z_1, z_2) \in \{0, 1, 2\} \times \{0, 1, 2\}$, the values of

$\text{Cov}(X, Y|Z = z_1)$ and $\text{Cov}(X, Y|Z = z_2)$ must satisfy

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

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 (4) 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). Ultimately, we have 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 the usual IV bounds by Balke and Pearl, Richardson and Robins from one-sample IV studies to obtain a bound for the ATE. If a large number of these bounds do not cover zero, then there is some evidence to suggest of a causal effect of the exposure and only reason we are not able to detect this effect is due to the limitations of the two-sample design. However, if majority of these IV bounds do cover zero, there is less evidence to suggest a causal exposure effect and/or that utilizing bounds to obtain some information about the ATE may be a hopeless exercise. In short, we are trying answer “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?”

The approach above can be thought of as using a quasi-empirical 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 nature as they are informed by data from two-sample MR.

4.2 Single Instrument

We illustrate the potential utility of the proposed method from the previous section by considering nine hypothetical MR studies, each using one instrument; see Section 4.3 for the case with multiple instruments. Table 2 presents nine different sets of values of the marginal distributions $P(Y|Z)$ and $P(X|Z)$ from nine hypothetical two-sample MR studies **Do you think we can find an empirical example to support some of these nine from MR-Base? I'm thinking about using popular exposures in the MR field (like CRP, cholesterol, or vitamin D?).**

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

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

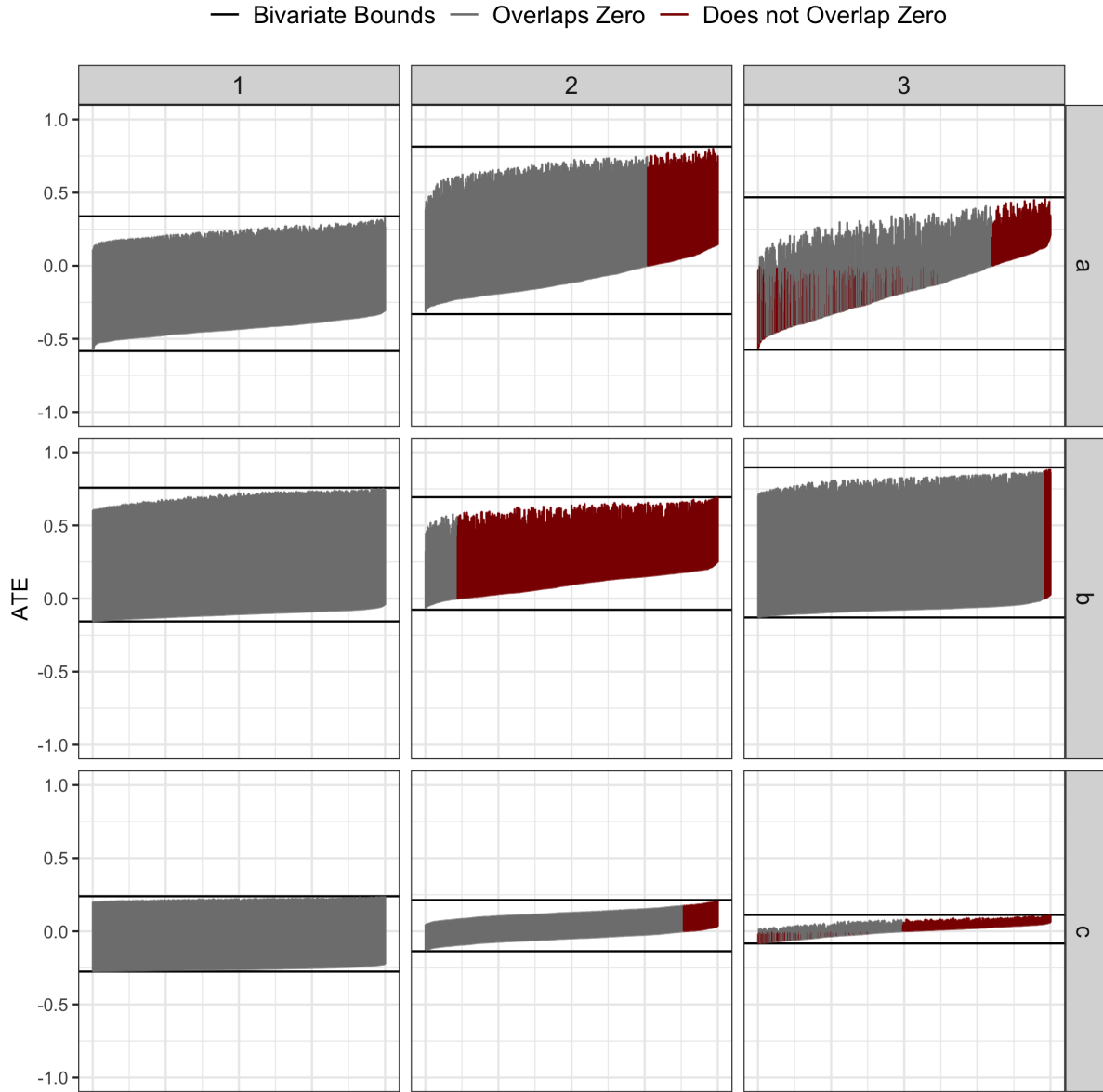


Figure 3: One-sample and two-sample bounds. Even similar bivariate distributions can result in very different insights.

Figure 3 show the resulting bounds only using two-sample data and the set of plausible one-sample IV bounds from our procedure. Row a 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 one-sample bounds would allow us to determine the presence of a non-zero causal effect. Column 2 indicates that about 24% of the one-sample IV bounds does not contain 0 while for column 3 that number is approximately 36.8%. However, while the direction of the effect is always the same for column 2 (positive), it varies for column 3.

Row b illustrates three scenarios where the two-sample bounds are centered well above zero and have 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 able to reveal some information about presence as well as the direction of the exposure effect.

We also remark that interpreting the proportion of one-sample bounds not containing 0 should be done with some caution. For example, a scenario like the one resulting in the bounds presented in row b, column 2 only provides information about the one-sample bounds under the assumption that all possible valid trivariate probability distributions are equally likely. Under this assumption, it tells us that it is much more likely that the ATE is positive. It does not, however, rule out a negative value of the ATE. What it does tell us is that trivariate bounds will not be able to determine direction *if the ATE is in fact negative*. This conclusion only hinges on the correctness of the marginal probabilities, $P(X = 1|Z = z)$ and $P(Y = 1|Z = z)$, and the assumptions presented in Section ??.

4.3 Multiple IV Case

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

The simplest extension to the multiple IV scenario, is to simply repeat the sampling procedure presented in Section 4.1 for each proposed instrument before creating the combined bounds by taking the intersection of the pairwise bounds. This builds on one main assumption in that the two sampling procedures are done independently, and so implicitly assume that the covariances of X and Y given Z_1 are independent of the covariances of X and Y given Z_2 .

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

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

5 Data Analysis

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

To be able to find non-parametric bounds, we need estimates of the marginal probabilities $P(Y = 1|Z = z)$ and $P(X = 1|Z = z)$. To do so, we use the **TwoSampleMR** R-package. This allows us to find studies that have explored the effects of genetic variants on the exposure and outcome variables we are interested in. Instruments were extracted, and LD based clumping ($r^2 \geq 0.001$ within a 10,000 kb window using $p < 5 \times 10^{-8}$ as the level of significance) performed such that only independent instruments with significant associations are

returned. The data is harmonized to make sure that the effects of the SNPs on exposure and outcome were measured with the same allele as reference. We obtain coefficients from GWAS experiments corresponding to the effects of the SNPs on the exposure, and the outcome from a logistic model. Since no intercept for these models are included in the reported results, but marginal proportions of the outcome, exposure, and allele frequencies are, we find the intercepts by solving $P(X = 1) = \sum_{z=0}^2 \text{logit}(\beta_0 + \hat{\beta}_1 \cdot z) \cdot P(Z = z)$ and $P(Y = 1) = \sum_{z=0}^2 \text{logit}(\gamma_0 + \hat{\gamma}_1 \cdot z) \cdot P(Z_j = z)$ for β_0 and γ_0 , respectively. This allows us to calculate $P(Y = 1|Z_j = z)$ and $P(X = 1|Z_j = z)$ for every j and $z = 0, 1, 2$. With these quantities, non-parametric bounds on the ATE can be calculated.

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

5.1 Smoking effect on depression

In our first example, we explore the effect smoking has as an exposure on the outcome depression. It has previously been suggested that smoking increases the risk of depression. Wootton et al. (2019) estimated the odds ratio using an inverse-variance weighted method to be 1.99 with a 95% confidence interval of [1.71, 2.32] suggesting a relatively strong causal effect.

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

The genetic markers that were identified here as potential instruments all look very similar in terms of the estimated conditional distributions of exposure and outcome given instruments. Figure 4 shows histograms of the values of $P(X = 1|Z = z)$ and $P(Y = 1|Z = z)$, $z = 0, 1, 2$, for all 84 instruments. As you can see, there is very little variation in the actual values. Especially the small change when moving from $z = 0$ through $z = 1$ to $z = 2$ on the three left panels is of interest here, as this is our first indication that these instruments might be rather weak.

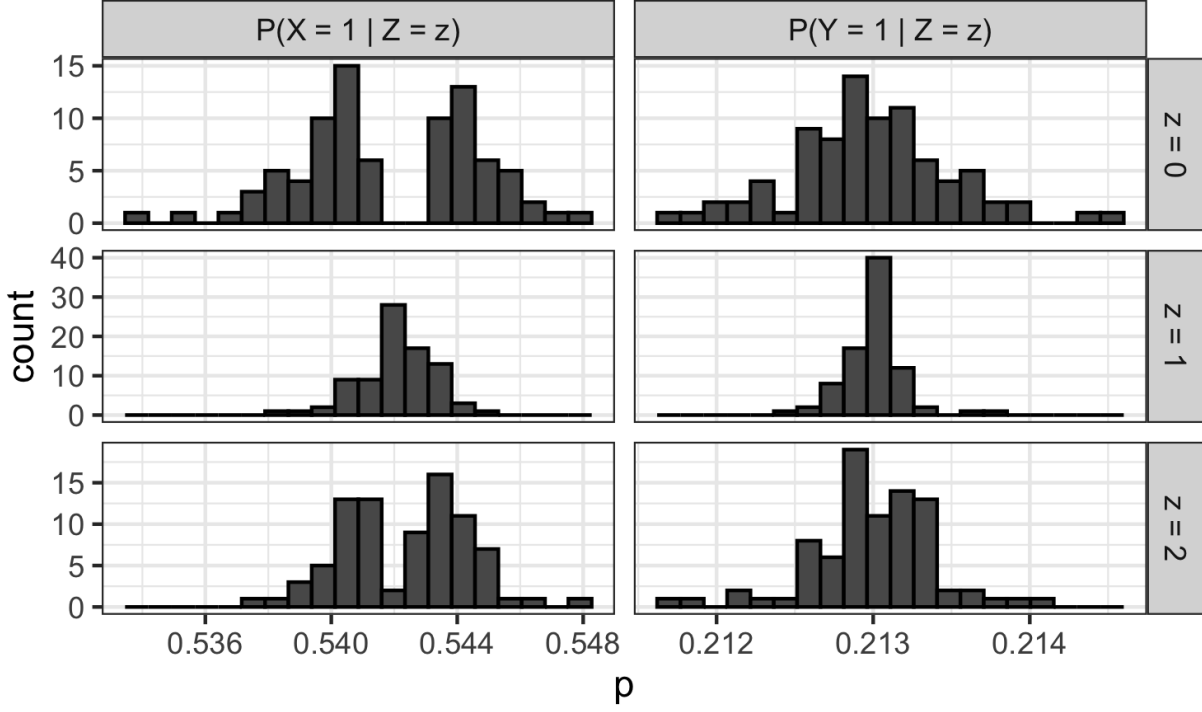


Figure 4: Histograms of the marginal conditional probabilities $P(X = 1 | Z = z)$, $z = 0, 1, 2$ and $P(Y = 1 | Z = z)$, $z = 0, 1, 2$.

Figure 5 shows a histogram of the strength of all the potential instruments. We see here that the strength of the strongest instrument is less than 0.01, which is much smaller than the 0.5 needed to guarantee narrow bounds, and well in line with the observation on Figure 4. More information on the instruments and summary statistics can be found in Appendix D.

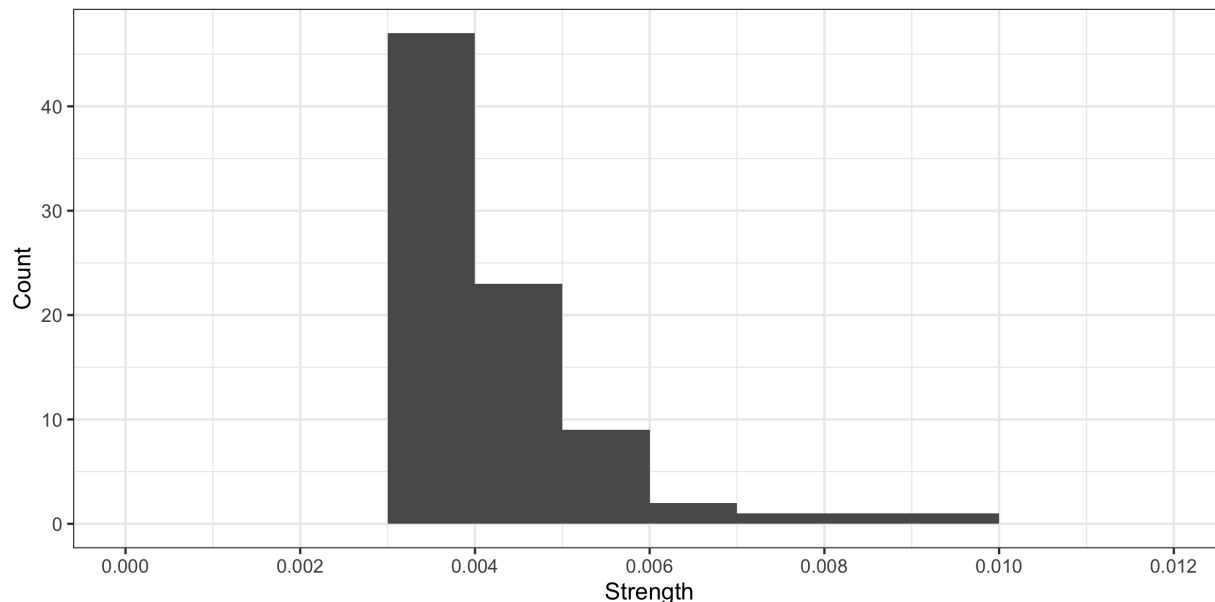


Figure 5: Histogram of strengths of IVs on the exposure. Here, SNPs are IVs, and smoking status (ever/never) is exposure. We see that all IVs are very weak, with the largest value just below 0.01.

From the 84 instrumental variables found, we obtain 84 sets of bounds using the values of $P(X = 1|Z_j = z)$, $P(Y = 1|Z_j = z)$, $z = 0, 1, 2$, $j = 1, 2, \dots, 84$. These are shown on Figure 6. From this figure, it is immediately clear that all the intervals are practically identical. This means that none of these instruments result in bounds that can help us determine direction of the ATE, and, in general, the amount of information they provide on the magnitude of the ATE is limited. This also tells us that trying to aggregate information from these instruments by simply creating intersection bounds will lead to essential no gains.

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

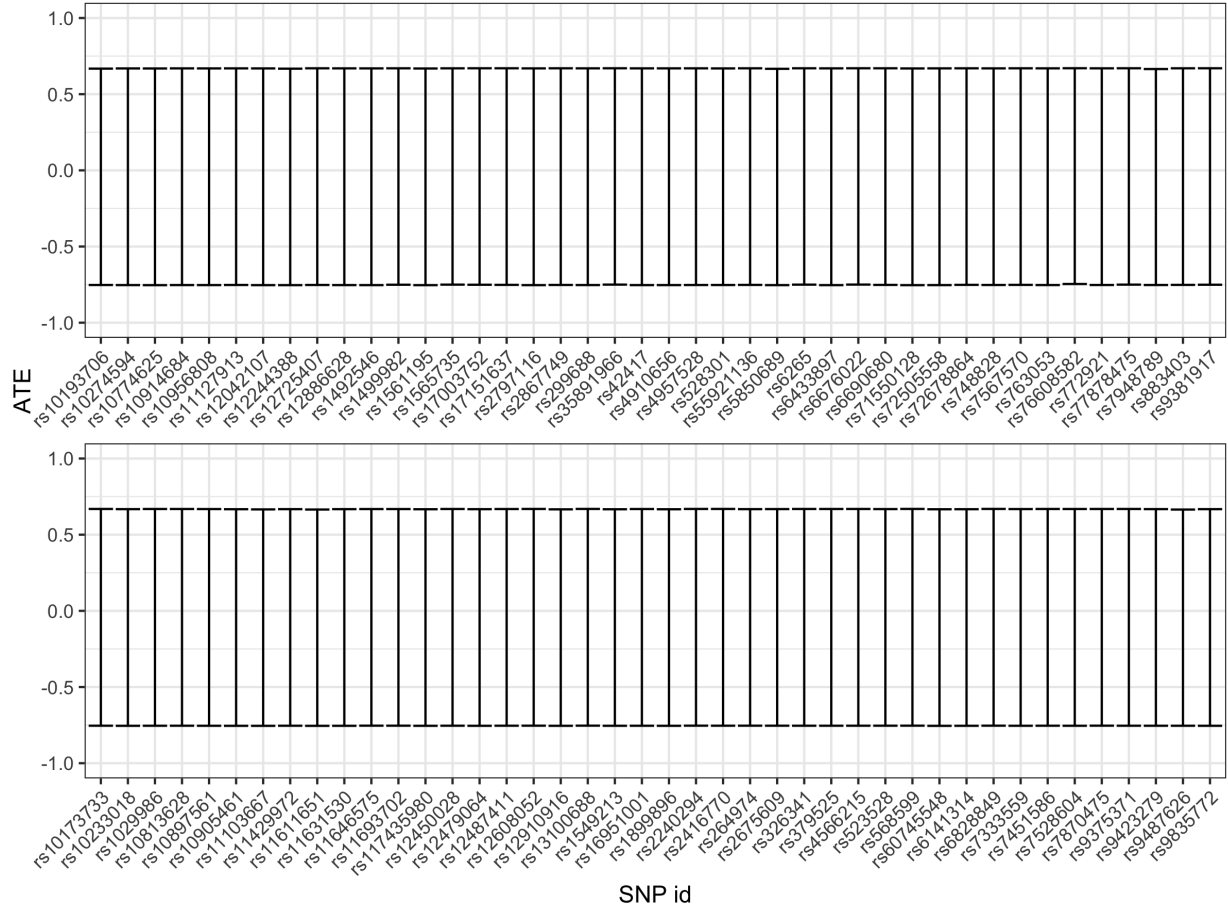


Figure 6: Non-parametric bounds for the 84 genetic variants identified as potential instruments for the effect of smoking on depression created based on the bivariate probabilities found from GWAS summary statistics.

With this in mind, we proceed to explore our quasi-bayesian approach. For each of the 84 genetic variants, we sample 500 potential trivariate distributions as described in Section 4. From these 500 trivariate distributions, non-parametric bounds are created. Figure 7 shows the resulting bounds.

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



Figure 7: 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.

Aggregating the information from multiple IVs through intersections is a simple idea, but everything we have seen so far points to this not being useful in practice. Figure 8 shows the results from doing exactly this for 9 pairs of SNPs, both when simply creating intersection of the bivariate bounds, and when using our quasi-bayesian approach to estimate the distribution of intersections of bounds from trivariate distributions as described in Section 4.3. Comparing Figure 8 to Figure 7, we notice that the intersection bounds are essentially the same width. As for intersections of trivariate bounds, these are narrower than the corresponding intersections of bivariate bounds, but we do not see any scenario where intersections of trivariate bounds would help us determine direction of the ATE.

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

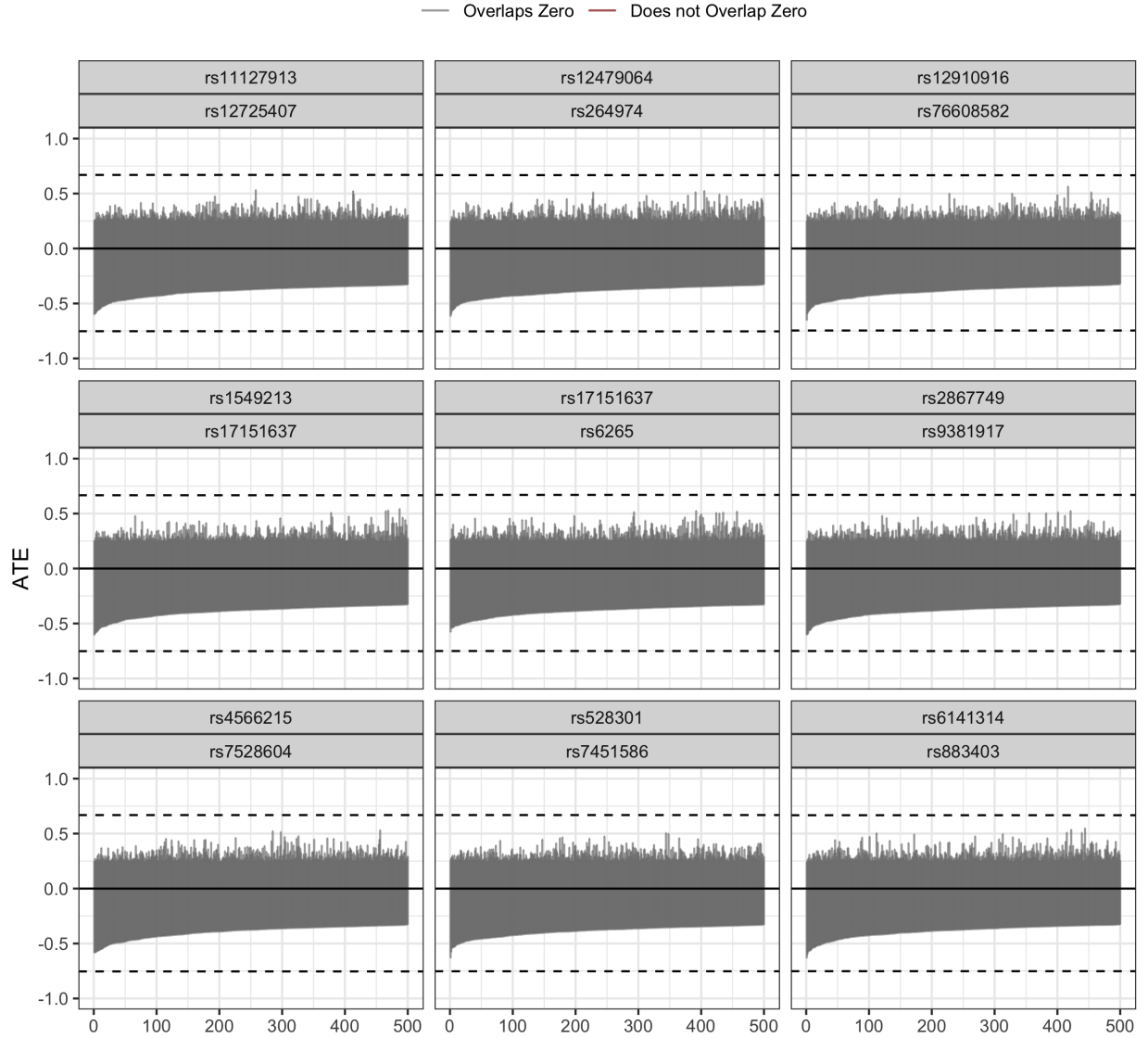


Figure 8: Intersection bounds of the average treatment effect of smoking on depression based on randomly sampled trivariate distributions from pairs of SNPs. These 9 pairs were randomly chosen from all possible pairs.

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

5.2 Smoking effect on lung cancer

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

The SNPs used here are the same as in Section 5.1, and therefore the marginal conditional distributions and distribution of strengths are the same. More information on the instruments and summary statistics can be found in Appendix D. Once again, the bivariate bounds (Figure 9) are rather wide (all have width greater than 1) meaning they convey no truly useful information about the ATE, and even if we were to obtain trivariate data, we will not be able to determine the direction of the ATE (Figure 10). Aggregating through intersections (Figure 11) does not lead to real gain in information, even if this is done using bounds based on trivariate distributions.

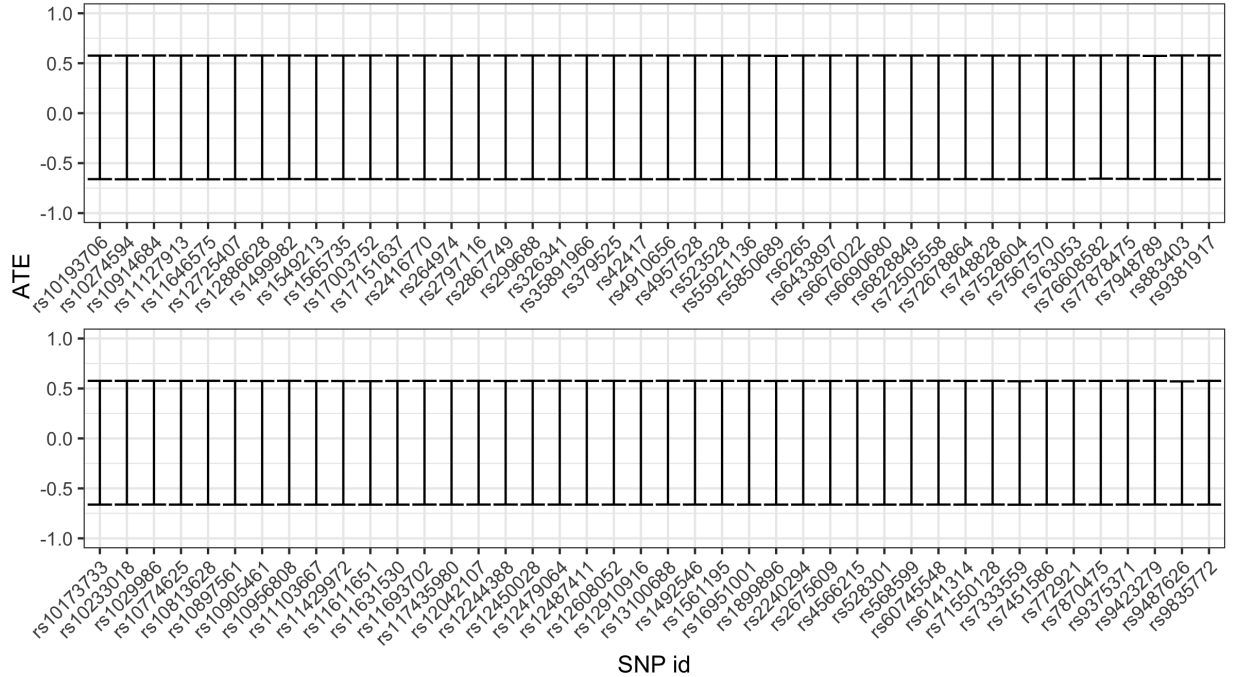


Figure 9: Non-parametric bounds on the average treatment effect of smoking on lung cancer.

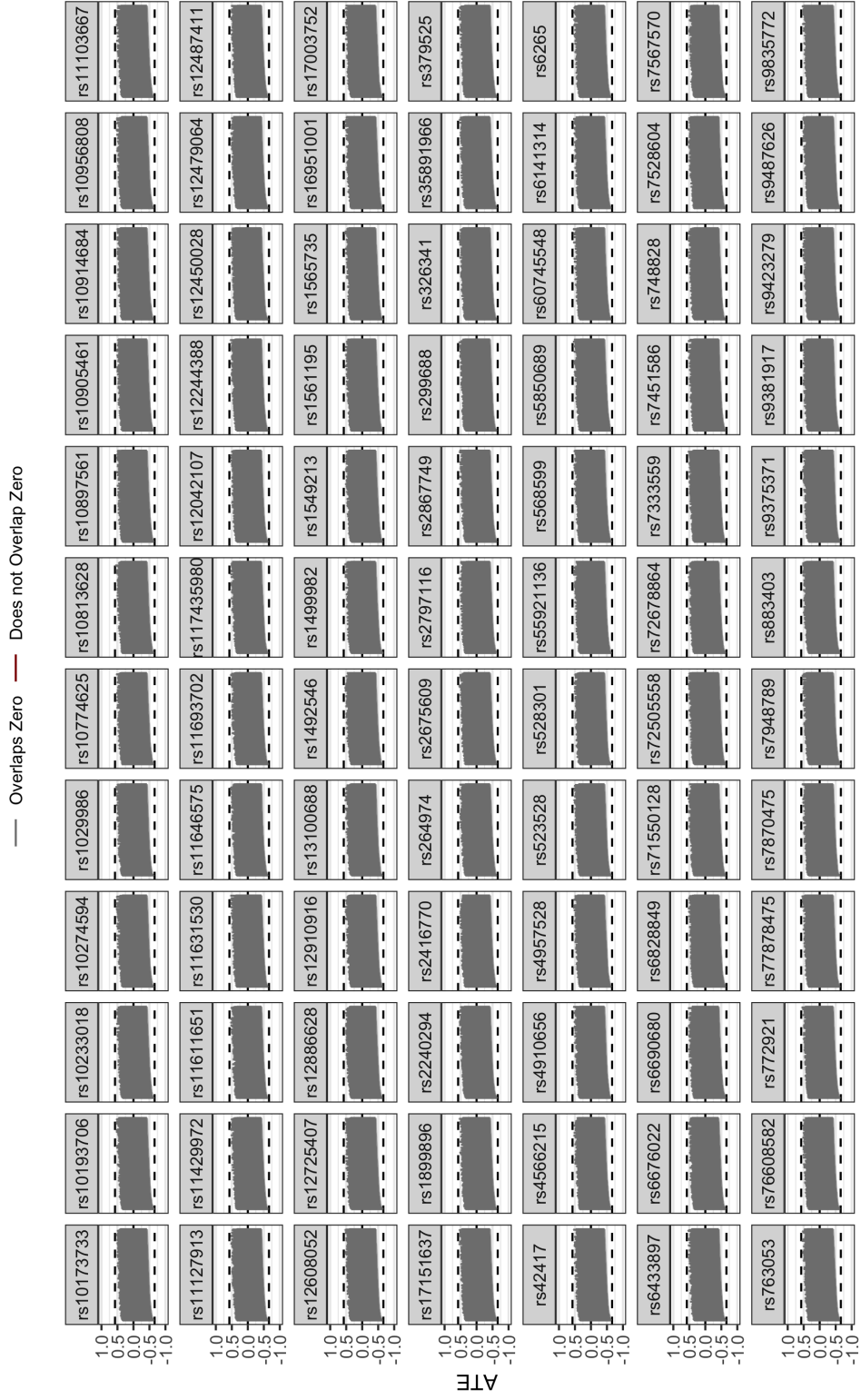


Figure 10: 500 sets of bounds of the average treatment effect of smoking on lung cancer for each of the 84 SNPs. Each bound is based on a set of values for the trivariate distribution randomly sampled. Bounds are color coded to show if they overlap 0 (grey) or do not (red). All bounds overlap 0.

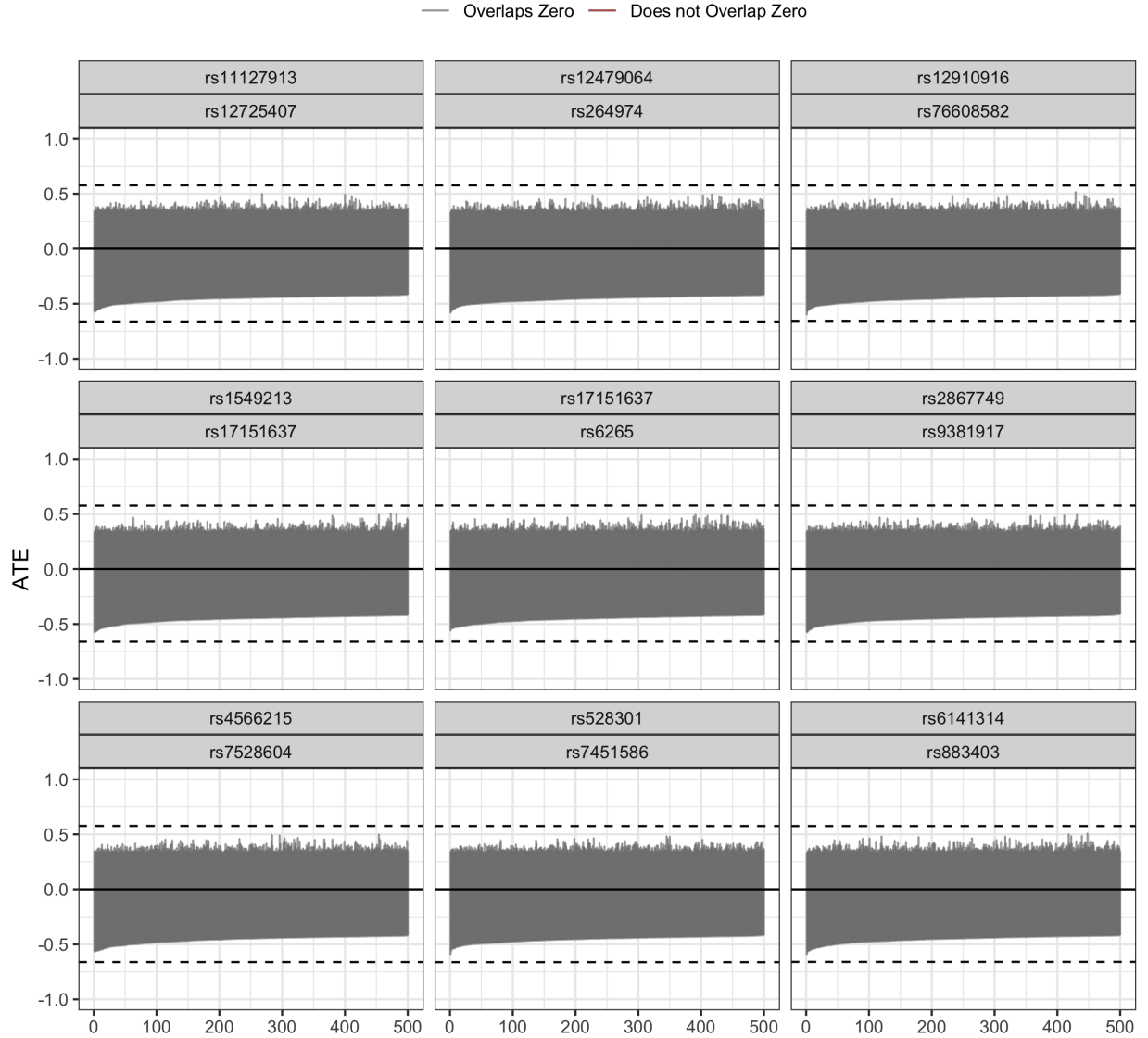


Figure 11: Intersection bounds of the average treatment effect of smoking on lung cancer based on randomly sampled trivariate distributions from pairs of SNPs. These 9 pairs were randomly chosen from all possible pairs.

This is a very concerning result. It is well established that smoking has a strong causal effect on the chances of developing lung cancer (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 bounds obtained using bivariate data. Even more concerning is the fact that trivariate distributions also are unsuccessful in determining the direction of the effect. Non-parametric bounds alone seem unable to give information about the direction of the effect, whether based on bivariate or trivariate data.

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 in a deterministic way – no probabilistic interpretations needed. It almost sounds too good to be true. As we have seen here, it turns out, in certain settings, it is.

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

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

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

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

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

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

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

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

but wish to get a better sense of the magnitude. Non-parametric bounds can provide an upper limit on this magnitude, which might in some scenarios be of use. For example in our second example, where the direction of the effect of smoking on lung cancer is well known, non-parametric bounds might help in providing an upper bound for the effect.

A Proof of Theorem 3.1

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

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

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

Width = U1 - L1

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

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

Width = U2 - L1

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

Width = U3 - L1

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

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

Width = U1 - L2

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

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

Width = U2 - L2

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

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

Width = U3 - L2

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

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

Width = U1 - L3

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

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

Width = U2 - L3

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

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

Width = U3 - L3

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

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

B Bounds on the Average Treatment Effect

Move this entire section to Appendix We review the method presented by Ramsahai (2012) to bound the average treatment effect using two-sample summary data. Let $\vec{\tau}^* = \left(P(Y = 1|X = 0, U), P(Y = 1|X = 1, U), P(X = 1|Z = 0, U), P(X = 1|Z = 1, U), P(X = 1|Z = 2, U) \right) \in [0, 1]^5$ and $\vec{v}^* = \left(P(Y = 0|Z = 0, U), P(Y = 0|Z = 1, U), P(Y = 0|Z = 2, U), P(X = 0|Z = 0, U), P(X = 0|Z = 1, U), P(X = 0|Z = 2, U), \alpha^* \right)$ where

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

Since $U \perp Z$, $E_U[P(X = x|Z = z, U)] = P(X = x|Z = z)$ and $E_U[P(Y = y|Z = z, U)] = P(Y = y|Z = z)$. Let $\vec{v} = E_U[\vec{v}^*] = \left(P(Y = 0|Z = 0), P(Y = 0|Z = 1), P(Y = 0|Z = 2), P(X = 0|Z = 0), P(X = 0|Z = 1), P(X = 0|Z = 2), \alpha \right)$, where

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

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

By the exclusion restriction, we have

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

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

$$f(y_0, y_1, x_0, x_1, x_2) = \begin{pmatrix} (1 - y_0) \cdot (1 - x_0) + (1 - y_1) \cdot x_0 \\ y_0 \cdot (1 - x_0) + y_1 \cdot x_0 \\ (1 - y_0) \cdot (1 - x_1) + (1 - y_1) \cdot x_1 \\ y_0 \cdot (1 - x_1) + y_1 \cdot x_1 \\ (1 - y_0) \cdot (1 - x_2) + (1 - y_1) \cdot x_2 \\ y_0 \cdot (1 - x_2) + y_1 \cdot x_2 \end{pmatrix}$$

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} .

I moved Section 3.2 into here

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
1	1	1	1	1

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

Table 4: Most extreme values of $P(Y = y|Z = z)$ and $P(X = x|Z = z, U)$. Here, $PYyZzU = P(Y = y|Z = z, U)$, $PXxZzU = P(X = x|Z = z, U)$, 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

PY0Z0	PY0Z1	PY0Z2	PY1Z0	PY1Z1	PY1Z2	PX0Z0	PX0Z1	PX0Z2	PX1Z0	PX1Z1	PX1Z2	α
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 $\sum_{z=0}^2 PX1Zz \cdot P(X = 1|Z = z) + \sum_{z=0}^2 PY0Zz \cdot P(Y = 0|Z = z) + PY1Z0 \cdot P(Y = 1|Z = 0) + c_\alpha \alpha \geq 0$.

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

PY0Z0	PY0Z1	PY0Z2	PY1Z0	PX1Z0	PX1Z1	PX1Z2	c_α
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
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

PY0Z0	PY0Z1	PY0Z2	PY1Z0	PX1Z0	PX1Z1	PX1Z2	c_α
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 $c_\alpha \neq 0$.

$$\max \left\{ \begin{array}{l} \max_{i \neq j} P(Y = 1|Z = i) - 2 \cdot P(Y = 1|Z = j) - 2 \cdot P(X = 1|Z = j) \\ \max_{i \neq j} P(Y = 1|Z = i) + P(X = 1|Z = i) - P(Y = 1|Z = j) - P(X = 1|Z = j) - 1 \\ \max_{i \neq j} 2 \cdot P(Y = 1|Z = i) + 2 \cdot P(X = 1|Z = i) - P(Y = 1|Z = j) - 3 \\ \max_i -P(Y = 1|Z = i) - P(X = 1|Z = i) \\ \max_i P(Y = 1|Z = i) + P(X = 1|Z = i) - 2 \end{array} \right\} \leq \alpha \leq \min \left\{ \begin{array}{l} \min_{i \neq j} P(Y = 1|Z = i) - 2 \cdot P(Y = 1|Z = j) + 2 \cdot P(X = 1|Z = j) + 1 \\ \min_{i \neq j} P(Y = 1|Z = i) + 2 \cdot P(Y = 1|Z = j) - 2 \cdot P(X = 1|Z = j) + 1 \\ \min_{i \neq j} P(Y = 1|Z = i) - P(X = 1|Z = i) + P(X = 1|Z = j) - P(Y = 1|Z = j) + 1 \\ \min_i P(X = 1|Z = i) - P(Y = 1|Z = i) + 1 \\ \min_i P(Y = 1|Z = i) - P(X = 1|Z = i) + 1 \end{array} \right\}$$

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

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

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:

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

C Exploration of Scenarios Where Bounds are Flipped

Of 10,000 randomly generated sets of values for $P(X = 1|Z = z), P(Y = 1|Z = z)$, $z = 0, 1, 2$, 123 resulted in bounds where the upper limit is smaller than the lower limit without violating any of the verifiable constraints presented in (4). 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 for Analyses Presented in Section 5

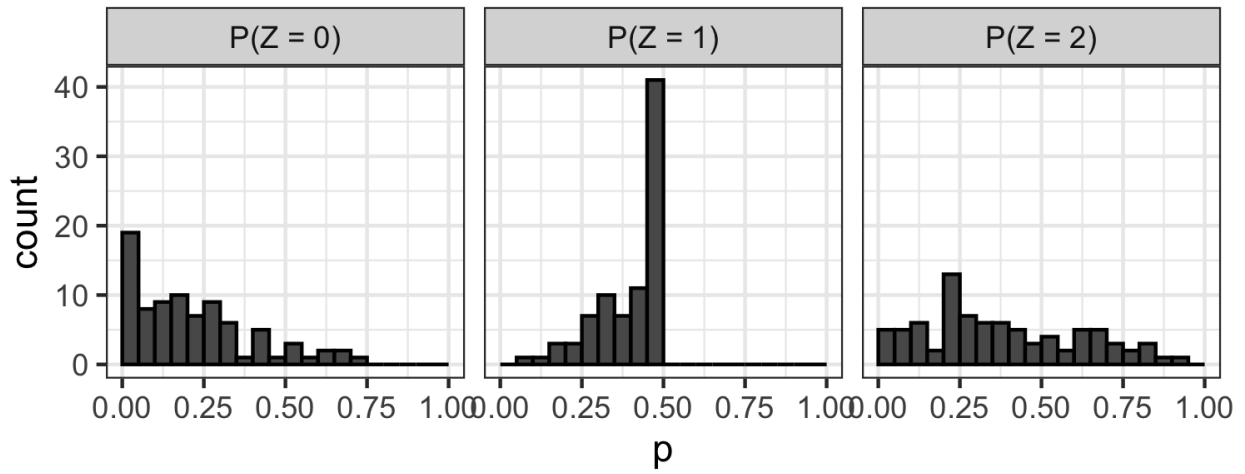


Figure 12: Histograms of the marginal distribution of instruments, $P(Z = z)$, $z = 0, 1, 2$, estimated after preprocessing for analysis in Section 5.1

Table 8: 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)	SNP	P(Z = 2)	P(Z = 1)	P(Z = 0)
rs10173733	0.3567595	0.4810680	0.1621726	rs2797116	0.5378179	0.3910856	0.0710965
rs10193706	0.2250921	0.4986932	0.2762147	rs2867749	0.4635738	0.4345775	0.1018487
rs10233018	0.2456177	0.4999613	0.2544211	rs299688	0.0809490	0.4071328	0.5119182
rs10274594	0.2534258	0.4999767	0.2465975	rs326341	0.2744742	0.4988573	0.2266685
rs1029986	0.1723555	0.4856034	0.3420411	rs35891966	0.8606480	0.1341263	0.0052257
rs10774625	0.2452793	0.4999550	0.2547657	rs379525	0.2693148	0.4992814	0.2314038
rs10813628	0.2353130	0.4995554	0.2651316	rs42417	0.0958938	0.4275468	0.4765594
rs10897561	0.4145906	0.4585930	0.1268164	rs4566215	0.2180425	0.4978154	0.2841421
rs10905461	0.0653045	0.3804860	0.5542095	rs4910656	0.4335363	0.4497969	0.1166669
rs10914684	0.4568603	0.4381082	0.1050314	rs4957528	0.0432628	0.3294687	0.6272685
rs10956808	0.3341139	0.4878239	0.1780622	rs523528	0.1717489	0.4853542	0.3428969
rs11103667	0.6529965	0.3101710	0.0368325	rs528301	0.2008634	0.4946289	0.3045076
rs11127913	0.3714083	0.4760490	0.1525428	rs55921136	0.6345353	0.3240838	0.0413808
rs11429972	0.1121109	0.4454375	0.4424516	rs568599	0.2093354	0.4963929	0.2942717
rs11611651	0.8320219	0.1602609	0.0077172	rs5850689	0.1341769	0.4642495	0.4015736
rs11631530	0.7776549	0.2083850	0.0139600	rs60745548	0.0747215	0.3972616	0.5280169
rs11646575	0.3152078	0.4924518	0.1923404	rs6141314	0.5745378	0.3668899	0.0585724
rs11693702	0.2857164	0.4976161	0.2166675	rs6265	0.6582044	0.3061871	0.0356085
rs117435980	0.6997059	0.2735567	0.0267374	rs6433897	0.0693904	0.3880603	0.5425494
rs12042107	0.2018720	0.4948594	0.3032687	rs6676022	0.7719180	0.2133413	0.0147407
rs12244388	0.4406271	0.4463408	0.1130321	rs6690680	0.7092842	0.2658119	0.0249040
rs12450028	0.4295142	0.4517182	0.1187675	rs6828849	0.3390095	0.4864715	0.1745191
rs12479064	0.6269478	0.3297051	0.0433471	rs71550128	0.2006117	0.4945706	0.3048177
rs12487411	0.2787537	0.4984352	0.2228111	rs72505558	0.3617365	0.4794177	0.1588458
rs12608052	0.2309196	0.4992427	0.2698378	rs72678864	0.6820022	0.2876641	0.0303337
rs12725407	0.6539829	0.3094184	0.0365987	rs7333559	0.0438714	0.3311672	0.6249614
rs12886628	0.1122813	0.4456055	0.4421132	rs7451586	0.3546216	0.4817591	0.1636193
rs12910916	0.6211224	0.3339816	0.0448960	rs748828	0.5136337	0.4060975	0.0802688
rs13100688	0.3932586	0.4676895	0.1390519	rs7528604	0.3204723	0.4912608	0.1882668
rs1492546	0.2020165	0.4948919	0.3030915	rs7567570	0.0300586	0.2866312	0.6833102
rs1499982	0.0222374	0.2537694	0.7239932	rs763053	0.6007027	0.3486949	0.0506025
rs1549213	0.1277548	0.4593465	0.4128986	rs76608582	0.9065935	0.0911171	0.0022894
rs1561195	0.2282248	0.4990080	0.2727672	rs772921	0.4307261	0.4511423	0.1181316
rs1565735	0.6370613	0.3221998	0.0407389	rs77878475	0.8356274	0.1569984	0.0073742
rs16951001	0.3381946	0.4867008	0.1751046	rs7870475	0.2766026	0.4986552	0.2247422
rs17003752	0.7422782	0.2385549	0.0191668	rs7948789	0.3779911	0.4736374	0.1483715
rs17151637	0.5169616	0.4040776	0.0789607	rs883403	0.7155911	0.2606702	0.0237388
rs1899896	0.4936293	0.4179166	0.0884542	rs9375371	0.5339661	0.3935275	0.0725064
rs2240294	0.3090443	0.4937465	0.1972092	rs9381917	0.8061282	0.1834365	0.0104354
rs2416770	0.2198025	0.4980570	0.2821405	rs9423279	0.1176593	0.4507114	0.4316293
rs264974	0.2632013	0.4996604	0.2371383	rs9487626	0.0333177	0.2984272	0.6682551
rs2675609	0.1388997	0.4675856	0.3935147	rs9835772	0.5732121	0.3677912	0.0589967

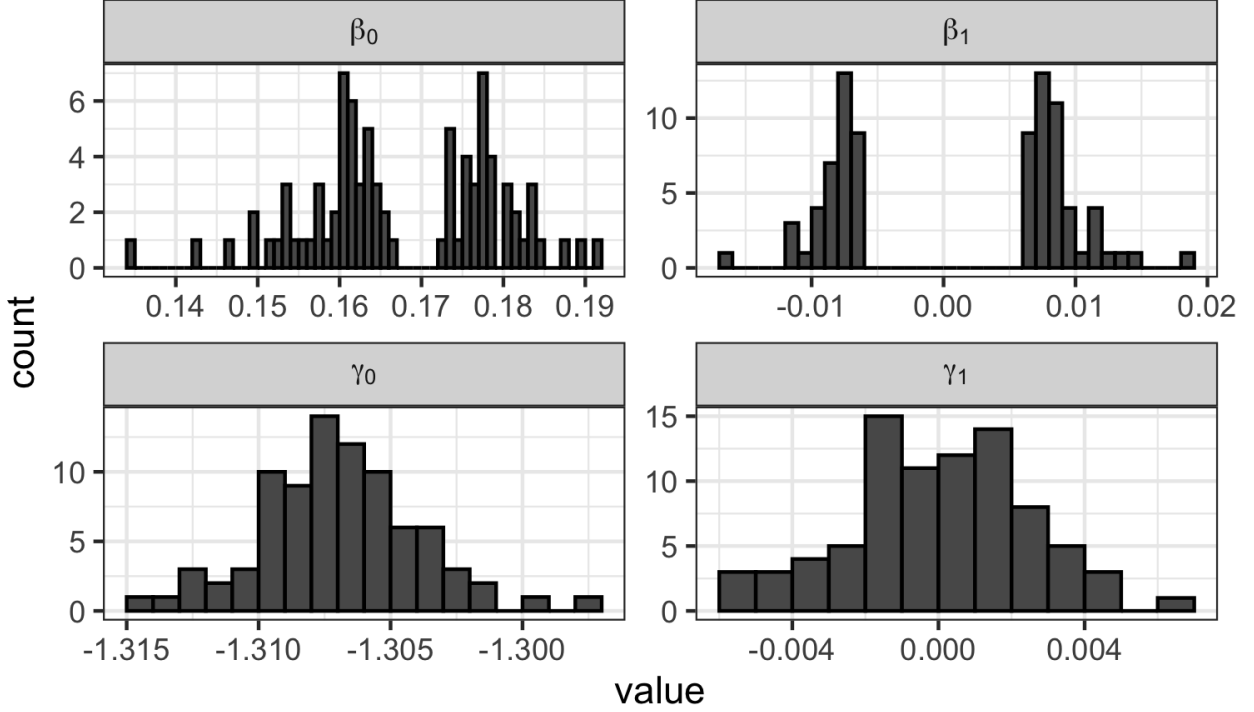


Figure 13: Histograms of the coefficients from GWAS results of logistic regression of the SNPs on smoking status and depression status, respectively. Intercepts (β_0 and γ_0) are inferred, while slopes (β_1 and γ_1) are as reported.

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

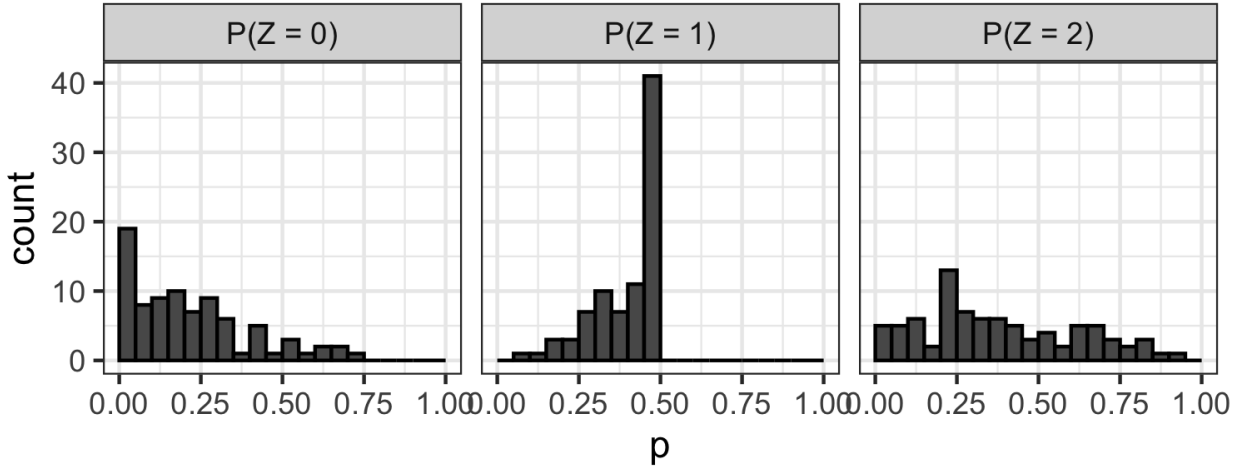


Figure 14: Histograms of the marginal distribution of instruments, $P(Z = z)$, $z = 0, 1, 2$, estimated after preprocessing for analysis in Section 5.2.

Table 10: Table of the marginal distribution of instruments, $P(Z = z)$, $z = 0, 1, 2$, estimated after preprocessing for analysis in Section 5.2

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

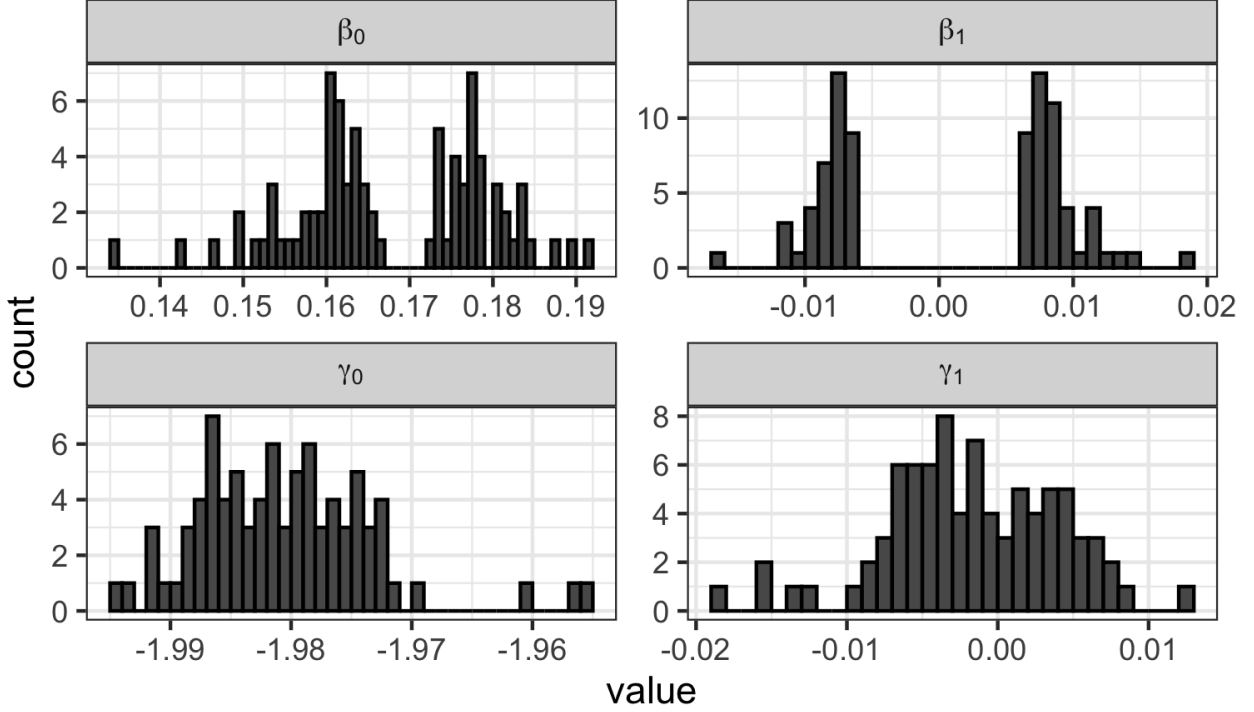


Figure 15: Histograms of the coefficients from GWAS results of logistic regression of the SNPs on smoking status and lung cancer status. Intercepts (β_0 and γ_0) are inferred, while slopes (β_1 and γ_1) are as reported.

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

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