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Average treatment effect of cholesterol-lowering medication and average systolic blood pressure (SBP), mm Hg.

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Summary: We investigate the average treatment effect among the treated (ATT) of cholesterol-lowering medication on the mean systolic blood pressure (mm Hg). Using data from the National Health and Nutrition Examination Survey (NHANES), we use the Inverse Probability Weighting method to estimate the ATT among adults living in the United States of America.

Key words: cholesterol-lowering medication,systolic blood pressure,blood pressure control.

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1. Introduction

Controlling blood pressure (BP) reduces the risk for cardiovascular disease. However, the prevalence of BP control (i.e., systolic BP $<$ 140 mmHg and diastolic BP $<$ 90 mmHg) among US adults with hypertension has decreased (CDC, CDC). In 2017-2018, prevalence of hypertension in the USA was 49.64% while the prevalence of blood control by medication is only 39.64% (Chobufo et al., 2020). Further interventions are needed to help improve the prevalence and hypertension control rates in the USA.

High blood pressure and high cholesterol often occur at the same time. According to survey, 60.7% to 64.3% of people with high blood pressure also have high cholesterol (Egan et al., 2013). The prescription of both anti-hypertensive and cholesterol-lowering drugs is generally required for these patients. It is recommended that doctors prescribe statin drugs like atorvastatin (Lipitor), and simvastatin (Zocor, FloLipid) for patients with high cholesterol or patients with high blood pressure (with or without high cholesterol) (Williams et al., 2020).

Statins (a chemical in cholesterol-lowering medication) have been proven to minimize the risk of cardiovascular adverse events since it block a substance the liver needs to make cholesterol (Liu et al., 2023). Thus statins have the potential to lower blood pressure. In many cases, simultaneously lower blood pressure and cholesterol level (Strazzullo et al., 2007).

Using a causal analysis approach, we aim to explore whether taking cholesterol-lowering medication have the potential to lower blood pressure. By analyzing the publicly available National Health and Nutrition Examination Survey (NHANES), we will estimate the average treatment effect of taking cholesterol-lowing medication among those who take the medication. Our exposure is whether or not a person has been taking any cholesterol-loweing medication at the time of the survey. Our primary outcome is the mean systolic blood pressure (DBP) at the time of the survey. The average treatment effect among the

treated (ATT) is the estimand of the different in DBP between taking cholesterol-lowering medication and not taking the medication. This estimand is conditioned on the exposed group.

With this causal question in mind, we want to control for demographics and a person bmi since high blood pressure disproportionately affect men, people of color, older people, obese people and people with diabetes and chronic kidney disease (Chobufo et al., 2020). Moreover, as stated before, if a patient have high BP, they are sometimes prescribed cholesterol-lowering medication along with anti-hypertensive medication to control for BP (Egan et al., 2013). In addition, if a person has high cholesterol, this has been shown to cause increase in BP. Moreover, smoking has been shown to increase BP. Furthermore, a person's BMI, smoking habit, and cholesterol may be a result of poor lifestyle habit. There are distinct cluster of lifestyle in different demographics. Patients with high BMI are also at risk of having high cholesterol.

2. Materials and methods

2.1 *Data*

The National Health and Nutrition Examination Survey (NHANES) combines interviews and physical examinations to assess the health and nutritional status of adults and children in the United States of America. The program started in the early 1960s and has been conducted every two years since 1999. The survey samples from a nationally representative 5,000 persons each year. The participants are located in counties across the country, 15 of which are visited each year. The interview asks questions about demographic, socioeconomic, dietary, and health-related questions. The examination consists of medical, dental, physiological measurements, and laboratory tests.

The NHANES dataset we are using is from the cardioStatsUSA R package. The dataset

contains information from the survey from 1999 to 2020 with a sample of 59,799 rows and 111 chosen columns focusing on cardiovascular disease. Each row is a noninstitutionalized US adults who participated in the survey between 1999 and 2020. The columns contain information about demographics, blood pressure levels, hypertension status, antihypertensive medication usage, and co-morbidities.

For this analysis, we had 38977 rows with NA values. We decided to deal with this by removing all the na values. We decided this was preferable to removing certain columns since we were still left with 20,822 data points which is still an extremely large data set. We also selected columns that represent our treatment, our outcome out interest, and the covariates we need to adjust for given the proposed causal directed acyclic graph in the Causal directed acyclic graphs section

2.1.1 *Exploratory data analysis.*

[Figure 1 about here.]

2.1.2 *Causal directed acyclic graphs.* We visualize the assumptions that we're making about the causal relationships between the use of cholesterol-lowering medication (the exposure), the mean systolic blood pressure (the outcome), and other possible confounders in the data set using a directed acyclic graph (DAG) (Figure @ref(fig:fig-dag)). The demographic variable include: age, gender, and race.

[Figure 2 about here.]

Given our assumptions, we obtained the adjustment set that will help us control for possible confounders (@ref(fig:fig_adjustment)). Our adjustment set only includes the amount of total cholesterol, demographics, and whether they use anti-hypertensive medication.

[Figure 3 about here.]

2.2 *Statistical methods*

We aim to answer our causal question by fitting an average treatment effect among the treated. Our causal question is as follows: Among those who take cholesterol lowering medication, does taking this cholesterol lowering medication change their systolic blood pressure?

We fitted a propensity score model with our DAGS adjustment set as our explanatory variable (Causal directed acyclic graphs), and whether a person was taking cholesterol medication as our response variable. We employed a logistic regression model for the propensity score model. We log transform our age variable since the distribution is usually skewed.

Subsequently, we used the propensity score as weight for our exposure variable (taking cholesterol medication). To estimate the average treatment effect among the treated, we fit a weighted linear regression model. We use the weighted cholesterol medication as our explanatory variable and systolic blood pressure as our response variable.

To assess the appropriateness of our propensity score model and proceed with our final model, we perform diagnostic using weighted mirrored histograms, empirical cumulative distribution function (ECDF) plots, and Love plots.

3. Results

3.1 *Study population*

Table 1: **Table 1. Survey Participant Characteristics**

Taking Cholesterol-lowering Medication	**No**, N = 21,071	**Yes**, N = 4,433	**Overall**, N = 25,504
Total cholesterol, mg/dL	192 (166, 221)	173 (149, 201)	189 (163, 218)

Taking Cholesterol-lowering Medication	**No**, N = 21,071	**Yes**, N = 4,433	**Overall**, N = 25,504
Unknown	237	64	301
Systolic blood pressure (SBP), mm Hg	119 (109, 131)	129 (117, 142)	120 (110, 133)
Unknown	914	171	1,085
Race/ethnicity			
Non-Hispanic White	8,639 (41%)	2,320 (52%)	10,959 (43%)
Non-Hispanic Black	4,430 (21%)	840 (19%)	5,270 (21%)
Non-Hispanic Asian	1,179 (5.6%)	244 (5.5%)	1,423 (5.6%)
Hispanic	5,973 (28%)	865 (20%)	6,838 (27%)
Other	850 (4.0%)	164 (3.7%)	1,014 (4.0%)
Gender			
Men	9,943 (47%)	2,356 (53%)	12,299 (48%)
Women	11,128 (53%)	2,077 (47%)	13,205 (52%)
Age at Screening Adjudicated - Recode	42 (28, 58)	66 (58, 75)	47 (31, 63)
Self-reported antihypertensive medication use	3,475 (17%)	2,880 (65%)	6,355 (25%)
Unknown	116	4	120

3.2 *Propensity score model and Diagnostics*

We fitted a propensity score model with "total cholesterol" in mg/dL as our explanatory variable and "taking cholesterol medication" as our response variable. We employed a Logistic Regression model for this purpose. Subsequently, we examined a Mirrored Histogram of our

propensity scores for both exposure groups. The table below demonstrates significant overlap in propensity scores across both groups, indicating very little evidence of a positivity violation in our model, which is promising.

Next, we used our propensity score model to generate weights for the average treatment effect among the treated (ATT), aligning with our causal question. To assess the appropriateness of our propensity score model and the resulting weights, we created a Weighted Mirror Histogram of our propensity scores. As shown below, we achieved sufficient balance between the exposed and unexposed groups. Furthermore, the distribution of the unexposed group now resembles that of the exposed group, which is the desired outcome when using ATT weights.

We also generated a love plot, displaying the standardized mean difference changes for the exposed and unexposed groups regarding our "total cholesterol" variable in both unweighted and weighted data. As expected, our weighted data exhibit a standardized mean difference of 0 for the "total cholesterol" variable, which is ideal and allows us to proceed.

Finally, we created a weighted empirical cumulative distribution function (eCDF) plot for our continuous variable, "total cholesterol." As shown below, the Weighted ECDF plot indicates balance not only in the mean across exposure groups but also across their respective distributions. No changes are required for our model, and we can now proceed to estimate our average treatment effect among the treated.

3.2.1 *Diagnostics.*

[Figure 4 about here.]

[Figure 5 about here.]

[Figure 6 about here.]

[Figure 7 about here.]

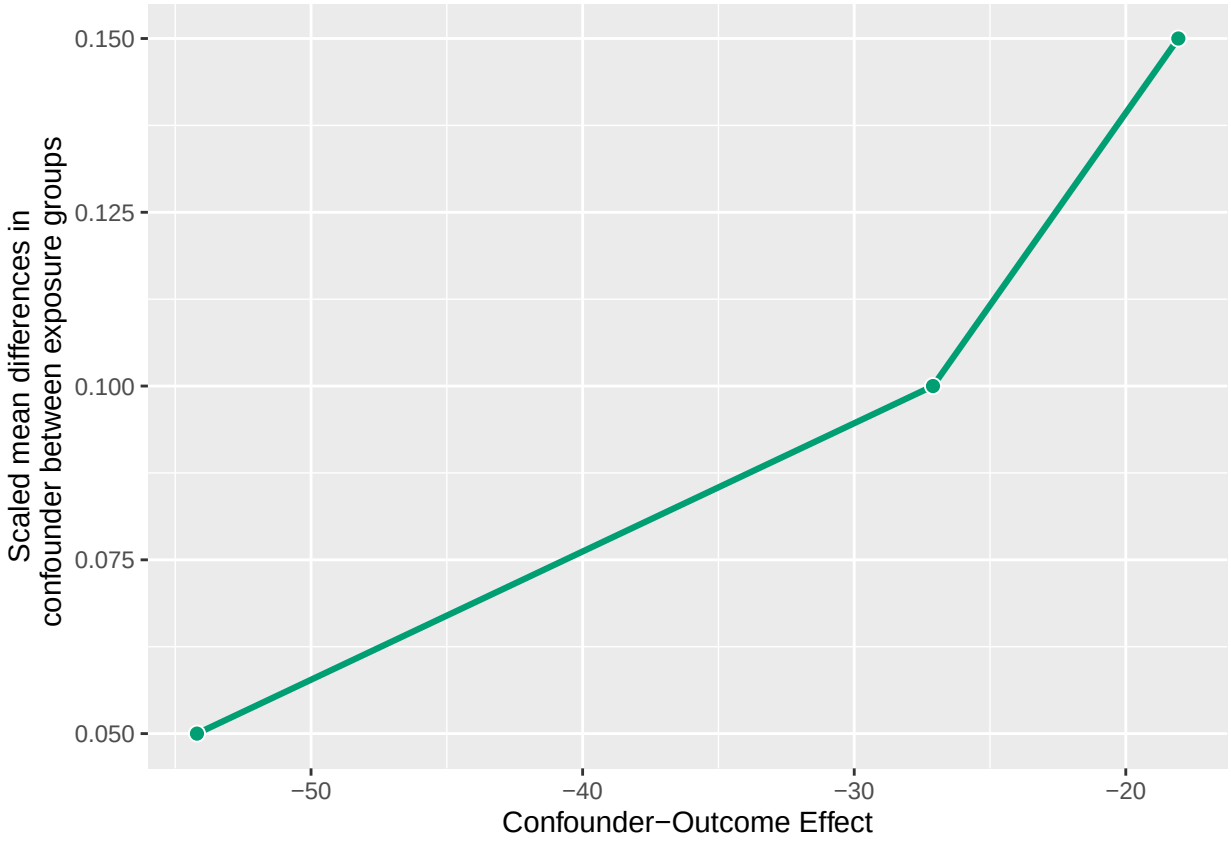
3.3 *Average treatment effect among the treated*

We estimated the average treatment effect of taking cholesterol-lowering medication. Our findings indicate that, on average, individuals who take cholesterol-lowering medication experience a decrease 3.911 mm Hg in their Systolic Blood Pressure (SBP). We are 95 percent confident that the average effect of taking this medication on SBP falls within the range of at least -4.960 mm Hg to at most -2.863 mm Hg.

Characteristic	**Beta**	**95% CI**	**p-value**
Taking a cholesterol-lowering medication			
No	—	—	
Yes	-3.9	-5.0, -2.9	<0.001

3.4 *Sensitivity analysis*

We conducted a sensitivity analysis to account for the possibility that our Directed Acyclic Graph (DAG) might not include all potential confounding variables. In this analysis, we calculated the necessary relationship between an unmeasured confounder and the change in weight required to shift the lower bound of the confidence interval to the null hypothesis level (5%). We considered exposure confounder effects of sizes 0.05, 0.10, and 0.15, which would necessitate confounder-outcome effects of 172, 85, and 57, respectively, to influence the interval. The smallest of these values, 57, is over 6 times greater than the estimated treatment effect. Therefore, it is reasonable to conclude that the Average Treatment Effect (ATT) we computed is robust against potential confounding factors.



4. Discussion

4.1 *Limitation*

Our dataset does not include information on when a person start taking the anti-hypertensive medication and the cholesterol-lowering medication in relation to a biophysical measurement.

Furthermore, in addition to pharmacotherapy, it is also important to adopt a lifestyle change include exercise, a healthy diet, regulating sodium, reducing alcohol use, reduce smoking, getting sleep, reducing stress, and regular health check-ups.

Even with prescribed medication, the barriers to effective blood control includes those that are under the control of the physician (patients' insufficient education and motivation, reluctance to initiate lifestyle changes or drug treatment) and those that are under the

control of the patients (failure to comply with recommended lifestyle modifications and poor medication compliance) (Düsing, 2006).

5. Conclusion

We conclude that for people taking cholesterol-lowering medication, they should continue to do so.

6. Supplementary information

The data can be downloaded from GitHub or accessed via the cardioStatsUSA R package. For both the file and information about the R package, see `https://github.com/jhs-hwg/cardioStatsUSA`.

All code for the analysis can be accessed at **link github**

7. Acknowledgement

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References

CDC. Prevalence of Hypertension and Controlled Hypertension — United States, 2007–2010.

Chobufo, M. D., Gayam, V., Soluny, J., Rahman, E. U., Enoru, S., Foryoung, J. B., Agbor, V. N., Dufresne, A., and Nfor, T. (2020). Prevalence and control rates of hypertension in the USA: 2017–2018. *International Journal of Cardiology Hypertension* **6,** 100044.

Düsing, R. (2006). Overcoming barriers to effective blood pressure control in patients with hypertension. *Current Medical Research and Opinion* **22,** 1545–1553. Publisher: Taylor & Francis _eprint: https://doi.org/10.1185/030079906X120995.

Egan, B. M., Li, J., Qanungo, S., and Wolfman, T. E. (2013). Blood Pressure and Cholesterol Control in Hypertensive Hypercholesterolemic Patients. *Circulation* **128,** 29–41. Publisher: American Heart Association.

Liu, H. T., Deng, N. H., Wu, Z. F., Zhou, Z. Y., Tian, Z., Liu, X. Y., Wang, Y. X., Zheng, H. Y., Ou, Y. S., and Jiang, Z. S. (2023). Statin's role on blood pressure levels: Meta-analysis based on randomized controlled trials. *The Journal of Clinical Hypertension* **25,** 238–250.

Strazzullo, P., Kerry, S. M., Barbato, A., Versiero, M., D'Elia, L., and Cappuccio, F. P. (2007). Do Statins Reduce Blood Pressure? *Hypertension* **49,** 792–798. Publisher: American Heart Association.

Williams, B., Masi, S., Wolf, J., and Schmieder, R. E. (2020). Facing the Challenge of Lowering Blood Pressure and Cholesterol in the Same Patient: Report of a Symposium at the European Society of Hypertension. *Cardiology and Therapy* **9,** 19–34.

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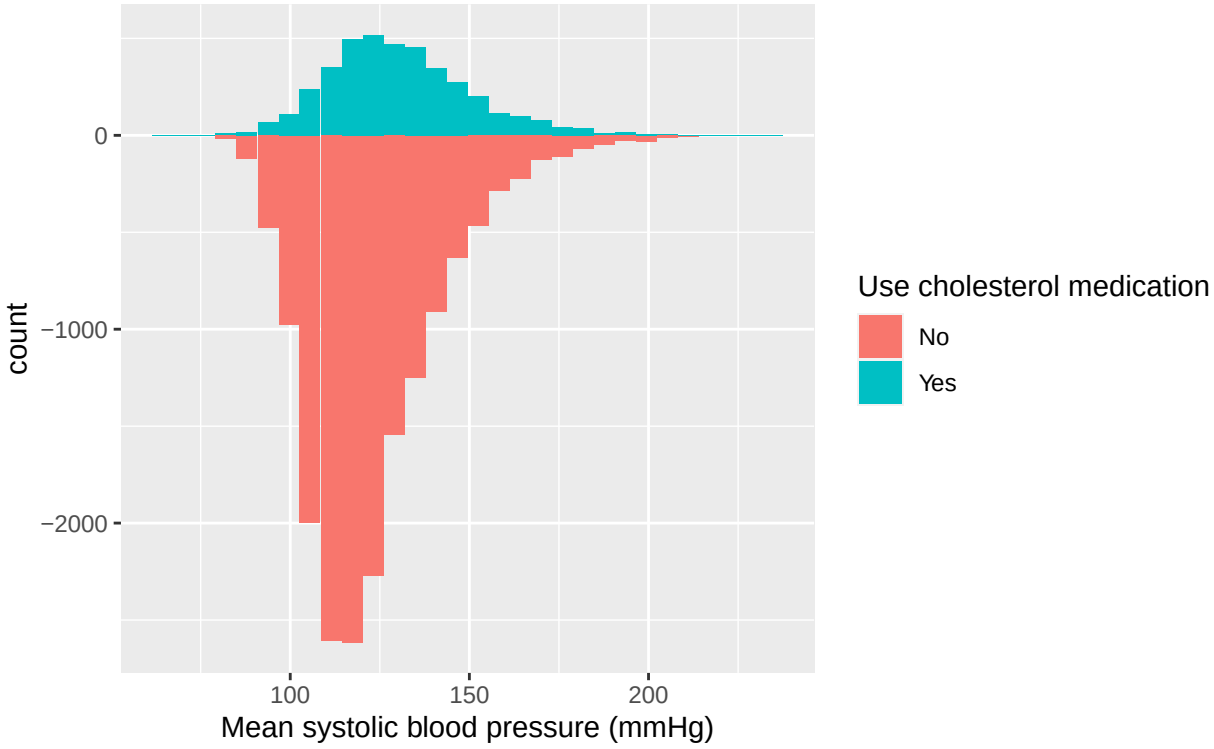

Figure 1. Mirror histogram by whether the participants use cholesterol medication

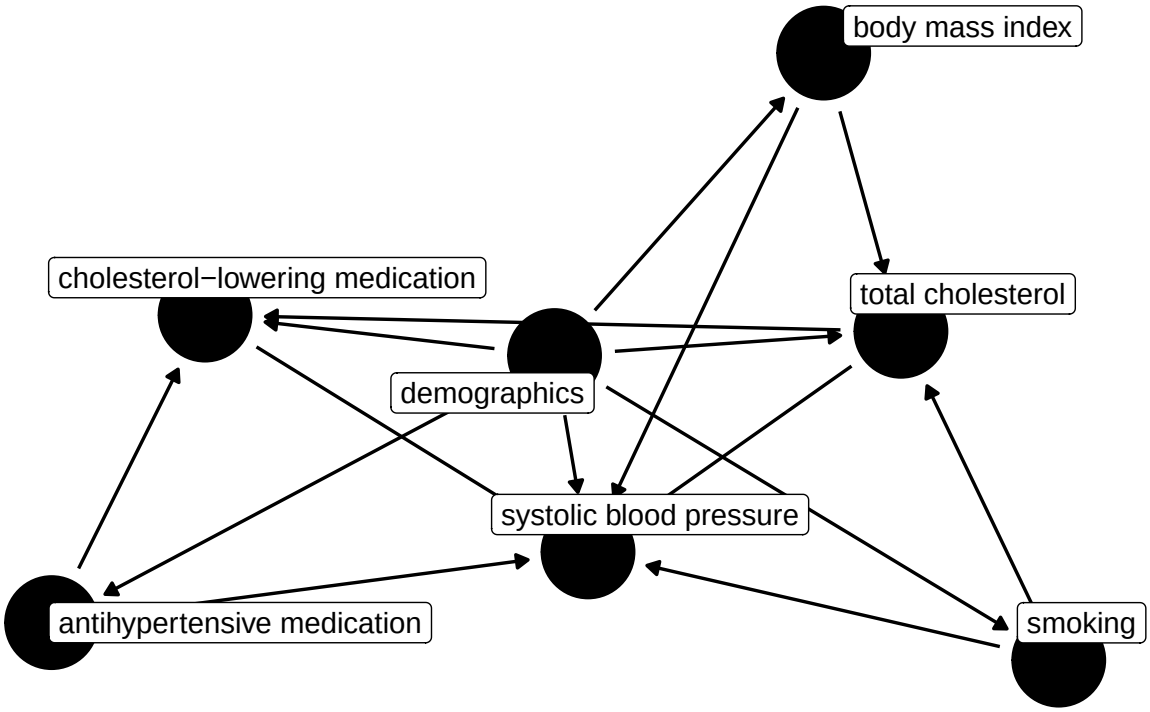

Figure 2. Causal direct acyclic graph between cholesterol-lowering medication and the mean systolic blood pressure

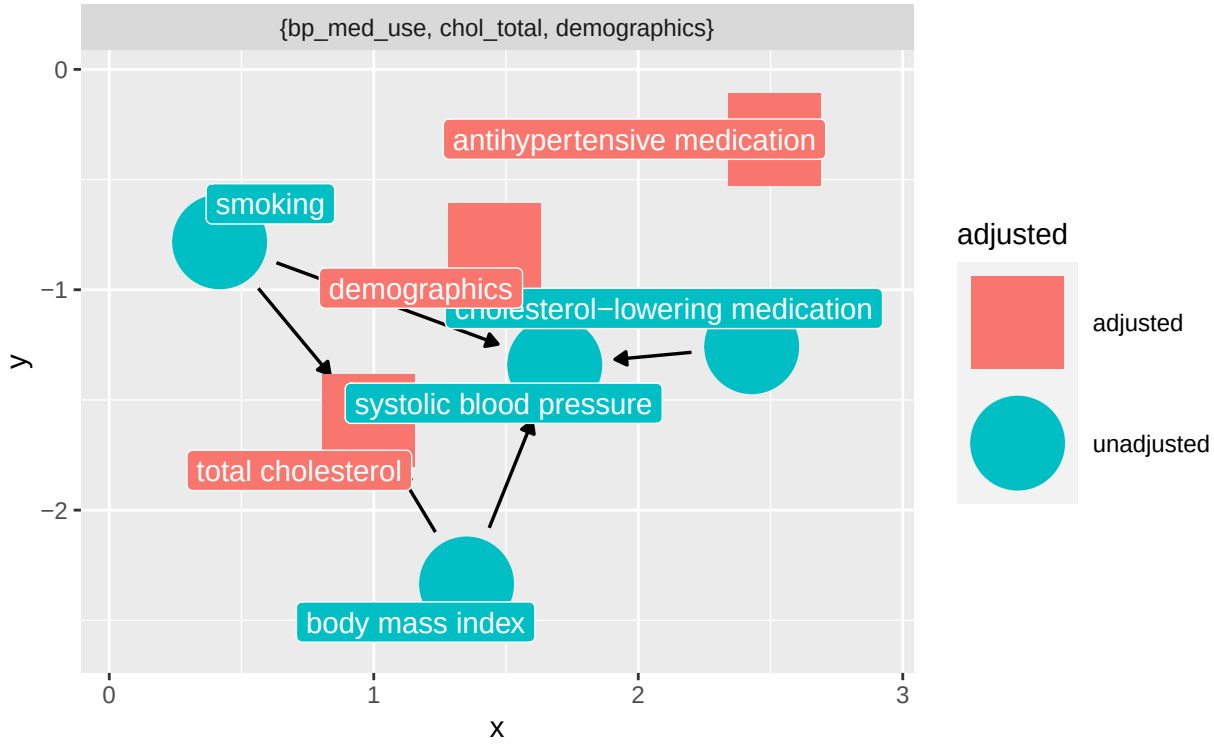

Figure 3. Causal adjustment set

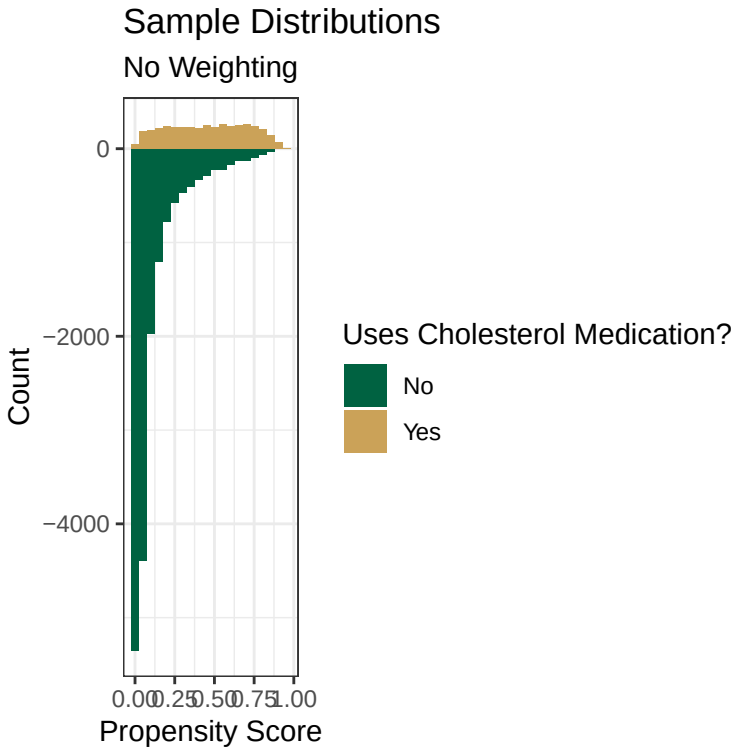

Figure 4. Mirror histogram of propensity score by treatment group

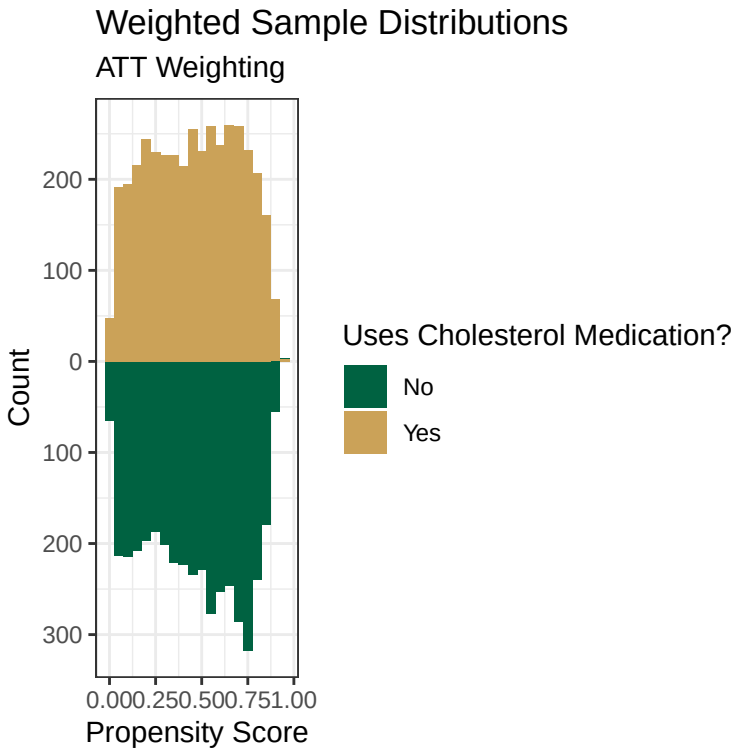

Figure 5. Mirror histogram by whether the participants use cholesterol medication using ATT weighting

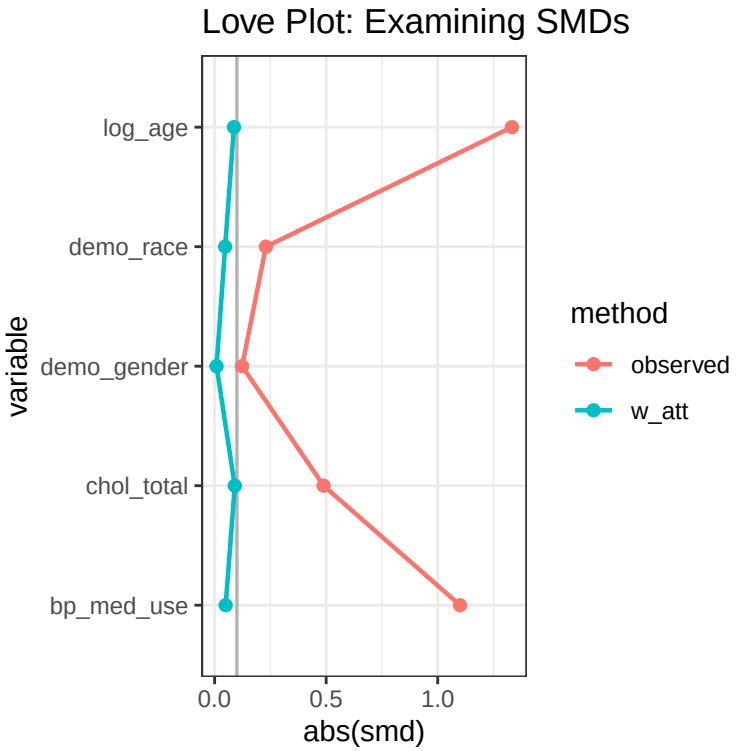

Figure 6. Love plot for covariates

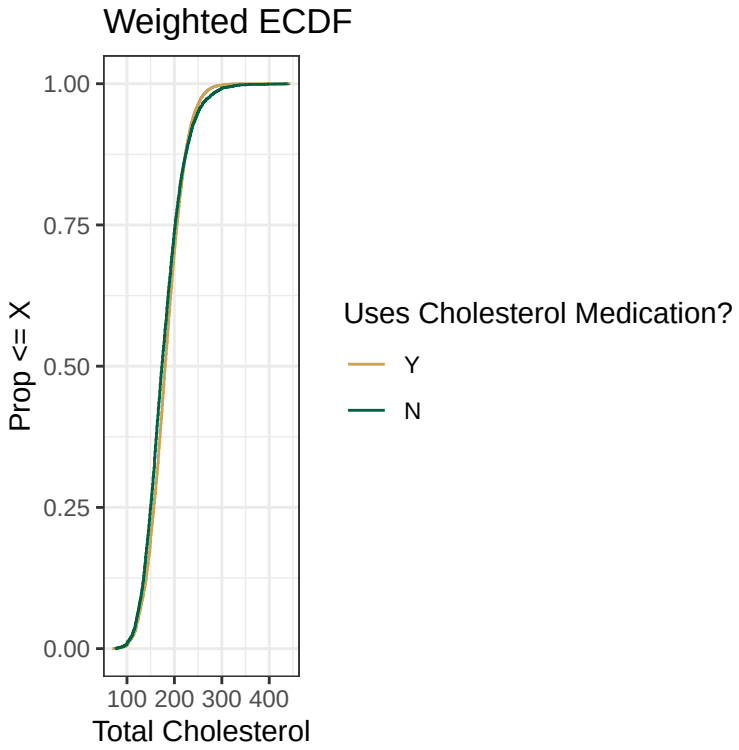

Figure 7. Empirical cummulative distribution function for numerical covariates