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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 fit a propensity score model to estimate the ATT among adults living in the United States of America.

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

This paper has been submitted for consideration for publication in *Biometrics*

talk more about population of dataset add ATT description, what it is for a non causal expert

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. The prescription of both antihypertensive 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). (Egan et al., 2013)

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).

explain our dags and why we include thing

We want to control for demographics since high blood pressure disproportionally

add short summary of methods here

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 among those who take cholesterol-lowering medication. Our exposure is whether or not a person take any cholesterol-loweing medication at the time of the survey. Our primary outcome is mean systolic blood pressure (DBP) at the time of the survey.

add short summary of results here

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 can be downloaded from **cite** . The dataset contains information from the survey from 1999 to 2020 with a sample of 59,799 rows and 111 chosen columns. Each row is a noninstitutionalized US adults participated in the survey between 1999 and 2020. Tahe 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.

[Figure 1 about here.]

2.2 *Statistical methods*

We fitted a propensity score model with "Total cholesterol" in mg/dL as our explanatory variable since this was the only variable, and "taking cholesterol medication" as our response variable, as it represents our exposure variable. We employed a Logistic Regression model for the propensity score model.

Subsequently, we used the propensity score model to fit our outcome model, estimating the average treatment effect among the treated. We utilized a linear regression model with "cholesterol medication" as our explanatory variable and "Systolic blood pressure (SBP)" in mm Hg as our response variable.

To assess the appropriateness of our propensity score model and proceed with our final model, we employed weighted mirrored histograms, ECDF plots, and Love Plots.

2.2.1 *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.

[Figure 2 about here.]

Given our assumptions, we need to adjust for the following adjustment set. The adjustment is given in Figure @ref(fig:fig_adjustment).

[Figure 3 about here.]

2.2.2 *Exploratory data analysis.*

```
## `stat_mirror_count()` using `bins = 30`. Pick better value with `binwidth`.
```

[Figure 4 about here.]

2.2.3 *Modeling.*

3. Results

3.1 *Study population*

We aim 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?

```
nhanes_data_selected |>
  select(-c(log_age)) |>
  tbl_summary(
    by = chol_med_use) |>
  # add an overall column to the table
  add_overall(last = TRUE)
```

Characteristic	**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)
Unknown	237	64	301
Systolic blood pressure (SBP), mm Hg	119 (109, 131)	129 (117, 142)	120 (110, 133)
Unknown	914	171	1,085
Self-reported antihypertensive medication use	3,475 (17%)	2,880 (65%)	6,355 (25%)
Unknown	116	4	120
Body mass index, kg/m2			
<25	7,002 (34%)	862 (20%)	7,864 (31%)
25 to <30	6,724 (33%)	1,521 (35%)	8,245 (33%)

Characteristic	**No**, N = 21,071	**Yes**, N = 4,433	**Overall**, N = 25,504
30 to <35	3,840 (19%)	1,069 (25%)	4,909 (20%)
35+	3,093 (15%)	871 (20%)	3,964 (16%)
Unknown	412	110	522
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)

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.

```
#check the vibes to think about an estimator
data <- nhanes_data |>
  as.data.frame() |>
  drop_na() |>
  mutate(log_age = log(demo_age_years)) |>
  select(chol_med_use, chol_total, bp_sys_mean, bp_med_use, cc_bmi, log_age, demo_race,


prop <- glm(chol_med_use ~ chol_total + bp_med_use + cc_bmi + log_age + demo_race + der
    data = data,
    family = binomial())
```

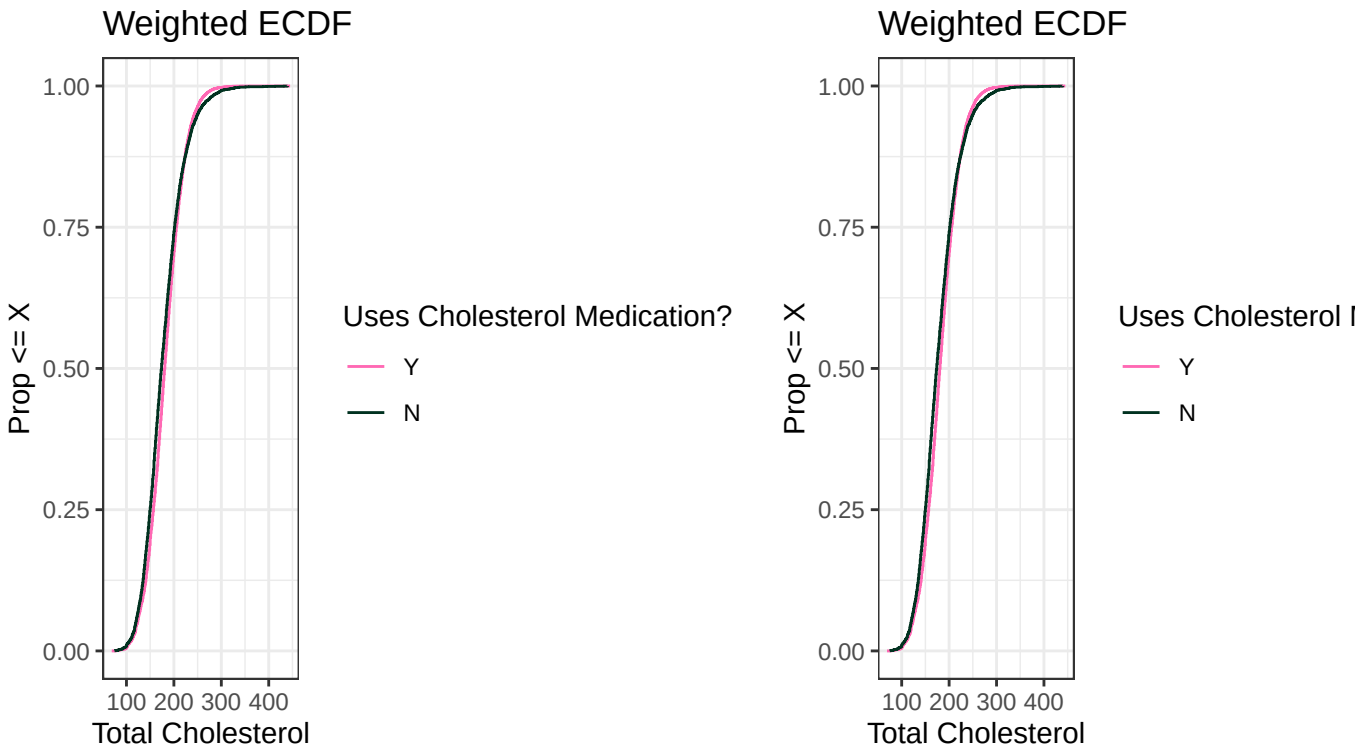
```
data <- prop |>
  augment(type.predict = "response", data = data)  |>
  select(-c(.resid, .hat, .sigma, .cooksd, .std.resid)) |>
  rename("prop" = ".fitted")
data <- data |>
  mutate(w_att = wt_att(prop, chol_med_use))
```

3.2.1 *Diagnostics.*

[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 an increase of 9.26 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 8.578 mm Hg to at most 9.941 mm Hg. Additionally, 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.

```
## [1] "The point estimate for the ATT is -3.746 with 95% CI (-4.782,-2.71)."
```

3.4 *Sensitivity analysis*

```
## # A tibble: 3 x 4
##   effect_observed exposure_confounder_effect confounder_outcome_effect
##             <dbl>                      <dbl>                      <dbl>
## 1           -2.71                       0.05                      -54.2
## 2           -2.71                       0.1                       -27.1
## 3           -2.71                       0.15                      -18.1
## # i 1 more variable: n_unmeasured_confounders <dbl>
```

4. Discussion

4.1 *Limitation*

will make lifestyle changes rather than take medication

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 () (Düsing, 2006)

not time sensitive

5. 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**

6. Acknowledgement

Thank Dr. Lucy D'Agostino McGowan for her guidance and assistance in preparing this manuscript.

7. Section title

Text with citations by **?**, (**?**).

7.1 *Subsection title*

as required (**??**). Don't forget to give each section and subsection a unique label (see Sect. 7).

Paragraph headings. Use paragraph headings as needed.

7.2 *Equations*

Here is an equation:

$$f_X(x) = \left(\frac{\alpha}{\beta}\right)\left(\frac{x}{\beta}\right)^{\alpha-1} e^{-\left(\frac{x}{\beta}\right)^{\alpha}}; \alpha, \beta, x > 0$$

Here is another:

$$a^2 + b^2 = c^2 \tag{1}$$

Inline equations: $\sum_{i=2}^{\infty}\{\alpha_i^{\beta}\}$

8. Figures and tables

8.1 *Figures coming from R*

Normal figure embedded in text.

[Figure 8 about here.]

8.2 *Tables coming from R*

```
print(xtable::xtable(head(mtcars)[,1:4],
caption = "Caption centered under table", label = "tab1"),
comment = FALSE, timestamp = FALSE, caption.placement = "top")
```

[Table 1 about here.]

Table 2 shows these numbers. Some of those numbers are plotted in Figure **??**.

```
head(mtcars[,1:4])
```

```
##                   mpg cyl disp  hp
## Mazda RX4         21.0   6  160 110
## Mazda RX4 Wag     21.0   6  160 110
## Datsun 710        22.8   4  108  93
## Hornet 4 Drive    21.4   6  258 110
## Hornet Sportabout 18.7   8  360 175
## Valiant           18.1   6  225 105
```

References

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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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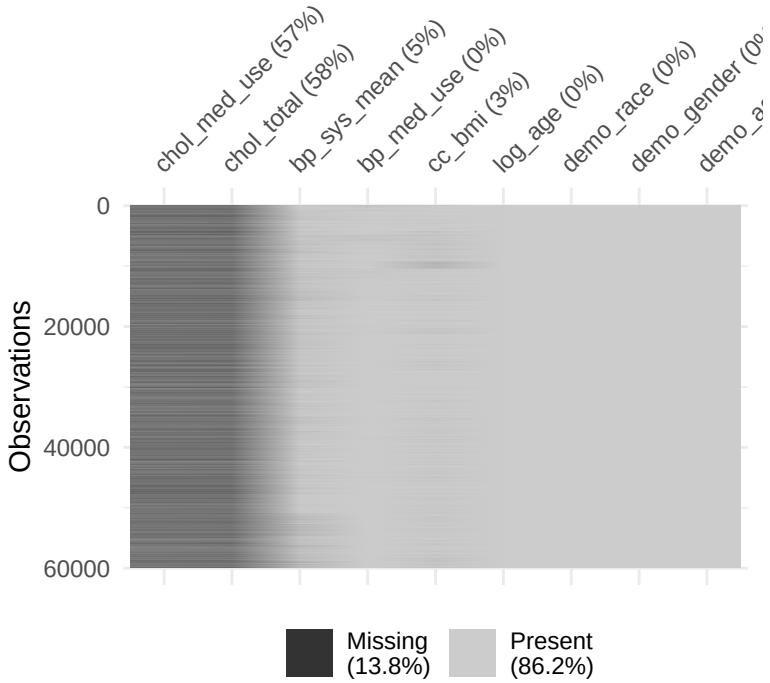

Figure 1. Missing data percentage for selected variables

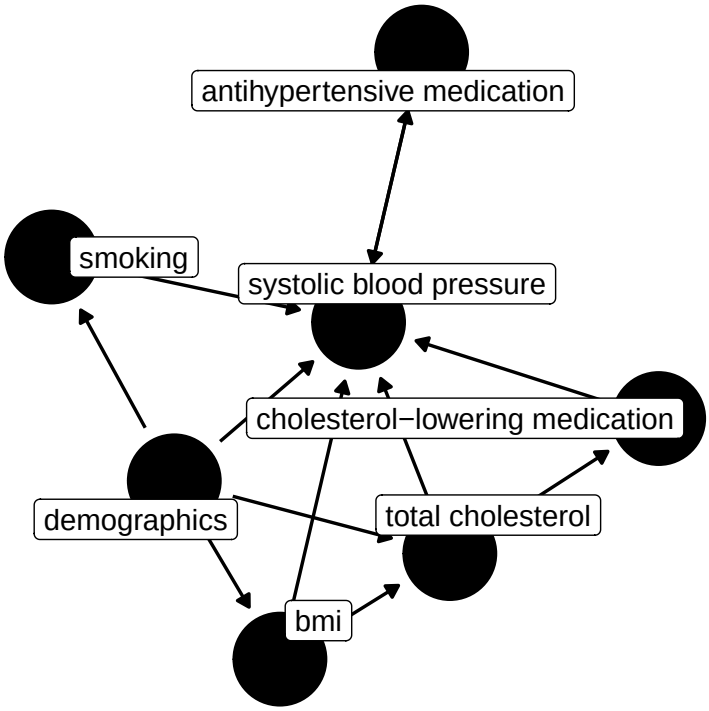

Figure 2. Causal direct acyclic graph between cholesterol-lowering medication and the mean systolic blood pressure

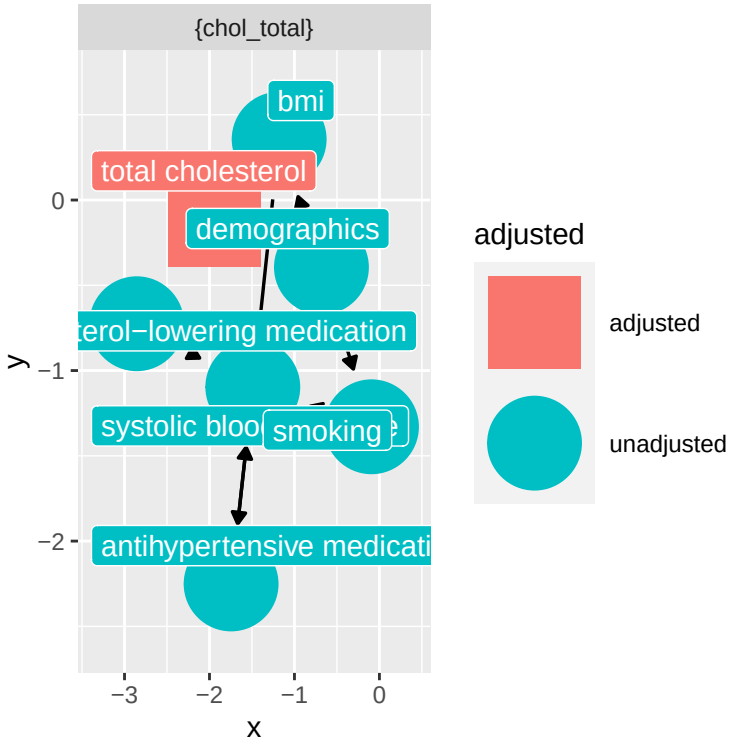

Figure 3. Causal adjustment set

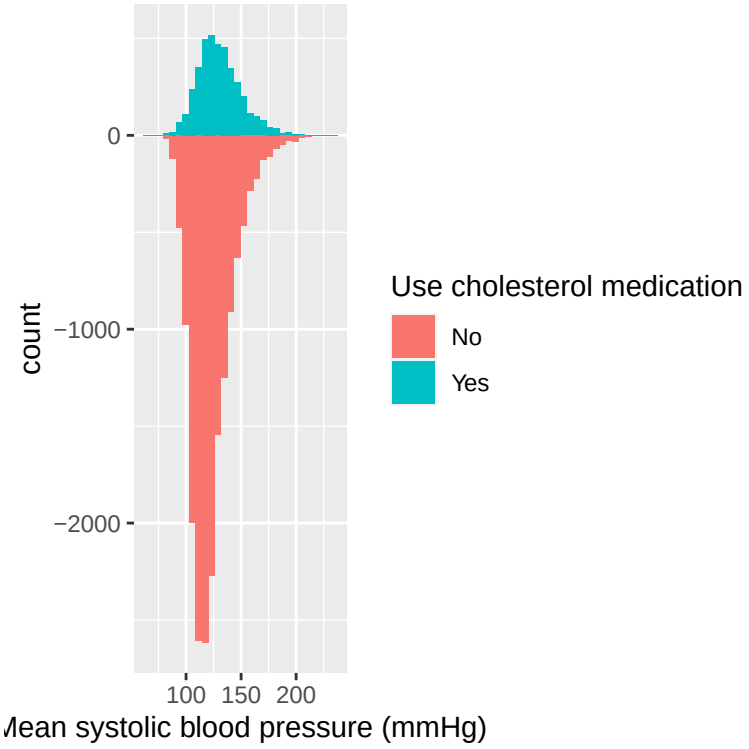

Figure 4. Mirror histogram by whether the participants use cholesterol medication

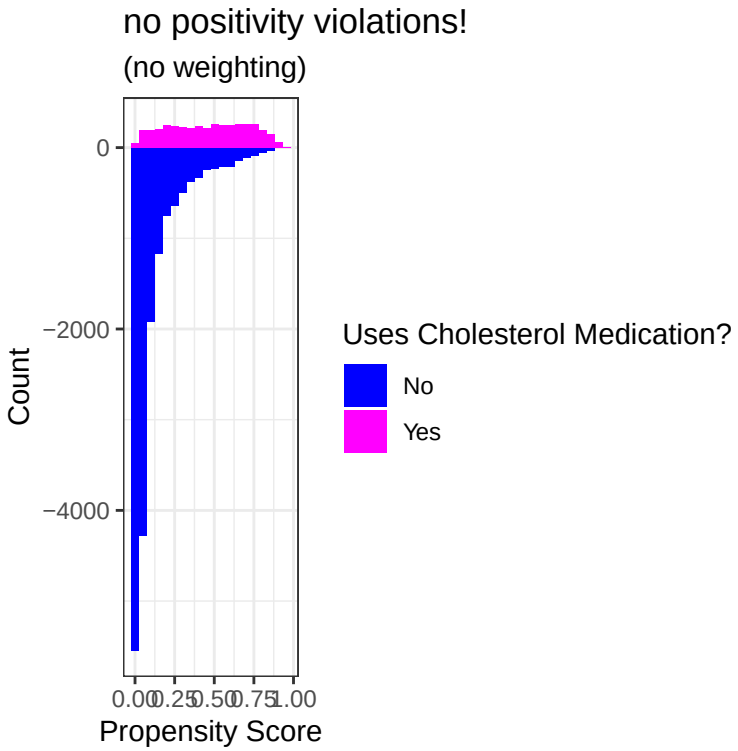

Figure 5. Mirror histogram of propensity score by treatment group

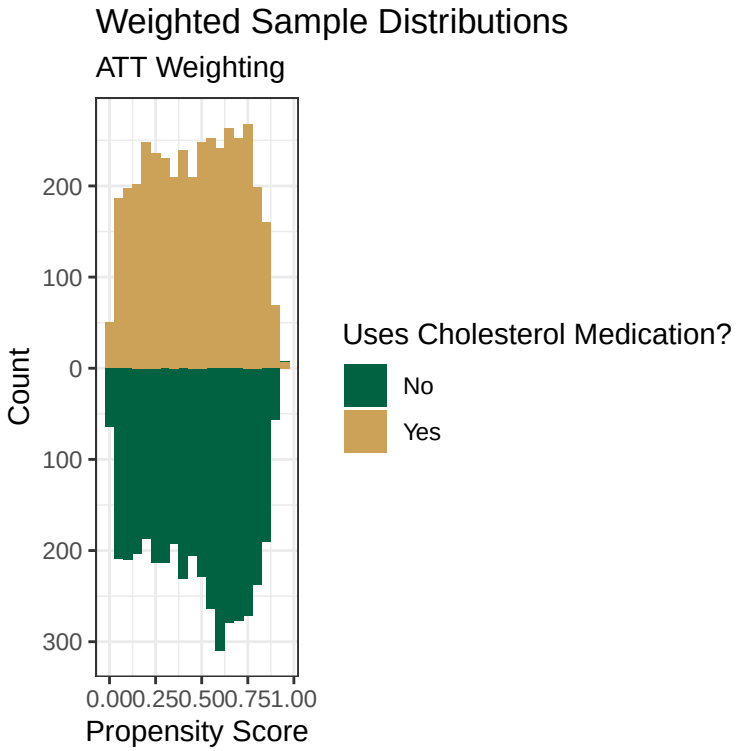

Figure 6. Mirror histogram by whether the participants use cholesterol medication

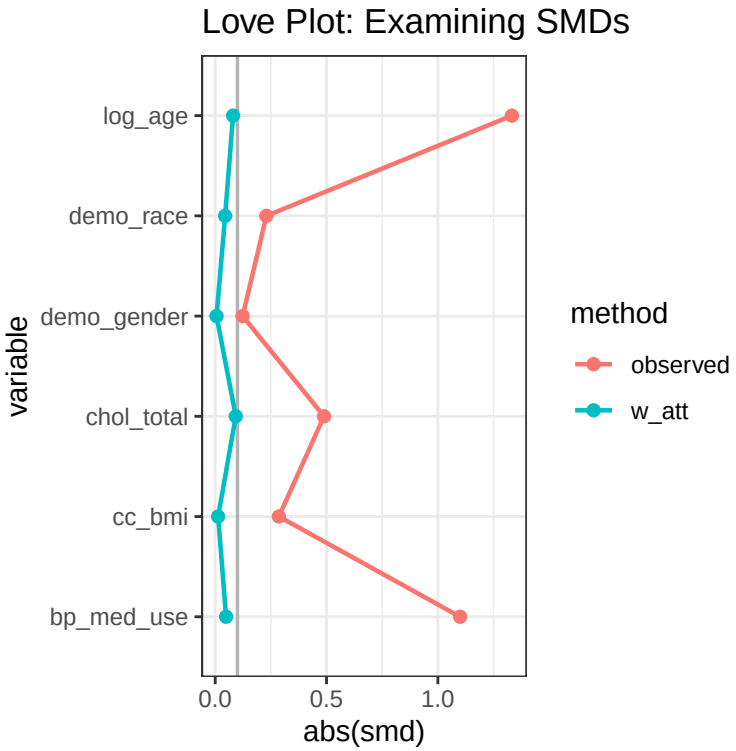

Figure 7. Love plot for covariates

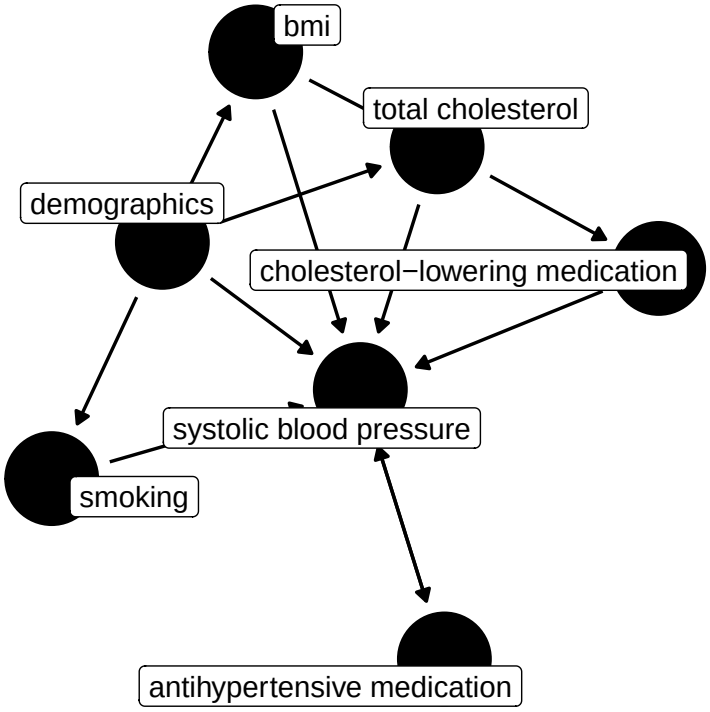

Figure 8. Output from `pdf()`

Table 2
Caption centered under table

	mpg	cyl	disp	hp
Mazda RX4	21.00	6.00	160.00	110.00
Mazda RX4 Wag	21.00	6.00	160.00	110.00
Datsun 710	22.80	4.00	108.00	93.00
Hornet 4 Drive	21.40	6.00	258.00	110.00
Hornet Sportabout	18.70	8.00	360.00	175.00
Valiant	18.10	6.00	225.00	105.00