

Causal Inference Final Project: Effect of Smoking on 10-year Development of Coronary Heart Disease

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Background Story

Coronary heart disease (CHD) is the leading cause of death and serious illness in the United States. The Framingham Heart Study's objective was to identify the common factors or characteristics that contribute to CHD by following its development over time in a large group of participants who had not yet developed overt symptoms of CHD or suffered a heart attack or stroke.

The researchers recruited 5,209 men and women between the ages of 30 and 70 from Framingham, Massachusetts, and began the first round of extensive physical examinations and lifestyle interviews that they would later analyze for common patterns related to CHD development. Over the years, careful monitoring of the Framingham Study population has led to the identification of the major CHD risk factors – high blood pressure, high blood cholesterol, smoking, obesity, diabetes, and physical inactivity. We are interested how the extent of smoking affects the development of CHD, specifically, it is not immediately obvious whether smoking 5 cigarettes per day affects the development of CHD differently than smoking 15 cigarettes per day does.

Causal Roadmap

Step 0: Specify the Scientific Question

What is the effect of smoking on the ten-year development of Coronary Heart Disease?

Target population

The target population is white middle-class men and women aged 30 to 70 in the US.

The sample in this study is white middle-class men and women aged 30 to 70 (at baseline) in Framingham, Massachusetts. The importance of the major CHD risk factors identified in this group have been shown in other studies to apply almost universally, even though the patterns of distribution may vary. Thus, we are willing to generalize to the target population.

Step 1: Specify a Causal Model

- Endogenous nodes: $X = (W, Z, A, Y)$, where
- W is age, gender, education
- Z is blood pressure (systolic and diastolic), total Cholesterol, prevalence of hypertension, prevalence of stroke, heart rate, BMI, Diabetes prevalence
- A is the number of cigarettes smoked per days
- Y is the ten-year development of coronary heart disease (CHD).

- Exogenous nodes: $U = (U_W, U_Z, U_A, U_Y) \sim \mathbb{P}_U$. We make no assumptions about the distribution \mathbb{P}_U .
- Structural equations F :

$$\begin{aligned} W &\leftarrow f_W(U_W) \\ Z &\leftarrow f_Z(W, A, U_Z) \\ A &\leftarrow f_A(W, U_A) \\ Y &\leftarrow f_Y(W, Z, A, U_Y) \end{aligned}$$

There are no exclusion restrictions or assumptions about functional form.

Causal Graph

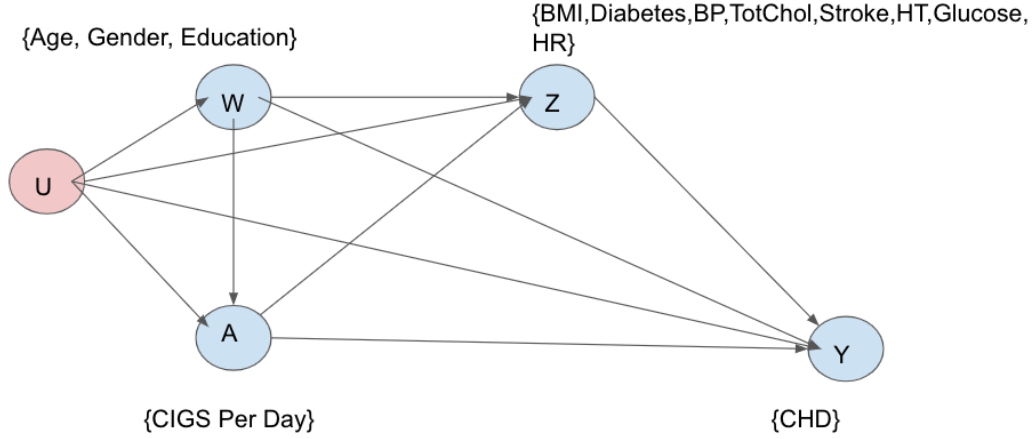


Figure 1: Causal Graph for the SCM

Step 2: Counterfactuals & Causal Parameter

Causal Parameter

$$\Psi^{*i}(\mathbb{P}^*) = \mathbb{E}^*[Y_i] \quad i \in \{1, 2, 3, 4\}$$

where i represent the bin of cigarettes smoked per day. Y_i denotes the counterfactual outcome (the ten-year development of cardiovascular disease), if possibly contrary to fact, a person's number of cigarettes smoked per day is within i^{th} bin.

Step 3. Specify your observed data and its link to the causal model

The dataset is adapted from Framingham Heart Study. We assume that Gender, Age, Education, and Number of Cigarettes per Day (A) were collected in a questionnaire at baseline. Then, BMI, Diabetes Status, Prevalence of Stroke, Prevalence of Hypertension, Indication of Blood Pressure Medication, Total Cholesterol Level, Blood Pressure, and Heart Rate were all collected after the questionnaire at a doctor's office. Our outcome, Coronary Heart Disease, is collected at a 10-year follow up. Note that this is unlike the original study. We assume our observed data were generated by sampling n from a system described by our structural causal model, so we have $n = 4211$ copies of $O \stackrel{i.i.d}{\sim} \mathbb{P}_O$. We place no restrictions on the statistical model \mathcal{M} , which is thereby non-parametric. BMI was binned using guidelines from the World

Health Organization. Total Cholesterol was binned using guidelines from the National Heart, Lung and Blood Institute (NHLBI). Table 1 below shows the counts for each variable in each bin of the exposure, as well as a χ^2 -test of independence.

Table 1: Number of Observations in Each Bin

	Level	[0,1)	[1,10)	[10,19)	[20,70]	p
n		2089	471	380	1168	
diabetes (%)	0	2022 (96.8)	463 (98.3)	372 (97.9)	1145 (98.0)	0.079
	1	67 (3.2)	8 (1.7)	8 (2.1)	23 (2.0)	
prevalentStroke (%)	0	2071 (99.1)	469 (99.6)	377 (99.2)	1166 (99.8)	0.095
	1	18 (0.9)	2 (0.4)	3 (0.8)	2 (0.2)	
prevalentHyp (%)	0	1337 (64.0)	338 (71.8)	293 (77.1)	860 (73.6)	<0.001
	1	752 (36.0)	133 (28.2)	87 (22.9)	308 (26.4)	
age (%)	[32, 42)	363 (17.4)	117 (24.8)	110 (28.9)	309 (26.5)	<0.001
	[42, 49)	464 (22.2)	137 (29.1)	125 (32.9)	401 (34.3)	
	[49, 56)	527 (25.2)	97 (20.6)	71 (18.7)	254 (21.7)	
	[56, 70]	735 (35.2)	120 (25.5)	74 (19.5)	204 (17.5)	
education (%)	1	915 (43.8)	188 (39.9)	137 (36.1)	470 (40.2)	0.003
	2	574 (27.5)	150 (31.8)	121 (31.8)	399 (34.2)	
	3	367 (17.6)	76 (16.1)	71 (18.7)	170 (14.6)	
	4	233 (11.2)	57 (12.1)	51 (13.4)	129 (11.0)	
BP (%)	0	1139 (54.5)	267 (56.7)	211 (55.5)	701 (60.0)	0.025
	1	950 (45.5)	204 (43.3)	169 (44.5)	467 (40.0)	
totChol (%)	[0, 200)	386 (18.6)	108 (23.4)	84 (22.3)	227 (19.7)	0.004
	[200, 240)	723 (34.9)	151 (32.7)	157 (41.8)	401 (34.9)	
	[240, 600]	962 (46.5)	203 (43.9)	135 (35.9)	522 (45.4)	
gender (%)	0	1400 (67.0)	346 (73.5)	222 (58.4)	386 (33.0)	<0.001
	1	689 (33.0)	125 (26.5)	158 (41.6)	782 (67.0)	
bmi (%)	[0, 18.5)	19 (0.9)	13 (2.8)	7 (1.8)	17 (1.5)	<0.001
	[18.5, 25)	785 (37.8)	245 (52.2)	225 (59.2)	568 (48.8)	
	[25, 30)	940 (45.3)	170 (36.2)	117 (30.8)	467 (40.1)	
	[30, 56.8]	333 (16.0)	41 (8.7)	31 (8.2)	112 (9.6)	
heartRate (%)	[0, 60)	122 (5.8)	27 (5.7)	19 (5.0)	28 (2.4)	<0.001
	[60, 143]	1967 (94.2)	444 (94.3)	360 (95.0)	1140 (97.6)	
CHD (%)	0	1784 (85.4)	420 (89.2)	320 (84.2)	958 (82.0)	0.002
	1	305 (14.6)	51 (10.8)	60 (15.8)	210 (18.0)	

Step 4. Identifiability

Since we made no independence assumptions on our exogenous background factors, we will need to make additional independence assumptions for identifiability. For the target causal parameter in the SCM \mathcal{M}^* to be identified from the observed data distribution, we need to make a randomization and a positivity assumption.

1) Randomization Assumption

We could assume that all unmeasured background factors in our SCM are independent, which is sufficient, but not minimally sufficient. In the augmented/working SCM (\mathcal{M}^{**}) that we selected, the unmeasured background factor of A (cigarettes smoked per day) is independent of the unmeasured background factor of Y (10yr CHD), the unmeasured background factor of W (baseline age, gender, education, diabetes, BMI), and the unmeasured background factor of Z (prevalence of stroke, hypertension, blood pressure, blood

pressure medication, heart rate). Thus, conditional on W , the counterfactual outcome is independent of the observed treatment: $Y \perp A|W$.

Since W, Z , and Y include SES and biological factors that affect human health, we avoid assuming independence between their unmeasured background factors. Thus, we consider it is more plausible to make the independence assumptions listed. We do not adjust the mediator Z to avoid opening a backdoor path. Under M^{**} , the backdoor criterion holds conditional on W . Additional data on factors that affect health status and determinants could help with identifiability, but those factors are not well-understood.

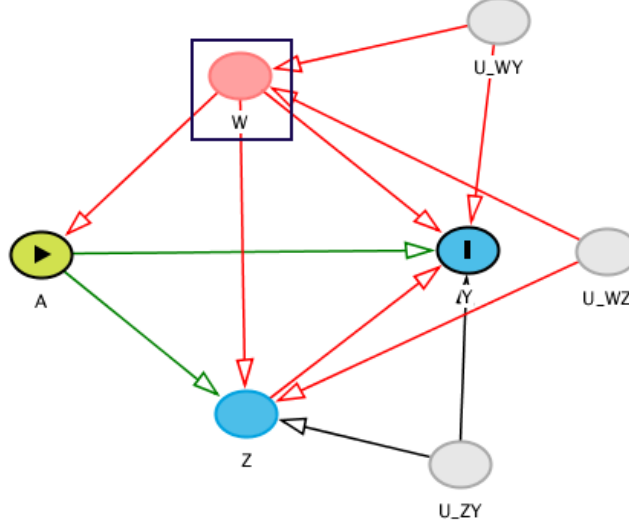


Figure 2: Causal Graph for an augmented SCM

$$U_A \perp U_Y, U_A \perp U_W, U_A \perp U_Z$$

2) Positivity Assumption

There must be a positive probability of each treatment condition within each possible strata of W . We need a positive probability of cigarettes smoked per day in bin i for each strata of W .

$$\min_{i \in A} \mathbb{P}_0(A = i | W = w) > 0$$

for all w for which $\mathbb{P}_0(W = w) > 0$

where i denote the index of a bin of A .

We are concerned about a positivity assumption violation since binning covariates could make particular stratas of W have low probabilities of smoking certain numbers of cigarettes per day, especially a bin with high numbers of cigarettes smoked per day. We can informally check for a positivity assumption violation from tables of A given a strata of W .

From the table from one of the stratas of W below, we can see that we have no female who smokes 10 to less than 20 cigarettes per day with missing education level in the age ranges $[42, 49)$ and $[56, 70]$ respectively.

Thus, we have some sparsity issue which could affect the estimator performance, particularly the inverse probability of treatment weighting (IPTW).

Table 2: Table for Gender = 0 (Female), cigsPerDay (A) = [10,20)

Strata	Education: 1	Education: 2	Education: 3	Education: 4	Education: NA
Age: [32, 42)	16	26	16	11	1
Age: [42, 49)	23	33	17	10	0
Age: [49, 56)	16	12	8	2	3
Age: [56, 70]	15	11	5	1	0

We also investigated the treatment mechanism by calculating the predicted probability of each bin of A (the number of cigarettes smoked per day) given a strata of W :

Table 3: Predicted Probabilities of A for each Strata of W

	Min	Mean	Max
0 cigarettes per day	0.2853671	0.5085200	0.7440546
[1,10) cigarettes per day	0.0612951	0.1146543	0.1733320
[10,19) cigarettes per day	0.0592084	0.0925024	0.1428044
[20,70] cigarettes per day	0.0765399	0.2843233	0.5630990

From the table's minimum probability column, we can see that some stratas of W have relatively low probabilities for the number of cigarettes smoked per day in the 2nd, 3rd, and 4th bin, which would results in those stratas having high weights in the IPTW estimator. However, the probabilities are not close to zero. Therefore, we do not have a practical violation of positivity assumption. Theoretically, randomizing the number of cigarettes smoked per day could rid of positivity assumption violation concerns, but it is not feasible.

Step 5. Statistical Model and Estimand

The target parameter of \mathbb{P}_0 , which equals the causal parameter in the augmented causal model \mathcal{M}^{**} is given by the G-Computation formula:

$$\begin{aligned}\Psi_0(\mathbb{P}_0^i) &= \mathbb{E}_0[\mathbb{E}_0[Y|A=i, W=w]] \\ &= \sum_w \mathbb{E}_0[Y|A=i, W=w] * \mathbb{P}_0(W=w)\end{aligned}$$

where i represent the bin of cigarettes smoked per day.

Step 6. Estimation

Classical Model Based on Chi-Squared

Simple Substitution

IPTW

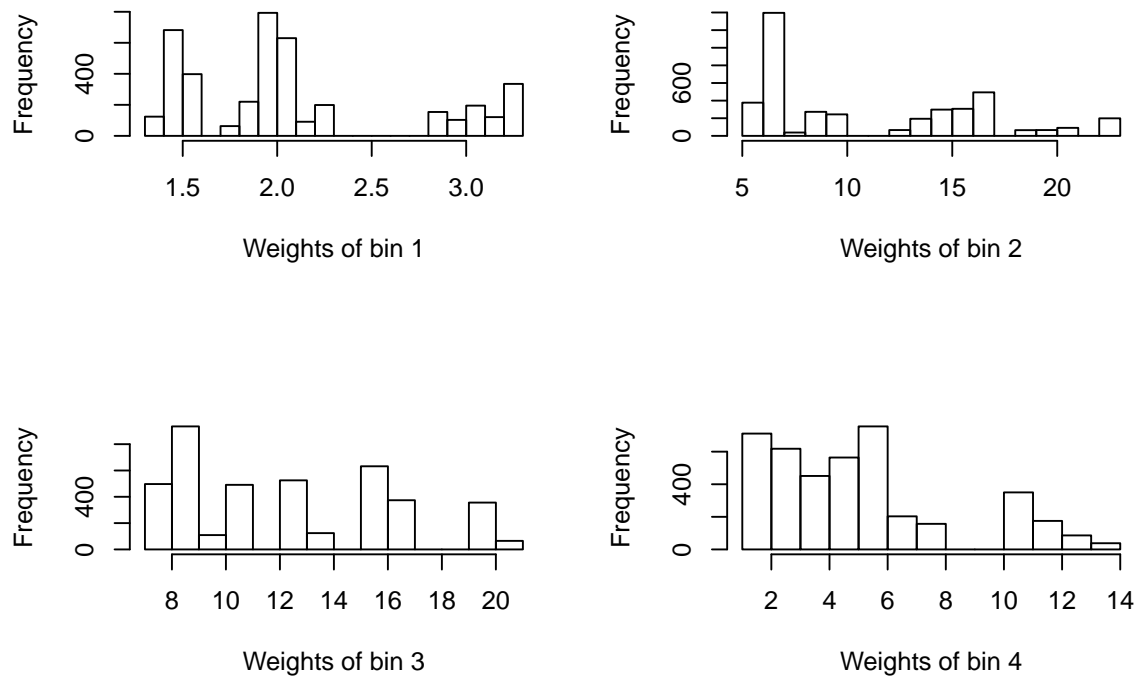


Figure 3: Distribution of Weights

Superlearner/TMLE

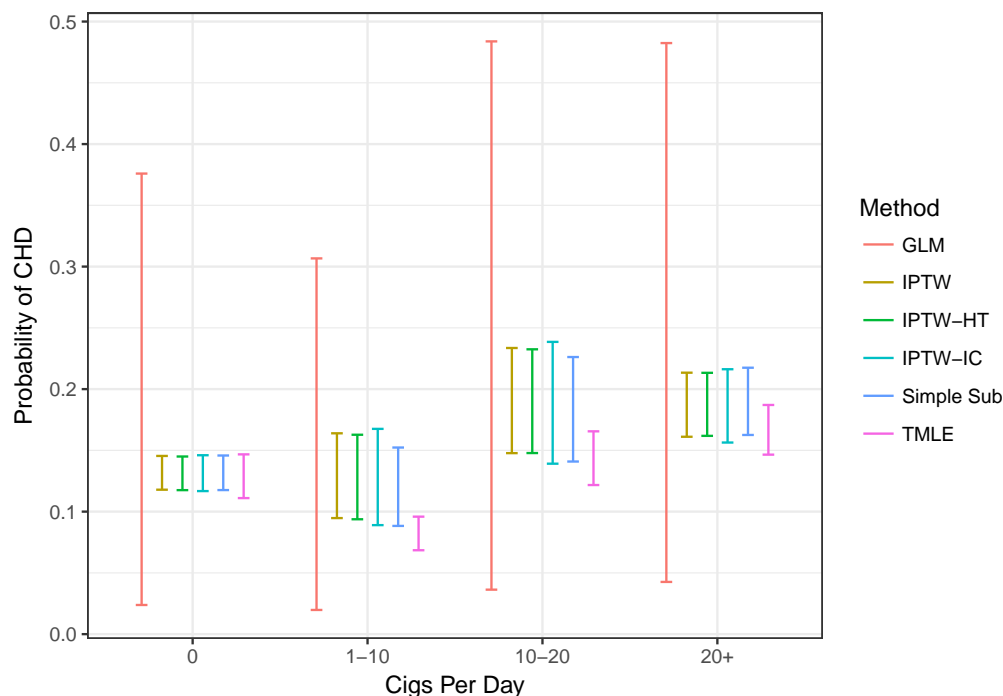


Figure 4: Confidence Intervals for Estimators

Step 7. Result Interpretation

Statistical

From the estimation of our statistical model \mathcal{M} , we found that the probability of developing coronary heart disease increases as the binned exposure (`cigsPerDay`) increases from, standardized to the distribution of baseline covariates W . However, in bin #2, corresponding to `cigsPerDay` $\in [1, 10)$, we found what seems to be a “protective” effect, in which smoking less than a pack of cigarettes as day is associated with a lower risk of CHD than not smoking at all. The difference risk in this bin is estimated at around 0.10-0.11, compared with . We argue that this may be due to *non-differential misclassification*, since participants may have not self-reported smoking due to the negative stigma associated with it. For `cigsPerDay` ≥ 20 , the probability of CHD plateaus near 0.2 (for the conditional mean outcome and IPTW estimators) and 0.16 (for TMLE).

Counterfactual

The estimated effect of the exposure is the counterfactual probability of developiong coronary heart disease in 10 years under the exposure category `cigsPerDay` ($A_i, i \in \{1, 2, 3, 4\}$), with the assumptions that conditioning on the baseline covariates W (age, sex, & education) and assuming certain independence assumptions satisfies the backdoor criterion, and said independence assumptions and positivity holds. The observed general increase in estimated risk of CHD as the (binned) exposure increases is certainly plausible; however, the estimated reduction in risk of CHD for `cigsPerDay` $\in [1, 10)$ is less plausible, again perhaps due to biased data from non-differential misclassification on the exposure, or could in fact be evidence for a protective effect of low degrees of smoking on risk of CHD.

Limitations

It is not likely that our target causal parameter is identifiable due to violations of the chosen independence assumptions, and thus our counterfactual estimation should not be accepted without some healthy skepticism. Many unmeasured confounders are possible, including pre-existing medical conditions not considered by the Framingham Heart Study patient surveys, diet and exercise habits, family history, genetic factors, and more. Future studies might expand the set of measured variables to include such information. As mentioned, we are also concerned about potential issues with reporting bias in the data. Finally, we did not have access to time-varying aspects of the data; e.g., smoking habits and biomarkers before or after baseline measurements were taken, many of which could contain information relevant to prediction of CHD outcomes.

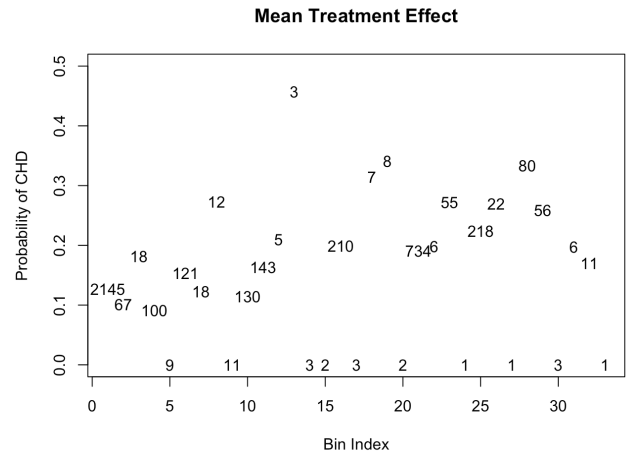


Figure 5: Expected Outcome

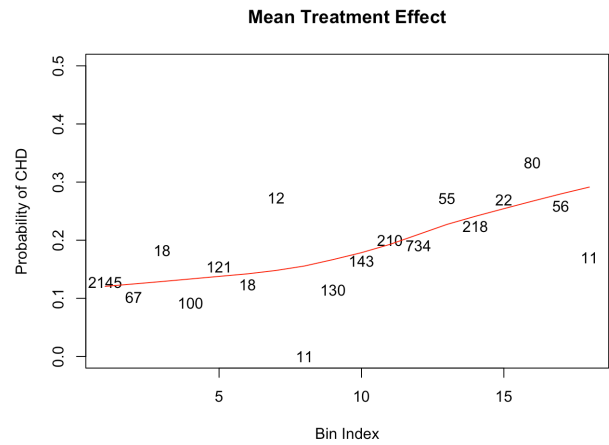


Figure 6: Expected Outcome

Team Member Contribution

Member	Contributions
Michael Attah	<ul style="list-style-type: none"> - group discussion of causal question - design of causal graph - design of descriptive table - categorize covariates: Z - interpretation: causal - references
Bianca Doone	<ul style="list-style-type: none"> - group discussion of causal question - design of causal graph - time-varying assumptions - chi-squared test of independence - categorize covariates: W (age, education, gender) - bootstrap confidence intervals: IPTW - interpretation: statistical - limitations
Casey Graham	<ul style="list-style-type: none"> - group discussion of causal question - design of causal graph - categorize covariates: <code>cigsPerDay</code> - computation of simple substitution - computation of IPTW - computation of Superlearner/TMLE - bootstrap confidence intervals: TMLE, GLM
Daniel Saunders	<ul style="list-style-type: none"> - group discussion of causal question - design of causal graph - design of descriptive table - statistical estimand: G-computation - bootstrap confidence intervals: TMLE, simple substitution - statistical estimand: G-computation
Nutcha Wattanachit	<ul style="list-style-type: none"> - group causal question - design of causal graph - background story and target population - specifying causal parameter - design of working SCM (\mathcal{M}^{**}) - specify observed data and link to SCM - identifiability: randomization assumption - identifiability: positivity assumption

References

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