Association of **Smoking Intensity** Overtime and Coronary Heart Disease

BS807 - Applied Causal Inference in Health Research

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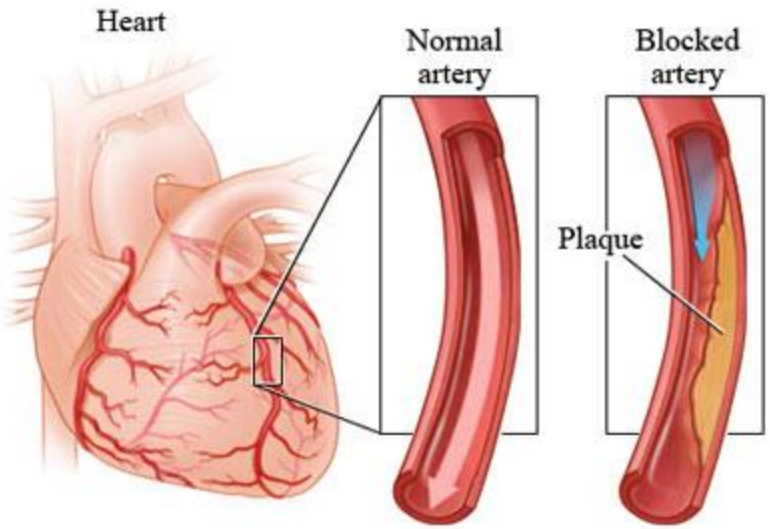
Coronary Heart Disease (CHD)

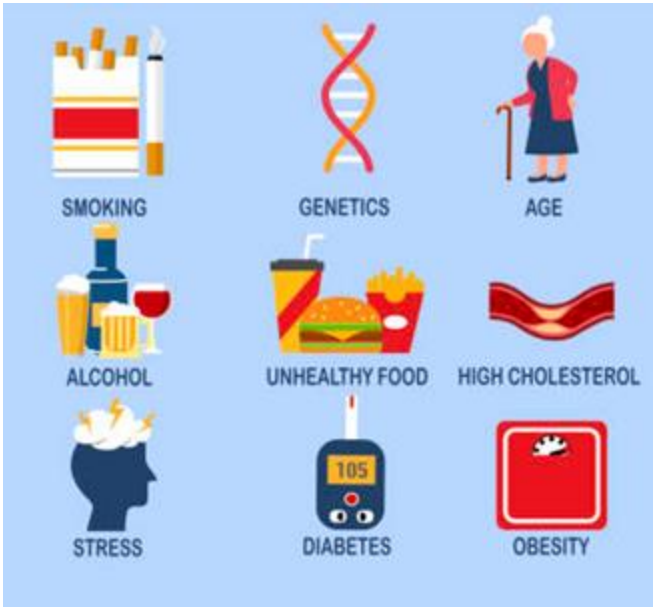
- “Catch-all” phrase for many conditions that affect the heart’s structure and function
  - Described as: Arteries of the heart cannot deliver enough oxygen-rich blood to the heart
- **Leading cause of the death in the U.S.**
  - Affects ~20 million adults per year
  - In 2020, CHD killed ~380,000 people



Risk Factors Related to Coronary Heart Disease (CHD)

- **Key Risk Factors:**
  - High blood pressure
  - High blood cholesterol
  - **Smoking**

- ***Other medical conditions and lifestyle choices can also put individuals at risk for CHD:***
  - Diabetes
  - Overweight and obesity
  - Unhealthy diet
  - Physical inactivity
  - Excessive alcohol use



Smoking in relation to Coronary Heart Disease (CHD)

- Cigarette smoke can interfere with important processes in the body – especially the delivery of oxygen-rich blood to the heart/body

- Smoking can also alter the body's chemistry, which can ultimately cause the build of plaque

- "**No safe level** of smoking exists for CHD" (Hackshaw et al., 2018).

- "**Consistent light smoking** throughout a lifetime also has a **large excess risk** for cardiovascular disease mortality" (Inoue-Cho et al., 2017)

But what about the smokers who find it hard to quit smoking?

The dataset: Framingham Heart Study (1956-1968)

- Longitudinal cohort study
- Began in 1948 with **5,209 initially enrolled participants** in the town of Framingham, MA
- Participants underwent **physical examinations**, gave **blood samples** for laboratory tests, and provided **lifestyle and medical history information** at regular intervals

Exposure: Smoking

- Number of cigarettes smoked each day

Outcome: Any coronary heart disease

- Angina Pectoris, Myocardial infarction (Hospitalized and silent or unrecognized), Coronary Insufficiency (Unstable Angina), or Fatal Coronary Heart Disease

Target Trial

Randomization

Adults 18+ w/ no history of CHD who are **smokers**

Light: 1-20 cigs. per day
Heavy: >20 cigs. per day

Light Smokers
1) P1 Light – P2 Heavy
2) P1 Light – P2 Light
Heavy Smokers
1) P1 Heavy – P2 Light
2) P1 Heavy – P1 Heavy

Assess if participants had any CHD after exposure was measured

Baseline confounders

12 years of follow-up

Period 1 **Period 3**

Cohort Design

Randomization

Adults 18+ w/ no history of CHD who are **smokers**

P1 Light
1-20 cigs. per day

P1 Heavy
>20 cigs. per day

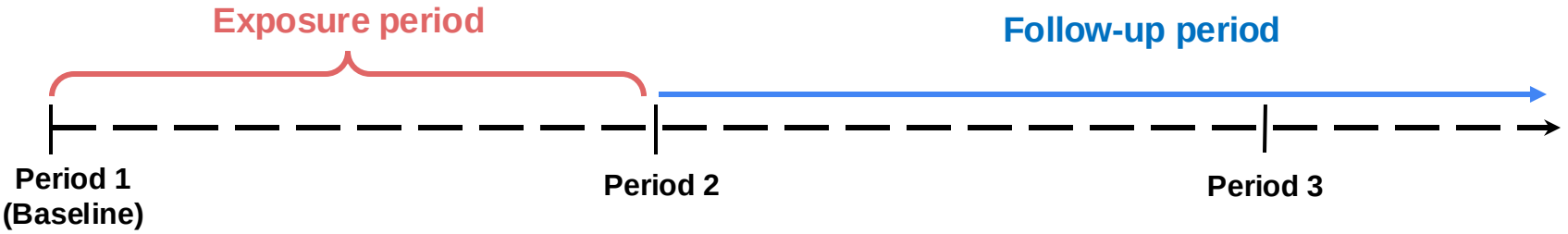
Baseline confounders
Age, Sex, Education, BMI

Treatment #1: Change **Light** to **Heavy**
Control Group: Light stays Light

Treatment #2: Change **Heavy** to **Light**
Control Group: Heavy stays Heavy

Measure exposure
1) **P1 Light – P2 Heavy**
2) P1 Light – P2 Light
3) **P1 Heavy – P2 Light**
4) P1 Heavy – P1 Heavy

Assess if participants had any CHD after exposure was measured



Causal Question

Among adults 18+ who have no history of any Coronary Heart Disease (CHD) who are smokers:

- **Question 1:** What is the risk of incident CHD among heavy smokers compared to light smokers adjusting for baseline confounders?
- **Question 2:** What is the risk of incident CHD among smokers who change their smoking intensity over 6-years compared to if everyone had instead kept their smoking intensity constant over 6-years adjusting for baseline confounders?

Outline of Methods

- Descriptive analysis
    - Stratified baseline covariates by four smoking exposure groups and median along with IQR was calculated for continuous variables while frequency and column percent was calculated for categorical variables.
- Main analytic methods
    - Stratified plug-in g-formula was used to estimate the average treatment effect.
    - Causal risk ratio and 95% confidence intervals were estimated using non-parametric bootstrap methods.

Directed Acyclic Graph (DAG)

Covariates were assessed at baseline; and therefore, only baseline covariates were adjusted for

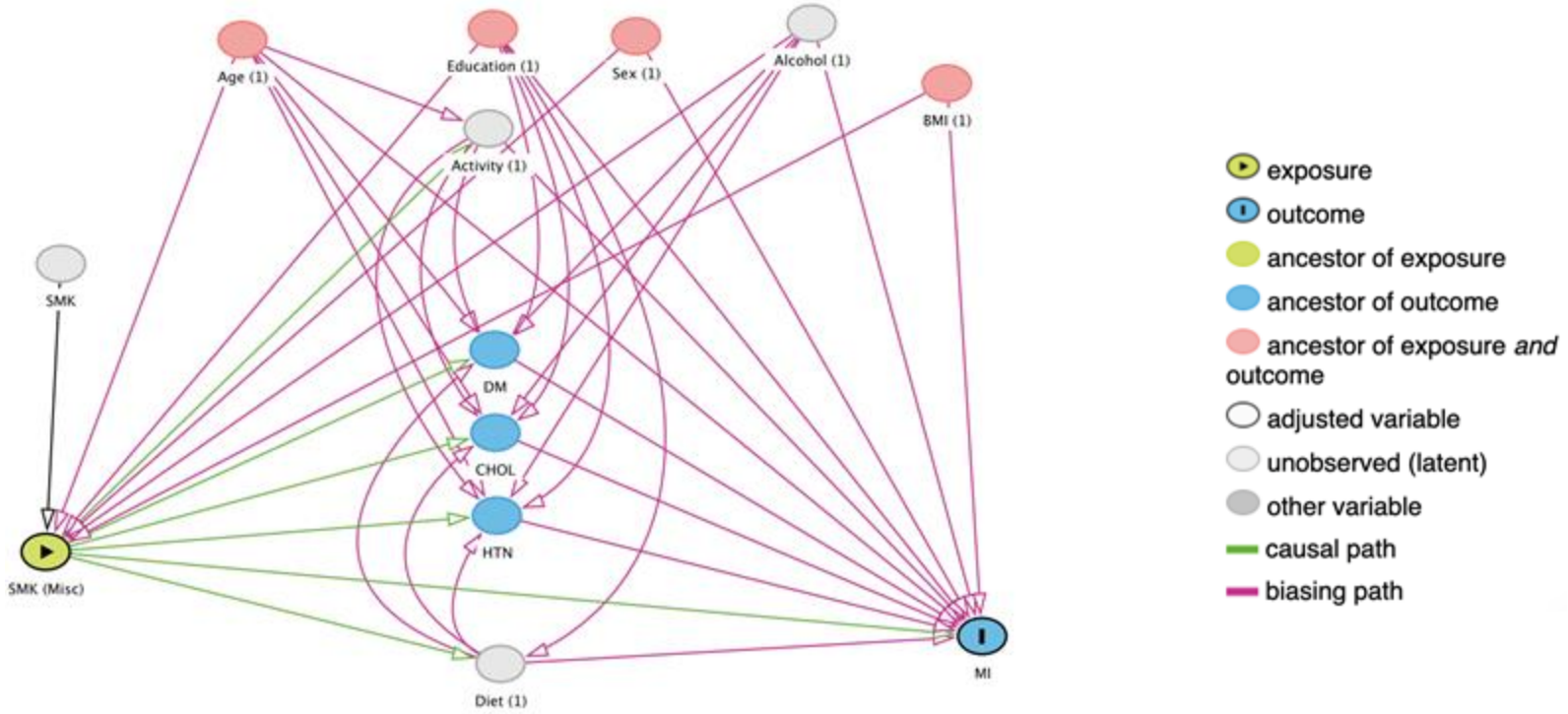


Table 1. Baseline Covariates

Characteristics	Total (n=1,743)	P1 Light[1] - P2 Light[2] (n=1,180)	P1 Light[1] - P2 Heavy[3] (n=196)	P1 Heavy[3] - P2 Light[2] (n=110)	P1 Heavy[3] - P2 Heavy[3] (n=257)
	Median (IQR[4])				
Cigarettes smoked per day at P1	20 (10-20)	15 (8-20)	20 (20-20)	30 (30-35)	30 (30-40)
Cigarettes smoked per day at P2	20 (7-25)	13.5 (3-20)	30 (30-35)	20 (0-20)	40 (30-40)
	n (column %)				
Sex					
Male	896 (51.1)	491 (41.6)	117 (59.7)	87 (79.1)	201 (78.2)
Age, *years*					
<55	1403 (80.5)	919 (77.9)	169 (86.2)	86 (78.2)	229 (89.1)
≥55	340 (19.5)	261 (22.1)	27 (13.8)	24 (21.8)	28 (10.9)
Body Mass Index (BMI)					
Underweight (<18.5)	33 (1.9)	27 (2.3)	2 (1.0)	0 (0.0)	4 (1.6)
Normal (18.5 – 24.9)	917 (52.6)	664 (56.3)	99 (50.5)	45 (40.9)	109 (42.4)
Overweight (25 – 29.9)	635 (36.4)	397 (33.6)	77 (39.3)	50 (45.5)	111 (43.2)
Obese (30+)	154 (8.8)	88 (7.5)	18 (9.2)	15 (13.6)	33 (12.8)
Missing	4 (0.23)	4 (0.34)	0 (0.0)	0 (0.0)	0 (0.0)
Prevalent Hypertension[5]	414 (23.8)	272 (23.1)	39 (19.9)	32 (29.1)	71 (27.6)
Prevalent Diabetes[6]	27 (1.6)	20 (1.7)	4 (2.0)	2 (1.8)	1 (0.4)
Total Cholesterol (mg/dL)[7]					
Borderline high to high (>200)	1337 (76.7)	890 (75.4)	157 (80.1)	85 (77.3)	205 (79.8)
Normal (<200)	381 (21.9)	277 (23.5)	34 (17.4)	23 (20.9)	47 (18.3)
Missing	25 (1.4)	13 (1.1)	5 (2.6)	2 (1.8)	5 (2.0)

Table 2a. Crude, non-causal adjusted, plug-in g-formula risk ratio (RR) estimates, and their 95% Confidence Intervals (CI) for the association of smoking behavior at Period 2 (P2) on any Coronary Heart Disease (CHD)					
	n	Events (%)	**Crude estimate** (95% CI)	**Non-causal adjusted estimate*** (95% CI)	**Plug-in g-formula estimate*** (95% CI)
P2 Smoking status group					
P2 Heavy	453	111 (24.5)	1.17 (0.96 – 1.42)	1.06 (0.87 – 1.30)	1.04 (0.84 – 1.27)
P2 Light	1,290	270 (20.9)	Ref.	Ref.	Ref.

**Adjusted for: age, sex, education, and BMI at baseline*

Table 2b. Non-causal adjusted, plug-in g-formula risk ratio (RR) estimates, and their 95% Confidence Intervals (CI) for the association of smoking behavior from Period 1 (P1) to Period 2 (P2) on any Coronary Heart Disease (CHD) by smoking status					
	N	Events (%)	Crude estimate (95% CI)	Non-causal adjusted estimate (95% CI)*	Plug-in g-formula estimate (95% CI)*
	Light Smokers P1				
P1 Light - P2 Heavy	196	46 (23.5)	1.15 (0.87 – 1.52)	1.07 (0.81 – 1.41)	**1.13 (0.81 – 1.49)**
P1 Light - P2 Light	1,180	241 (20.4)	Ref.	Ref.	Ref.
	Heavy Smokers P1				
P1 Heavy - P2 Light	110	29 (26.4)	1.04 (0.72 – 1.52)	0.93 (0.63 – 1.36)	**0.98 (0.65 – 1.45)**
P1 Heavy - P2 Heavy	257	65 (25.3)	Ref.	Ref.	Ref.
	Heavy Smokers P1 (to assess effect modification)				
P1 Heavy - P2 Heavy	257	65 (25.3)	0.96 (0.66 – 1.40)	1.08 (0.74 – 1.57)	**1.02 (0.70 – 1.57)**
P1 Heavy - P2 Light	110	29 (26.4)	Ref.	Ref.	Ref.

**Adjusted for: age, sex, education, and BMI at baseline.*

Discussion

1) The risk of CHD for heavy smokers with no history of CHD was 1.04 times as high as that of light smokers.

2) Participants with no history of CHD who changed their smoking behavior *from light to heavy smoking over the exposure period were 1.13 times* more likely to develop CHD than light smokers who did not change their smoking behavior.

3) Limitations of the observed data

   a) No information of unmeasured confounders such as alcohol consumption, dietary habits, and physical activity.

   b) FHS data might not be a good representation of every population because the participants were predominantly white.

Conclusion

- No adverse effect of heavy smoking on the incidence of CHD.
- There is an adverse effect of heavy vs. light smoking in those with a history of light smoking.
- Compared to those who remained light smokers over time, those who changed to heavy smoking reported an increased risk of CHD.
- When stratified by the effect modifier smoking status at period 1, the risk of CHD for heavy smoking compared to light smoking was higher for those who were light smokers compared to those who were heavy smokers at period 1.

Thank You!