Leiden University
Medical Center

# Confounding adjustment and estimating treatment effects

## Without models

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# Scope of this lecture

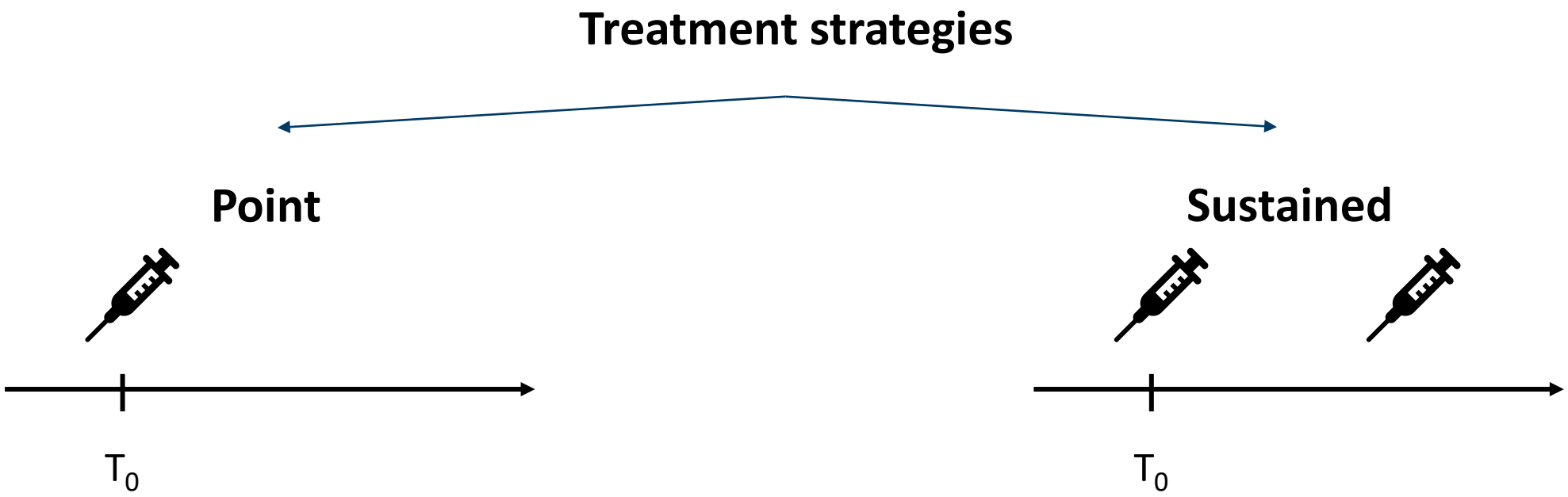

1. Make treatment groups correctly
2. Adjust for baseline and time-varying confounding
3. Estimate your treatment effect of interest

Target trial emulation

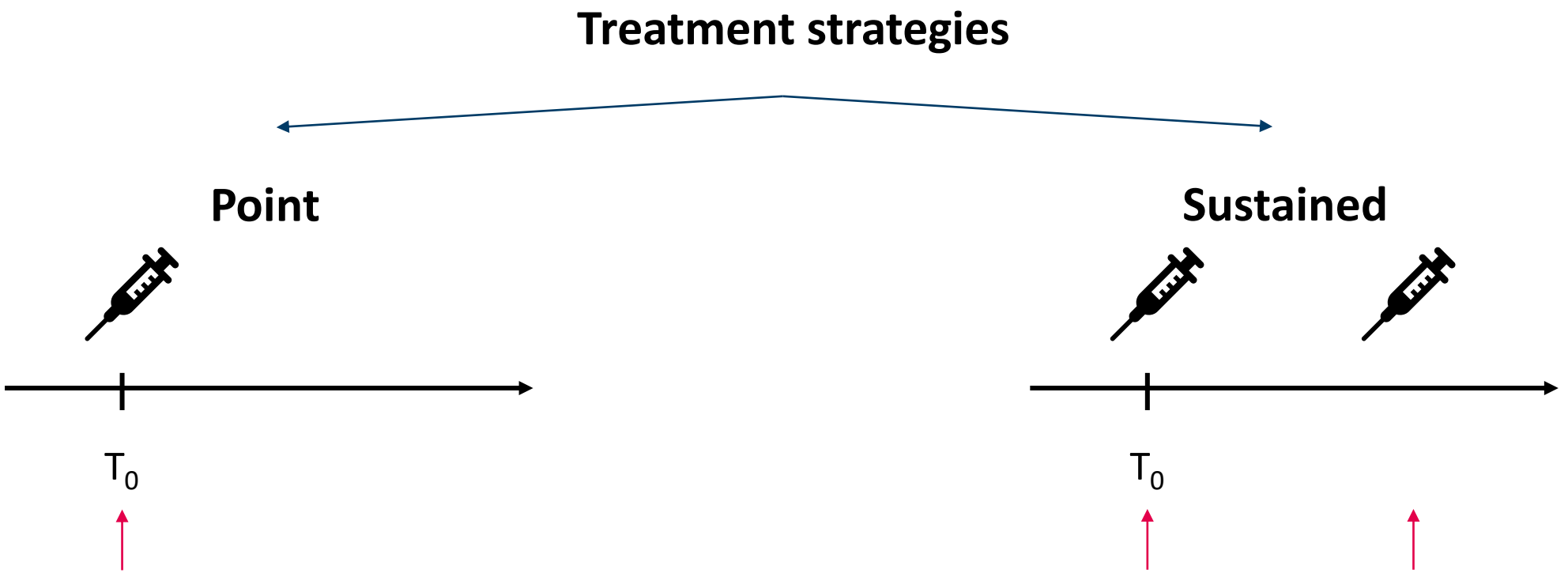
- This is going to be an interactive lecture

- Go to **classpoint.app** and fill in the classcode at the top right corner of this slide

# Classification of treatment strategies



# Baseline vs. time-varying confounding




- Groups need to be similar at time zero
- Only baseline confounding

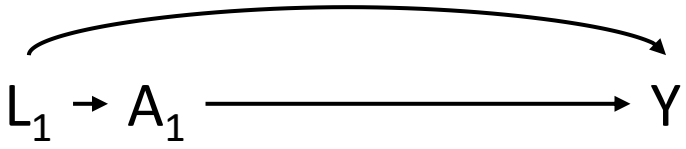
- Groups need to be similar at time zero & during follow-up
- Baseline & time-varying confounding

# Baseline vs. time-varying confounding

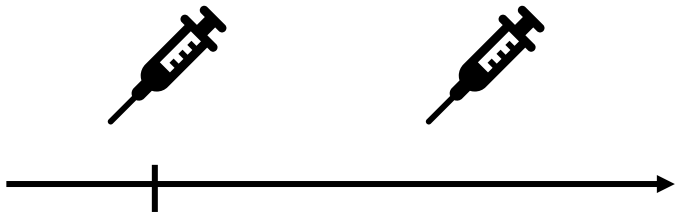
**Treatment strategies**

**Point**

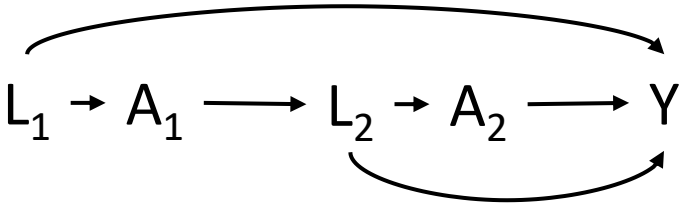

- Groups need to be similar at time zero
- Only baseline confounding




**Sustained**




- Groups need to be similar at time zero & during follow-up
- Baseline & time-varying confounding



# Let’s practice with classifying treatment strategies

Go to classpoint.app

Point strategy or sustained treatment strategy?

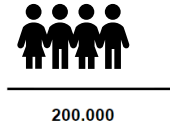
1. Receive bariatric surgery
2. Receive Pfizer first dose now, and second dose 3 weeks later
3. Start SGLT-2i within 3 months from now
4. Never start SGLT-2i
5. Start GLP-1RA when a cardiovascular event develops

A: point strategy

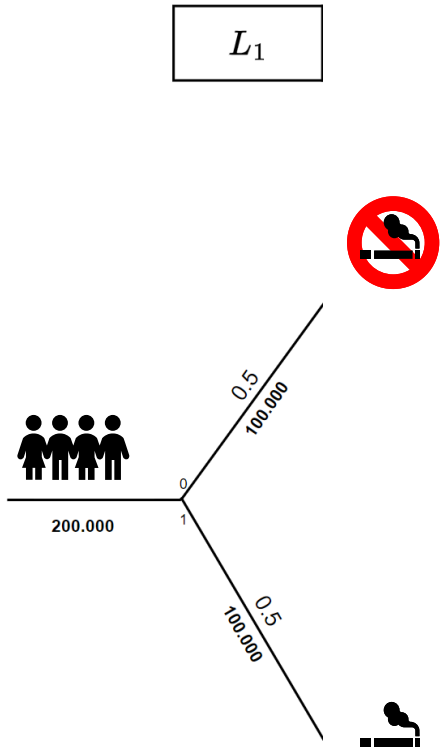
B: sustained strategy

Multiple Choice

# Visualizing the history of a population in a tree graph

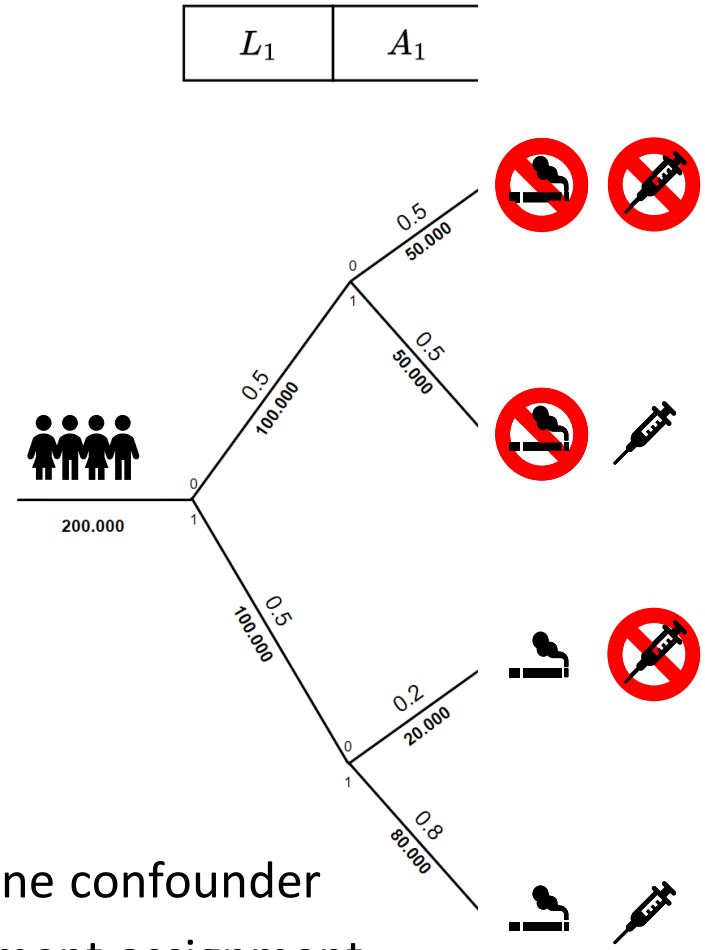


# Visualizing the history of a population in a tree graph




$L_1$: Baseline confounder

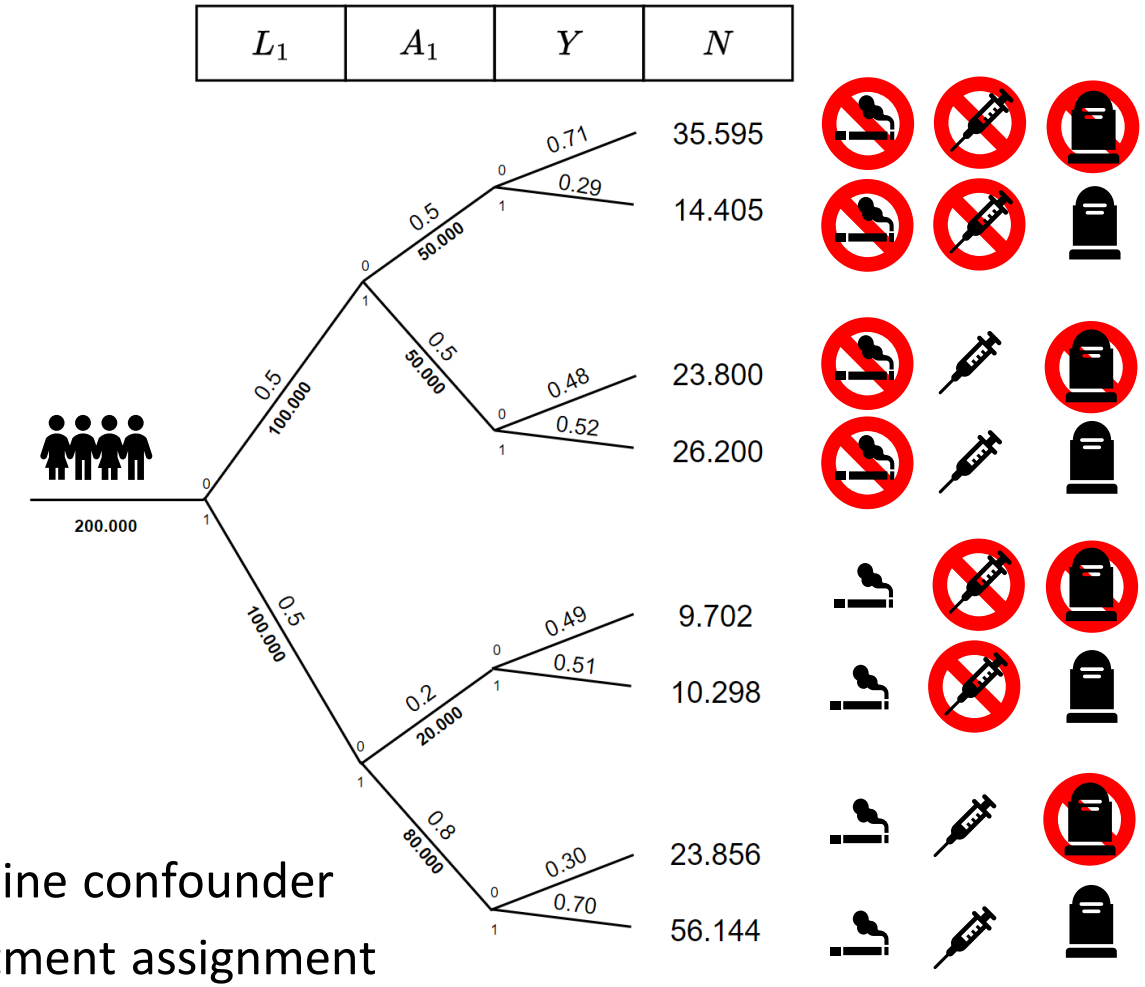
# Visualizing the history of a population in a tree graph




$L_1$: Baseline confounder

$A_1$: Treatment assignment

# Visualizing the history of a population in a tree graph



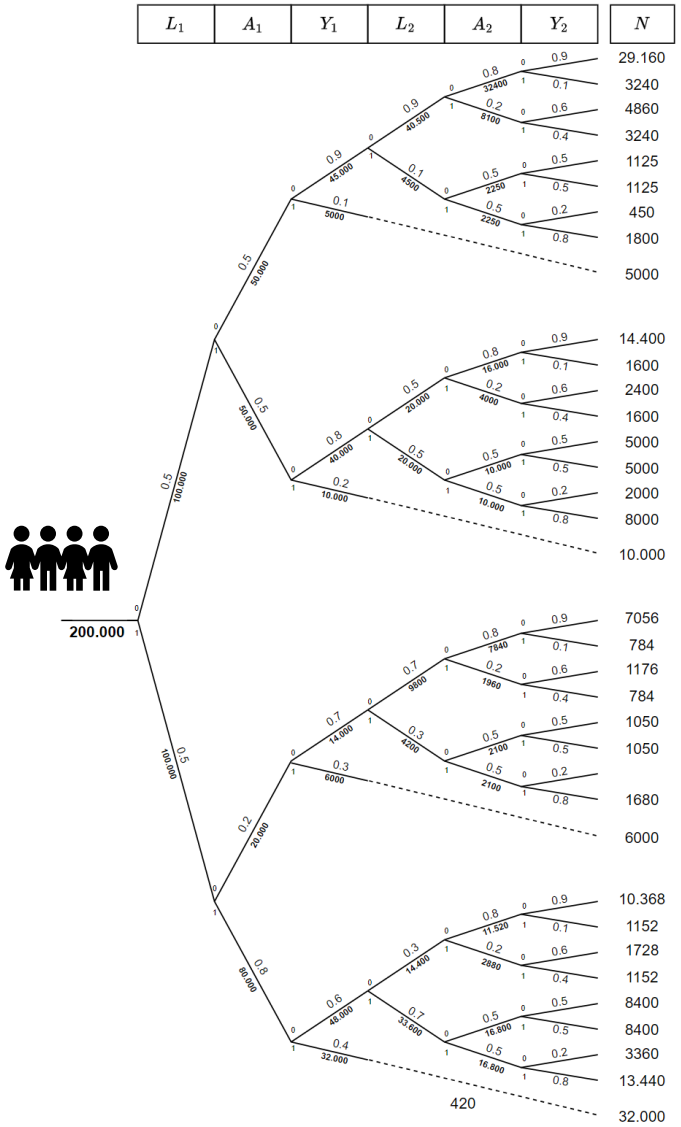

$L_1$: Baseline confounder

$A_1$: Treatment assignment

Y: Outcome

This is the whole tree of a **point intervention** because we only have treatment at single point in time!

# Visualizing the history of a population as a tree




Quickly becomes more complex for **sustained strategies** because of multiple $A_t$

$L_1$: Baseline confounder

$A_1$: Treatment at time t=1

$Y_1$: Outcome at time t=1

$L_2$: Time-varying confounder

$A_2$: Treatment at time t=2

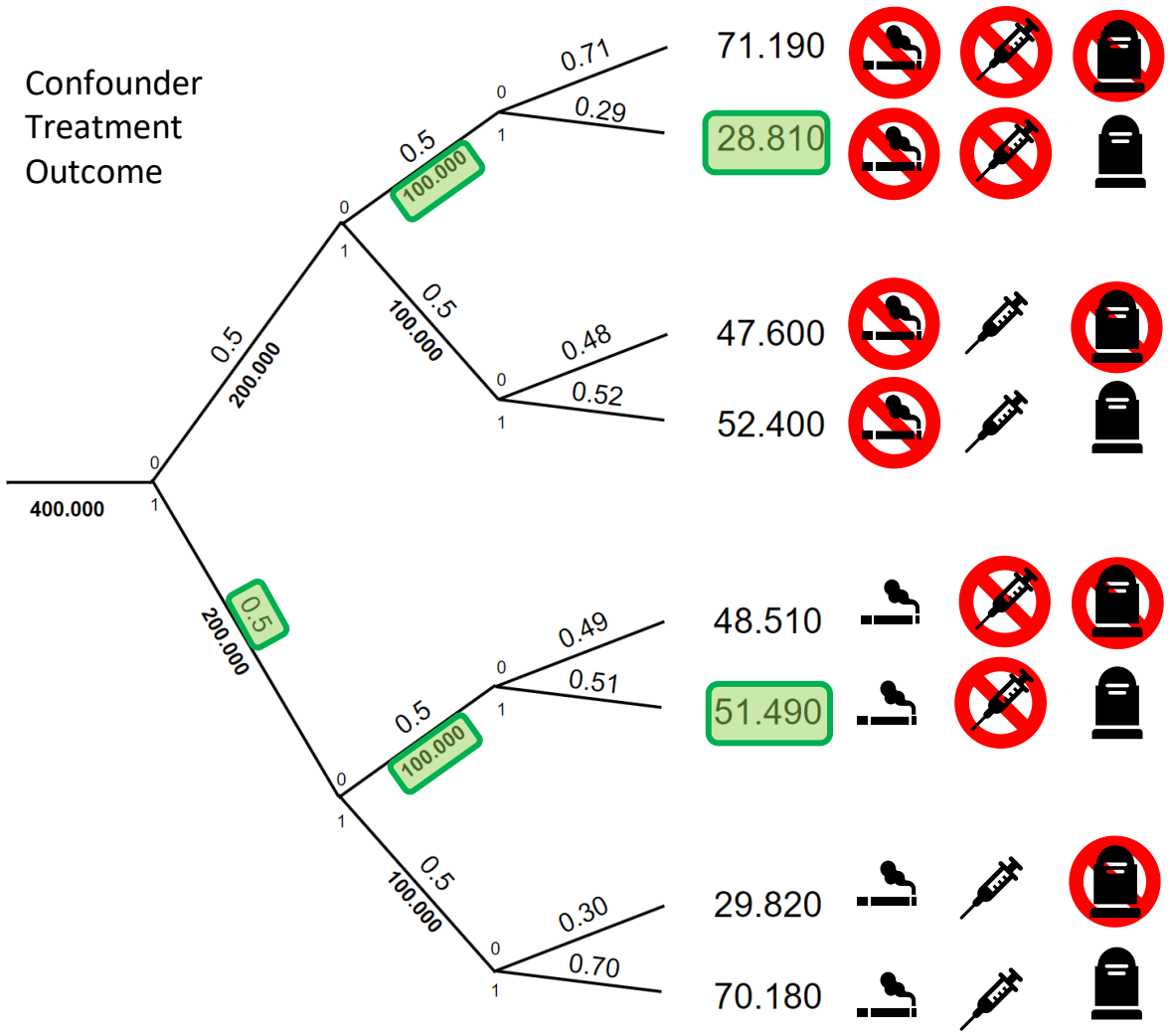
$Y_2$: Outcome at time t=2

# Some exercises

Go to classpoint.app

| $L_1$ | $A_1$ | $Y$ | $N$ |
|---|---|---|---|

L: Confounder
A: Treatment
Y: Outcome




**Instructions on reading the tree**

1 binary confounder L (smoking)

1 binary treatment A (medication)

1 binary outcome Y (death)

Number above the lines represent proportions

Number below the lines represent number of patients

Short Answer

**Question 1:**

What is the probability that $L_1$=1? **0.5**

**Question 2:**

How many are **untreated**? **100.000 + 100.000 = 200.000**

**Question 3:**

How many die among **untreated**? **28.810 + 51.490 = 80.300**

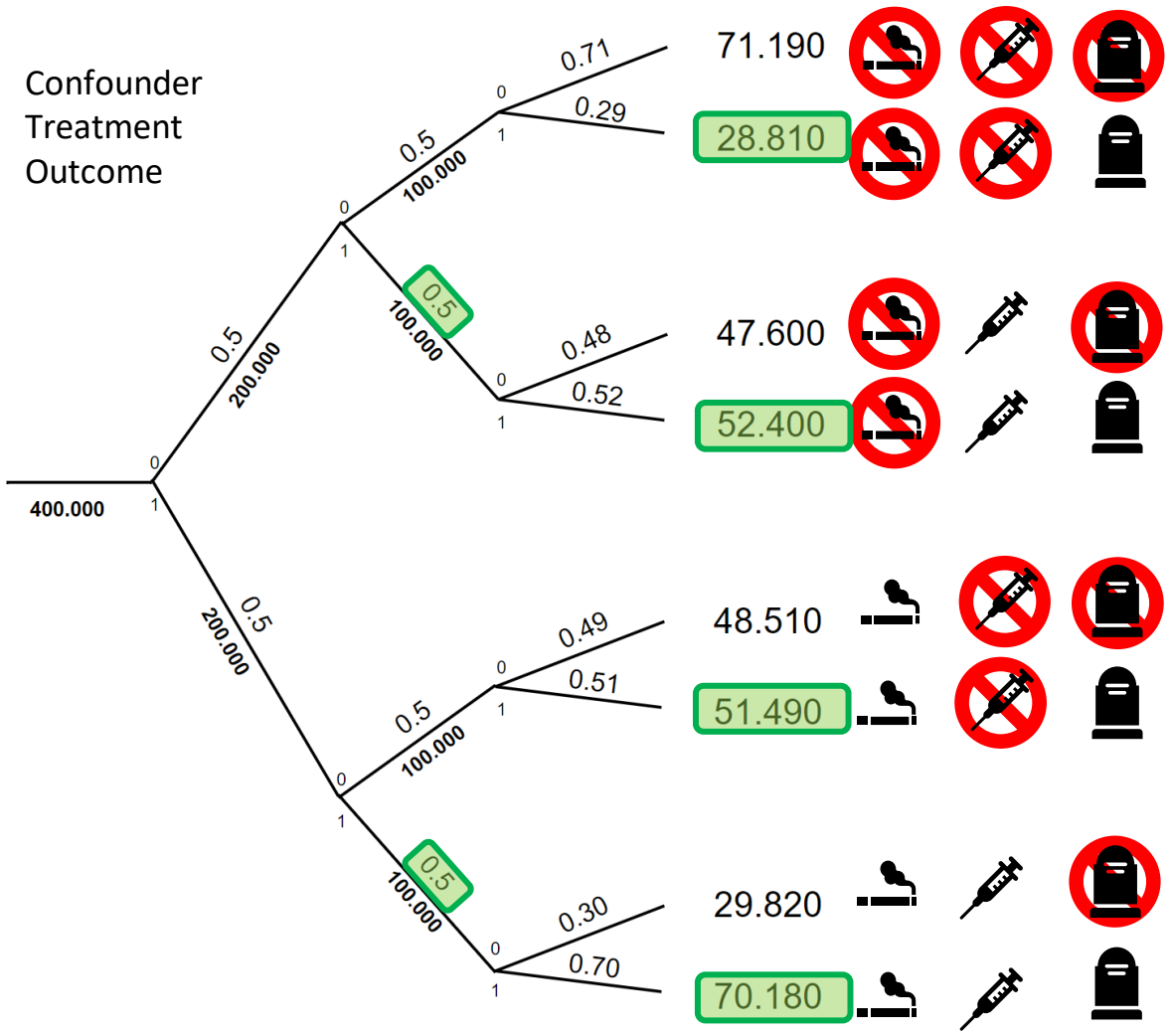
**Question 4:**

What is risk of death among **untreated**? **80.300/200.000 = 0.402**

# Some exercises

| $L_1$ | $A_1$ | $Y$ | $N$ |
|---|---|---|---|

L: Confounder
A: Treatment
Y: Outcome




**Instructions on reading the tree**

1 binary confounder L (smoking)

1 binary treatment A (medication)

1 binary outcome Y (death)

Number above the lines represent proportions

Number below the lines represent number of patients

**Question 5:**

Does $L_1$ predict $A_1$?

**No**

**$Pr[A_1 = 1 | L_1 = 1] = 0.5$**

**$Pr[A_1 = 1 | L_1 = 0] = 0.5$**

**Question 6:**

Does $L_1$ predict Y?

**Yes:**

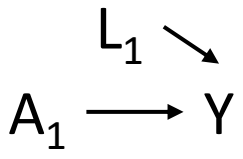
**$Pr[Y = 1 | L_1 = 1] = (51.490+70.180)/200.000 = 0.61$**

**$Pr[Y = 1 | L_1 = 0] = (28.810+52.400)/200.000 = 0.41$**

**Question 7:**

Is $L_1$ a confounder?

**No**

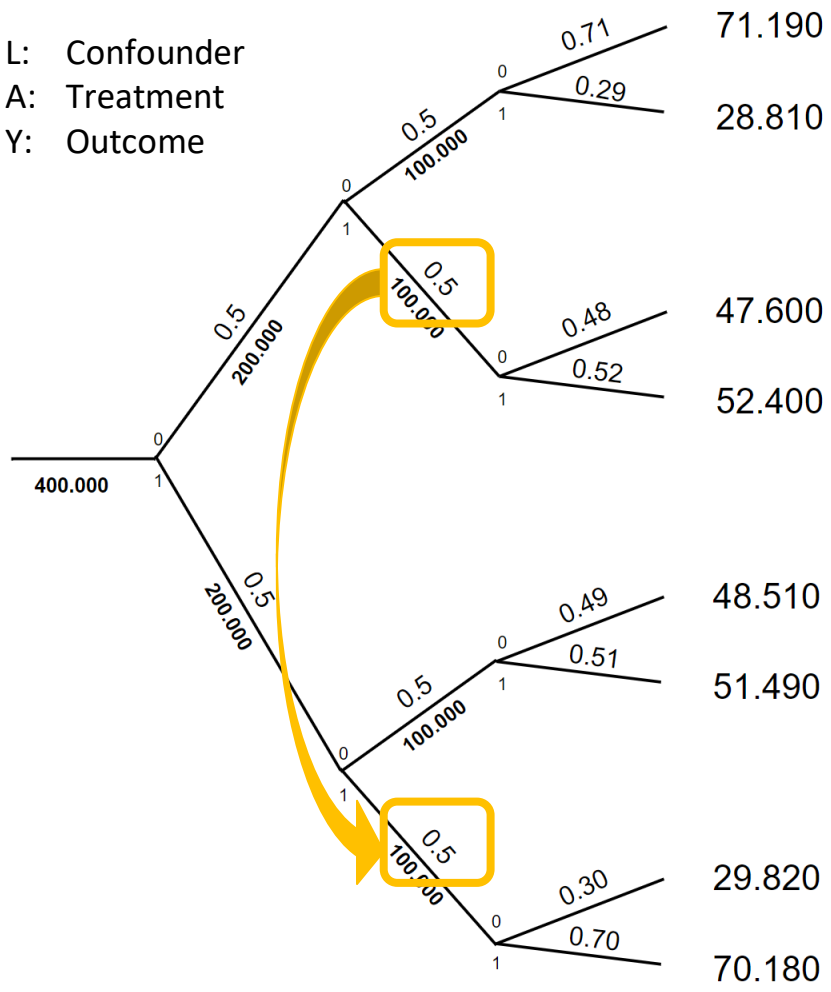


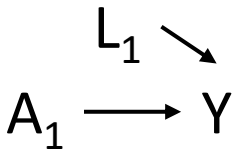
# Baseline confounding

# Let's check that these data indeed come from a randomized trial

| $L_1$ | $A_1$ | $Y$ | $N$ |
|---|---|---|---|

L: Confounder
A: Treatment
Y: Outcome




**In a randomized trial**

- Prognostic factor does not determine whether someone receives treatment or not

- Association is causation in randomized trial

**Step 3: Effect estimation**

**Risk among untreated**
(28.810+51.490)/(100.000+100.000) = 0.40

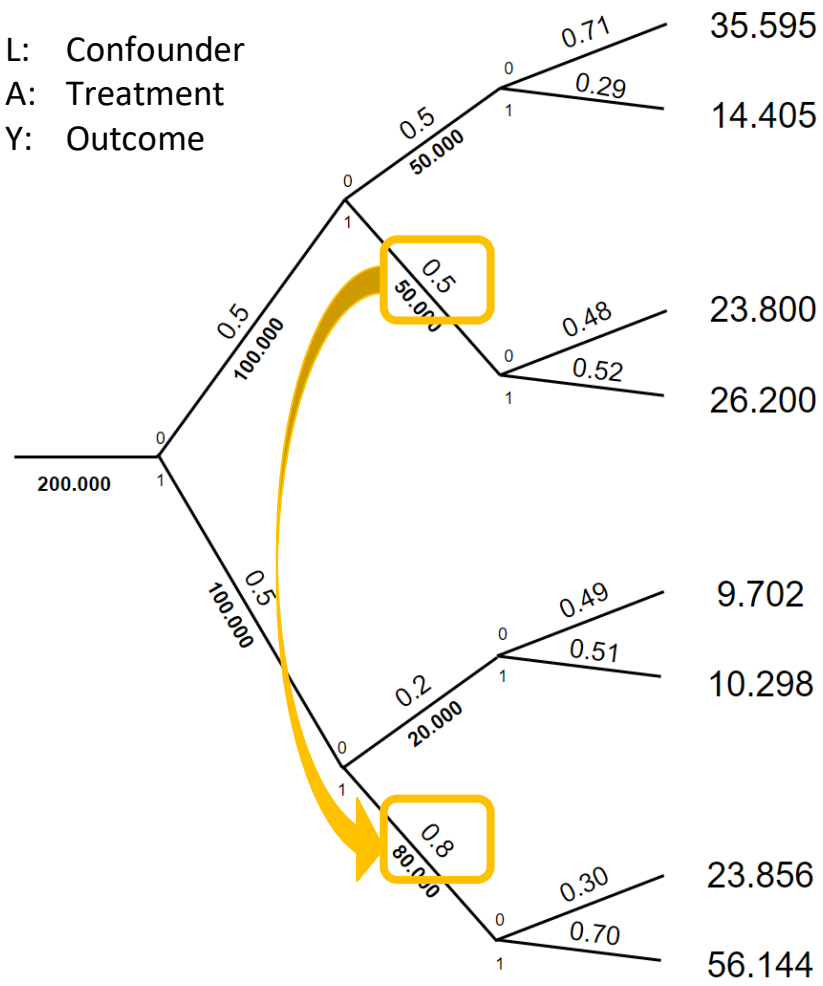
**Risk among treated**
(26.200+56.144)/(50.000+80.000) = 0.61

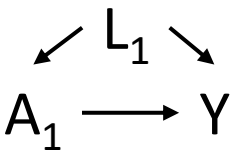
**Causal risk difference**: 0.61-0.40 = 0.21 (= 21%)
**Causal risk ratio**: 0.61/0.40 = 1.52

# New tree graph. Do these new data come from a randomized trial?

| $L_1$ | $A_1$ | $Y$ | $N$ |
|---|---|---|---|

L: Confounder
A: Treatment
Y: Outcome




**In observational studies**

- Prognostic factor determines whether someone receives treatment or not ($L_1$ = confounder)
- Association is NOT causation

**Step 3: Effect estimation without adjustment for baseline confounding**

**Risk among untreated**
(14.405+10.298)/(50.000+20.000) = 0.35 ≠ 0.40

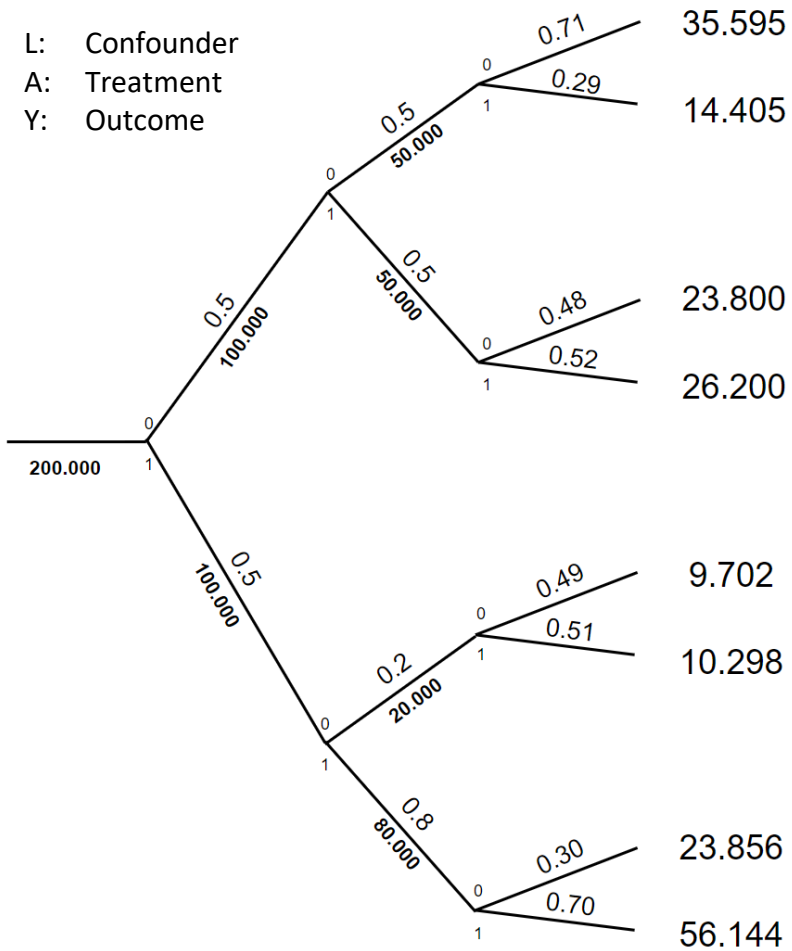
**Risk among treated**
(26.200+56.144)/(50.000+80.000) = 0.63 ≠ 0.61

**Confounded risk difference**: 0.63-0.35 = 0.28 (= 28%) ≠ 0.21
**Confounded risk ratio**: 0.63/0.35 = 1.80 ≠ 1.52

# Adjusting for baseline confounding with weighting (IPTW)

| $L_1$ | $A_1$ | $Y$ | $N$ |
|---|---|---|---|

L: Confounder
A: Treatment
Y: Outcome



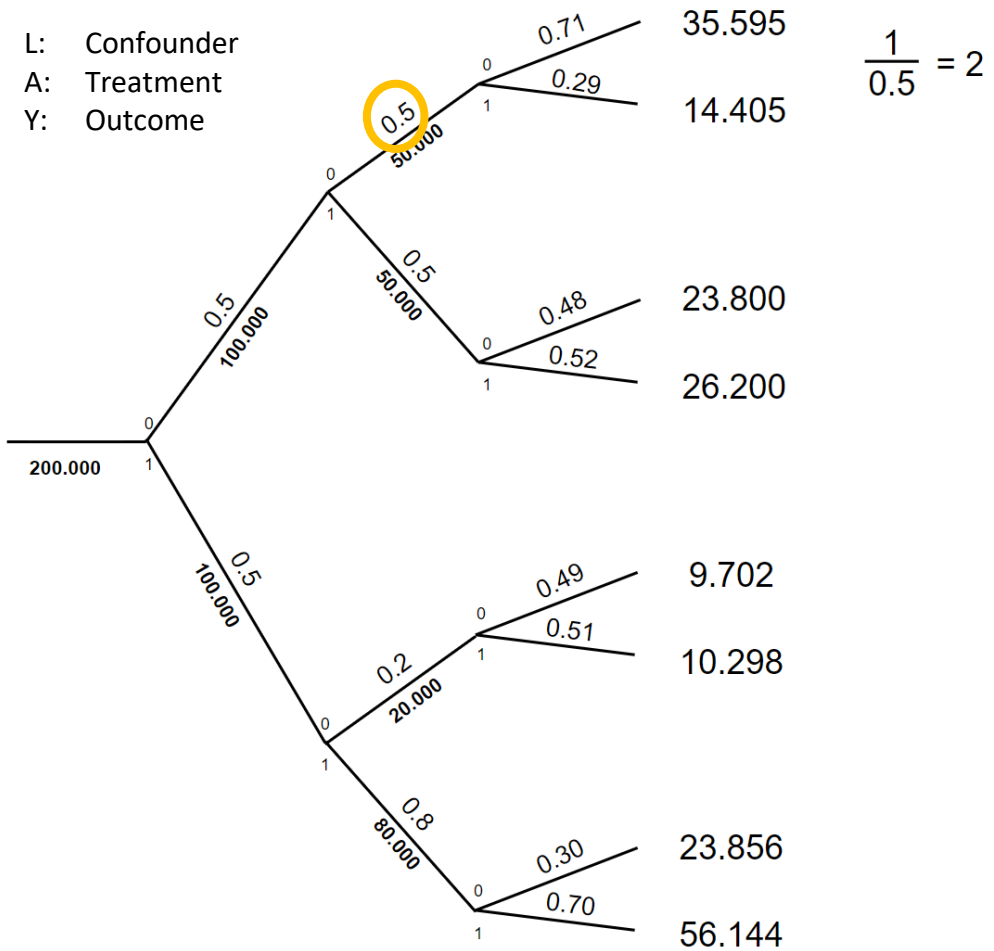

Inverse Probability of Treatment Weights are the inverse of the probability of having received your treatment history given confounders

Here: $w_t = \frac{1}{\Pr[A_1|L_1]}$

# Adjusting for baseline confounding with weighting (IPTW)

| $L_1$ | $A_1$ | $Y$ | $N$ | $w_t$ | $N_w$ |
|---|---|---|---|---|---|

L: Confounder
A: Treatment
Y: Outcome




$$\frac{1}{0.5} = 2$$

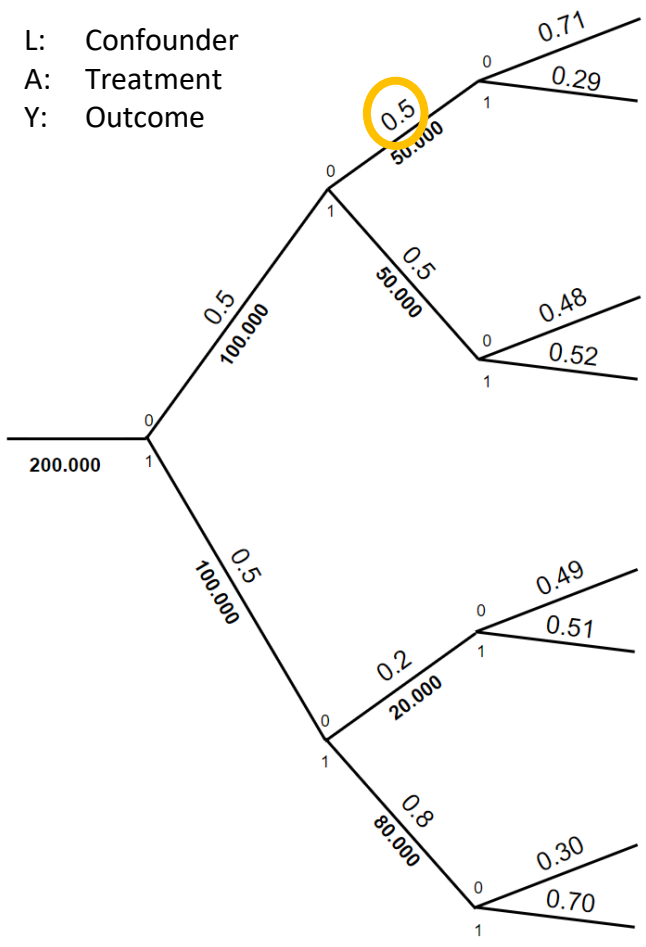
Inverse Probability of Treatment Weights are the inverse of the probability of having received your treatment history given confounders

Here: $w_t = \frac{1}{\Pr[A_1|L_1]}$

# Adjusting for baseline confounding with weighting (IPTW)

| $L_1$ | $A_1$ | $Y$ | $N$ | $w_t$ | $N_w$ |
|---|---|---|---|---|---|
| | | | 35.595 | $\frac{1}{0.5} = 2$ | 71.190 |
| | | | 14.405 | | 28.810 |
| | | | 23.800 | ? | |
| | | | 26.200 | | |
| | | | 9.702 | ? | |
| | | | 10.298 | | |
| | | | 23.856 | ? | |
| | | | 56.144 | | |

L: Confounder
A: Treatment
Y: Outcome




Inverse Probability of Treatment Weights are the inverse of the probability of having received your treatment history given confounders

Here: $w_t = \frac{1}{\Pr[A_1|L_1]}$

# Adjusting for baseline confounding with weighting (IPTW)

| $L_1$ | $A_1$ | $Y$ | $N$ | $w_t$ | $N_w$ |
|---|---|---|---|---|---|
| | | | 35.595 | $\frac{1}{0.5} = 2$ | 71.190 |
| | | | 14.405 | | 28.810 |
| | | | 23.800 | $\frac{1}{0.5} = 2$ | 47.600 |
| | | | 26.200 | | 52.400 |
| | | | 9.702 | $\frac{1}{0.2} = 5$ | 48.510 |
| | | | 10.298 | | 51.490 |
| | | | 23.856 | $\frac{1}{0.8} = 1.25$ | 29.820 |
| | | | 56.144 | | 70.180 |

L: Confounder
A: Treatment
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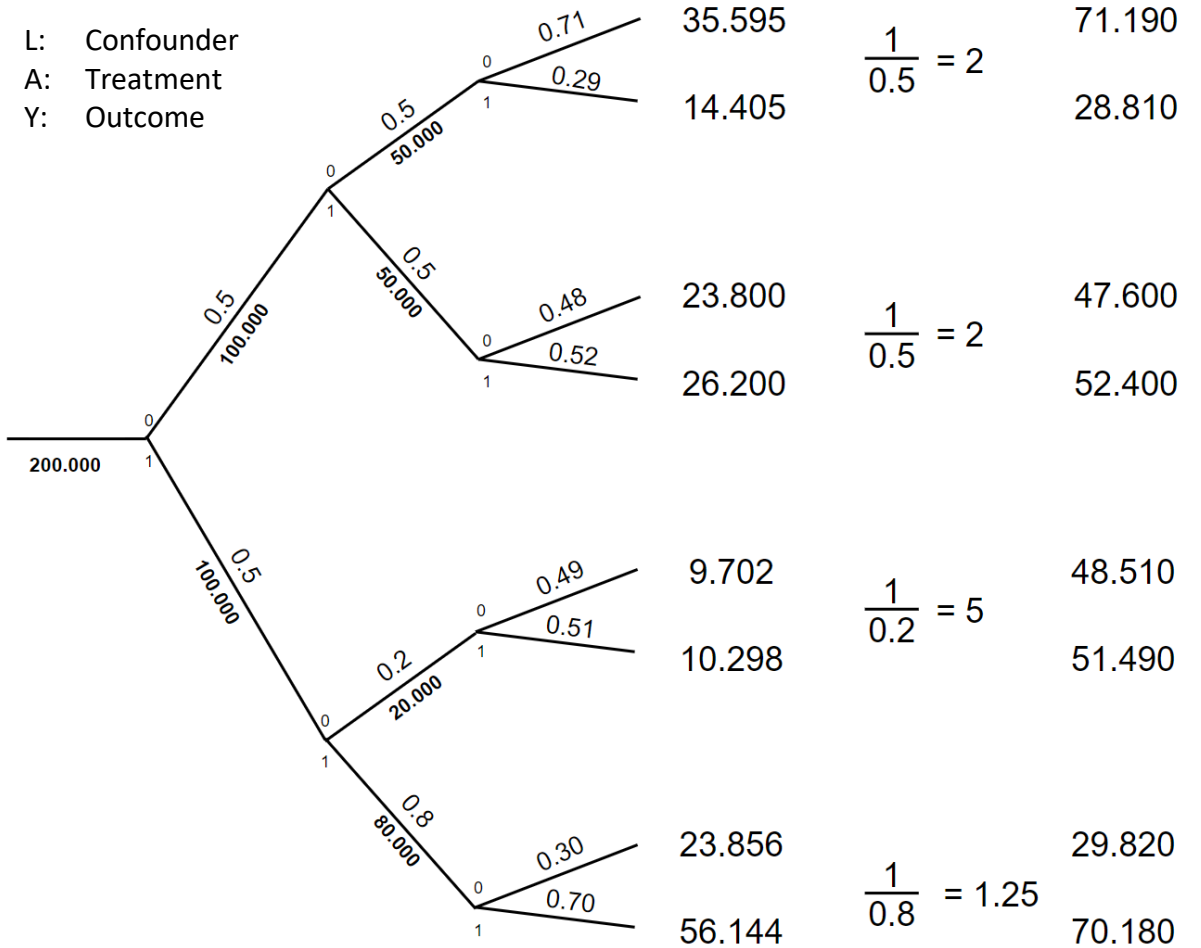


Inverse Probability of Treatment Weights are the inverse of the probability of having received your treatment history given confounders

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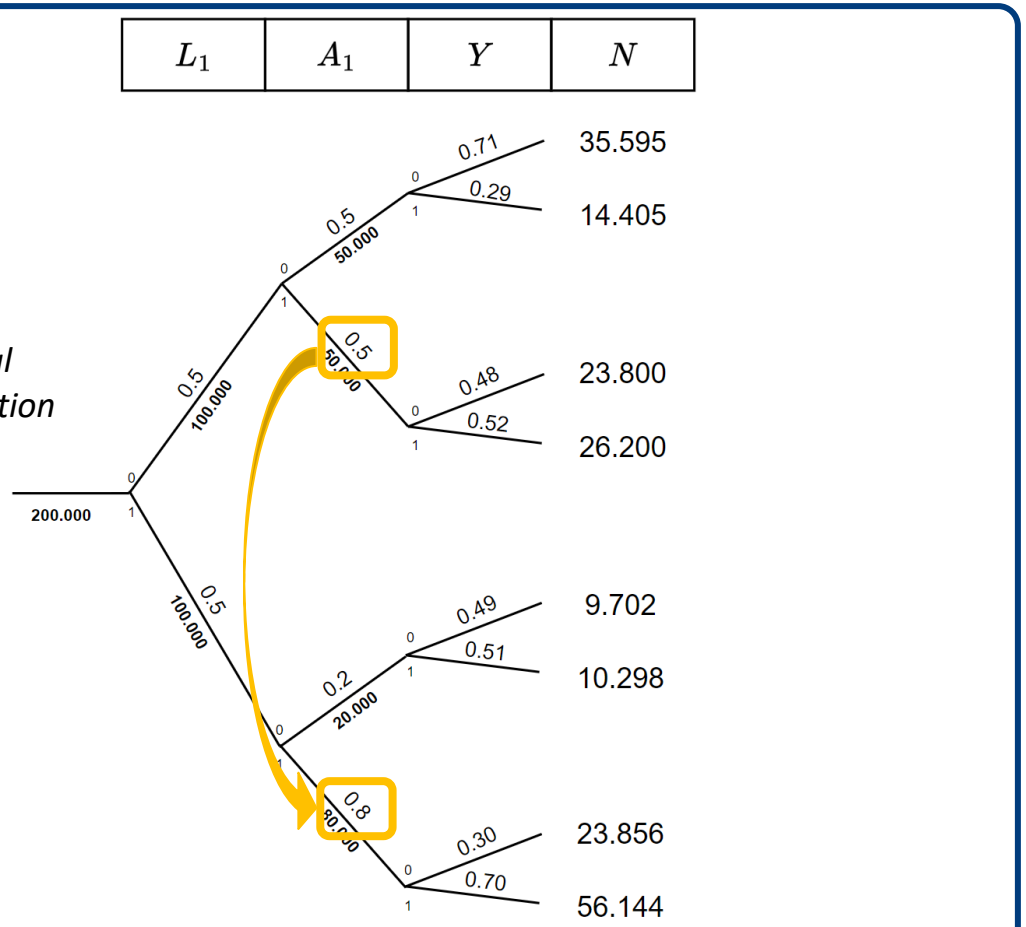
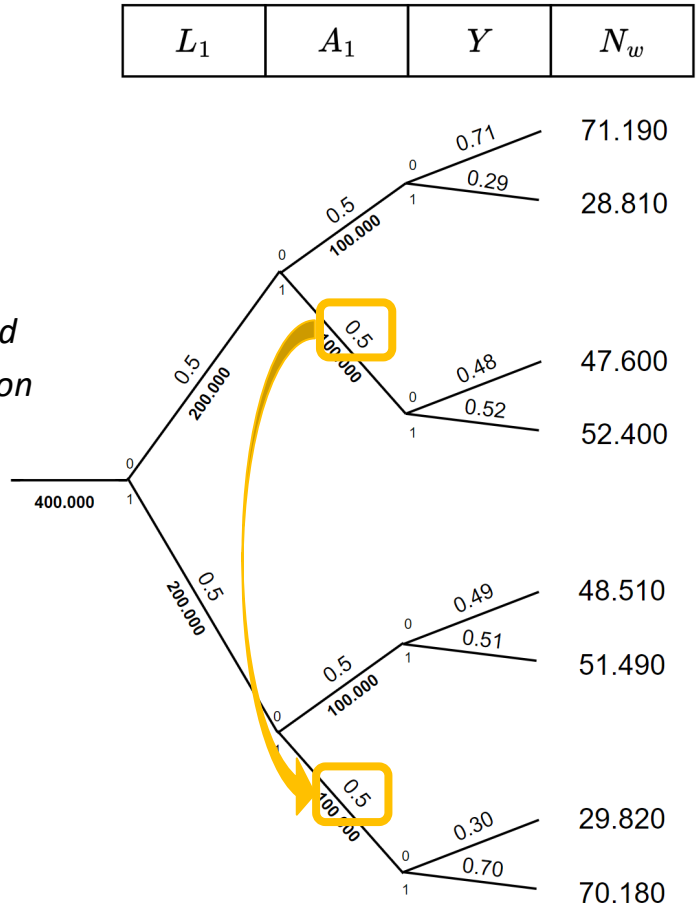
# Turning our observational study into a randomized trial

*Original population*




In the original population, treatment is predicted by confounder $L_1$

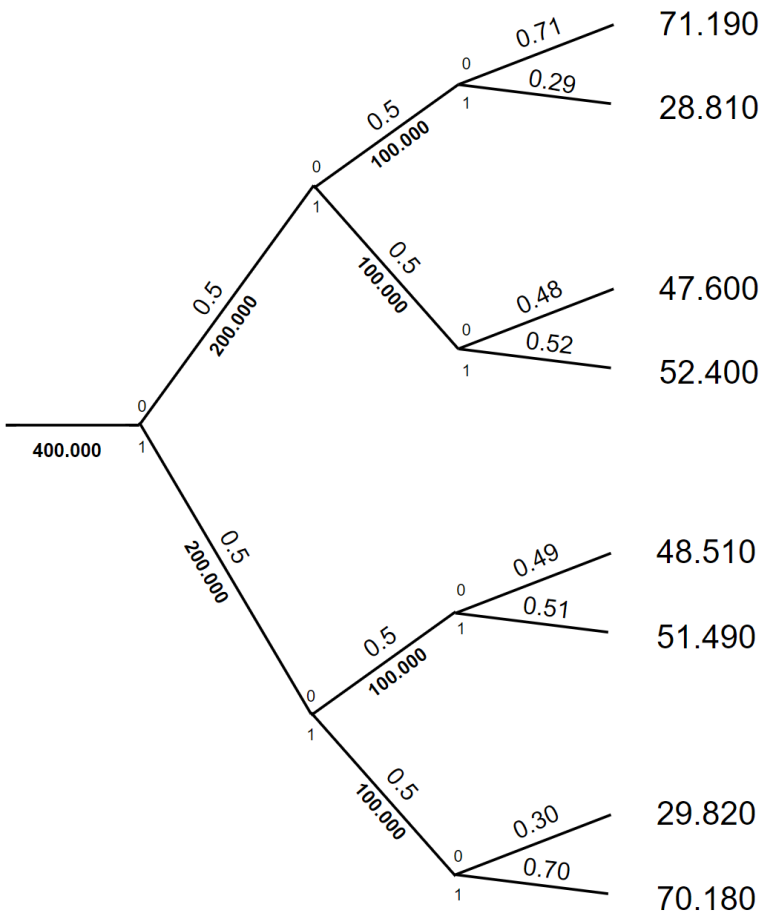
*Weighted population*

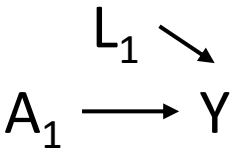



In the weighted population, treatment is no longer predicted by confounder $L_1$

# Treatment effect estimation in the weighted pseudopopulation

| $L_1$ | $A_1$ | $Y$ | $N_w$ |
|---|---|---|---|




**In weighted pseudopopulation**

- Confounder no longer determines whether someone receives treatment or not

- Association is causation in the weighted pseudopopulation

**Effect estimation**

**Risk among untreated**
(28.810+51.490)/(100.000+100.000) = 0.40 ✓

**Risk among treated**
(52.400+70.180)/(100.000+100.000) = 0.61 ✓

**Causal risk difference**: 0.61-0.40 = 0.21 (= 21%) ✓
**Causal risk ratio**: 0.61/0.40 = 1.52

# Some comments on weighting

- Note that we only assumed 1 binary confounder – So we could calculate the weights nonparametrically (i.e., without models)

- In practice, there may be many confounders, which may be categorical and continuous → need to **fit models** to estimate the weights (e.g. logistic regression model)

- Note that if there are unmeasured confounders (e.g. if we had not measured $L_1$), we cannot use them to estimate our inverse probability of treatment weights, and our resulting treatment effects will be biased (then we have not turned our observational study into a randomized trial)

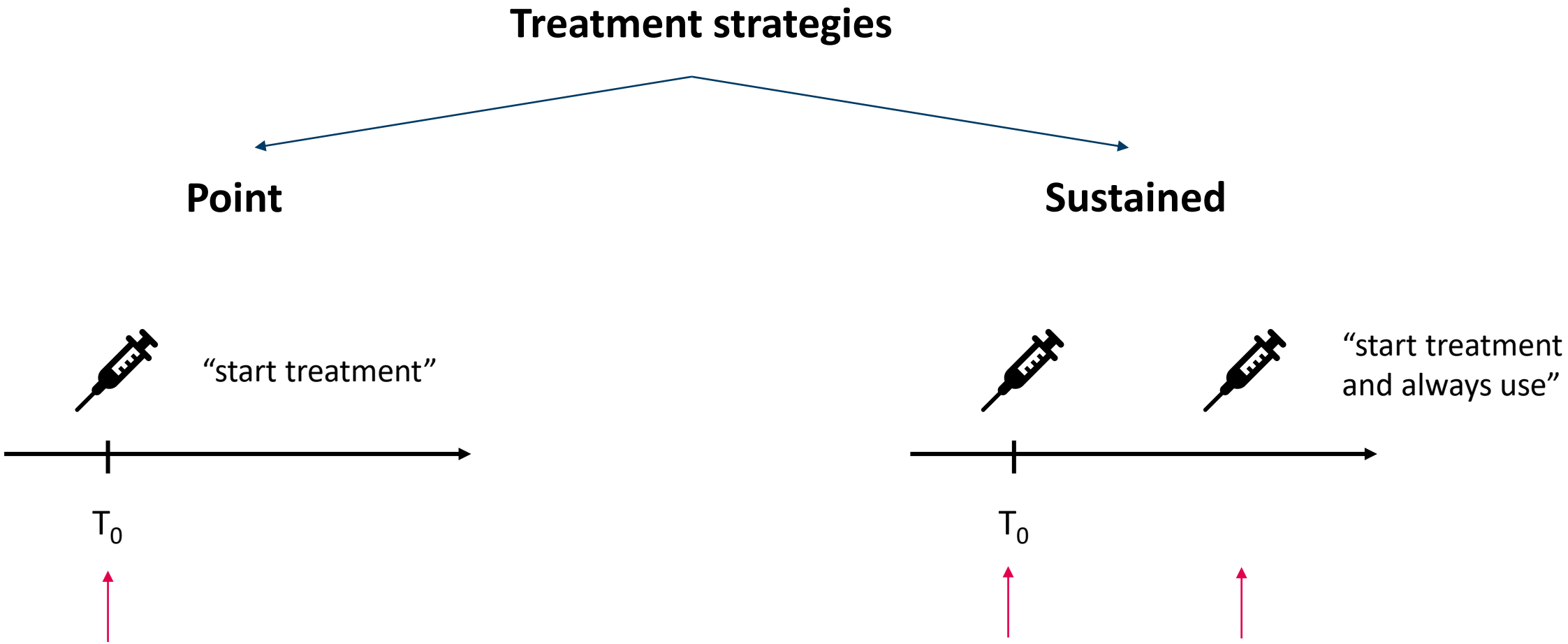
# Some comments on outcome model

- In practice, we also fit a model for the outcome (e.g. a *weighted* Cox regression) since survival times are not observed for everyone (there is censoring)

- To obtain correct confidence intervals we need to take into account the weighting, e.g. with robust standard error or bootstrapping

# Time-varying confounding

# Recap baseline vs. time-varying confounding



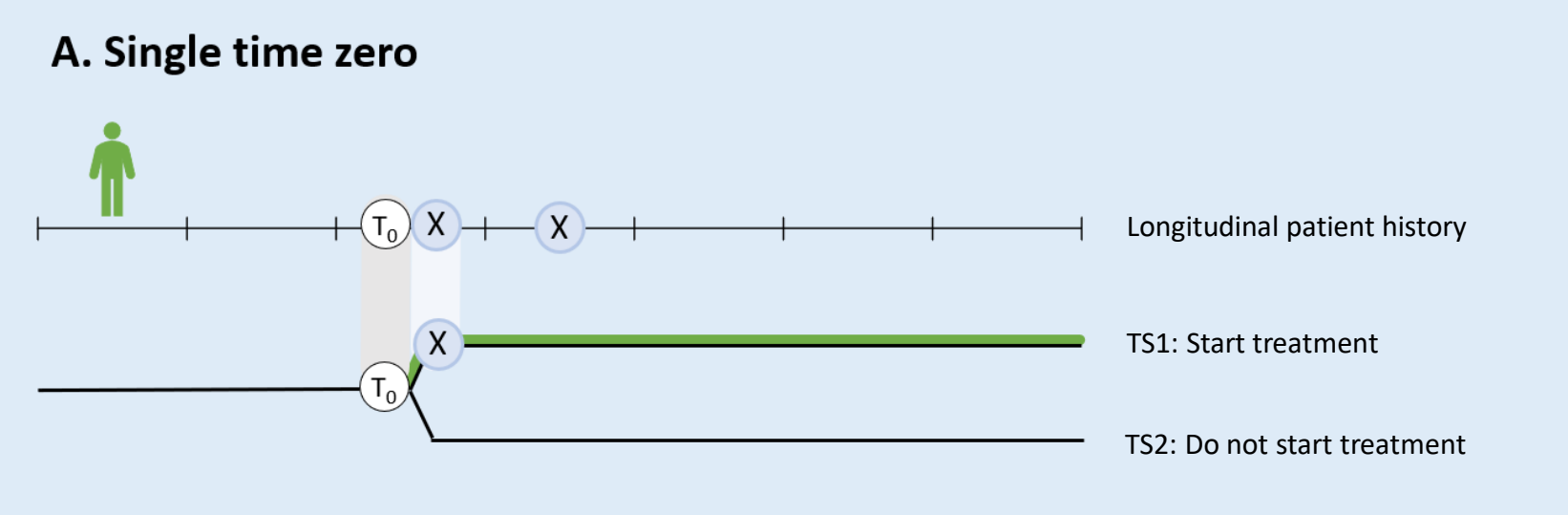

- Groups need to be similar at time zero
- Only baseline confounding

- Groups need to be similar at time zero & during follow-up
- Baseline & **time-varying confounding**

# Why the effects of sustained strategies are more interesting

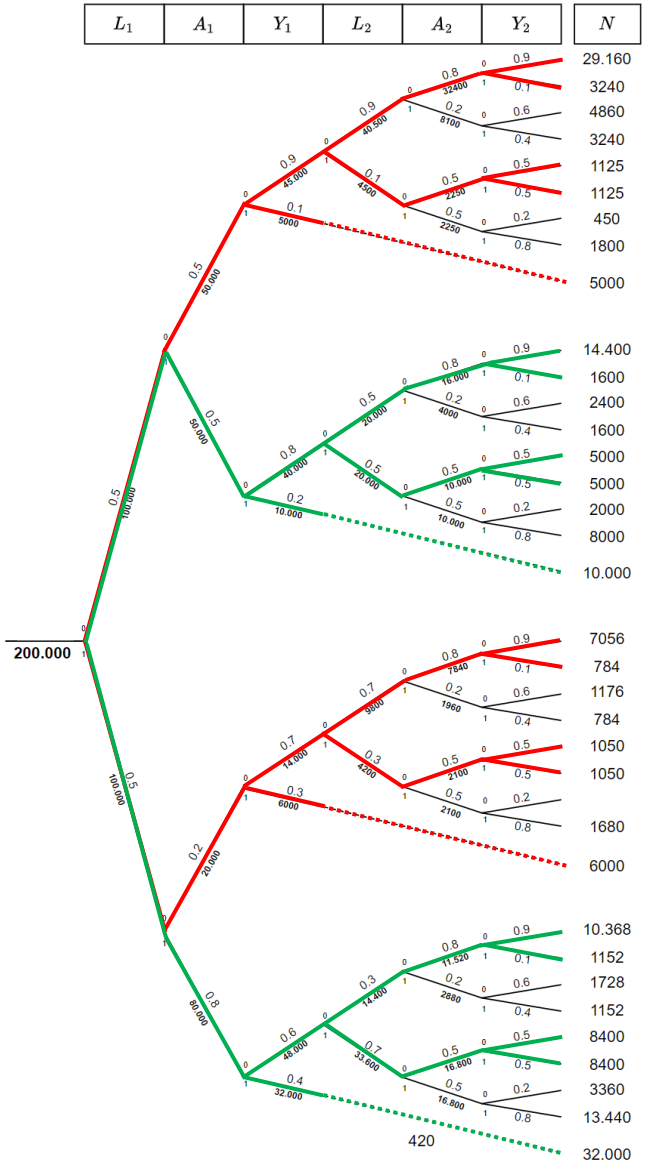
If we compare the point strategies “start treatment” vs. “do not start treatment”, what problems arise?

- Many people in “start treatment” group may stop treatment during follow-up
- Conversely, many people in “do not start treatment” group may start it during follow-up
- We may then find a hazard ratio of 1.0 even for a treatment known to have benefits



# Sustained strategies: tree graph with 2+ timepoints

Go to classpoint.app




Let's say we are interested in the sustained strategies:

- "always treat"
- "never treat"

Multiple Choice

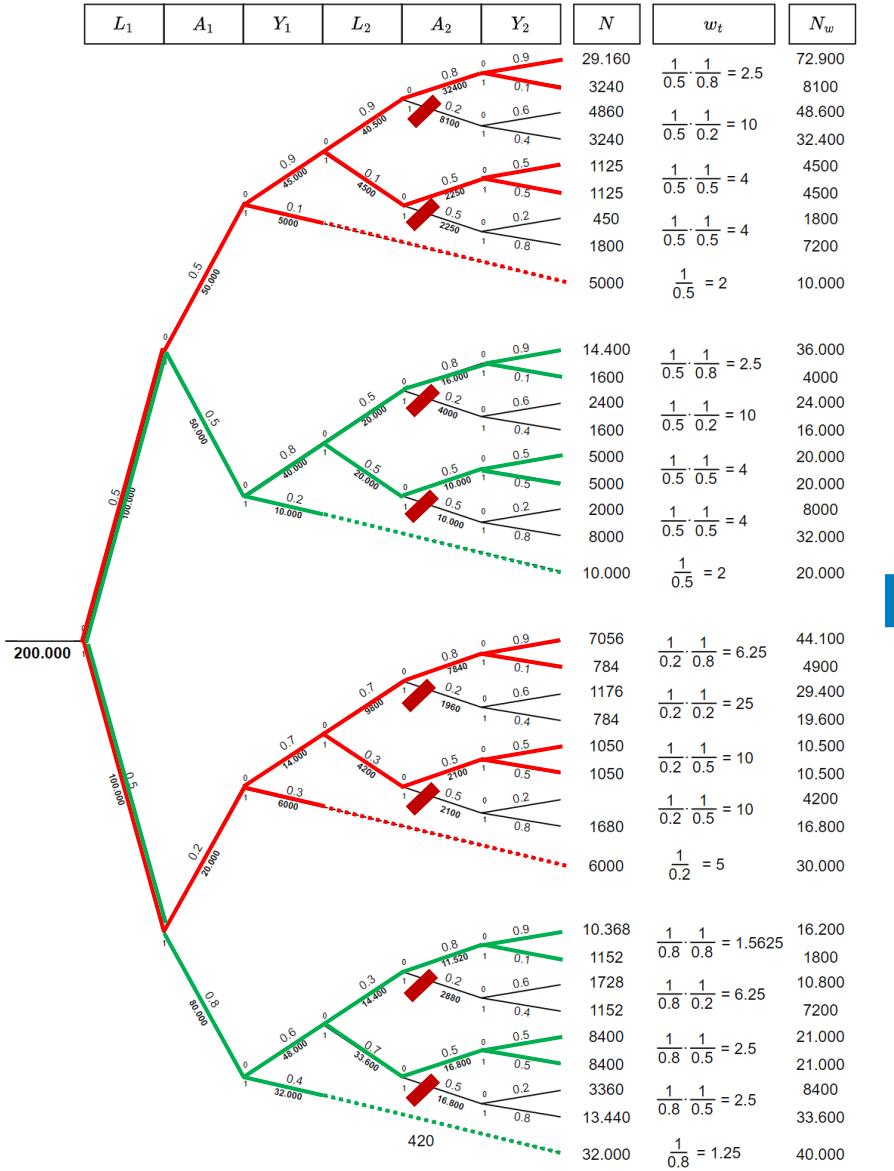
Which strategy is highlighted in the tree?

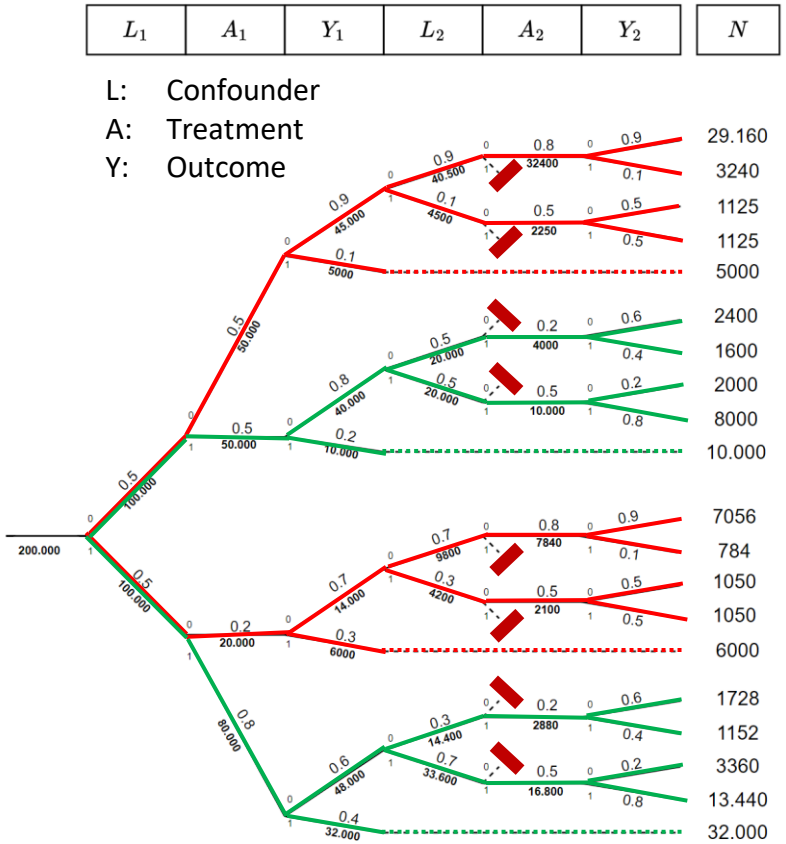
A: Always treat

B: Never treat

C: Neither

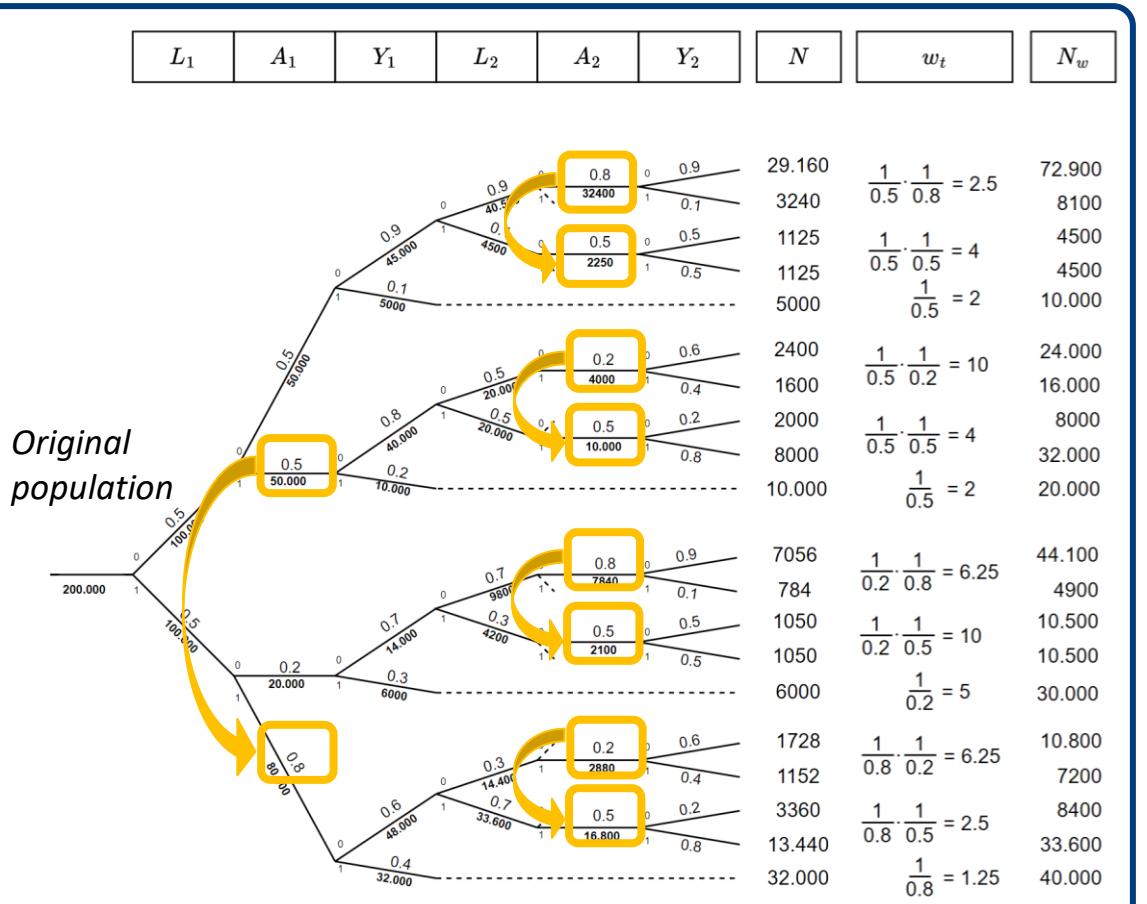
# Censoring: focus only on branches of interest




Censor patients who deviate from the strategies of interest

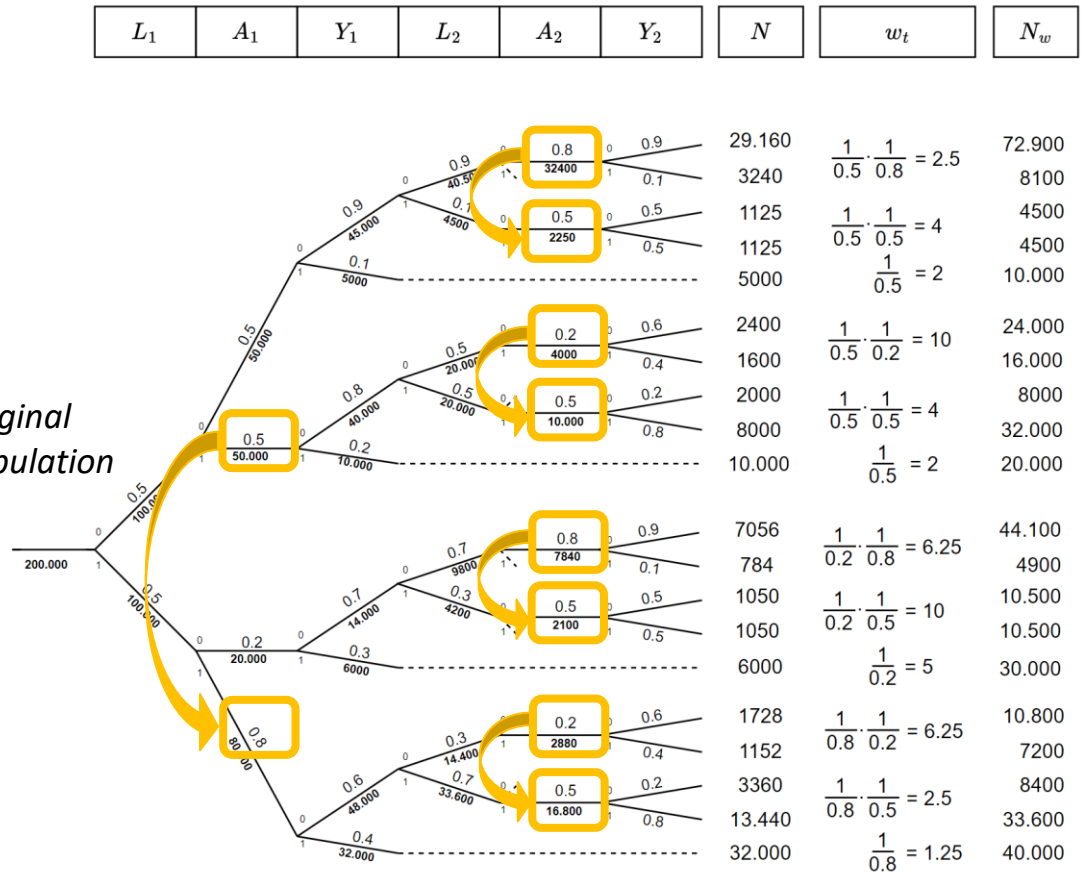
# Turning our observational study into a sequentially randomized trial




In the original population, treatment $A_k$ is predicted by confounder $L_k$

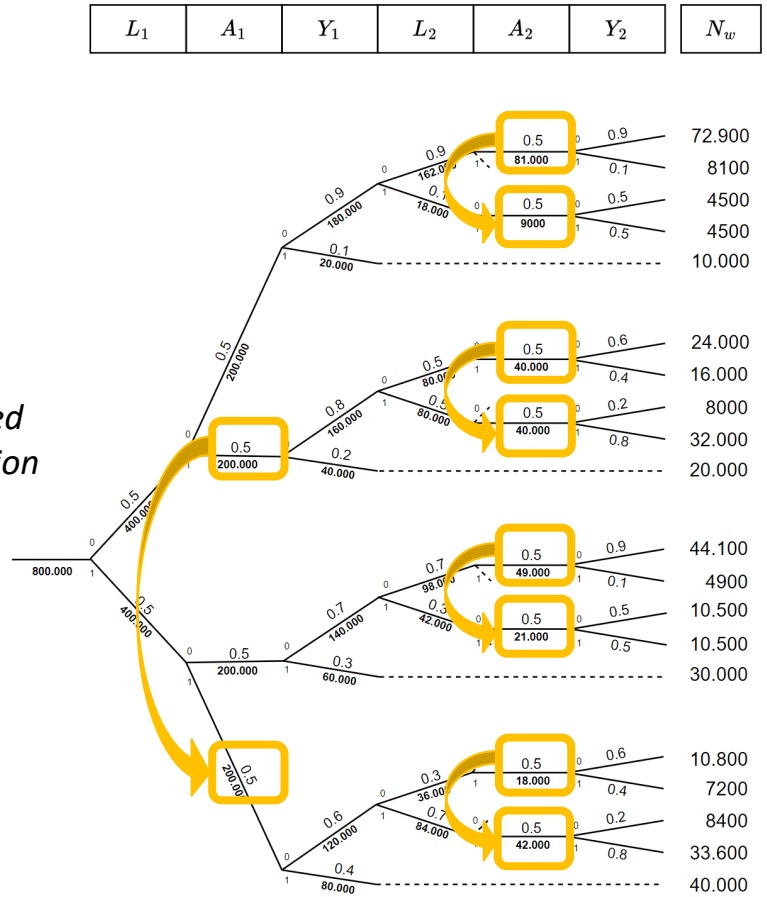
# Turning our observational study into a sequentially randomized trial

*Original population*




In the original population, treatment $A_k$ is predicted by confounder $L_k$

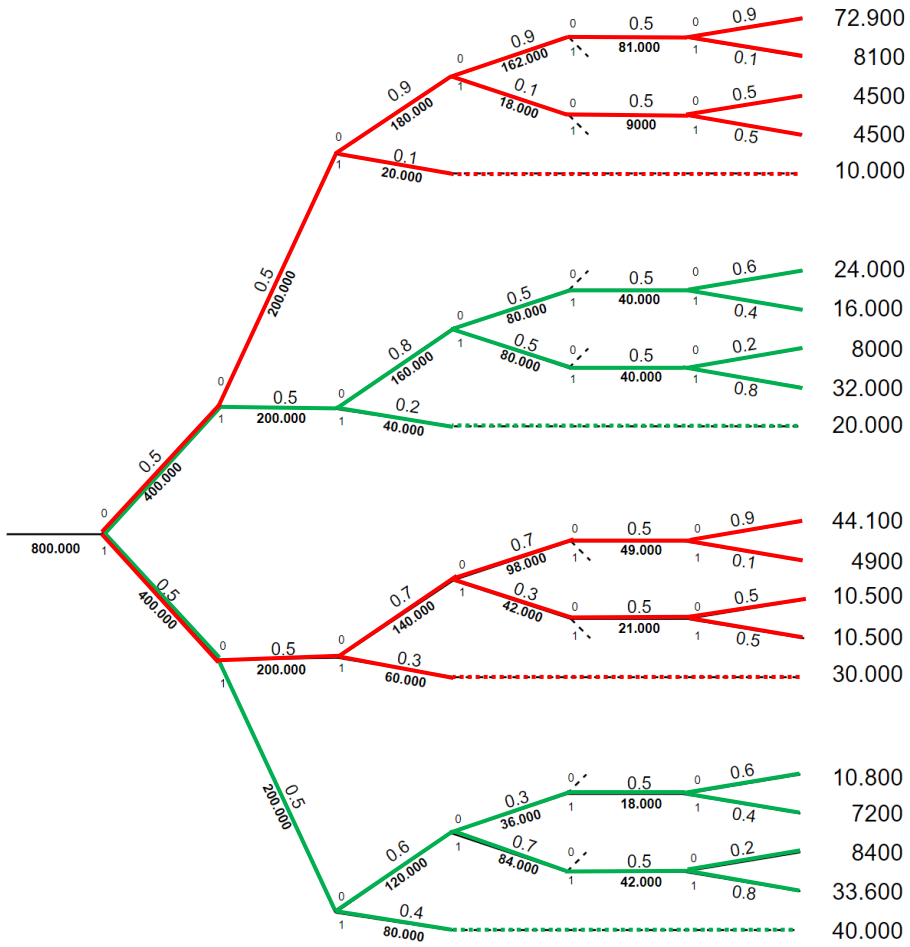
*Weighted population*




In the weighted population, treatment $A_k$ is no longer predicted by confounder $L_k$

# Treatment effect estimation in the weighted pseudopopulation

| $L_1$ | $A_1$ | $Y_1$ | $L_2$ | $A_2$ | $Y_2$ | $N_w$ |
|---|---|---|---|---|---|---|




## Effect estimation sustained strategies

**Risk among never treated**
(8100+4500+10.000+4900+10.500+30.000)/(200.000) = 0.34

**Risk among always treated**
(16.000+32.000+20.000+7200+33.600+40.000)/(200.000) = 0.74

**Causal risk difference**: 0.74-0.34 = 0.40 (= 40%)
**Causal risk ratio**: 0.74/0.34 = 2.19

## Effect estimation point strategies

**Risk among untreated**
(28.810+51.490)/(100.000+100.000) = 0.40

**Risk among treated**
(52.400+70.180)/(100.000+100.000) = 0.61

**Causal risk difference**: 0.61-0.40 = 0.21 (= 21%)
**Causal risk ratio**: 0.61/0.40 = 1.52

# Conclusions

1. Important distinction between point vs. sustained strategies

2. Always need to adjust for baseline confounding

3. If interested in sustained strategies, also need to adjust for time-varying confounding

4. We showed how weighting can be used to turn the observational data into a randomized or sequentially randomized trial

5. Results are biased if there are unmeasured confounders

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# Questions

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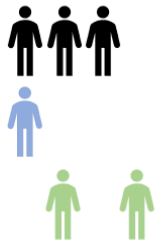
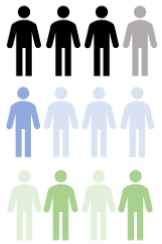
# Censoring & weighting on a group-level

Artificial censoring



Censored during follow-up if not following strategy of interest

Weighting



Uncensored replicates (dark color) are upweighted to account for censored replicates (light color) with similar characteristics