Leiden University Medical Center

Using IPW to adjust for confounding

Edouard Fu

Department of Clinical Epidemiology, LUMC

- 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

What you will learn

1. Distinction between point vs. sustained treatment strategies
2. Baseline vs. time-varying confounding
3. How tree graphs work
4. How IPW adjusts for confounding

The setting

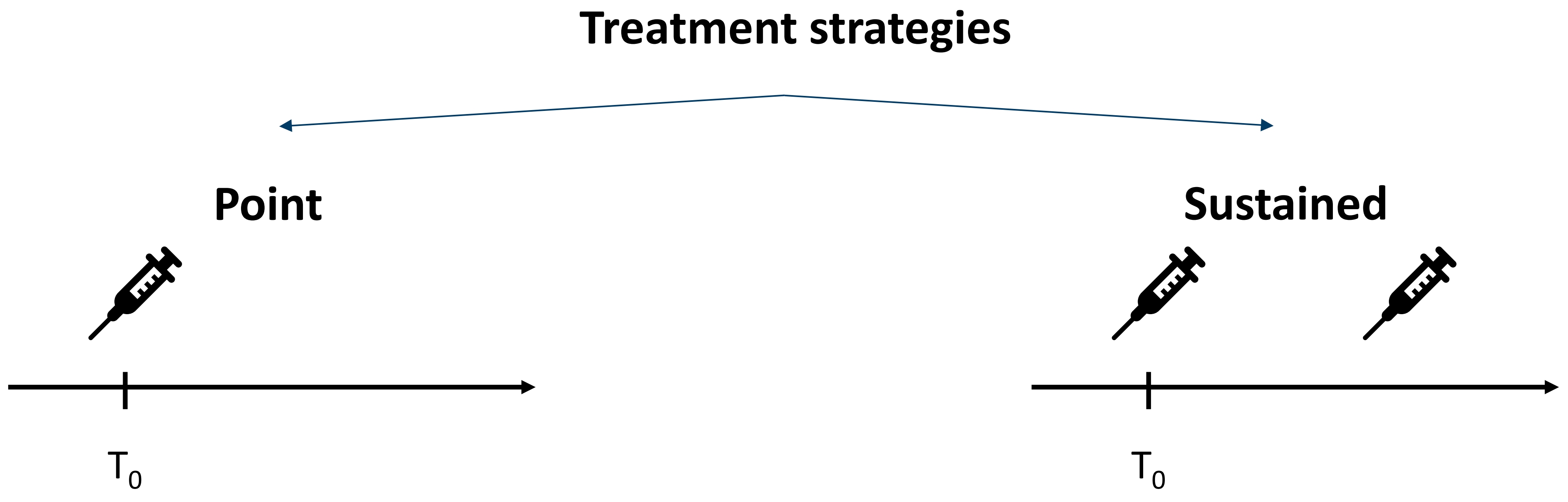
- We are interested in estimating the causal effect of a binary intervention on a binary outcome, using observational data
    - In the next examples, we focus on 1 binary confounder (adjusting for this confounder is sufficient to ensure exchangeability)

- We can imagine the hypothetical target trial that would answer this question

- E.g., the causal effect of metformin use on cardiovascular outcomes in patients with type 2 diabetes

- We make a target trial protocol, and specify eligibility criteria, treatment strategies, outcomes, start and end of follow-up, causal contrast (ITT/PP), data analysis

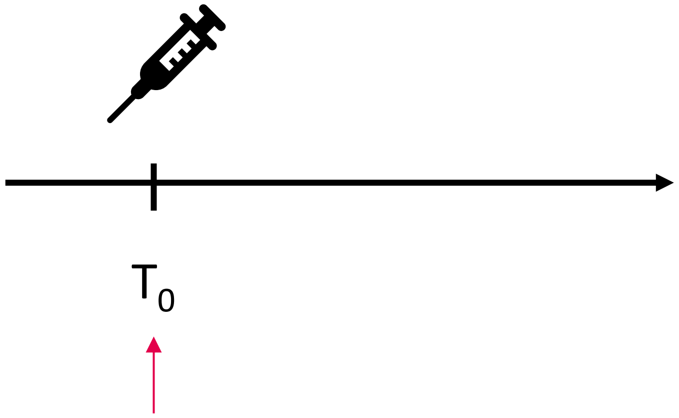
Classification of treatment strategies



Baseline vs. time-varying confounding

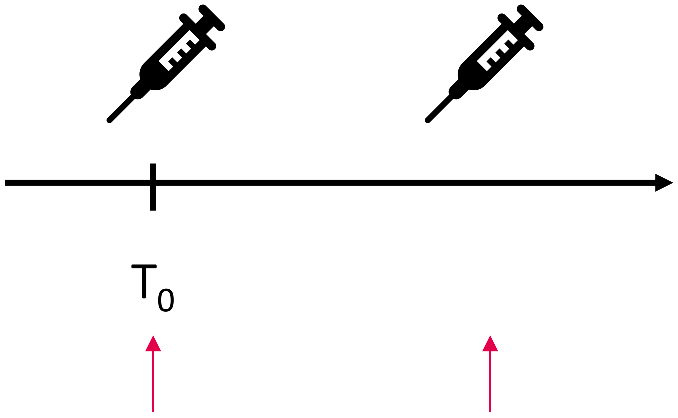
Treatment strategies

Point



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

Sustained

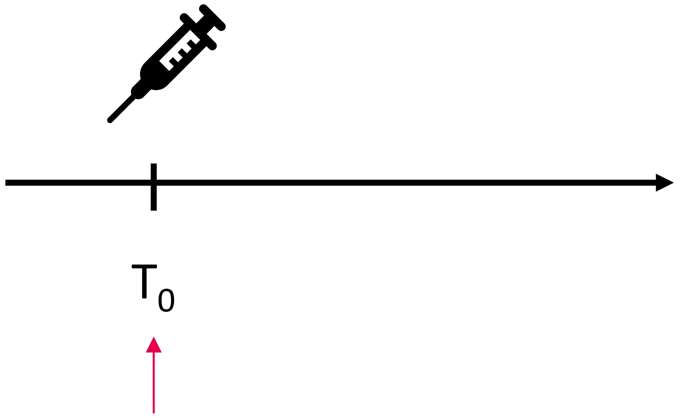


- Groups need to be similar at time zero & during follow-up
- Baseline & time-varying confounding

Baseline vs. time-varying confounding

Treatment strategies

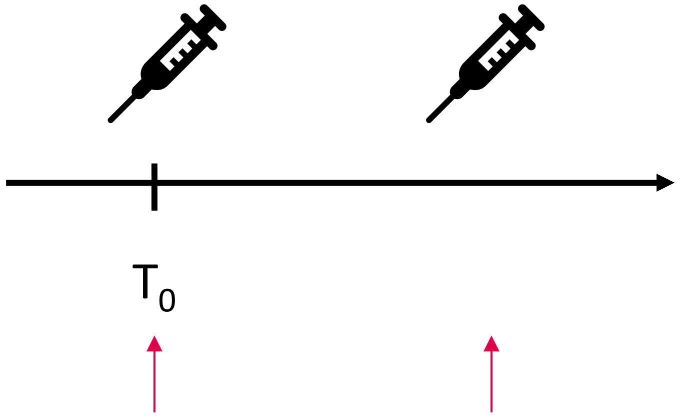
Point



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

$$\begin{tikzcd} L_1 \arrow[r] \arrow[rr, bend left] & A_1 \arrow[r] & Y \end{tikzcd}$$

Sustained



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

$$\begin{tikzcd} L_1 \arrow[r] \arrow[rrrr, bend left] & A_1 \arrow[r] & L_2 \arrow[r] \arrow[rr, bend right] & A_2 \arrow[r] & Y \end{tikzcd}$$

Let’s practice with classifying treatment strategies

Go to classpoint.app

Point strategy or sustained treatment strategy?

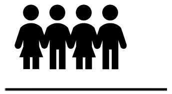
1. Receive bariatric surgery
2. Receive Pfizer first dose now, and second dose 3 weeks later
3. Start SGLT-2i within 3 months from now
4. Never start SGLT-2i
5. Start GLP-1RA when a cardiovascular event develops

A: point strategy

B: sustained strategy

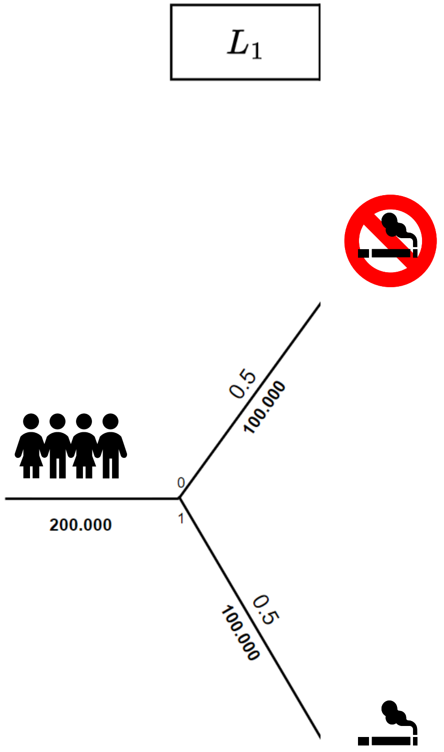
Multiple Choice

Visualizing the history of a population in a tree graph



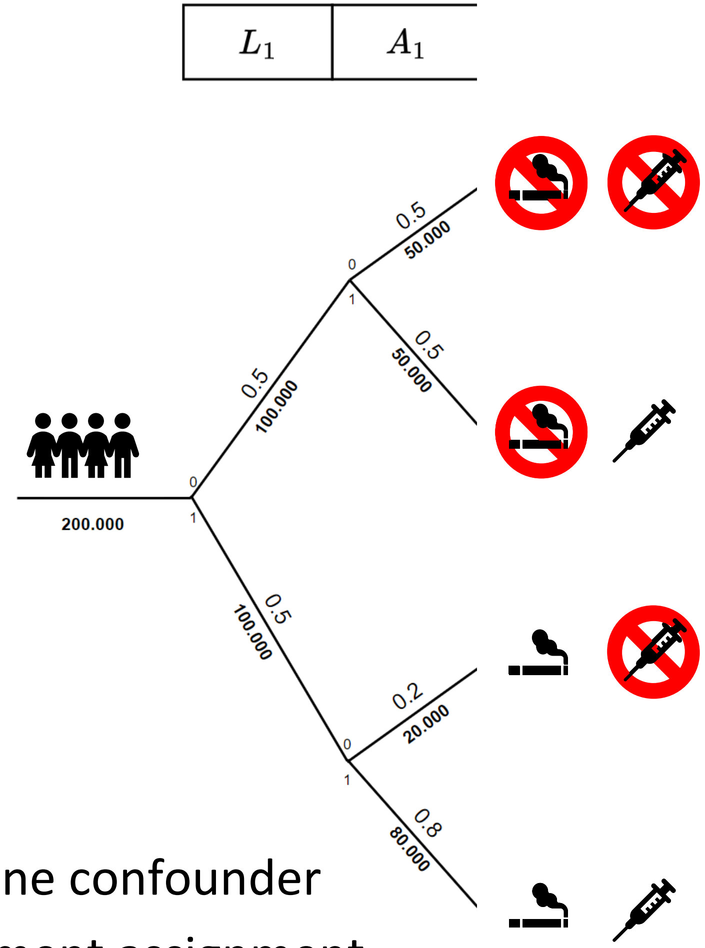
200.000

Visualizing the history of a population in a tree graph



L_1: Baseline confounder

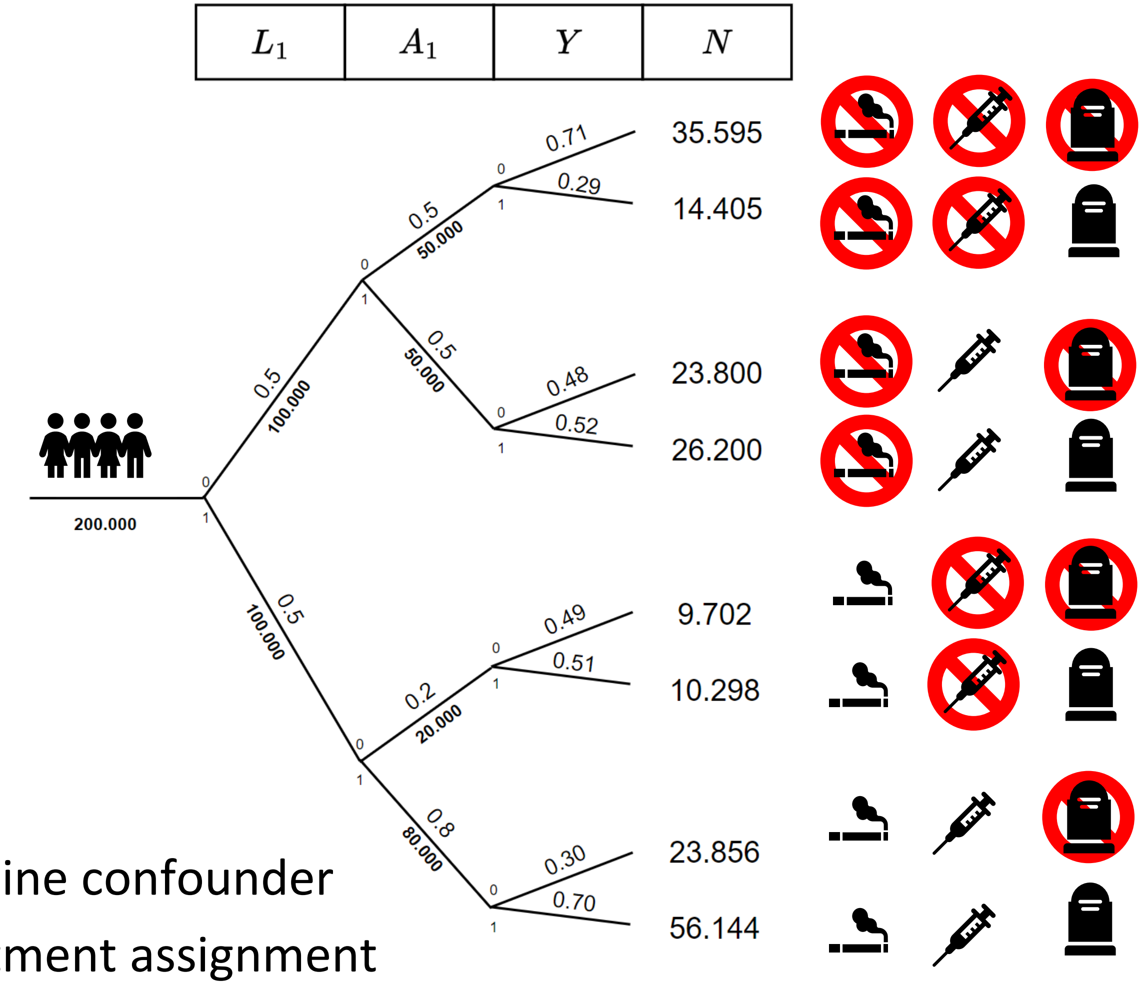
Visualizing the history of a population in a tree graph



L_1: Baseline confounder

A_1: Treatment assignment

Visualizing the history of a population in a tree graph



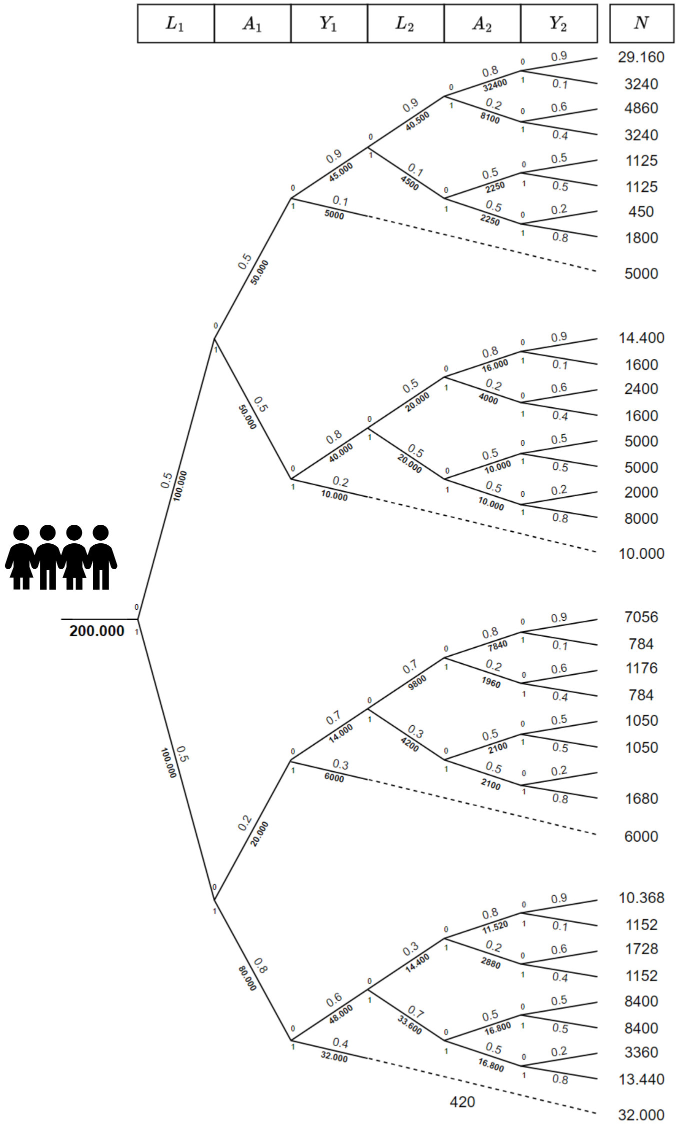
This is the whole tree of a **point intervention** because we only have treatment at single point in time!

L_1: Baseline confounder

A_1: Treatment assignment

Y: Outcome

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

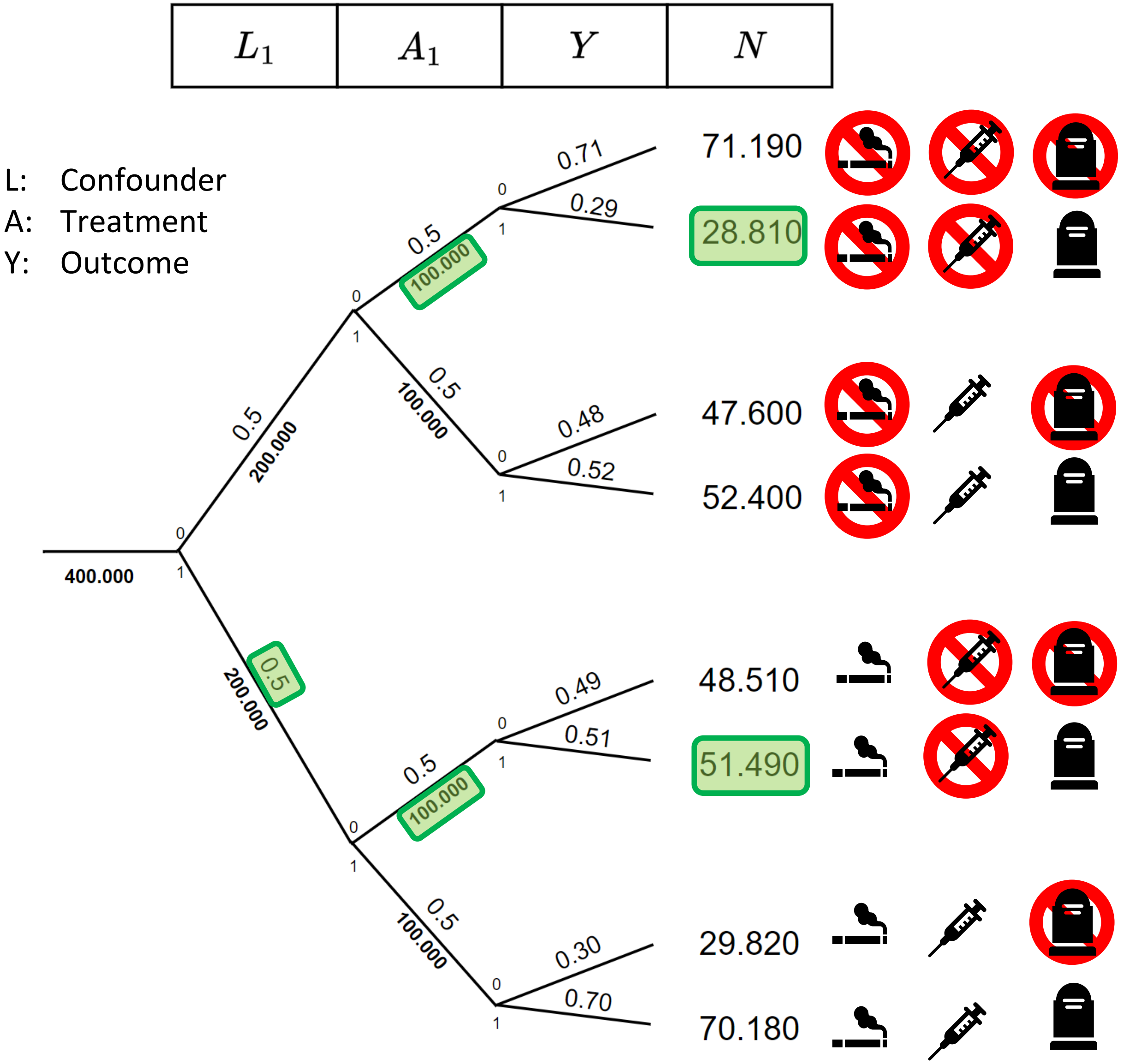
L_2: Time-varying confounder

A_2: Treatment at time t=2

Y_2: Outcome at time t=2

Some exercises

Go to classpoint.app



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:

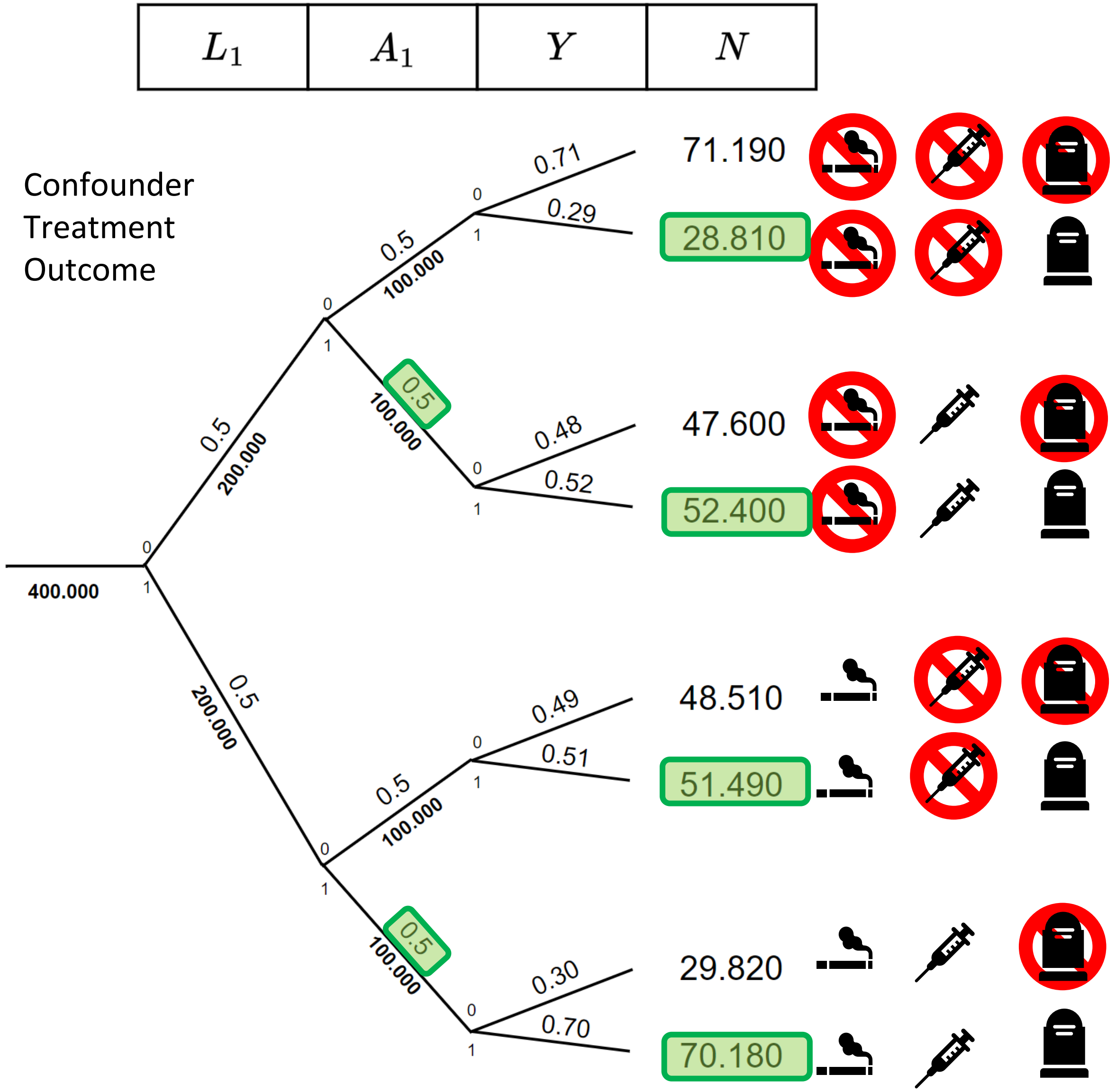
How many die among **untreated**? **28.810 + 51.490 = 80.300**

Question 4:

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

Some exercises

L: 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:

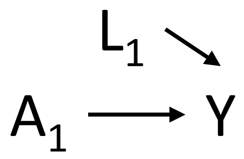
$Pr[Y = 1 | L_1 = 1] = (51.490+70.180)/200.000 = 0.61$

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

Question 7:

Is L_1 a confounder?

No



Baseline confounding

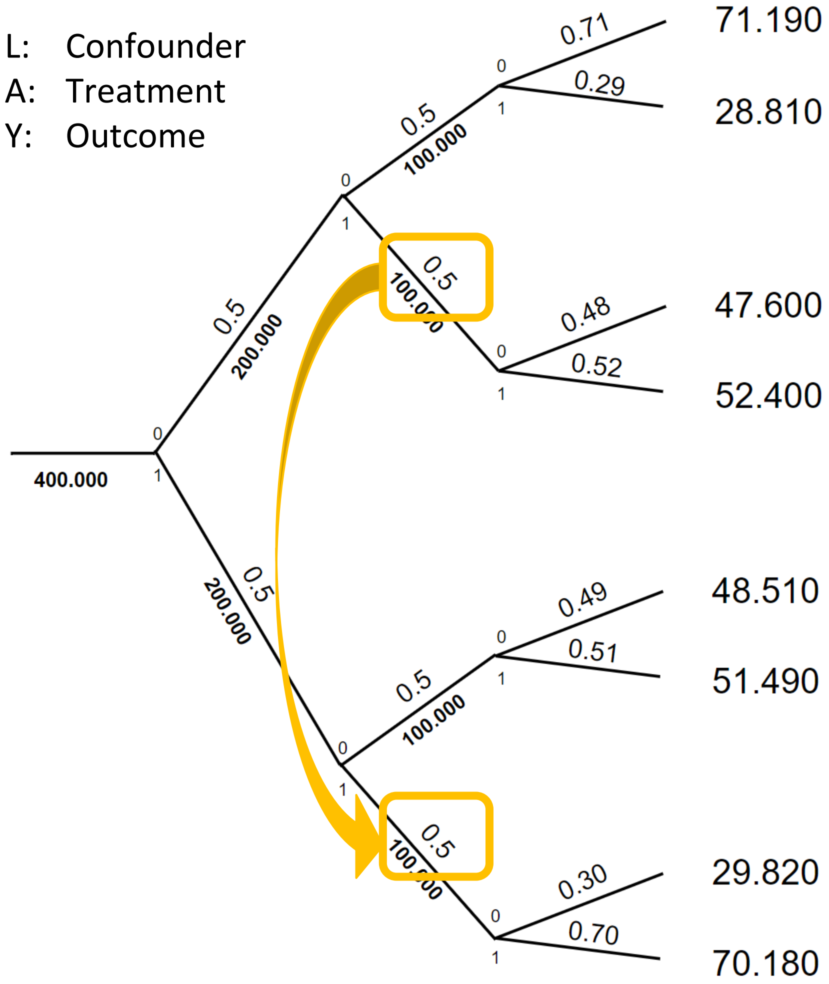
Setting

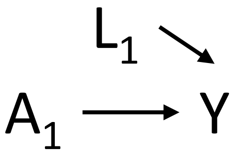
- 1 binary treatment (metformin yes vs. no)
- 1 binary outcome (myocardial infarction yes vs. no)
- 1 binary confounder

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

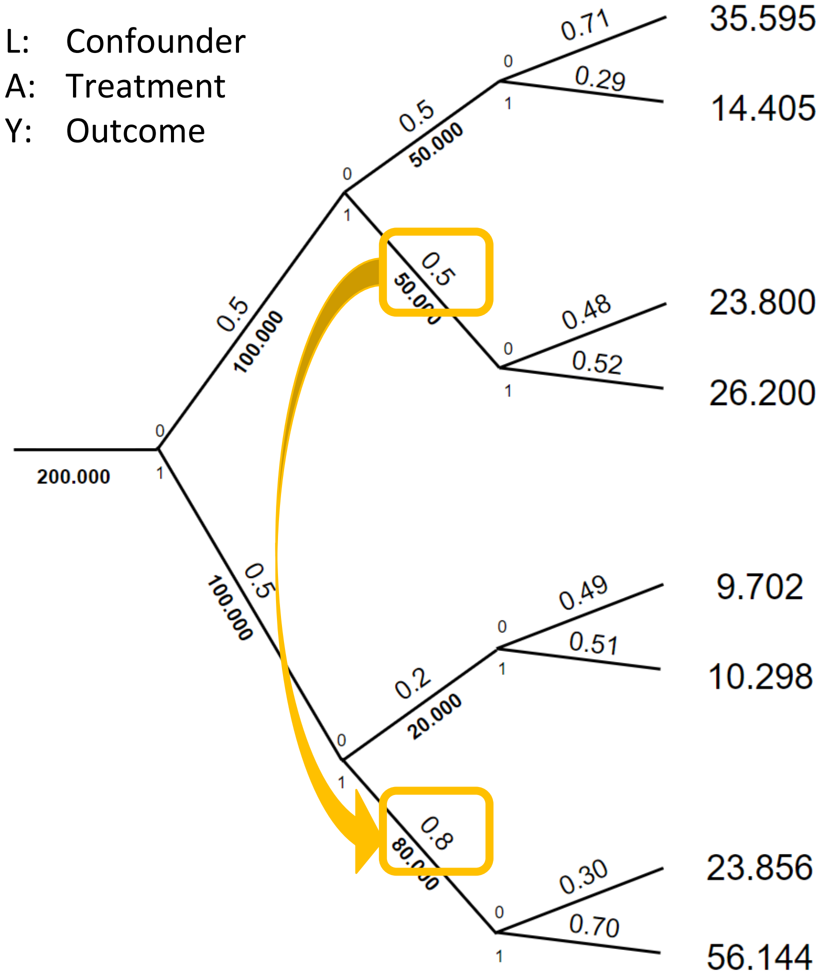
Risk among treated
(52.400+70.180)/(100.000+100.000) = 0.61

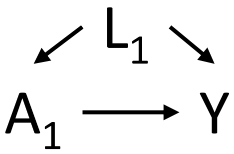
Causal risk difference: 0.61-0.40 = 0.21 (= 21%)
Causal risk ratio: 0.61/0.40 = 1.52

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

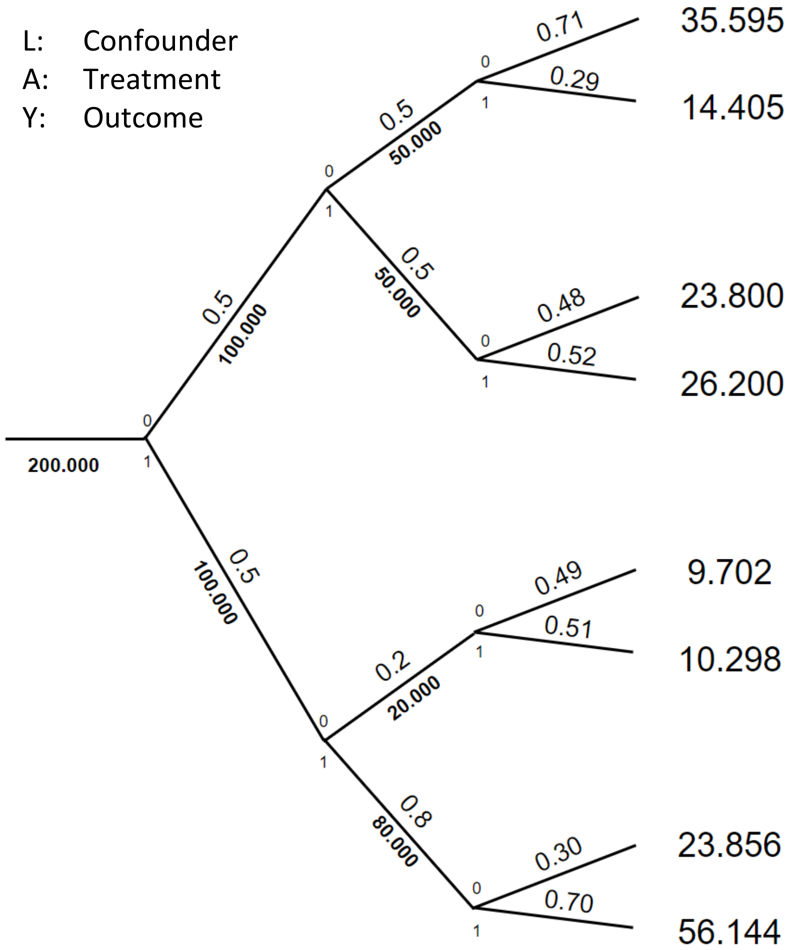
Risk among treated
(26.200+56.144)/(50.000+80.000) = 0.63 ≠ 0.61

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

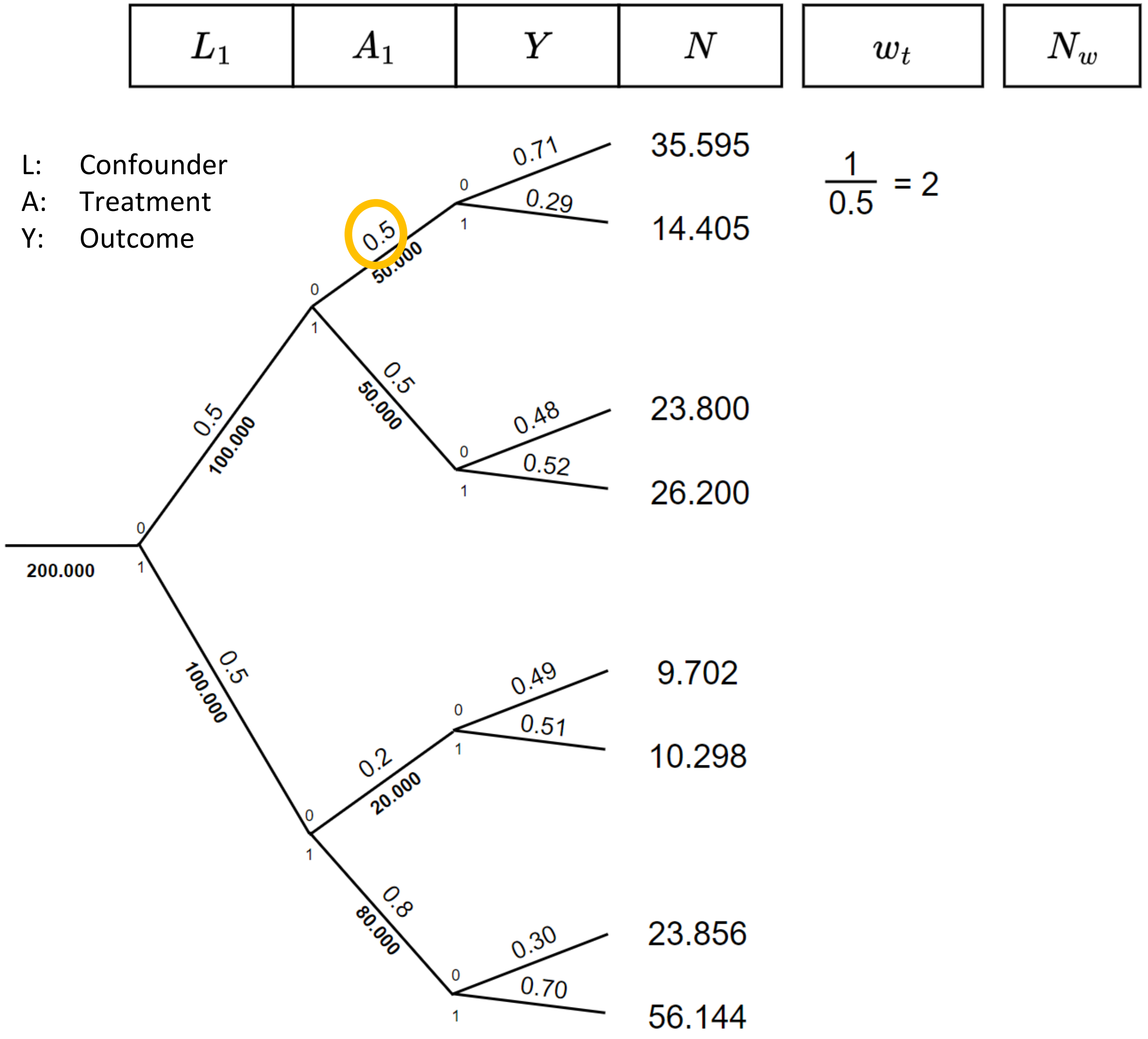
L: Confounder
A: Treatment
Y: Outcome



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

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

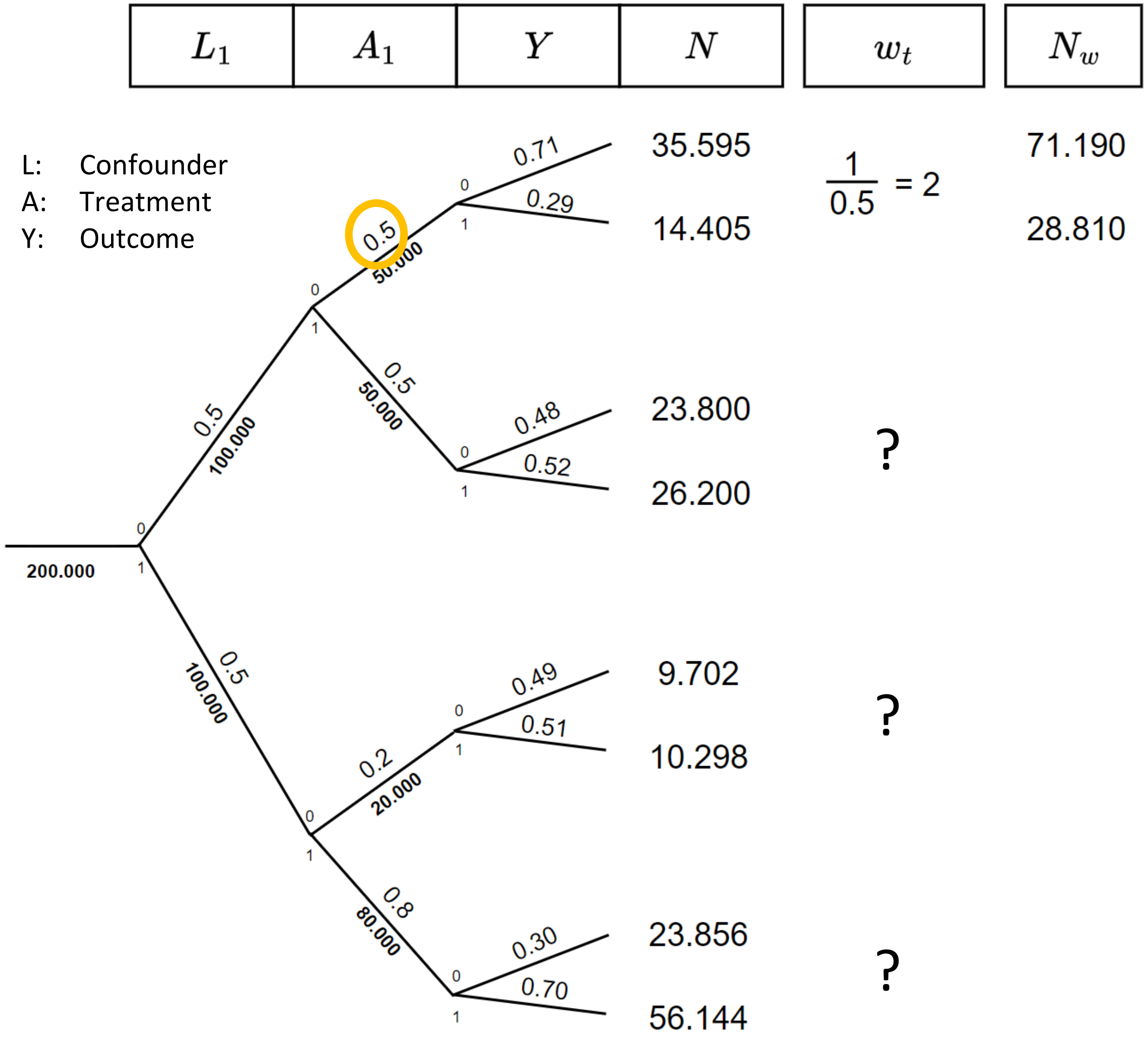
Adjusting for baseline confounding with weighting (IPTW)



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

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

Adjusting for baseline confounding with weighting (IPTW)

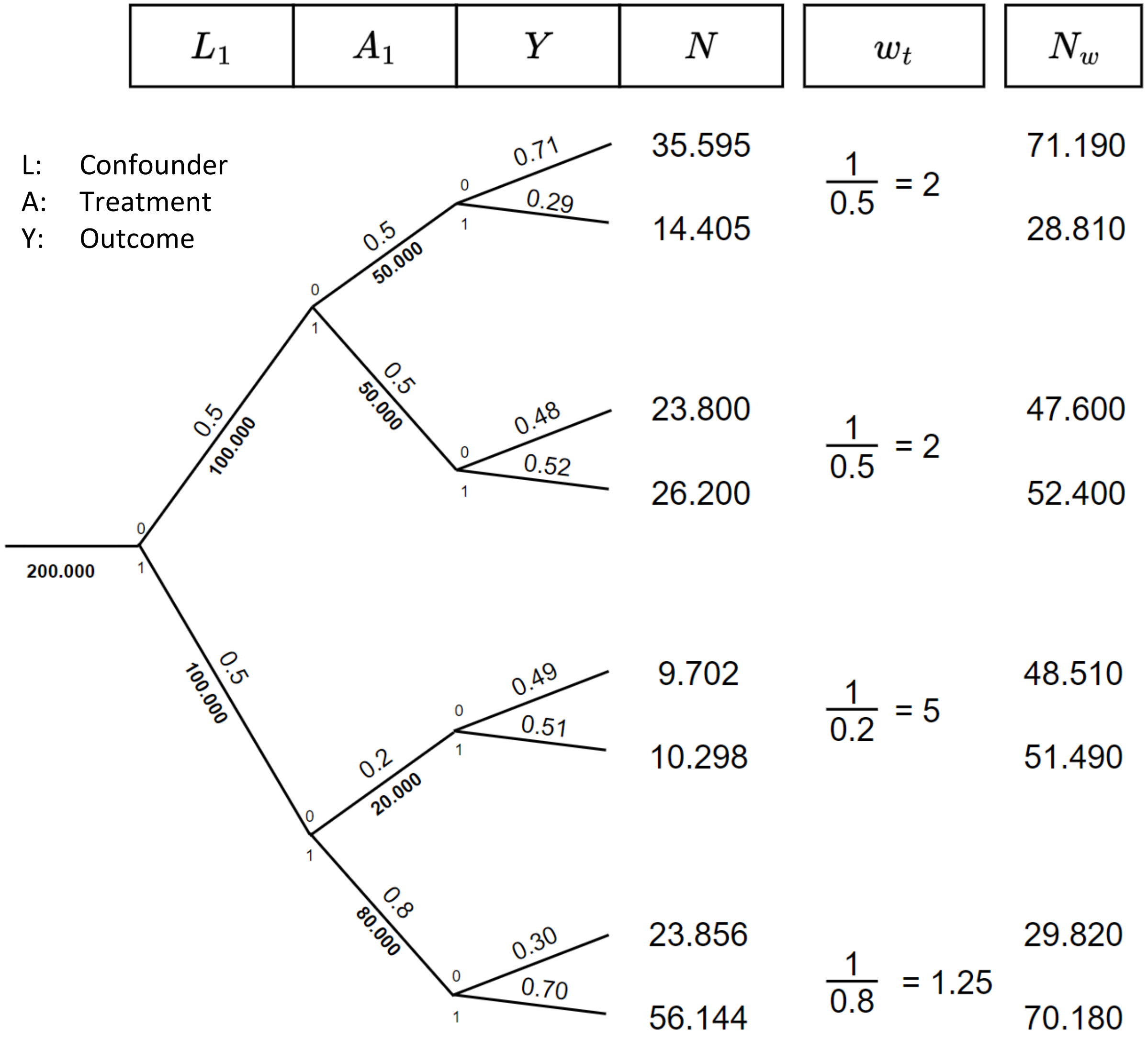


Inverse Probability of Treatment Weights are the inverse of the probability of having received your treatment history given confounders

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

Adjusting for baseline confounding with weighting (IPTW)

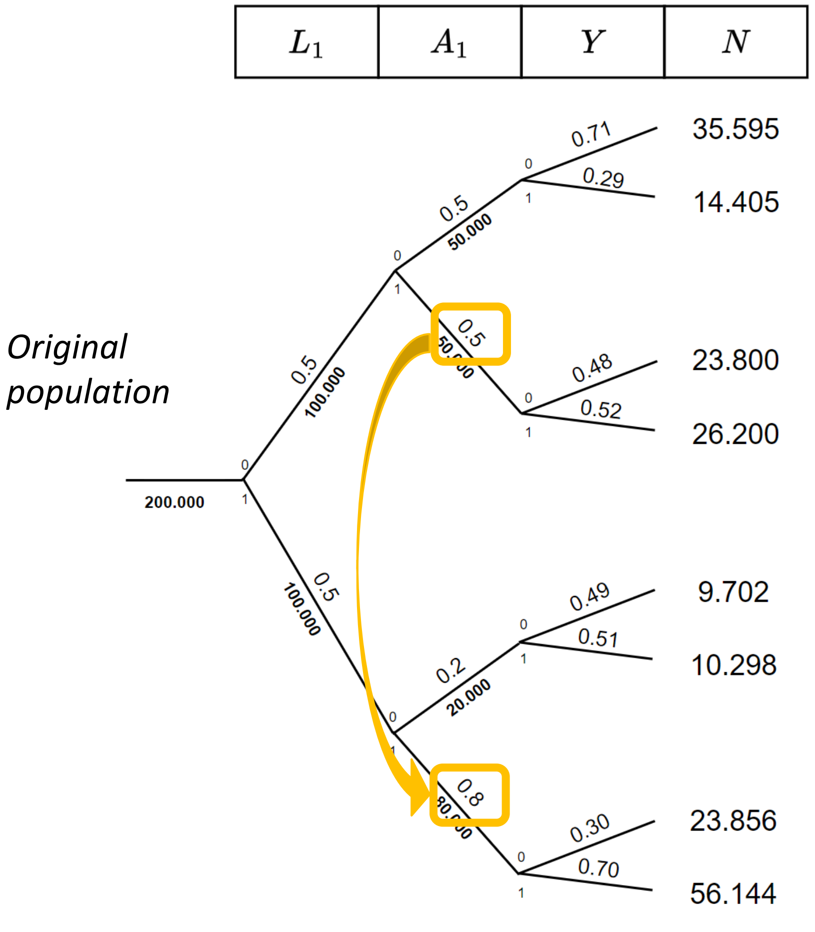
L: Confounder
A: Treatment
Y: Outcome

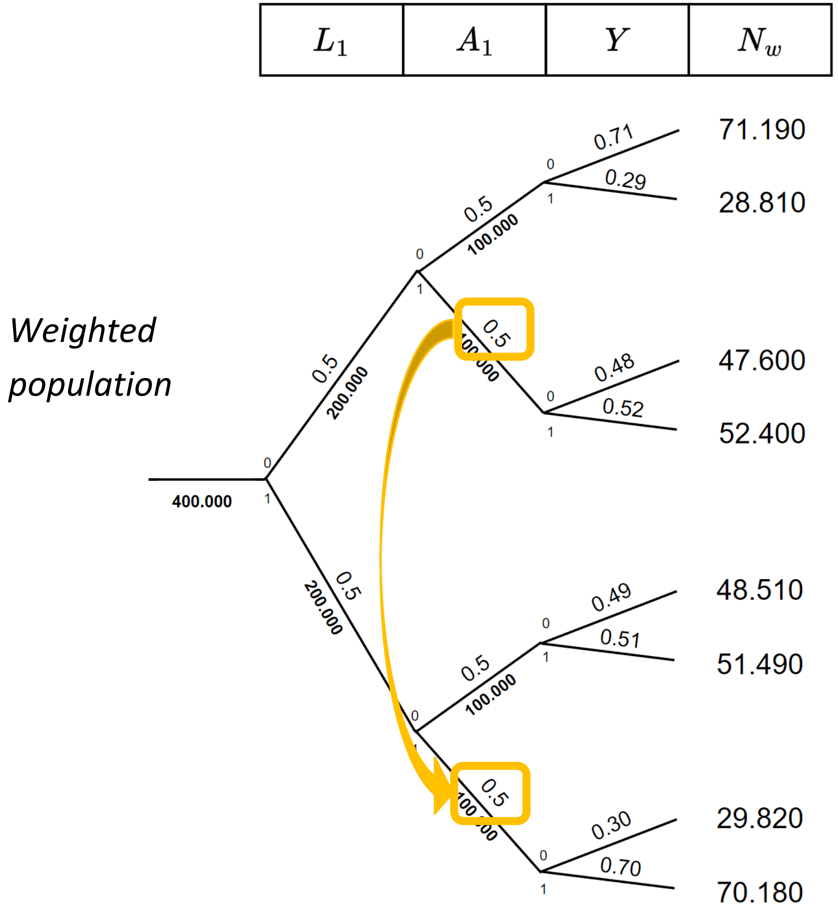


Inverse Probability of Treatment Weights are the inverse of the probability of having received your treatment history given confounders

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

Turning our observational study into a randomized trial

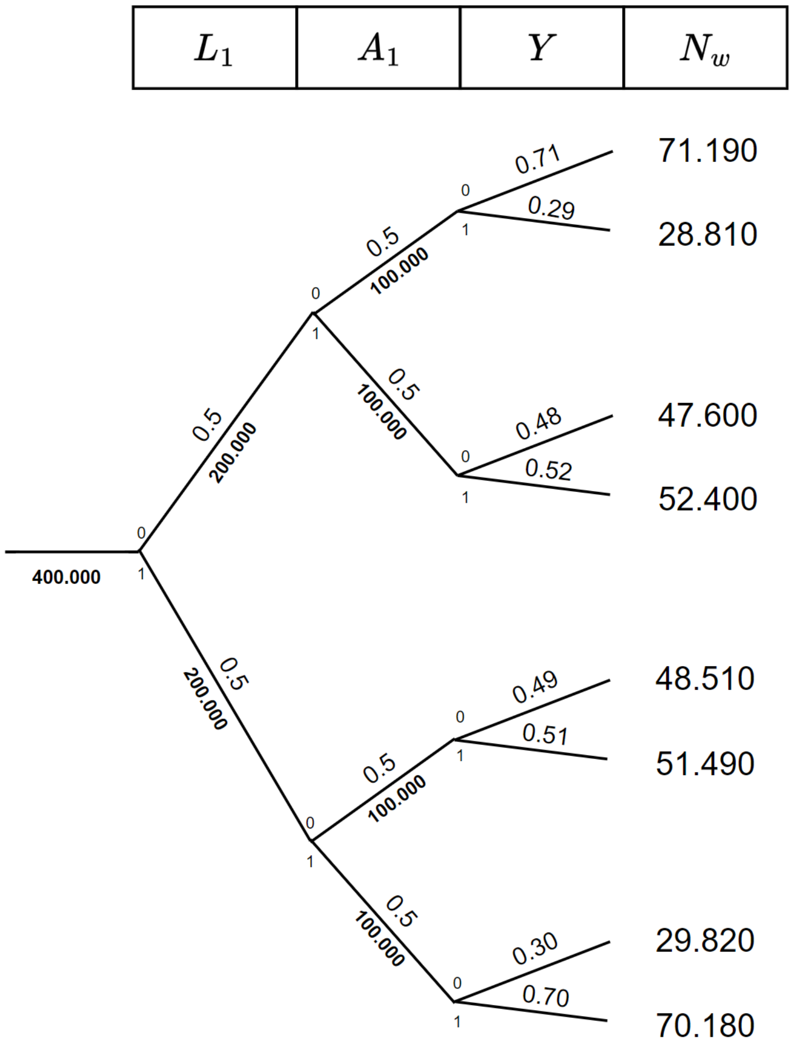


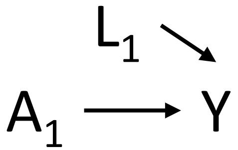


In the original population, treatment is predicted by confounder L_1

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

Treatment effect estimation in the weighted pseudopopulation





In weighted pseudopopulation

- Confounder <u>no longer</u> 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

<u>Causal</u> risk difference: 0.61-0.40 = 0.21 (= 21%)
<u>Causal</u> 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

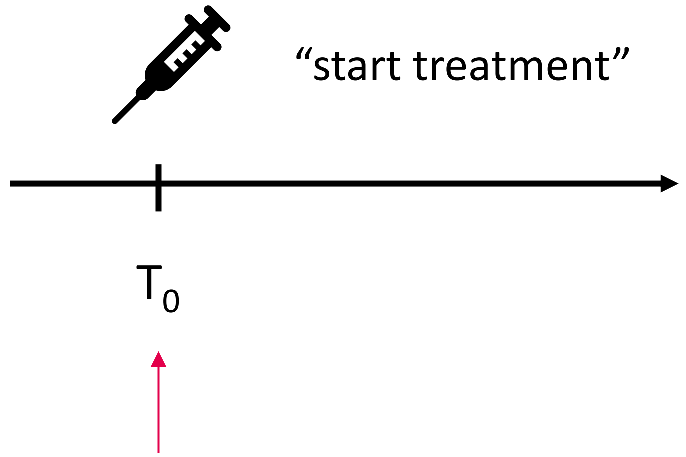
Time-varying confounding

Recap baseline vs. time-varying confounding

Treatment strategies

Point

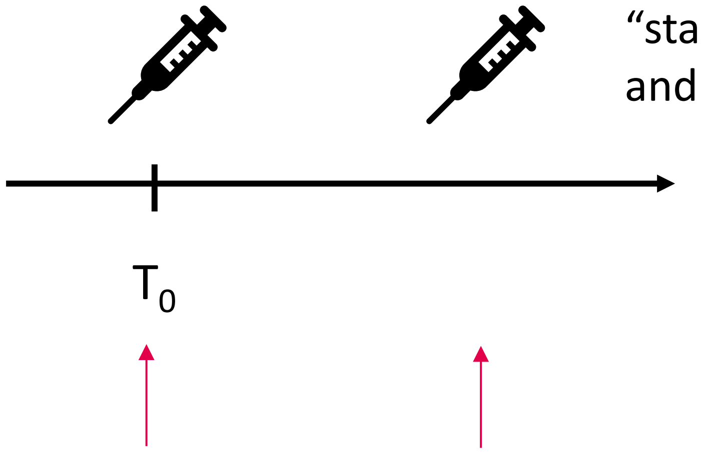
“start treatment”



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

Sustained

“start treatment and always use”

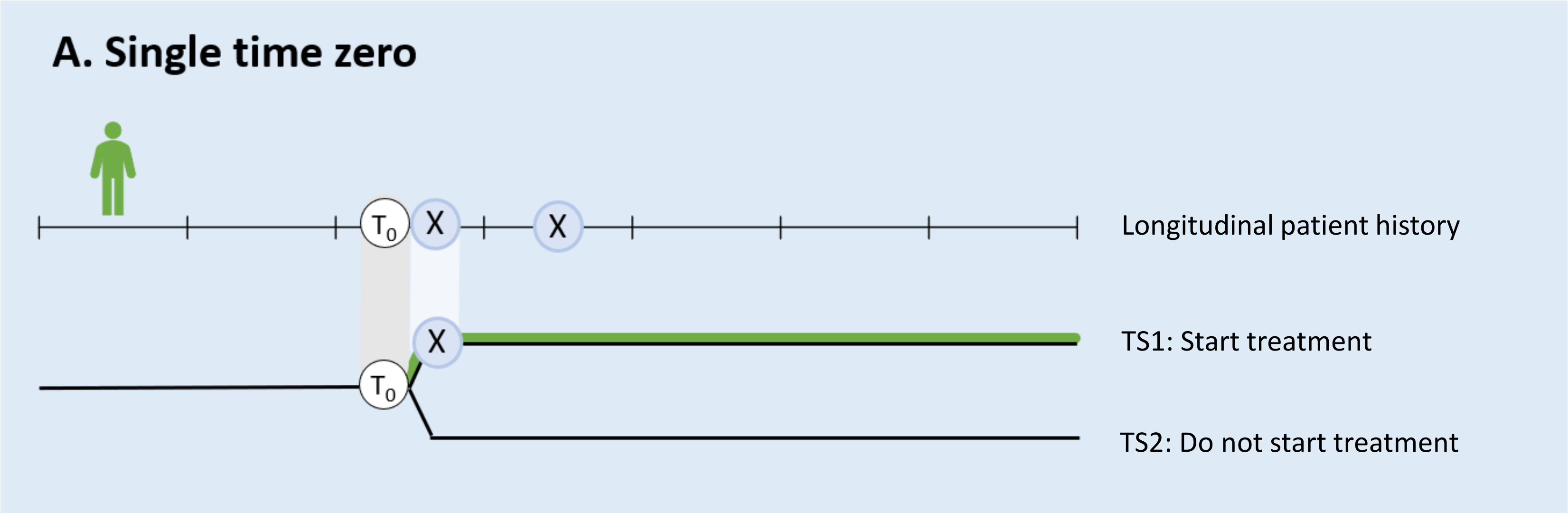


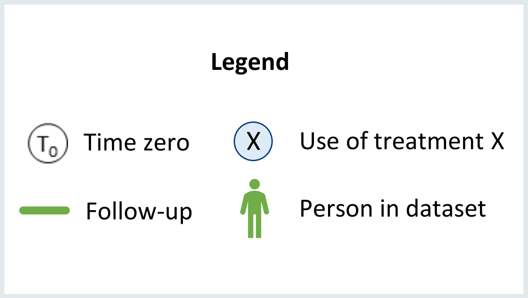
- Groups need to be similar at time zero & during follow-up
- Baseline & **time-varying confounding**

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?

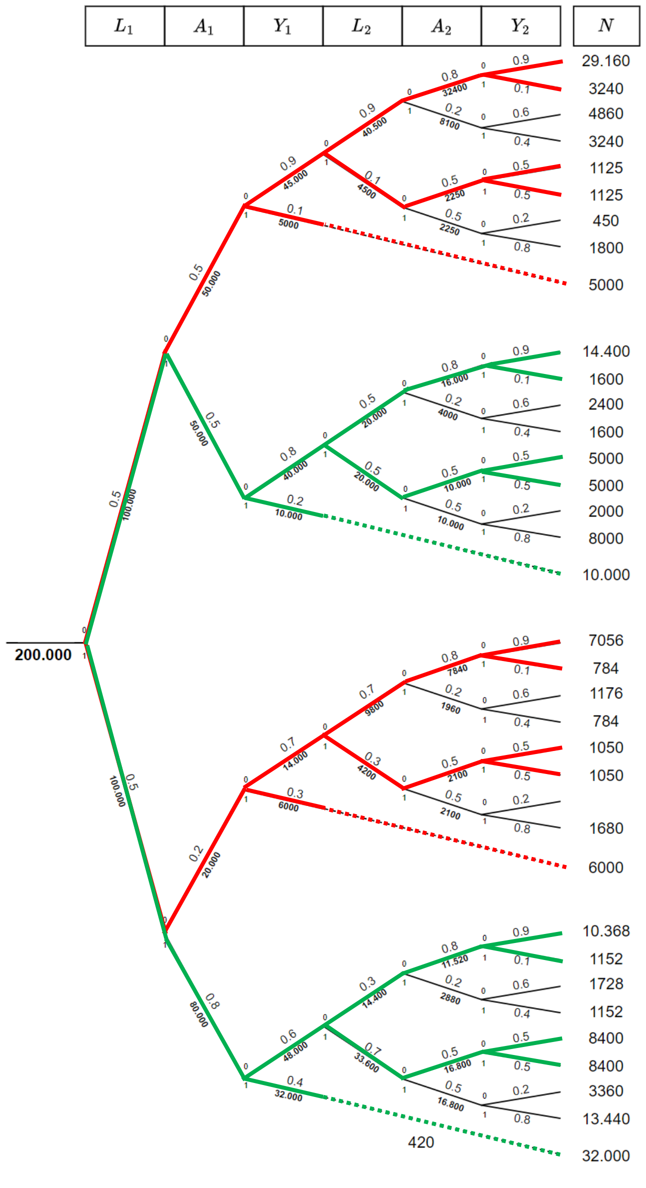
- Many people in “start treatment” group may stop treatment during follow-up
- Conversely, many people in “do not start treatment” group may start it during follow-up
- We may then find a hazard ratio of 1.0 even for a treatment known to have benefits





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

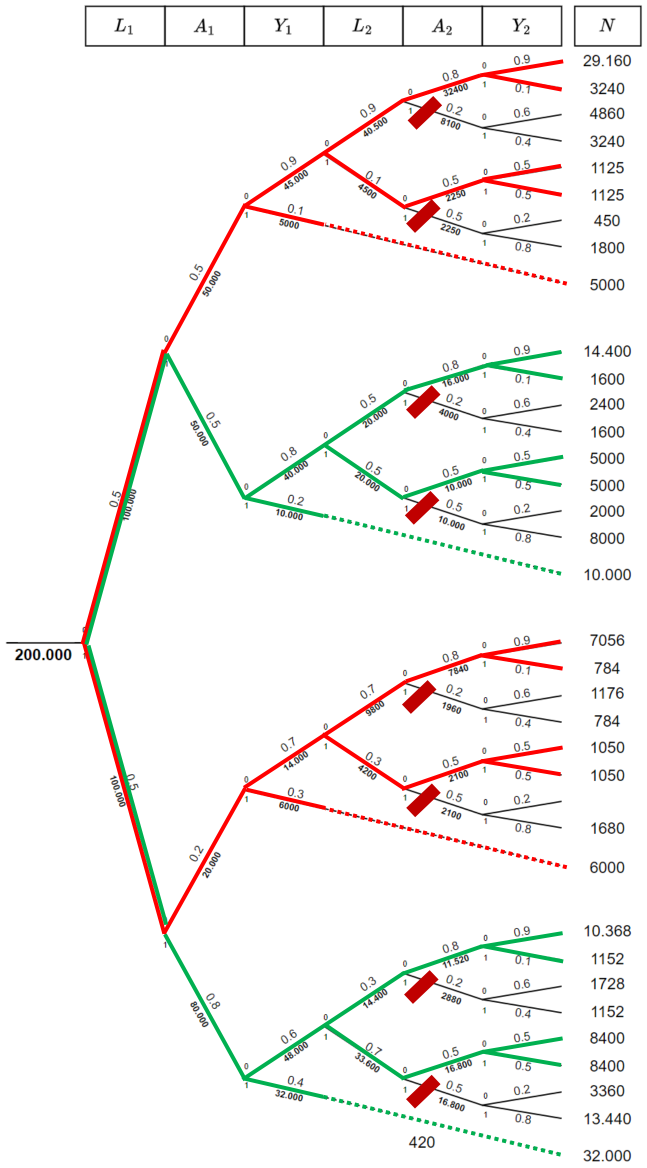
Which strategy is highlighted in the tree?

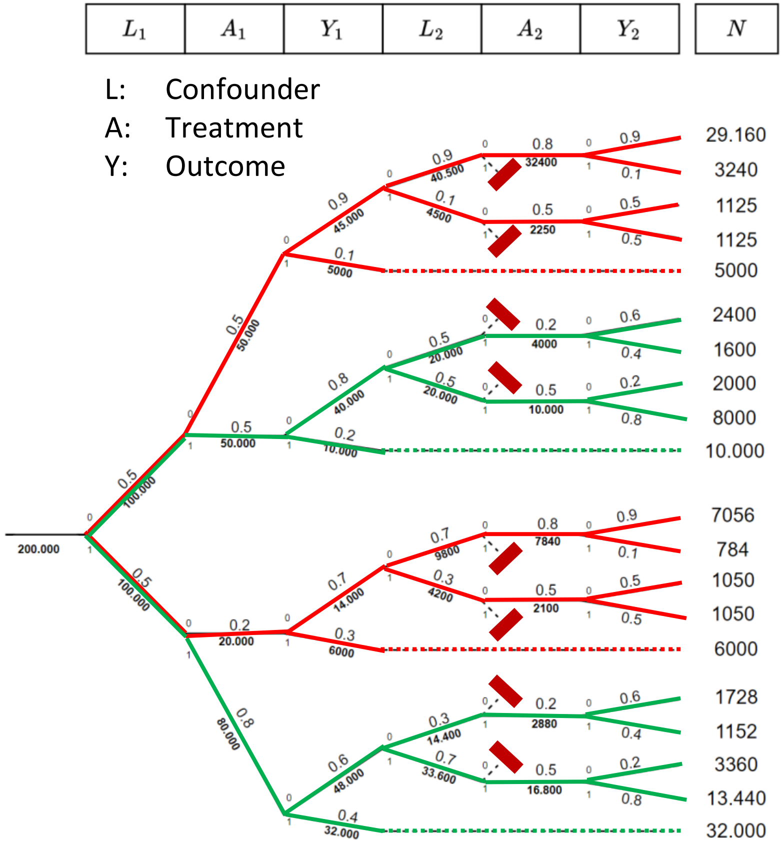
A: Always treat

B: Never treat

C: Neither

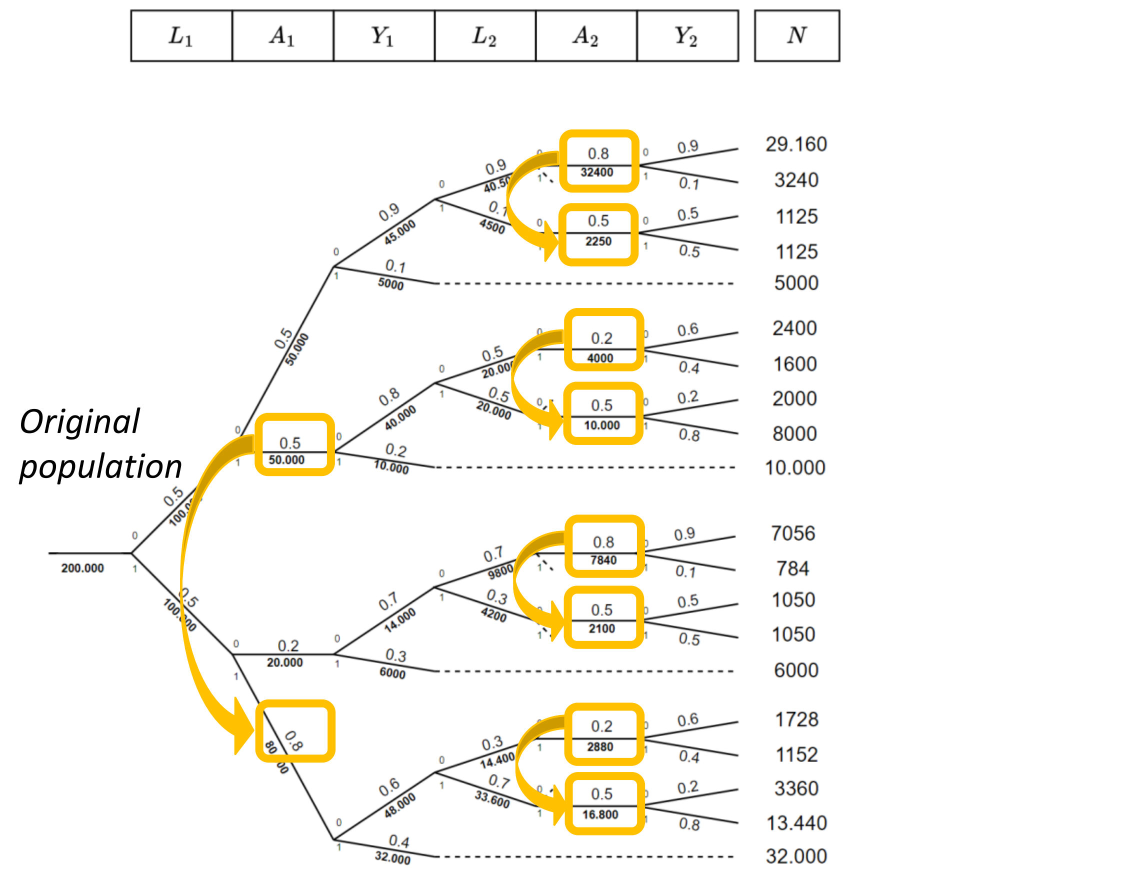
Censoring: focus only on branches of interest





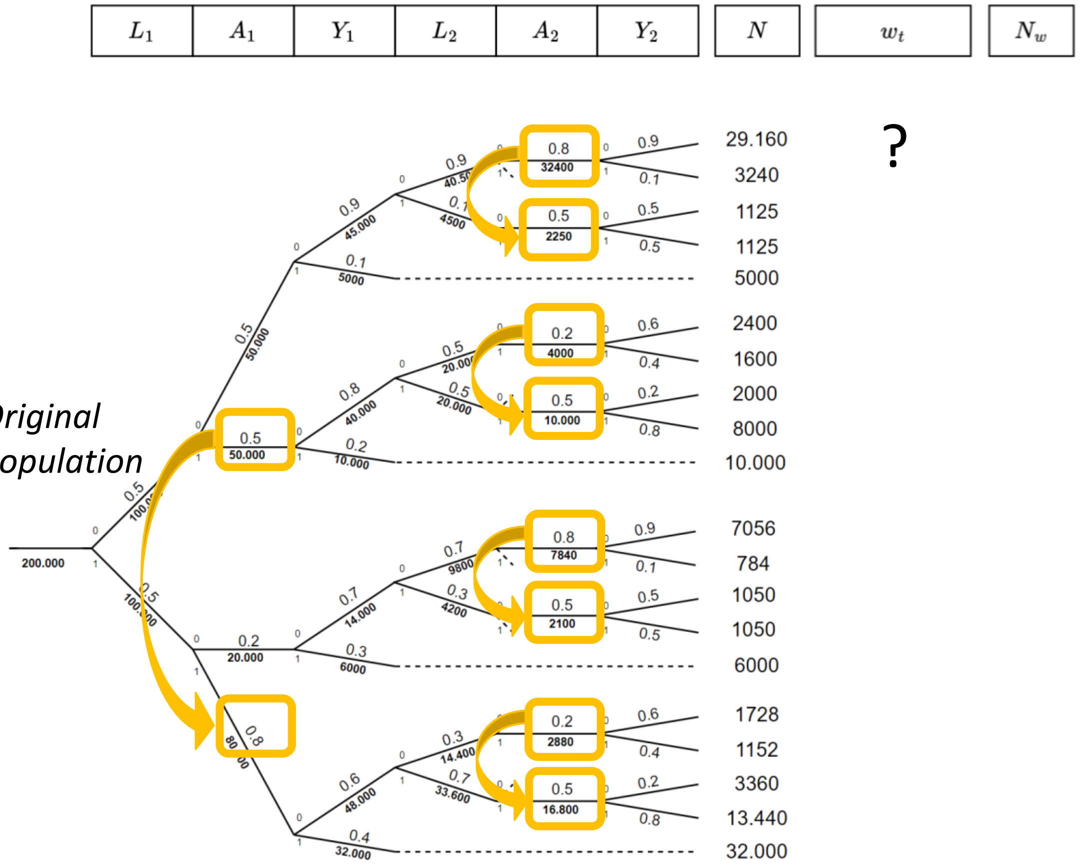
Censor patients who deviate from the strategies of interest

We cannot compare outcomes among those always vs. never using the treatment due to baseline and time-varying confounding



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

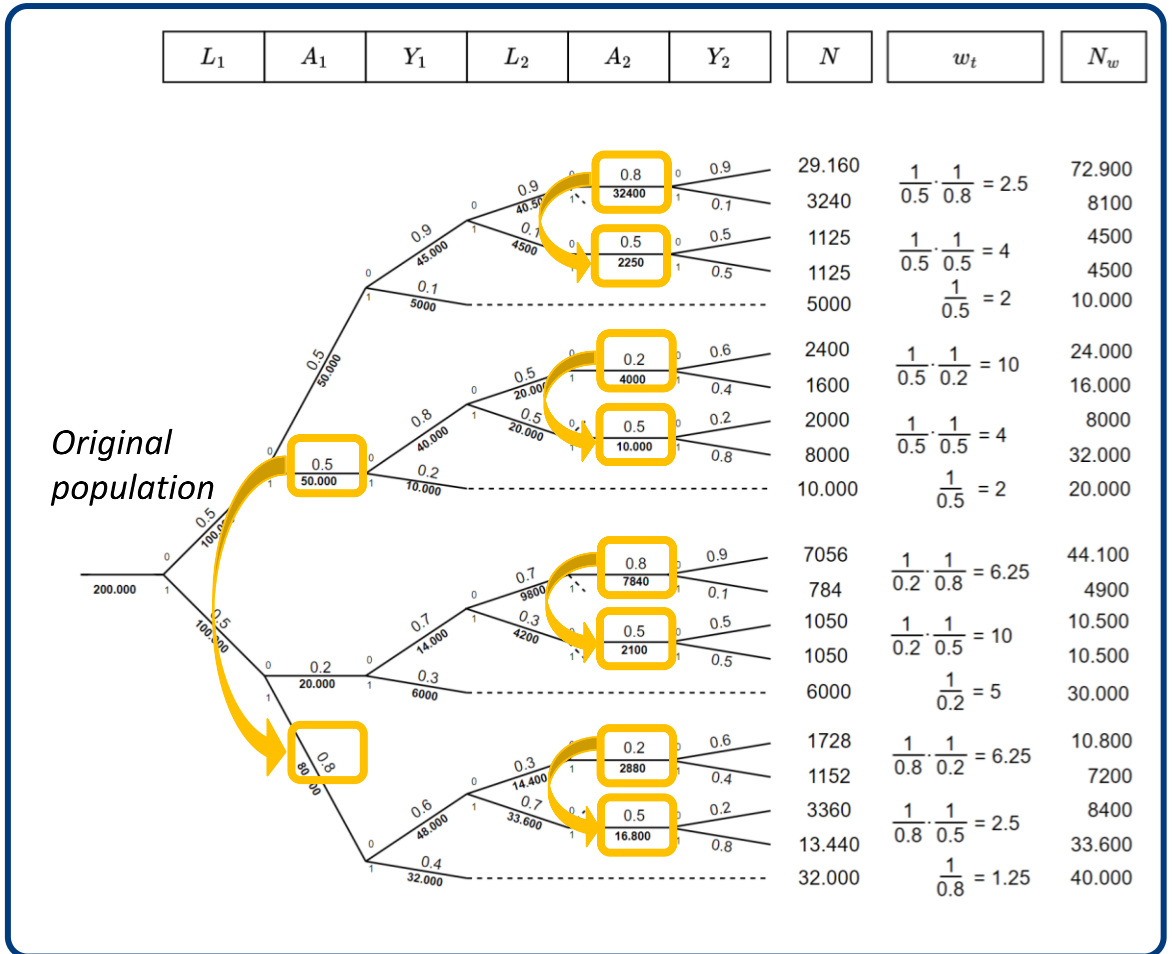
But we can use IPW to turn our observational study into a **sequentially** randomized trial



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

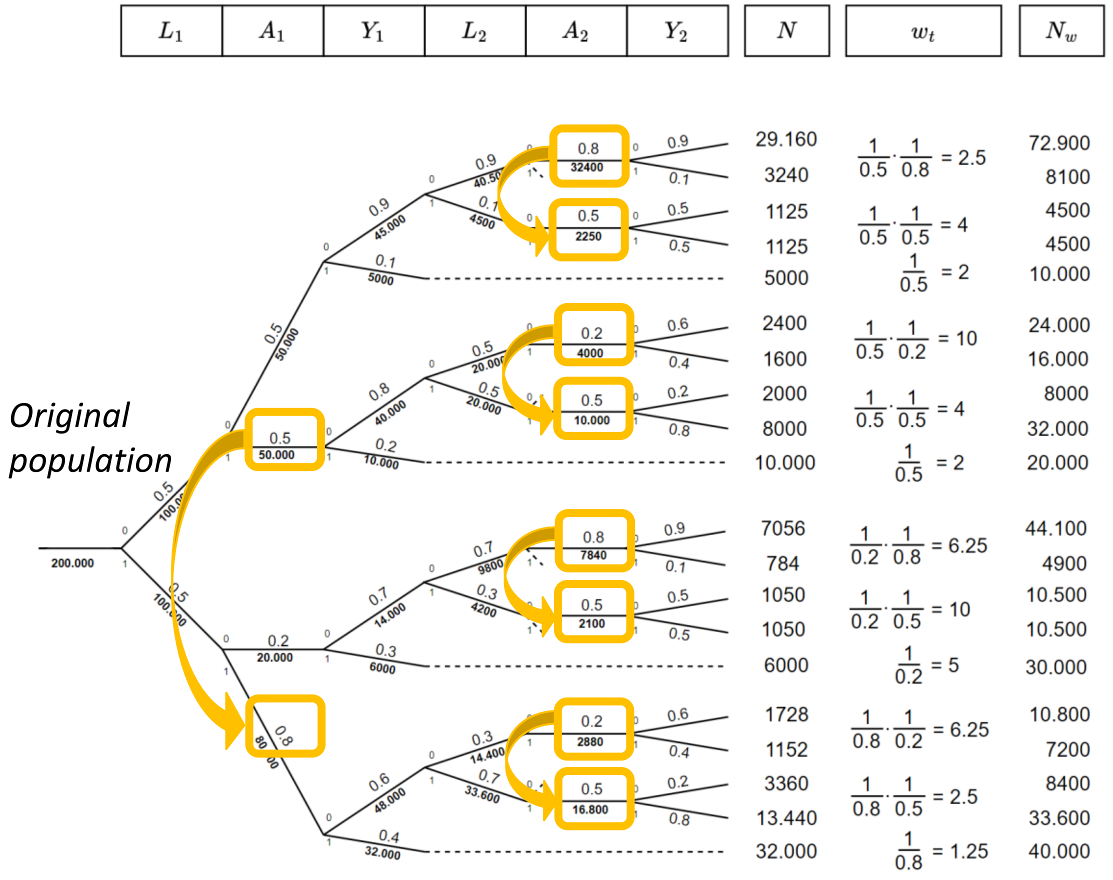
What weight do we need to give the people in the first two branches?

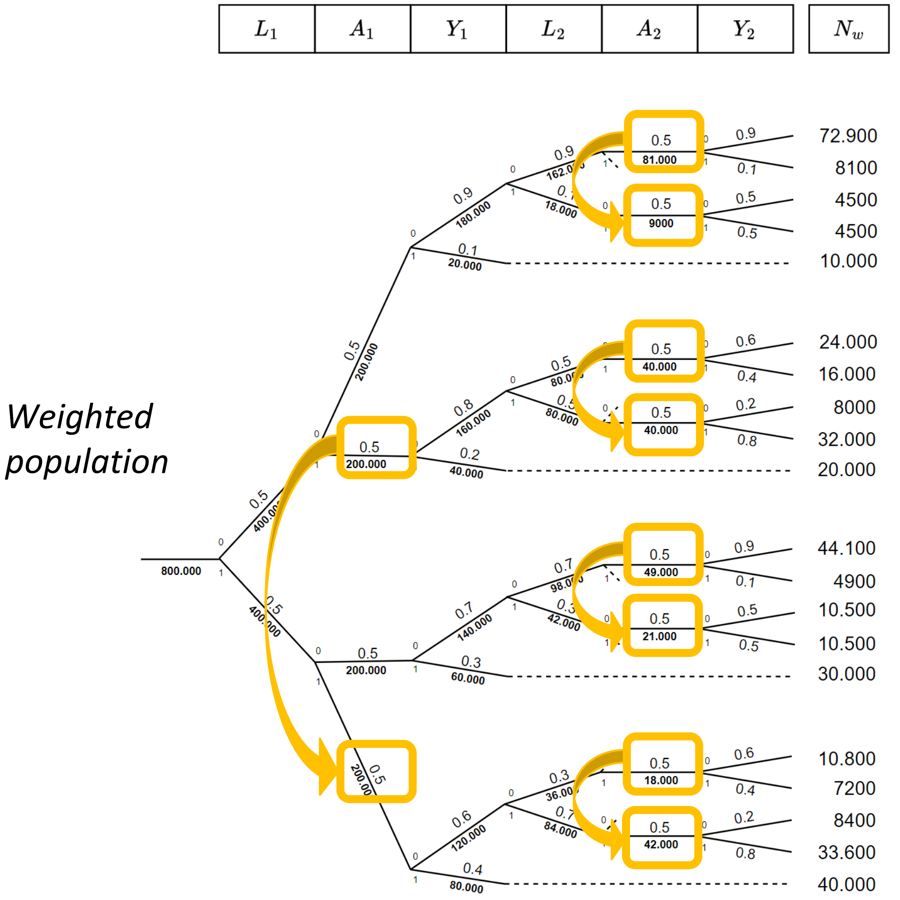
But we can use IPW to turn our observational study into a **sequentially** randomized trial



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

Turning our observational study into a sequentially randomized trial





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

In the weighted population, treatment A_k is no longer predicted by confounder L_k at each moment in time!

Before and after IPW

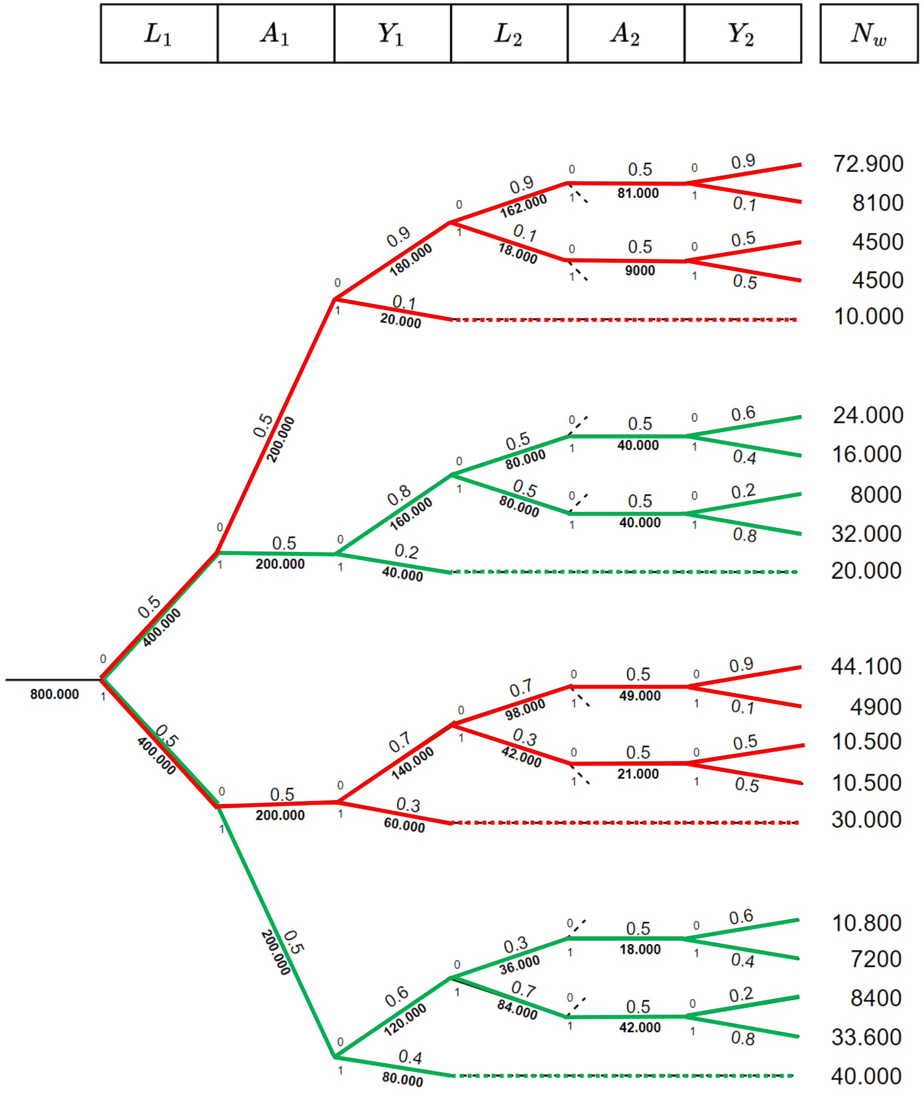
Before IPW

$$
\begin{tikzcd}
L_1 \arrow[r] \arrow[rrrr, bend left] & A_1 \arrow[r] & L_2 \arrow[r] \arrow[rr, bend right] & A_2 \arrow[r] & Y
\end{tikzcd}
$$

After IPW

$$
\begin{tikzcd}
L_1 \arrow[rrrr, bend left] & A_1 \arrow[r] & L_2 \arrow[rr, bend right] & A_2 \arrow[r] & Y
\end{tikzcd}
$$

Treatment effect estimation in the weighted pseudopopulation



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

<u>Causal</u> risk difference: 0.74-0.34 = 0.40 (= 40%)
<u>Causal</u> 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

<u>Causal</u> risk difference: 0.61-0.40 = 0.21 (= 21%)
<u>Causal</u> 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

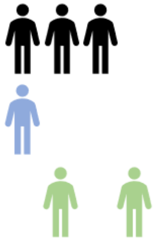
5. Results are biased if there are unmeasured confounders

Questions

e.l.fu@lumc.nl

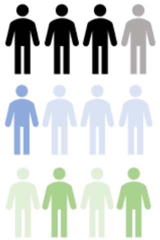
Censoring & weighting on a group-level

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