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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Methods to control for confounding
- Introduction & Overview -

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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Learning Objectives

At the end of this confounding control overview, you will be able to:

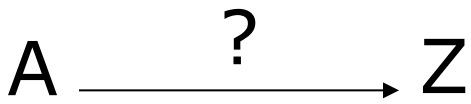
- Understand how confounding arises in pharmacoepidemiology and the problem it poses for causal inference
- Differentiate (exposure probability) weighting approaches to confounding control, including propensity score control, matching, and stratification, and inverse probability weighting
- Relate these weighting approaches to randomization
- List key assumptions necessary for these approaches to estimate causal effects
- Distinguish between point treatment and time-dependent confounding

Outline

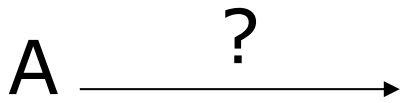
- Ideal comparisons for causal inference
- How confounding impedes causal inference
- The gold standard
- Mimicking ideal comparisons without randomization:
  - Typical multivariate regression
  - Propensity score methods
  - Inverse probability weighting (IPW)
- Practical considerations
- Take home messages

Aim of comparative pharmacoepidemiology studies

Does drug A protect against outcome Z?

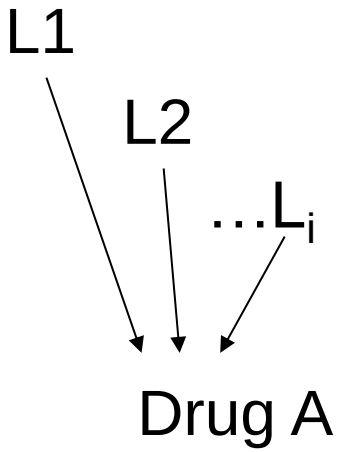


Does drug A cause outcome Y?



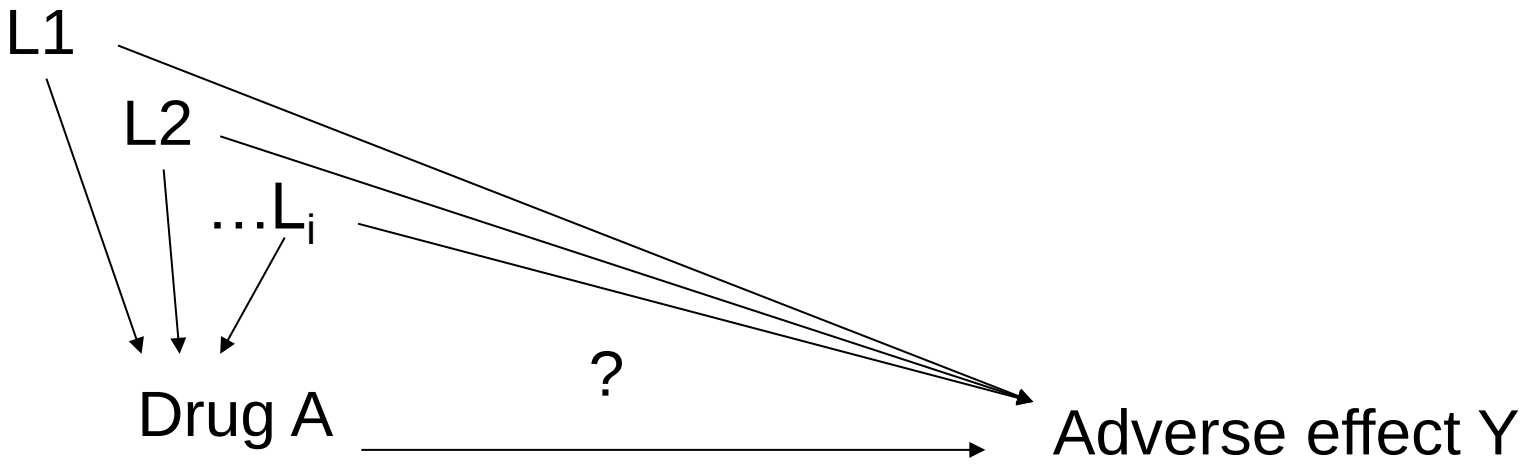
Here, the exposure of interest, A, is a "point-treatment"

The essential problem



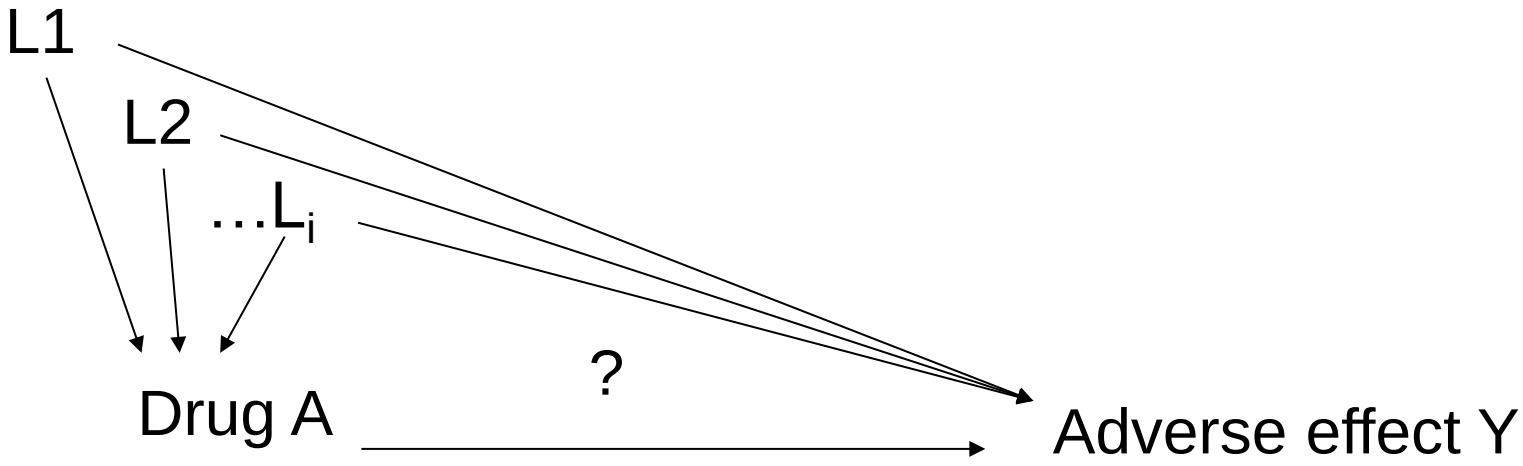
- Outside the context of study, many reasons people take one medication over another

The essential problem



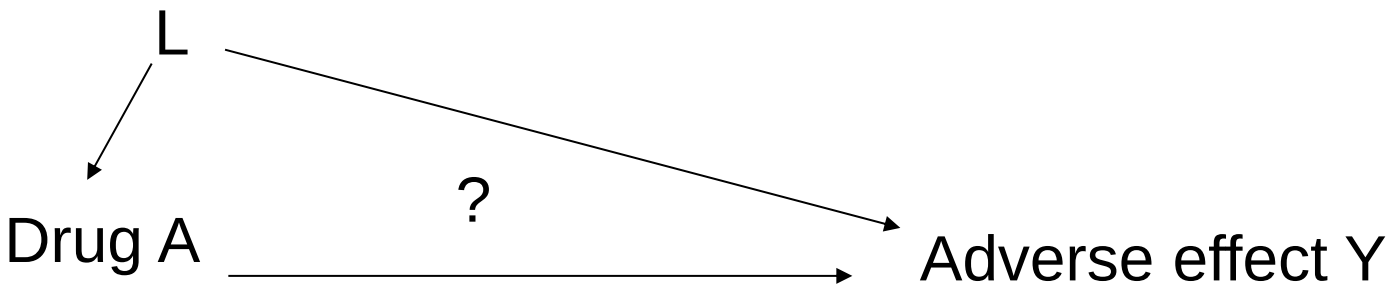
- These reasons are often related to outcomes of interest

The essential problem



- Confounding: When risk factors for the disease are associated with use of the medication of interest

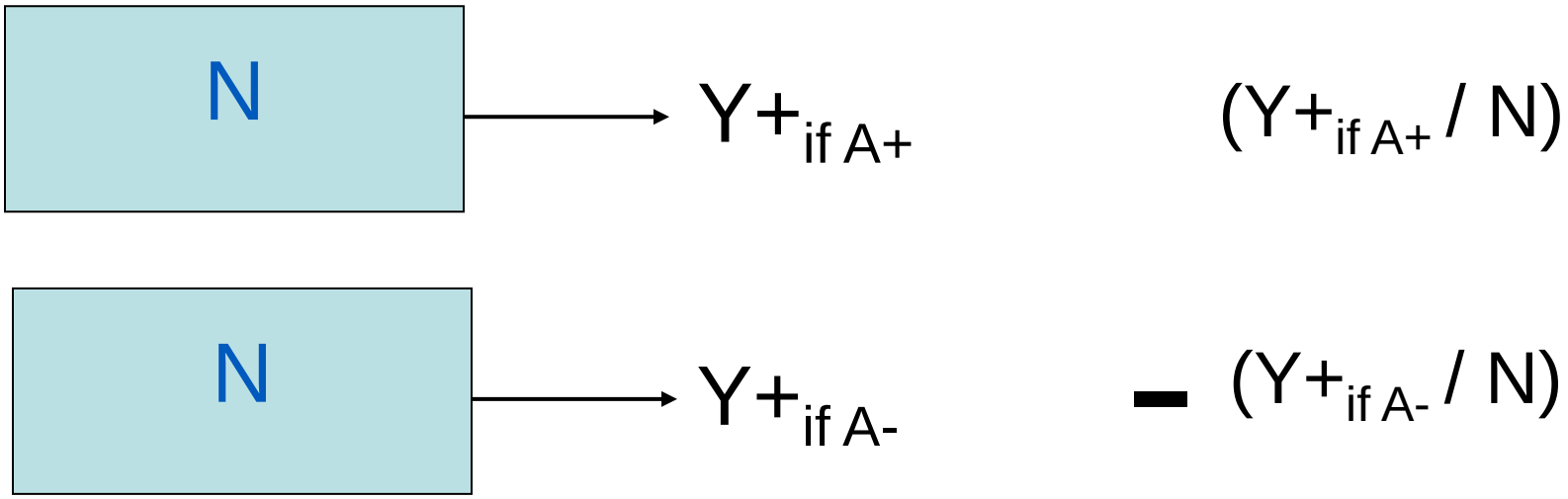
The essential problem



- For simplicity let's consider L as the totality of confounding
- "Point-treatment" confounding

The ideal (hint: it's not the RCT)

Target Population N



A type of counterfactual comparison

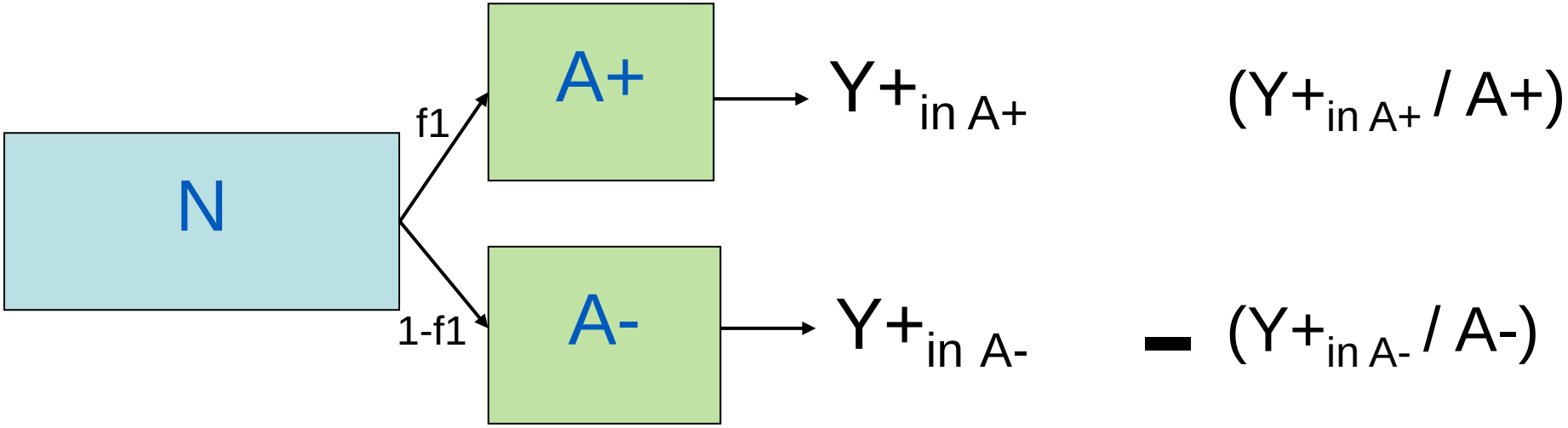
$= RD_{causal}$

The ideal (hint: it's not the RCT)

- We've defined RD_{causal} (for now) as the effect – with all else equal - in the total population if everyone was exposed versus no one was exposed
- But at least one of these conditions is counter-to-fact
- Instead we use substitutes for the ideal risks

The real world substitute

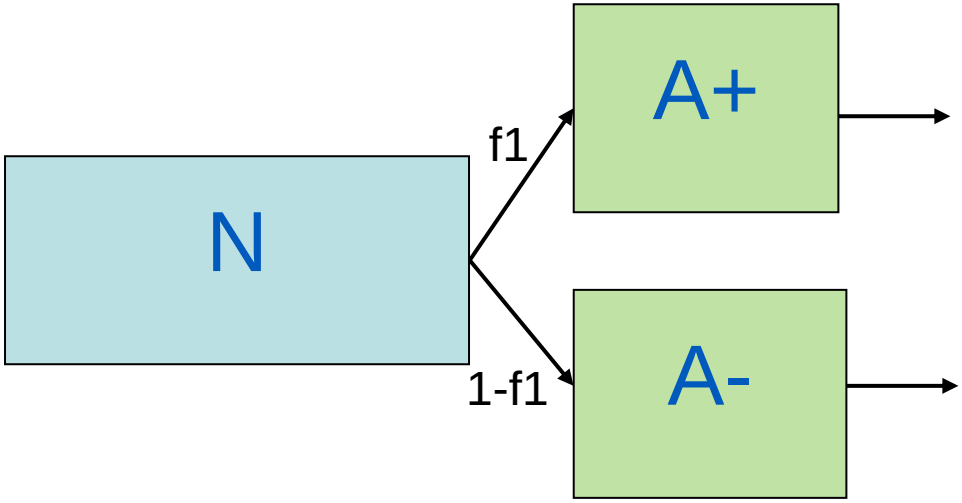
In target Population N, people become A+ or A-



An observable estimate

The real world substitute

In target Population N, people become A+ or A-



$Y+_{\text{in A+}}$ $(Y+_{\text{in A+}} / [f_1 N])$

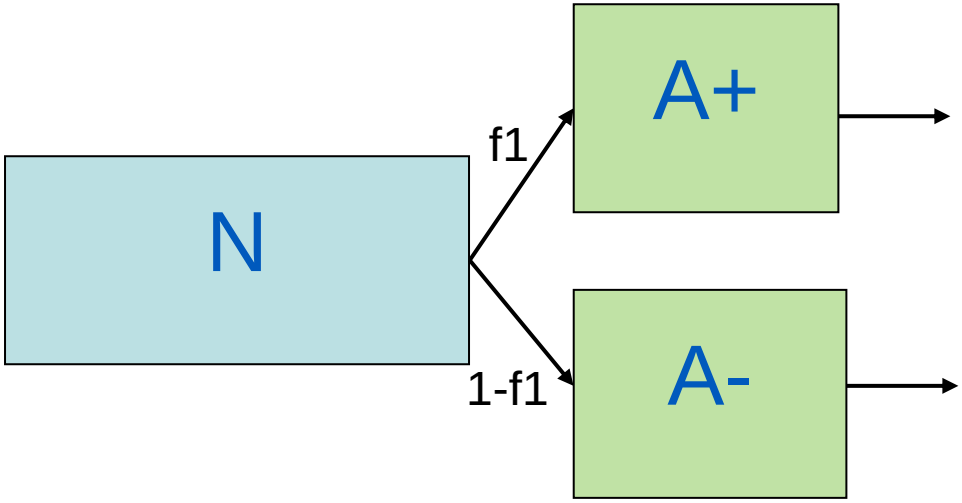
$Y+_{\text{in A-}}$ $-$ $(Y+_{\text{in A-}} / A-)$

An observable estimate ➡

$= RD_{crude}$

The real world substitute

In target Population N, people become A+ or A-



$Y+_{\text{in A+}}$ $(Y+_{\text{in A+}} / [f_1 N])$

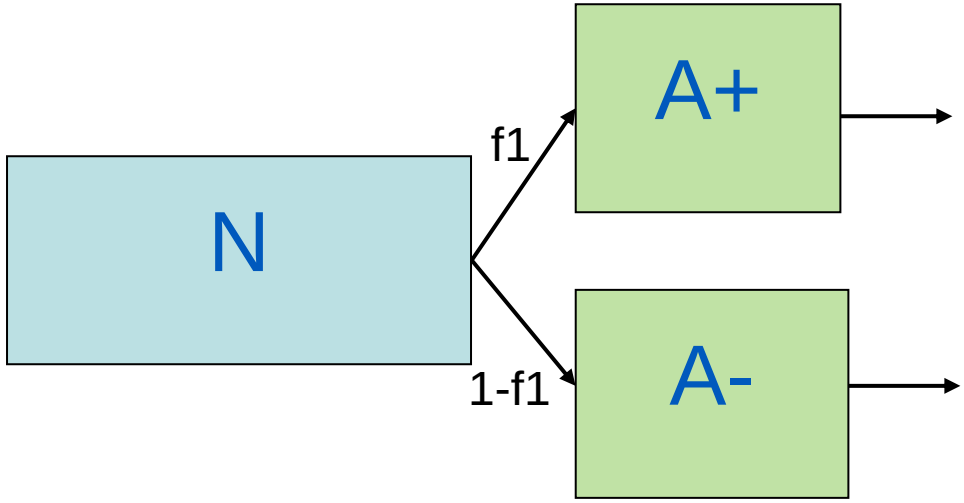
$Y+_{\text{in A-}}$ $-(Y+_{\text{in A-}} / [(1-f_1)N])$

An observable estimate ➡

$= RD_{\text{crude}}$

The real world substitute

In target Population N, people become A+ or A-



$Y+_{\text{in A+}}$ $([f_2 f_1 Y+_{\text{if A+}}] / [f_1 N])$

$Y+_{\text{in A-}}$ $-(Y+_{\text{in A-}} / [(1-f_1)N])$

An observable estimate ➡

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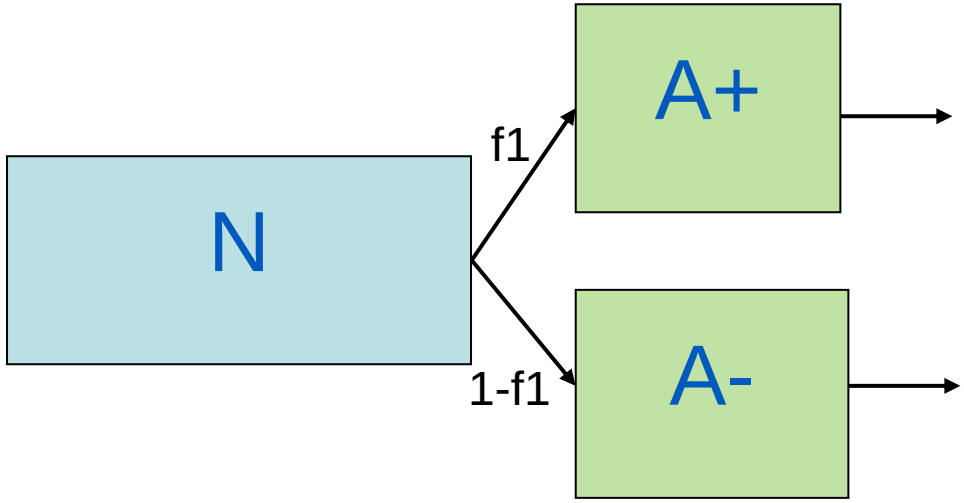


$Y+_{\text{in A+}}$ $([f_2 f_1 Y+_{\text{if A+}}] / [f_1 N])$

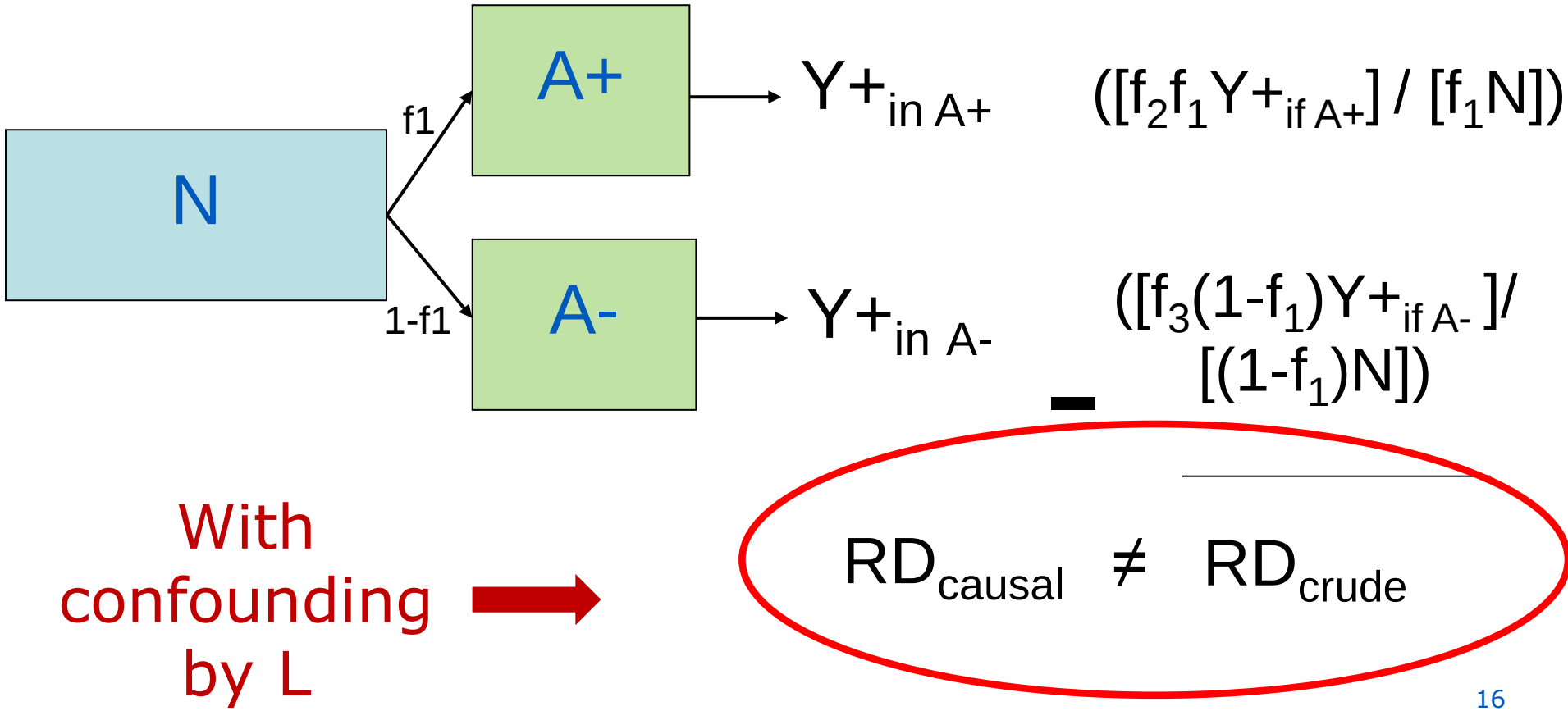
$Y+_{\text{in A-}}$ $([f_3(1-f_1)Y+_{\text{if A-}}]/[(1-f_1)N])$

$=$ RD_{crude}

An observable estimate

The real world substitute

In target Population N, people become A+ or A-

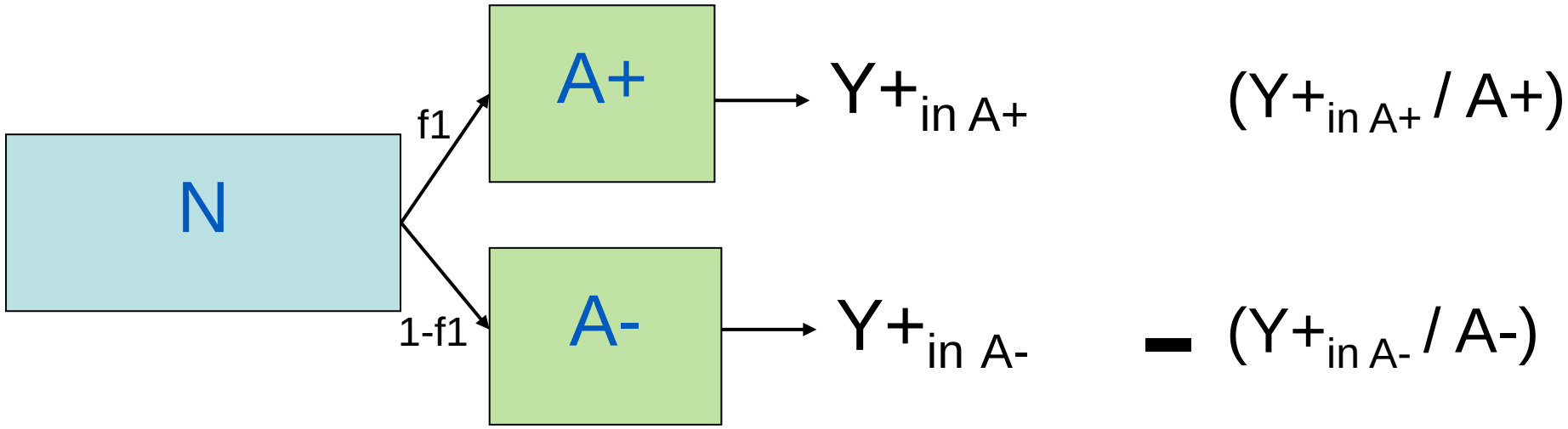


Possible solutions

- Try to avoid confounding through design, e.g.
  - Randomize
  - Match
  - Restrict
- Try to control confounding through analysis, e.g.:
  - Traditional analysis methods
  - Techniques that weight by causes of the treatment (aka mimic randomization)
  - Techniques that weight by causes of the outcome

Why randomization is "the gold standard"

Target Population N, randomized 1:1 to A+ or A-



An observable estimate

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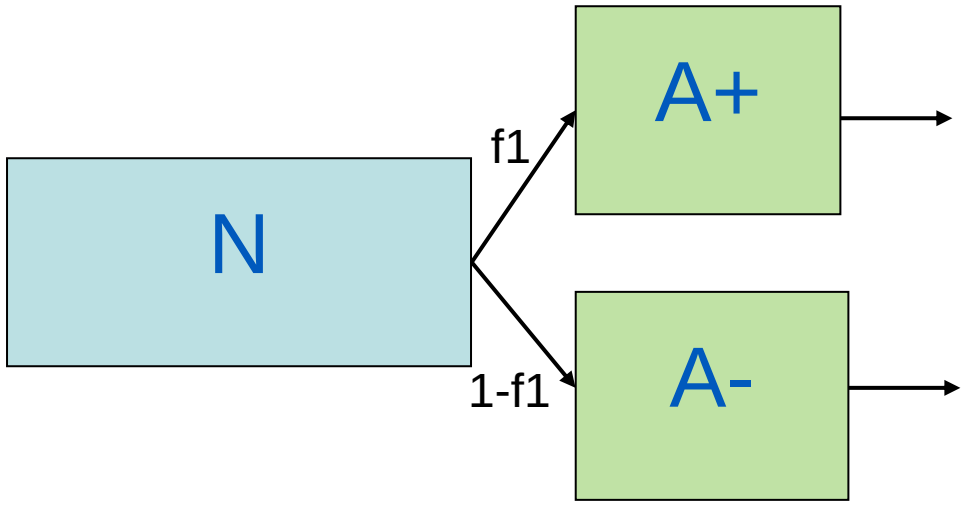
Target Population N, randomized 1:1 to A+ or A-



$Y+_{\text{in A+}}$ $(Y+_{\text{in A+}} / 0.5N)$

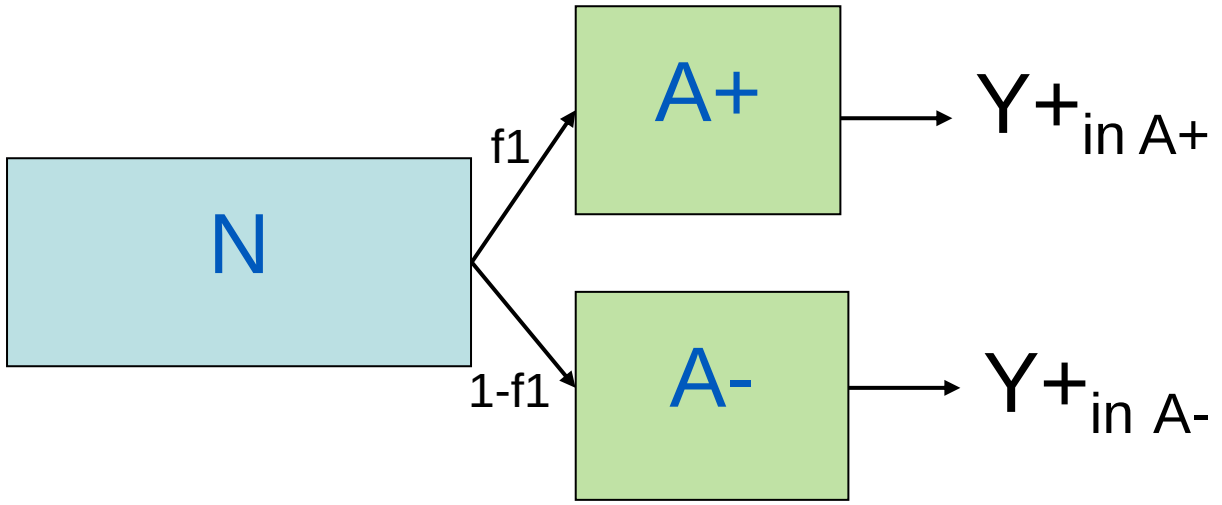
$Y+_{\text{in A-}}$ $-$ $(Y+_{\text{in A-}} / A-)$

An observable estimate ➡

$= RD_{crude}$

Why randomization is "the gold standard"

Target Population N, randomized 1:1 to A+ or A-



$Y+_{\text{in A+}}$ $(0.5Y+_{\text{if A+}} / 0.5N)$

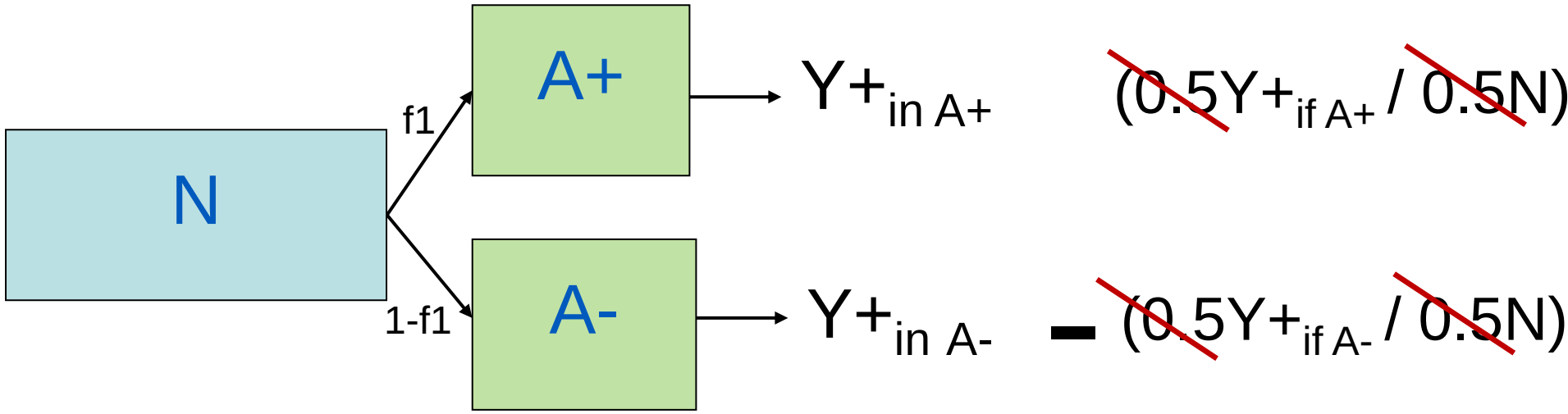
$Y+_{\text{in A-}}$ $- (Y+_{\text{in A-}} / A-)$

$= RD_{\text{crude}}$

An observable estimate ➡

Why randomization is "the gold standard"

Target Population N, randomized 1:1 to A+ or A-

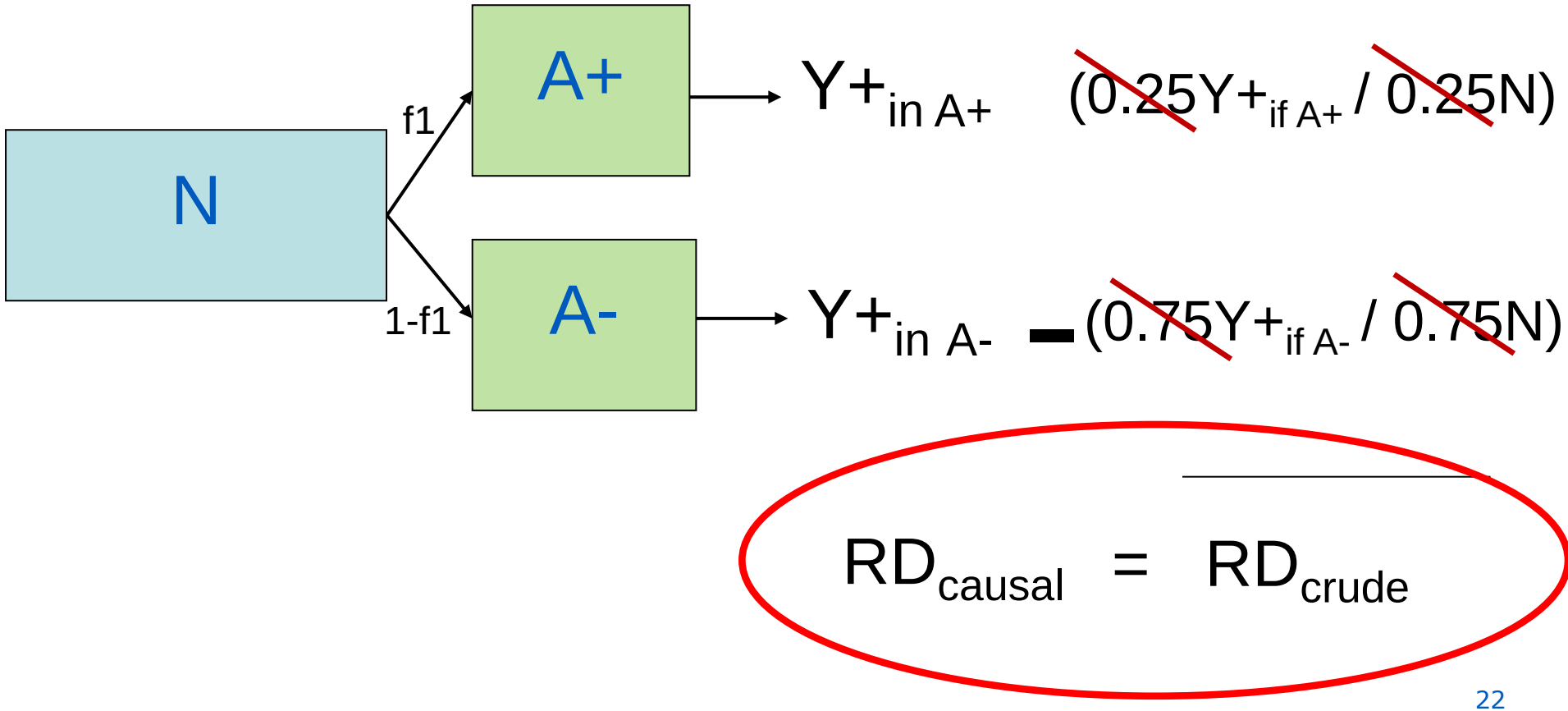


An observable estimate

$$RD_{causal} = RD_{crude}$$

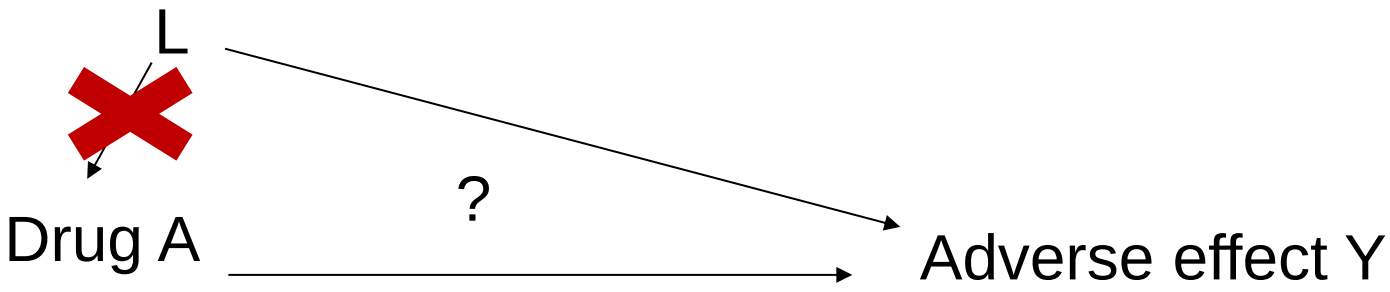
Why randomization is "the gold standard"

Target Population N, randomized 1:3 to A+ or A-



$$RD_{causal} = RD_{crude}$$

Why randomization is "the gold standard"



- If randomization is successful, no confounding at baseline

Possible solutions

- Try to avoid confounding through design, e.g.
  - Randomize
  - Match
  - Restrict
- Try to control confounding through analysis, e.g.:
  - Traditional analysis methods
  - Techniques that weight by causes of the treatment (aka mimic randomization)
  - Techniques that weight by causes of the outcome

Basic requirements of these methods

- Appropriately hypothesize factors that contribute to confounding
- Can measure these factors (validly)

...'there is no unmeasured confounding'

Option 1: Traditional confounding control

- For example, multivariate regression analysis
- Estimates RD_{causal}? Yes, when:
  - All variables that contribute to confounding are included in the model
  - Statistical model is specified correctly
  - Effect of A→Y across strata of confounding variables is homogeneous

Option 2: Propensity score (PS) methods

- Estimates RD_{causal}? Yes, when:
  - All variables that contribute to confounding are included in the model
  - Statistical model is specified correctly
  - Effect of A→Y across strata of confounding variables is homogeneous
    - (to estimate RD_{causal} as we've defined it: the total population effect)

Option 3: Inverse probability weighting (IPW)

- Estimates RD_{causal}? Yes, when:
  - All variables that contribute to confounding are included in the model
  - Statistical model is specified correctly
  - Positivity holds
    - There are no strata of L for which there are no subjects who received a particular exposure level

To estimate RD_{causal} in total population

Characteristic	Traditional methods	Propensity score control	IPW
Requires all confounding factors measured?	Yes	Yes	Yes
Statistical correctly specified	Yes	Yes	Yes
Can handle large number of confounding variables?	No	Yes	Yes
Requires homogeneity?	Yes	Yes	No
Requires positivity?	No	No	Yes

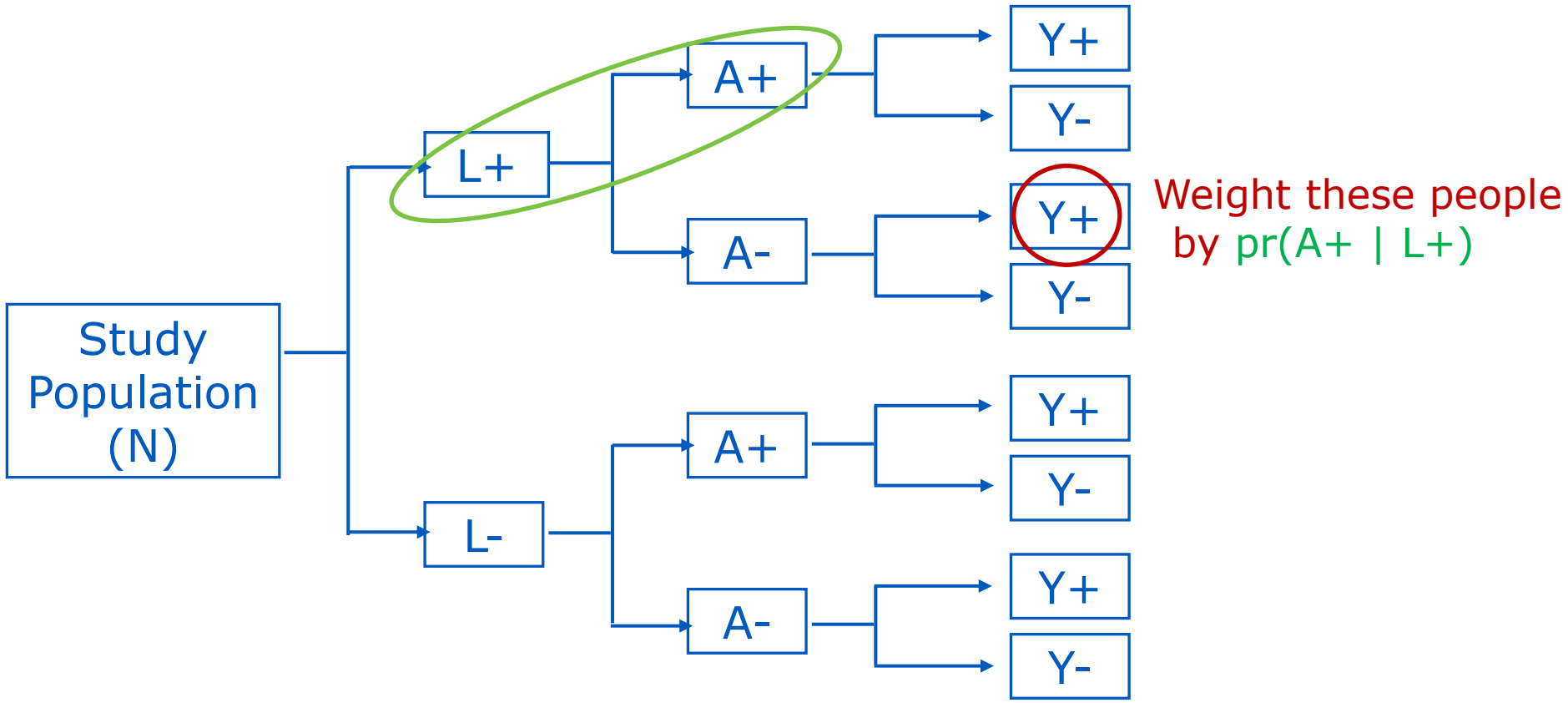
Estimating the propensity score

- Traditional PS: probability of being exposed conditional on predictors of exposure
- Minimally sufficient PS: probability of being exposed conditional on variables that contribute to confounding

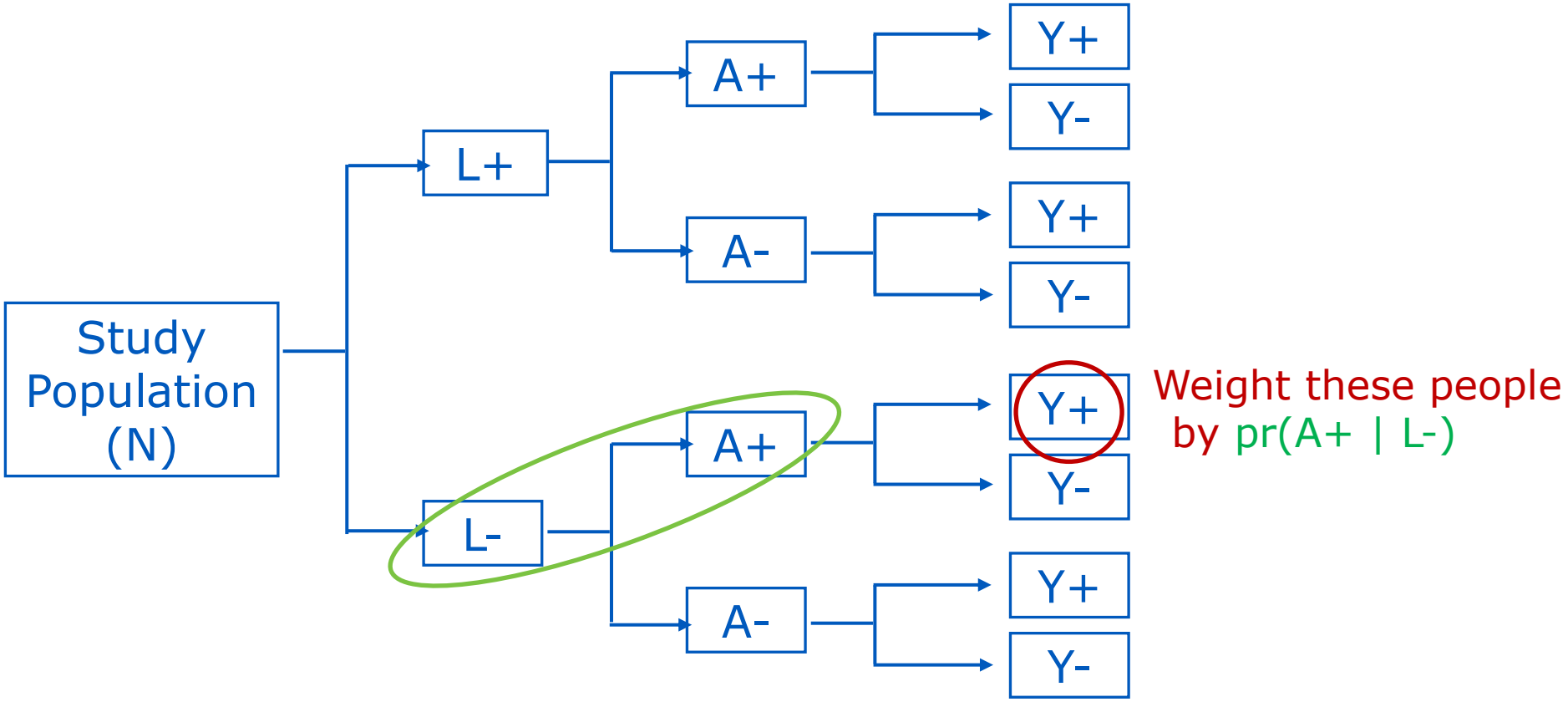
Estimating the propensity score

- Traditional PS: probability of being exposed conditional on predictors of exposure
- Minimally sufficient PS: probability of being exposed conditional on variables that contribute to confounding
  - A weight is assigned to each person according to the conditional probability of exposure given the confounder(s)

Estimating the propensity score: Example 1



Estimating the propensity score: Example 2



Estimating the propensity score

Example SAS code:

```
**estimate propensity scores**;
proc logistic descending data=dataset1;
        model A=L1 L2 L4 L5 L7 L8;
        output out=probA1_PS p=prA1_PS  xbeta=logit_ps;
run;
```

Applying the propensity score

- Options: PS control, stratification & matching
- After estimating PS for each person, use it to control confounding by:
  - Adjusting for the PS as a covariate
  - Stratifying the effect estimate by the PS
  - Matching A+ and A- people by PS

Applying the propensity score

Example SAS code:

```
**PS adjusted (as covariate) RR**;
proc genmod data=probA1_PS;
            model Y=A prA1_PS / dist=poisson;
run;
```

Applying the propensity score

Example SAS code:

```
**PS quintile stratification for CMH RR**;
proc rank data=probA1_PS groups=5 out=tempPS;
        ranks rnks;
        var prA1_PS;
run;

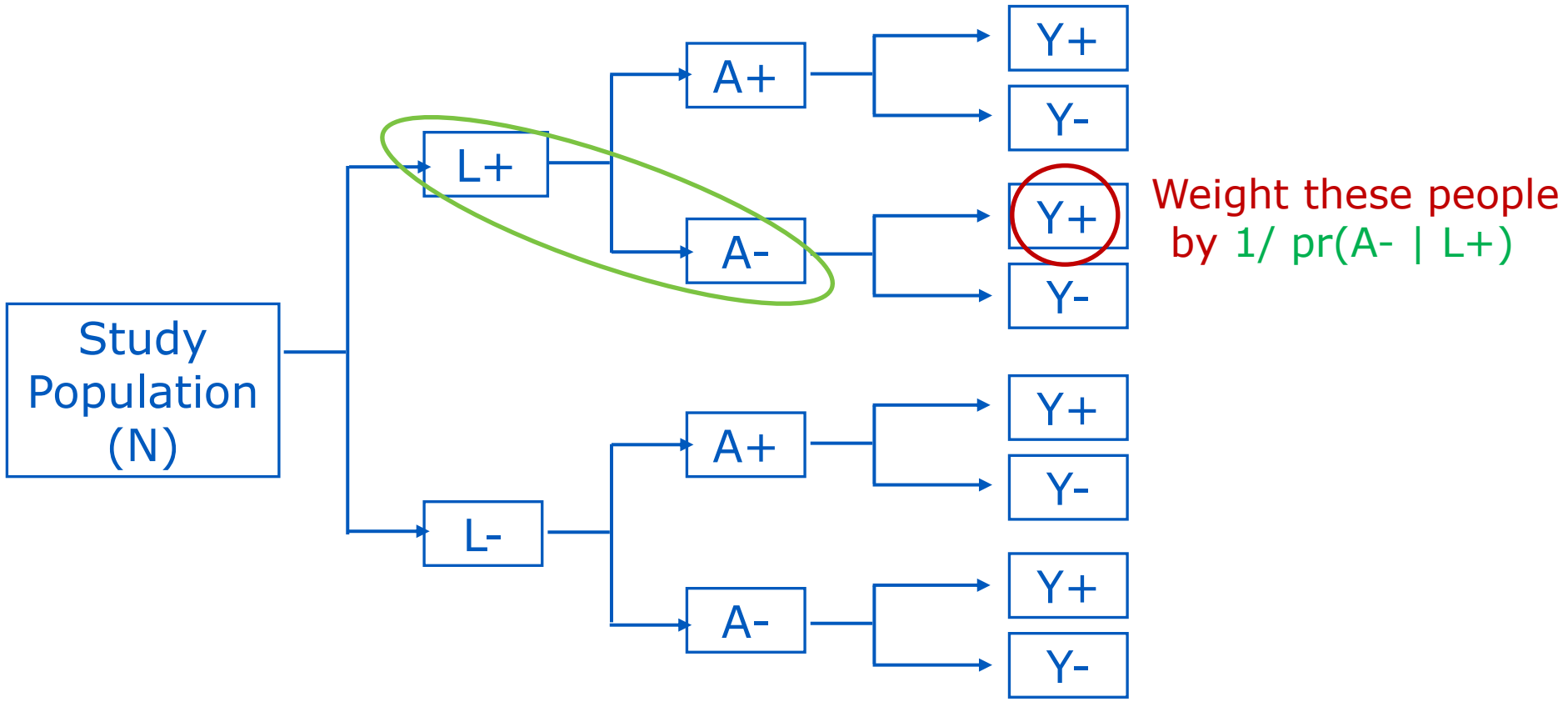
proc sort data=tempPS;
        by A Y;
proc freq data=tempPS order=data;
        tables rnks*A*Y / cmh;
        output out=tempPS1 mhrrc2 lgrrc2;
run;

data PSstrat_5;
        set tempPS1;
        beta=log(1/_MHRRC2_);
        SE=(log(U_MHRRC2)-log(L_MHRRC2))/3.92;
run;
```

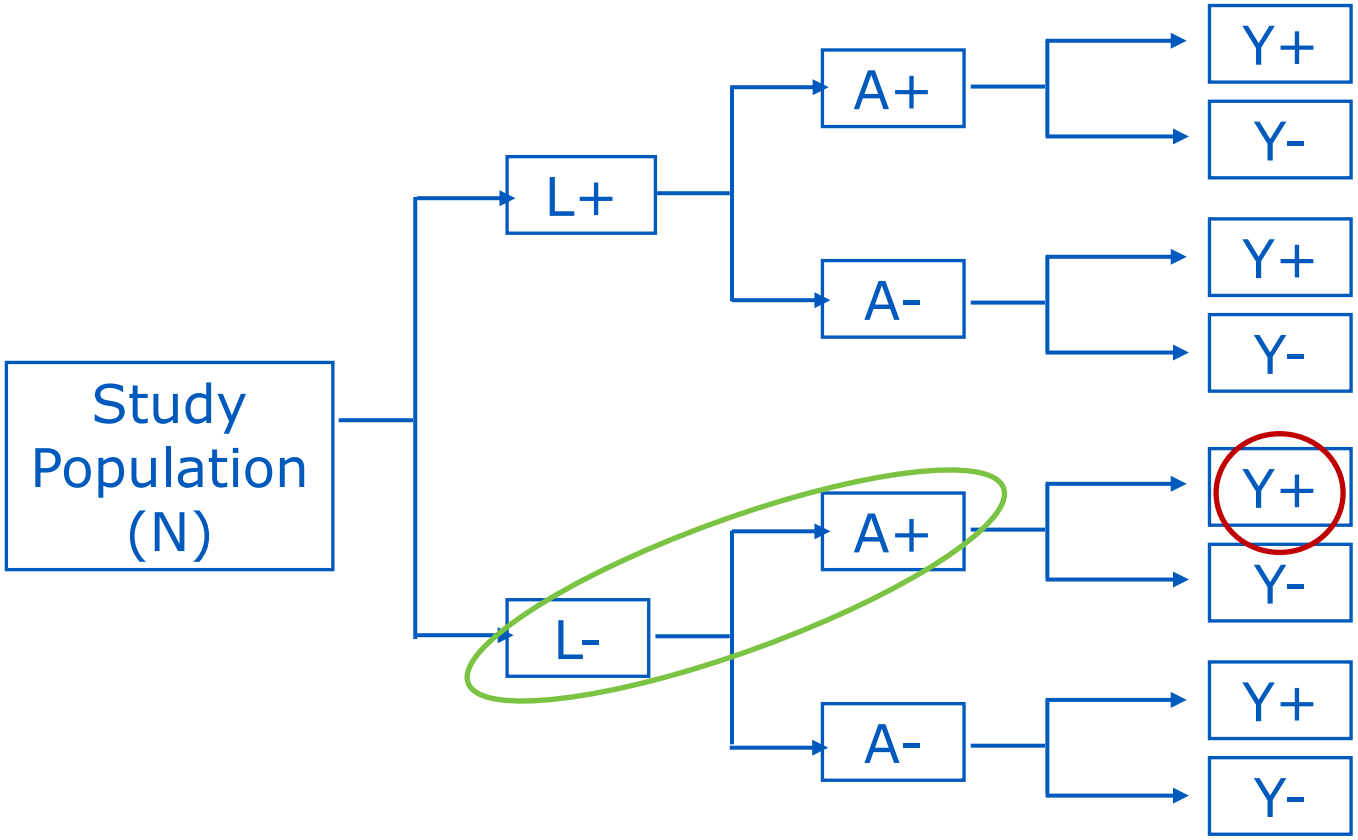
Estimating the inverse probability weight

- Another way to use the propensity score!
- IPW: Inverse of the exposure probability conditional on variables that contribute to confounding
  - A weight is assigned to each person according to the inverse of the conditional probability of his/her exposure status given the confounder(s)

Estimating the IPW: Example 1



Estimating the IPW: Example 2



Weight these people by 1 / pr(A+ | L-)

Estimating the IPW

Example SAS code:

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**estimate propensity scores**;
proc logistic descending data=dataset1;
        model A=L1 L2 L4 L5 L7 L8;
        output out=probA1_PS p=prA1_PS  xbeta=logit_ps;
run;

data weights_PS;
        set probA1_PS;
        prA0_PS=1-prA1_PS;
        if A=1 then IPW=1/prA1_PS;
        else IPW=1/prA0_PS;
run;
```

Applying the IPW

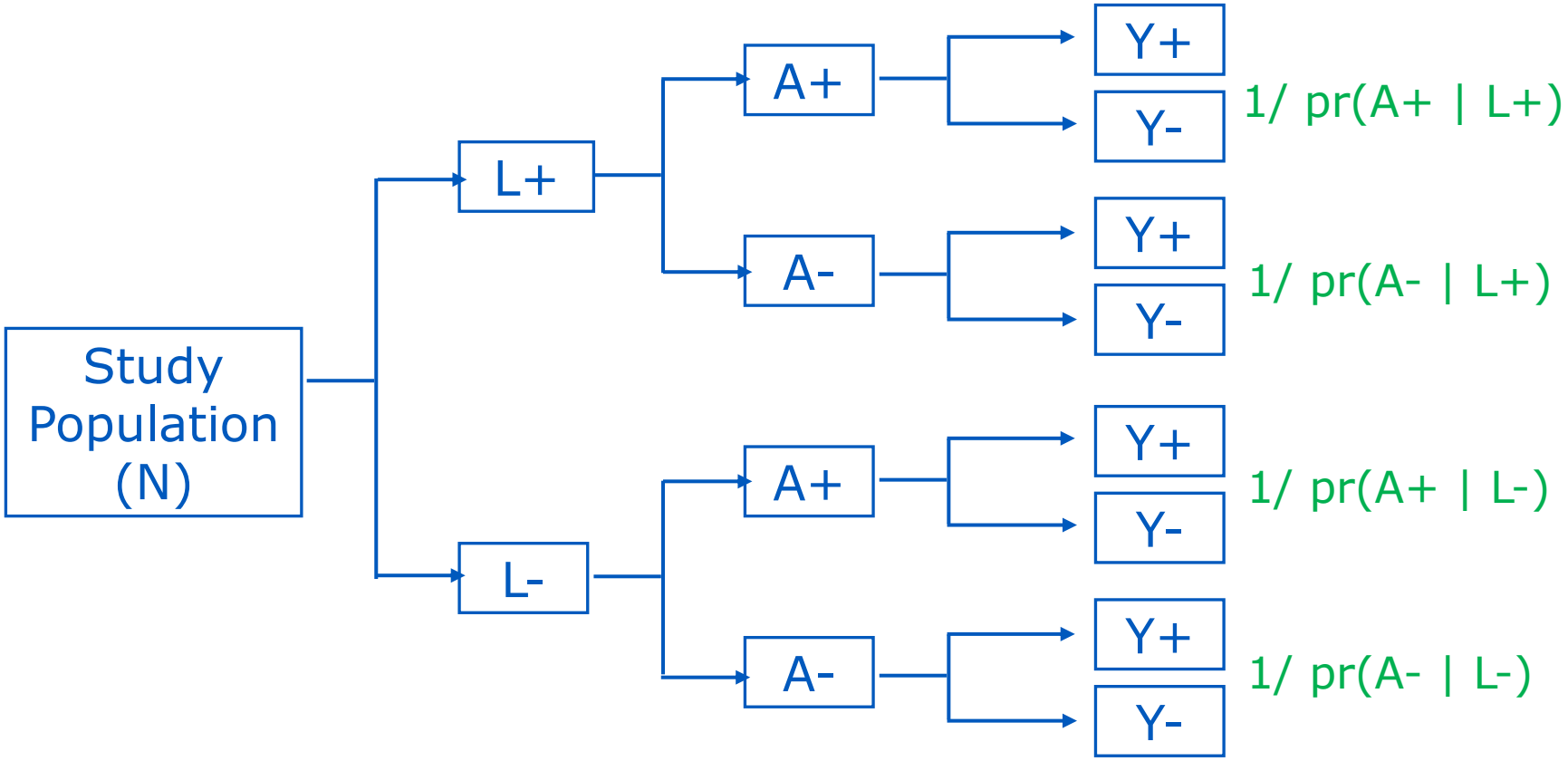
Example SAS code:

```
**IP weighted RR in total population**;
proc genmod data=weights_PS;
            class ID;
            model Y=A /dist=poisson;
            weight IPW;
            repeated subject=id;
            estimate 'beta' A 1;
run;
```

How do these methods relate to RCTs?

- They use weighting to mimic randomization
- PS methods estimate effect using weighting across *x* number of 'new populations'
- IPW weights people by the IPW, creating a pseudo-population

The pseudo-population



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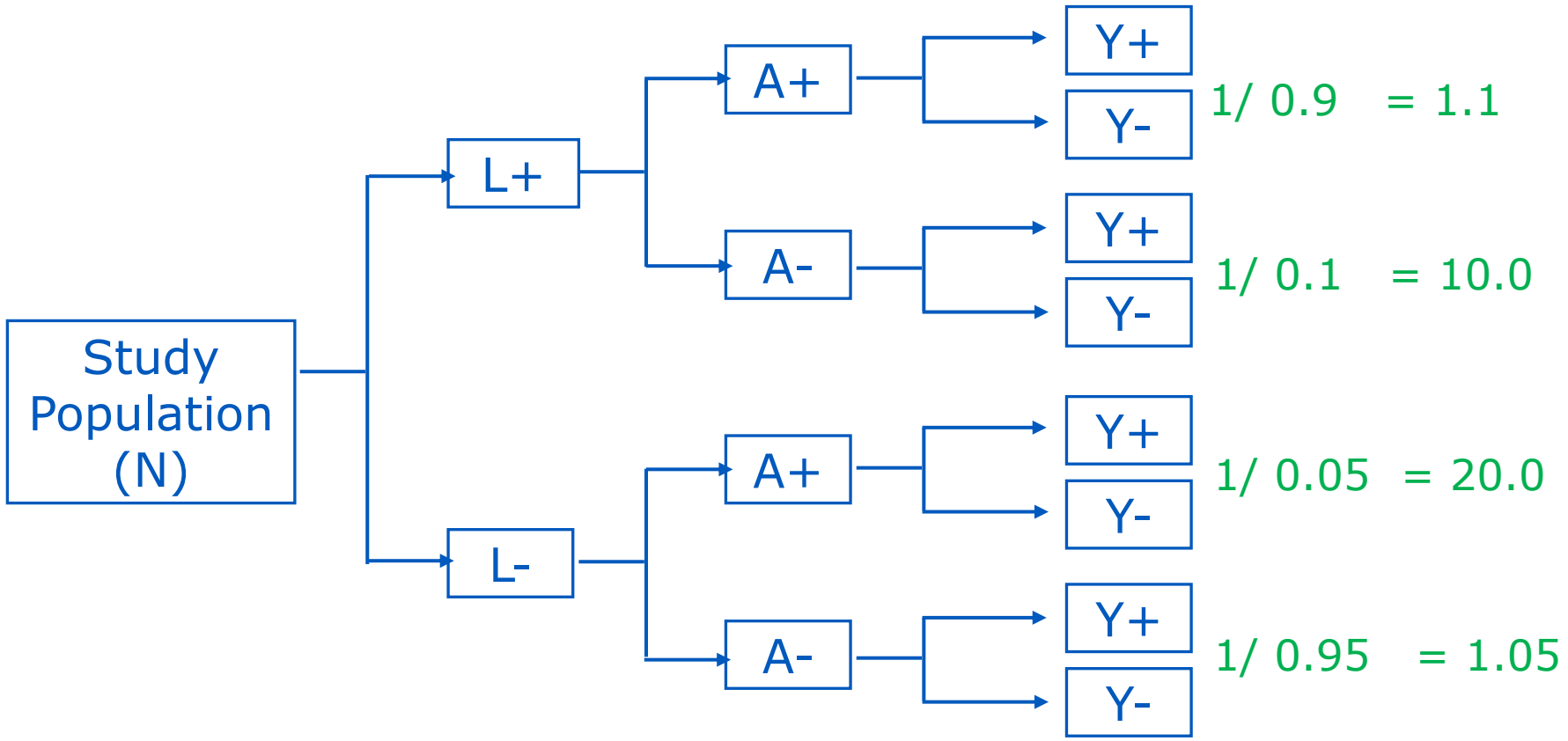

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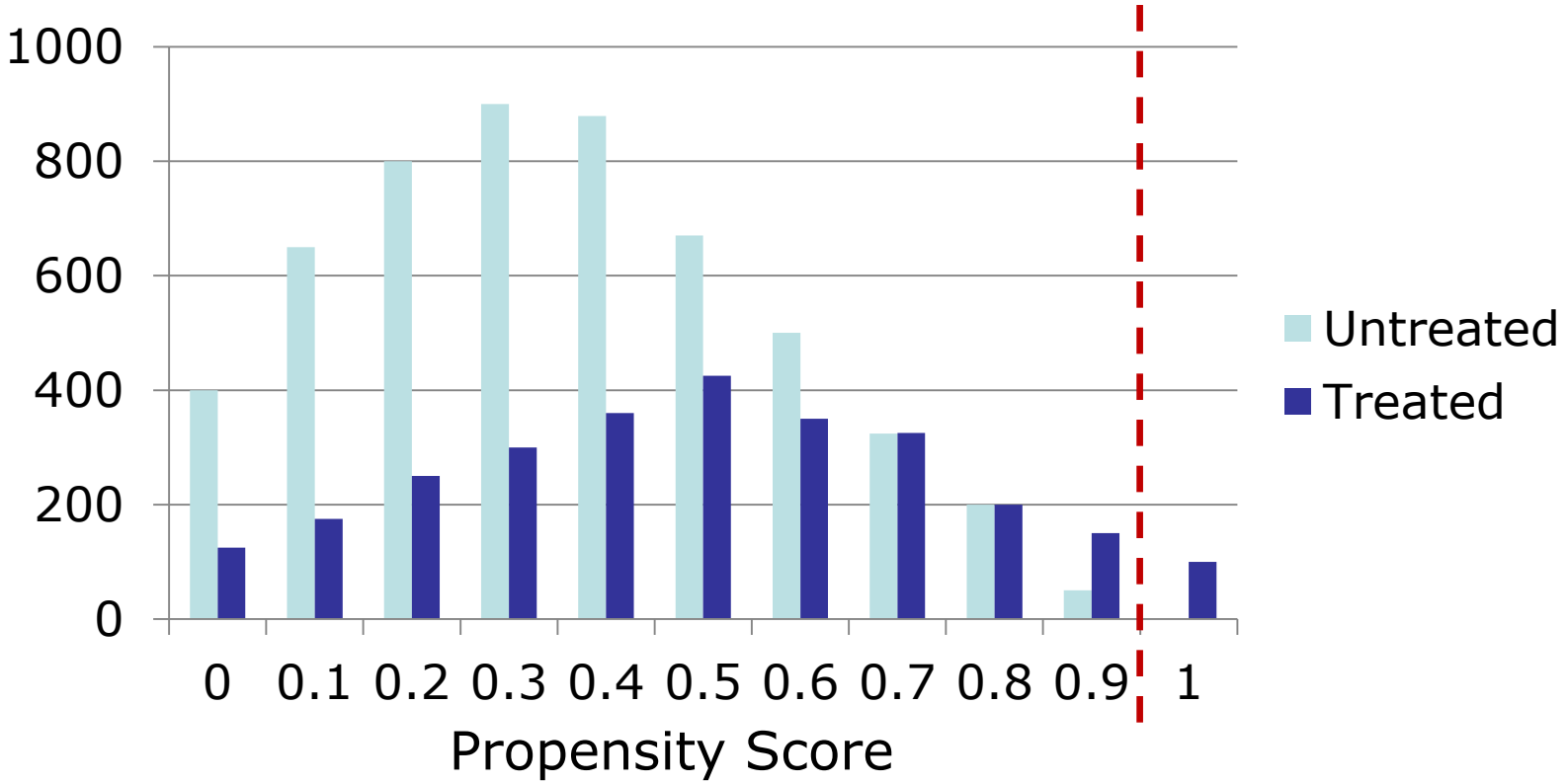
Some practical considerations

Propensity score balancing



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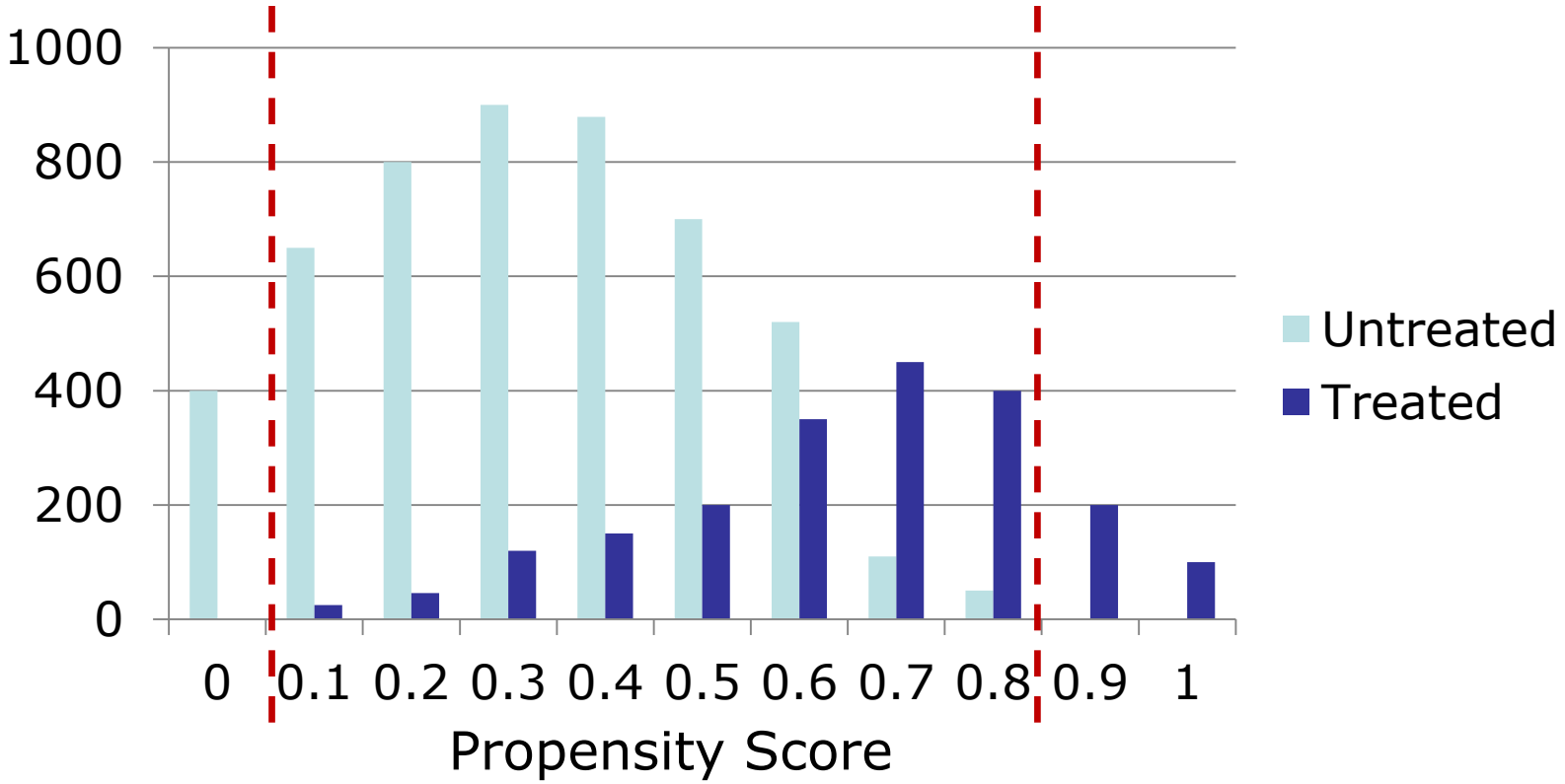

How will PS be estimated?

For example:

- Covariates to be included
- Interaction terms to be included
- Type of model used to estimate the probability of exposure
- Type of regression used to model the outcome

How will IPW be estimated?

For example:

- Covariates to be included
- Interaction terms to be included
- Type of model used to estimate the probability of exposure
- Type of regression used to model the outcome
- Stabilized or unstabilized weights
- Robust variance estimation

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To estimate RD_{causal} in total population

Characteristic	Traditional methods	Propensity score control	IPW
Requires all confounding factors measured?	Yes	Yes	Yes
Statistical correctly specified	Yes	Yes	Yes
Can handle large number of confounding variables?	No	Yes	Yes
Requires homogeneity?	Yes	Yes	No
Requires positivity?	No	No	Yes

To estimate RD_{causal} in treated

Characteristic	Traditional methods	Propensity score control	IPW
Requires all confounding factors measured?	Yes	Yes	Yes
Statistical correctly specified	Yes	Yes	Yes
Can handle large number of confounding variables?	No	Yes	Yes
Requires homogeneity?	Yes	No*	No#
Requires positivity?	No	No	Yes

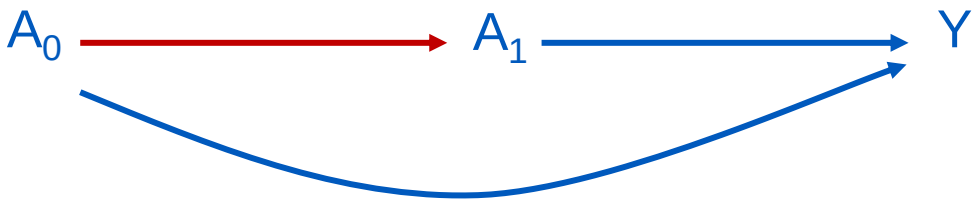
* If PS matching or SMR weighting to combine PS strata

\# If SMR weighting used to create pseudo-population

Instrumental variable analysis: A solution?

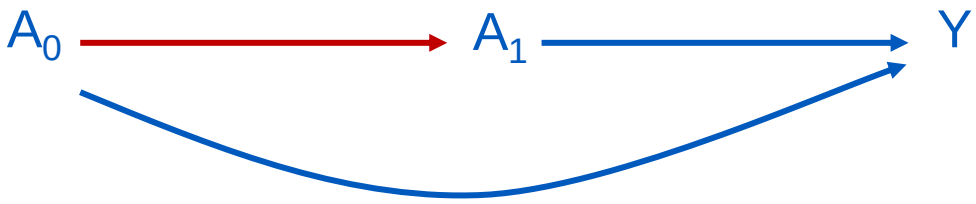
- Stay tuned...

What if we are interested in a time varying treatment effect?



- Treatment (A) varies with time

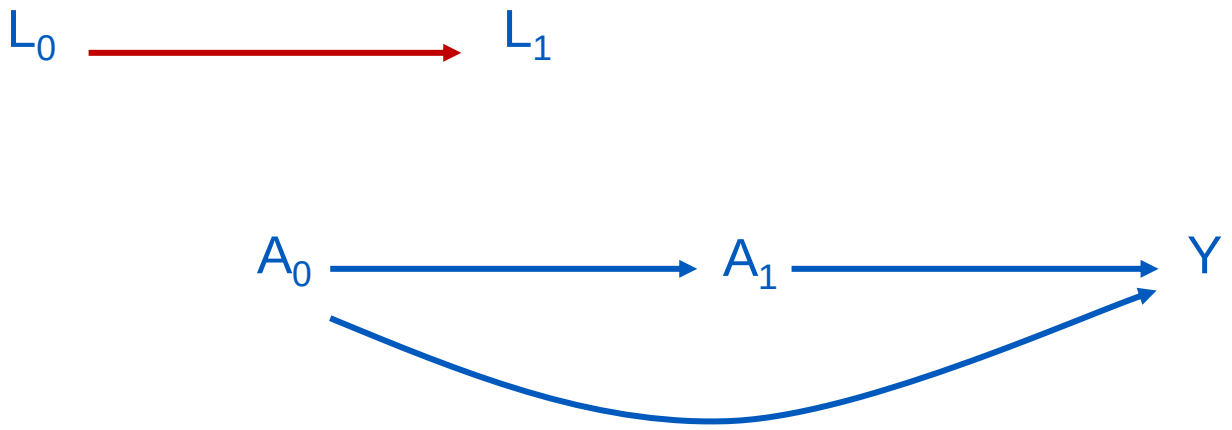
What if we are interested in a time varying treatment effect?



- Treatment (A) varies with time

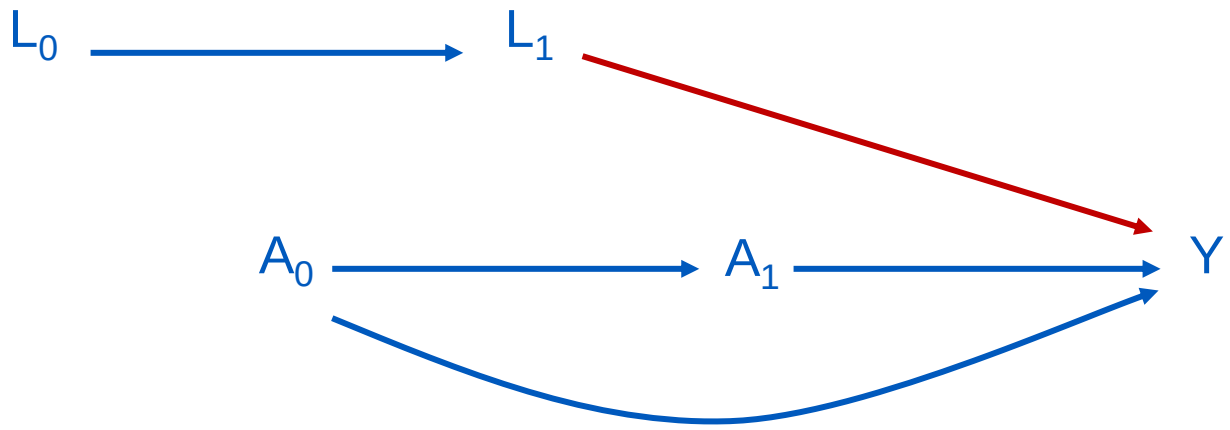
the causal effect if everyone in the population had been A_{++} versus if everyone had been A_{--}

What if we are interested in a time varying treatment effect?



- Treatment (A) varies with time
- Covariate (L) varies with time

What if we are interested in a time varying treatment effect?



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- Covariate (L) varies with time and:
  - Predicts the outcome

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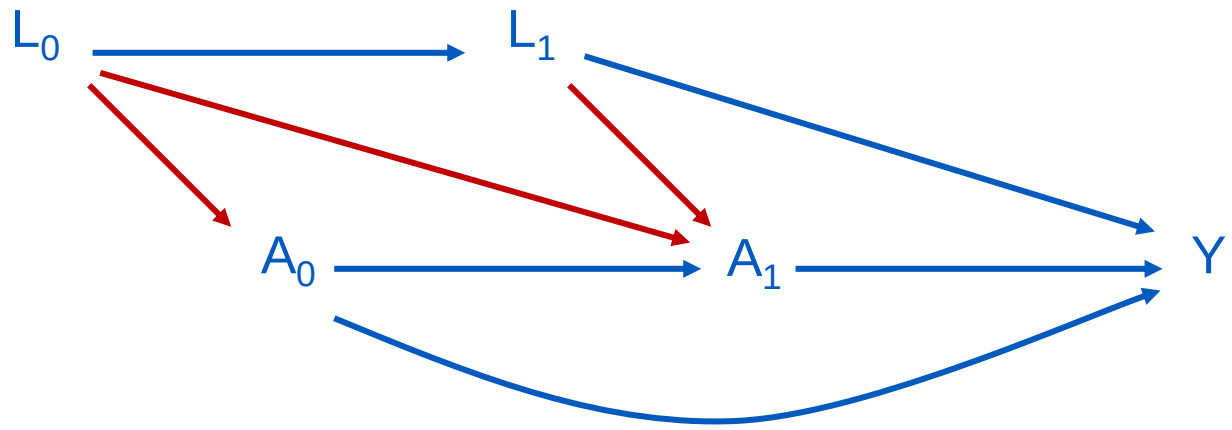

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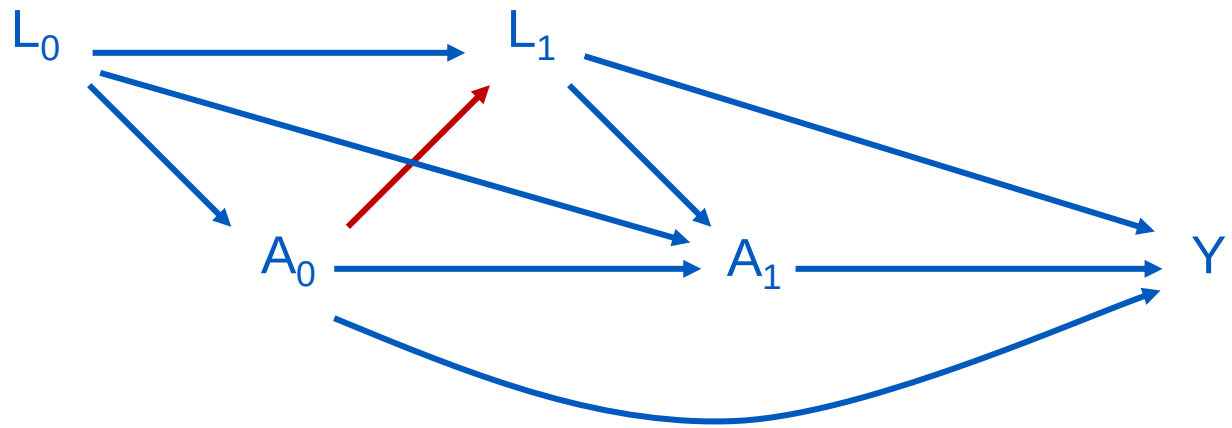
  - Predicts exposure

What if we are interested in a time varying treatment effect?



- Treatment (A) varies with time
- Covariate (L) varies with time and:
  - Predicts the outcome
  - Predicts exposure
  - Is affected by previous exposure

How do we address the confounding and mediational effects of L?

Inverse probability weighting: A solution?

- Stay tuned...

Take home messages

- These weighting approaches require all confounding factors are hypothesized and measured
- To estimate the causal effect in the total population, only IPW does not require homogeneity of the treatment effect
- The choice of confounding control method for point-treatment confounding should be driven by:
  - Causal question / target population
  - Practical considerations

References

Hernan MA and Robins JM. Estimating causal effects from epidemiological data. J Epidemiol Community Health 2006;60:578-86

Hernan MA et al. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology 2000;11:561-70

Robins JM et al. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550-60

Sato T and Matsuyama Y. Marginal Structural Models as a Tool for Standardization. Epidemiology 2003;14:680-6

Sturmer T, Rothman KJ, Glynn RJ Insights into different results from different causal contrasts in the presence of effect-measure modification. Pharmacoepidemiol Drug Saf 2006; 15, 698-709

Thank you