
# Causation and causal inference in randomised experiments and observational studies

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# Introduction

- Many - if not most - scientific questions concern causality.
- E.g.
  - what are the effects of smoking on health?
  - what are the effects of schooling on knowledge?
  - which genes are related to a plant's yield?
  - what is the best treatment to give to a given patient?
  - what explains differences in cancer stage at diagnosis by SES?
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  yet statistical developments in this field are relatively recent.
- There are several reasons for that.
- For decades, the feeling was that in most empirical studies,
  except for randomised experiments,
  it is too ambitious to infer cause-effect relationships.

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'it would take about 0.4 kg of chocolate per capita per year to increase the number of Nobel laureates in a given country by 1.'

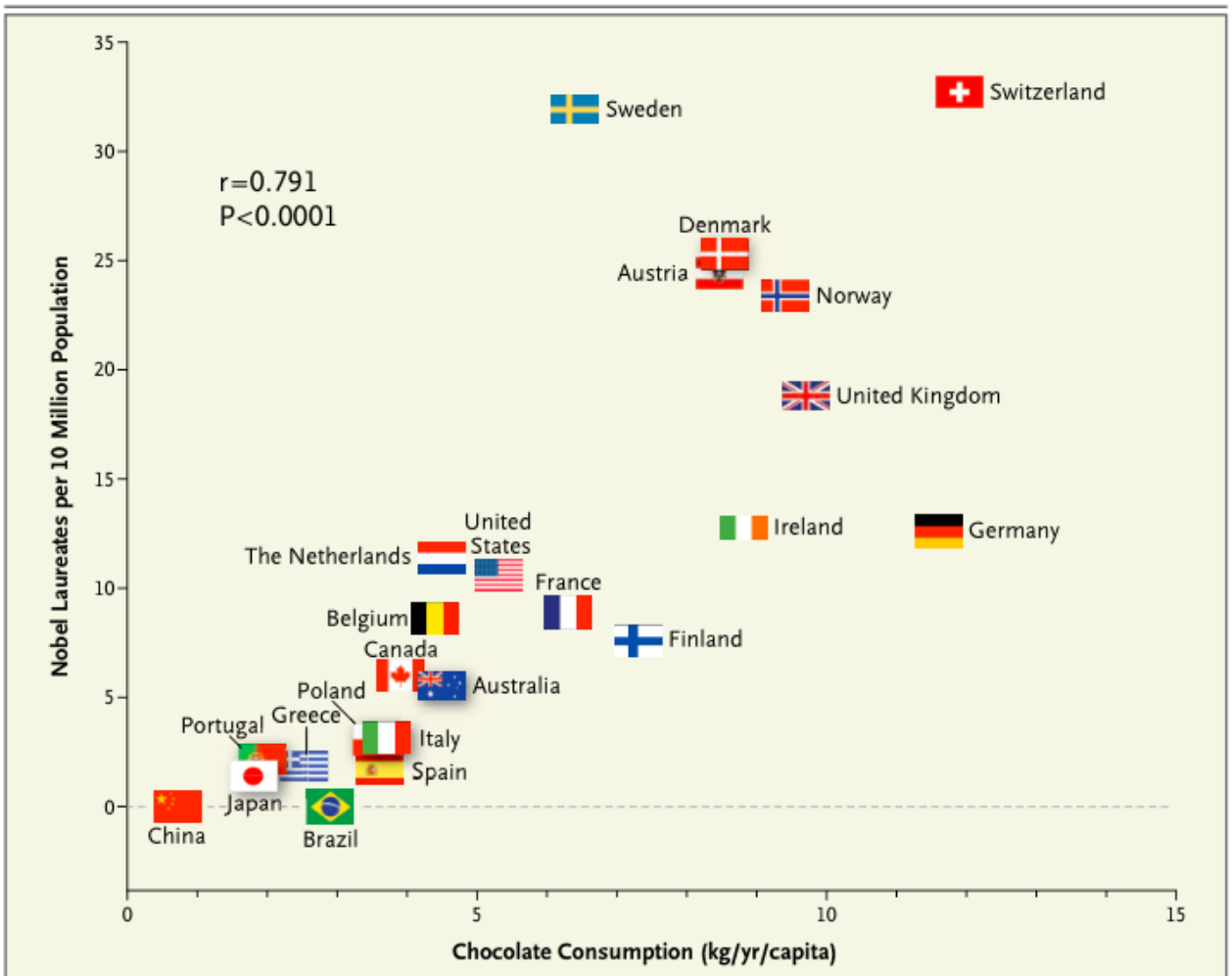
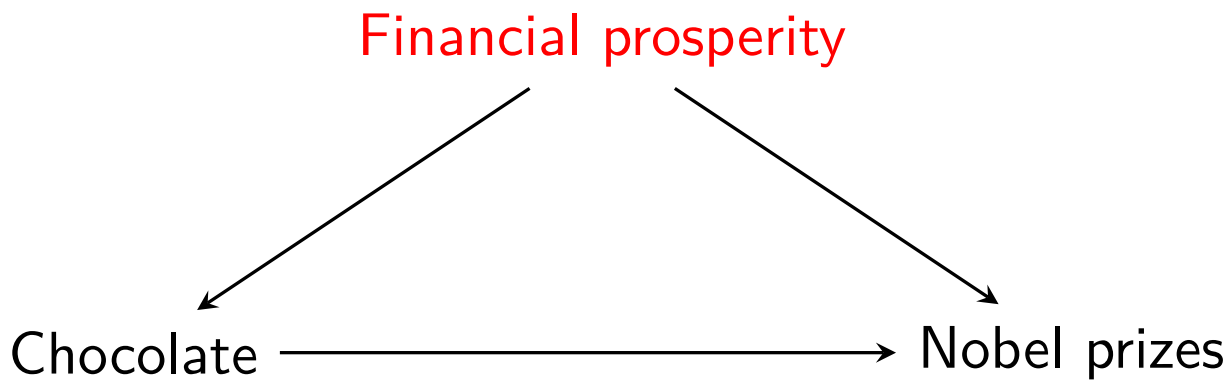



**Figure 1.** Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.

# Confounding: Are these countries comparable?

# Confounding bias...

... typically arises as a result of ignoring (hidden) common causes.



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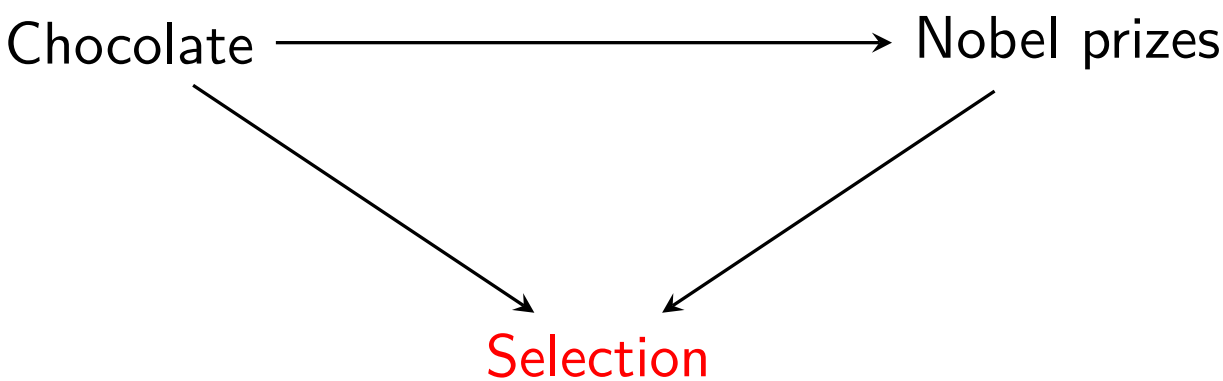
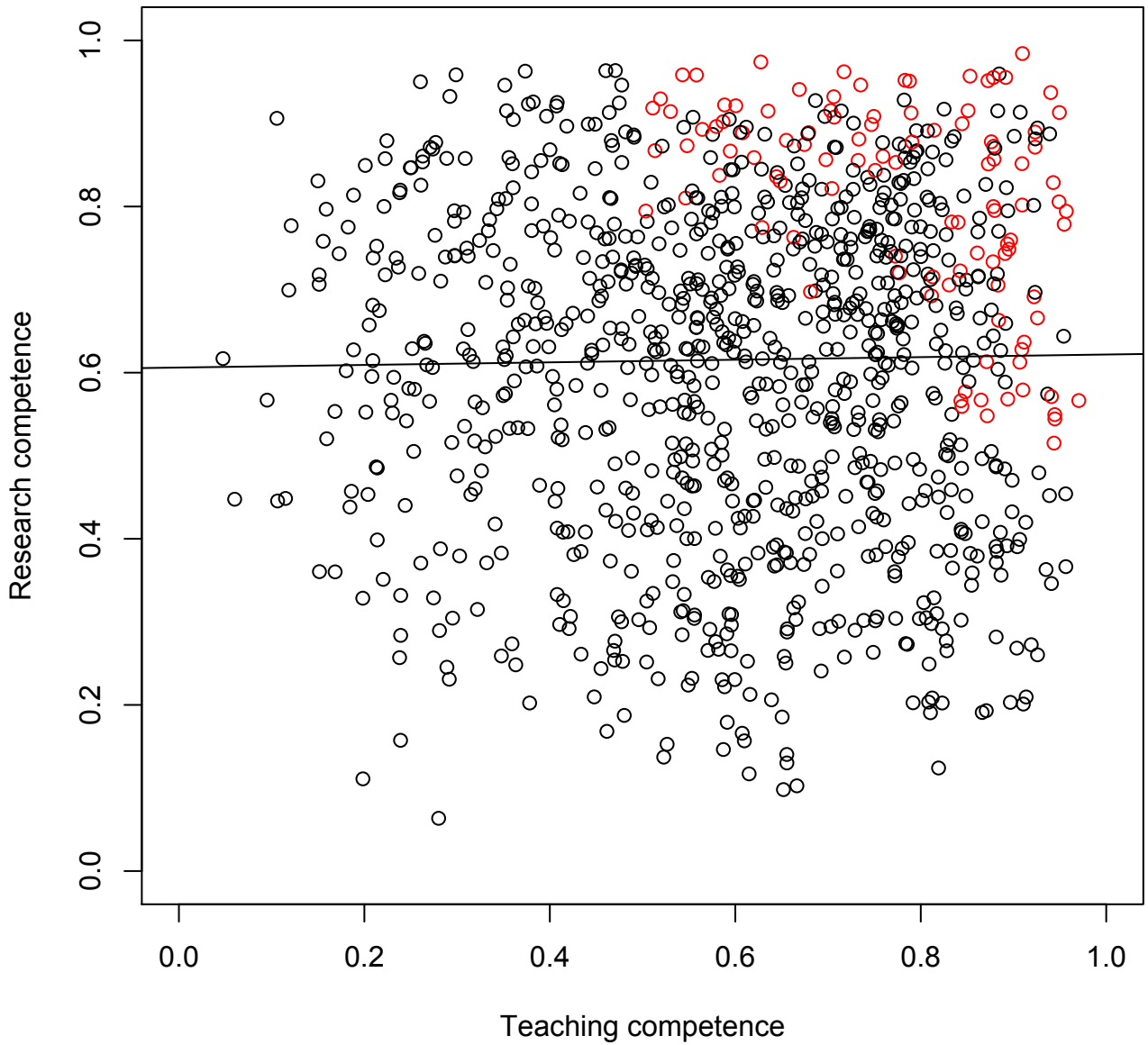
Selection bias typically arises as a result of selecting measurements in function of exposure and outcome.



# Selection bias is a source of much error

Black: Assistant and Associate Professors; Red: Full Professors



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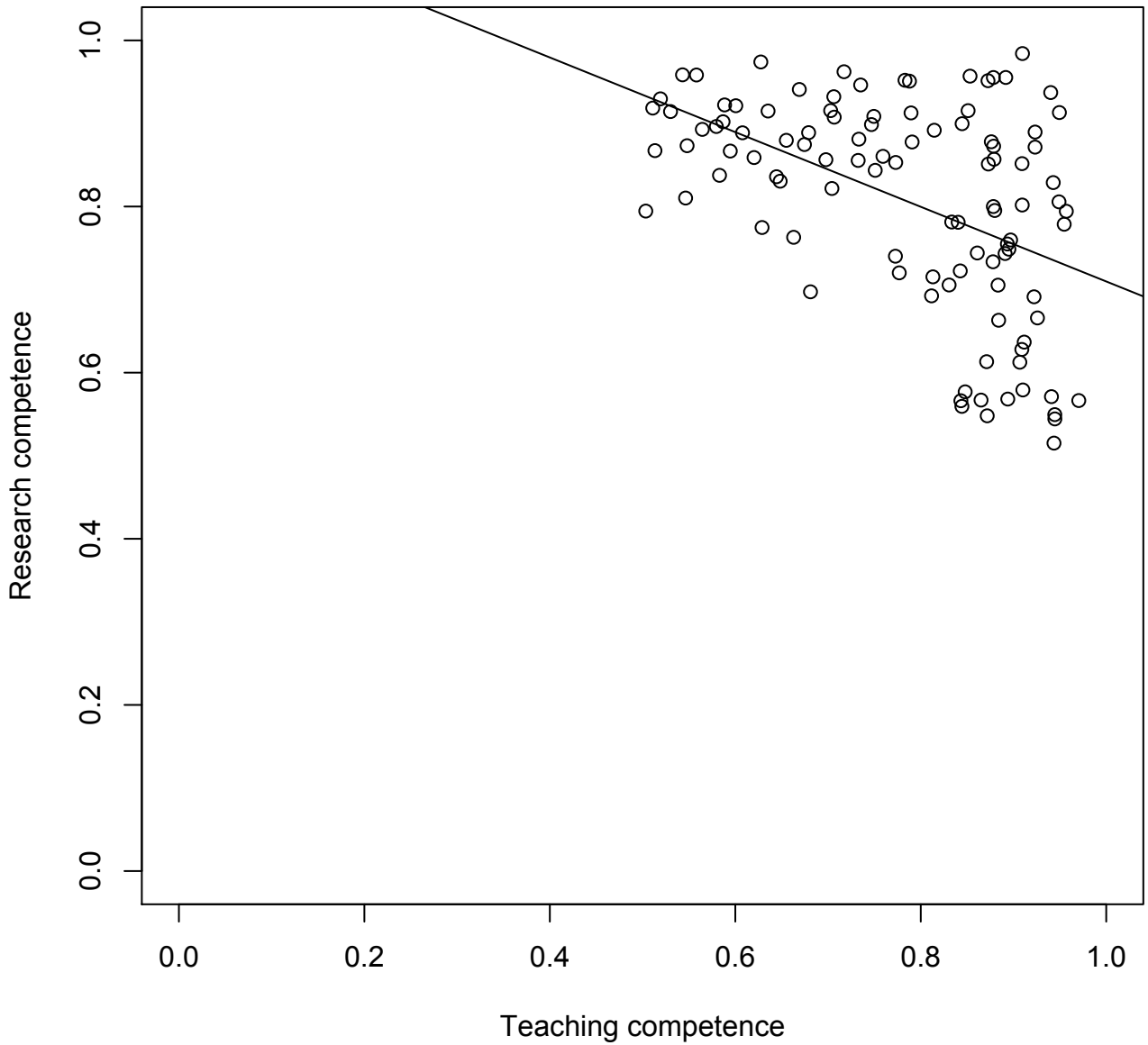
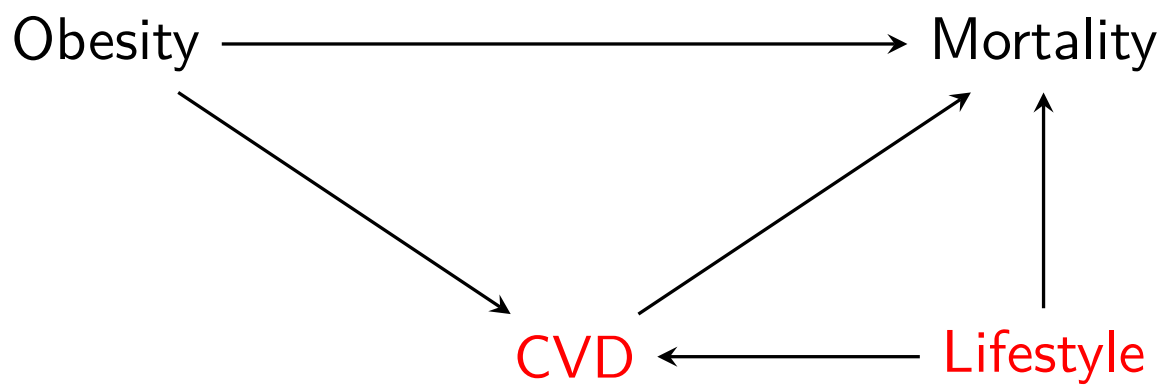


# Selection bias and the obesity paradox

Mortality rates are lower in obese than non-obese cardiovascular patients.



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Our statistical methods are subject to debate.[17] Other more sophisticated advanced approaches, such as marginal structural models, aim to address causality but necessitate additional assumptions.[18] Our methods are correct in terms of statistical association, because they adequately acknowledge the chronological order of all factors and do not need further assumptions.

## Discussion

Health-care-associated infections cause high excess mortality in critically ill patients, although antimicrobial resistance has a comparatively low additional effect.

*Lancet Infect Dis* 2011; 11: 30–38

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Use statistical methods designed to answer that question,
e.g.

- adopt variable selection strategies to detect 'confounders';
- be clear about the effect of interest
  and target the fitting of prediction models
  towards estimation of the considered effect;
- distinguish cause from effect in the analysis.

# The plan for today...

Today, I will touch upon 2 case studies in causal inference:

- Should we adjust for covariates or not in RCTs?

  Vermeulen, K., Thas, O. and Vansteelandt, S. (2015). Increasing the power of the Mann-Whitney test in randomized experiments through flexible covariate adjustment. Statistics in Medicine, 34, 1012-1030.

- What is the effect of hospital-acquired infection on mortality?

  Bekaert, M., Timsit, J.-F., Vansteelandt, S., Depuydt, P., Vésin, A., Garrouste-Orgeas, M., Decruyenaere, J., Clec'h, C., Azoulay, E., Benoit, D. (2011). Attributable Mortality of Ventilator Associated Pneumonia: A Reappraisal Using Causal Analysis. American Journal of Respiratory and Critical Care Medicine, 184, 1133-1139.

# Part I. To adjust or not to adjust...?

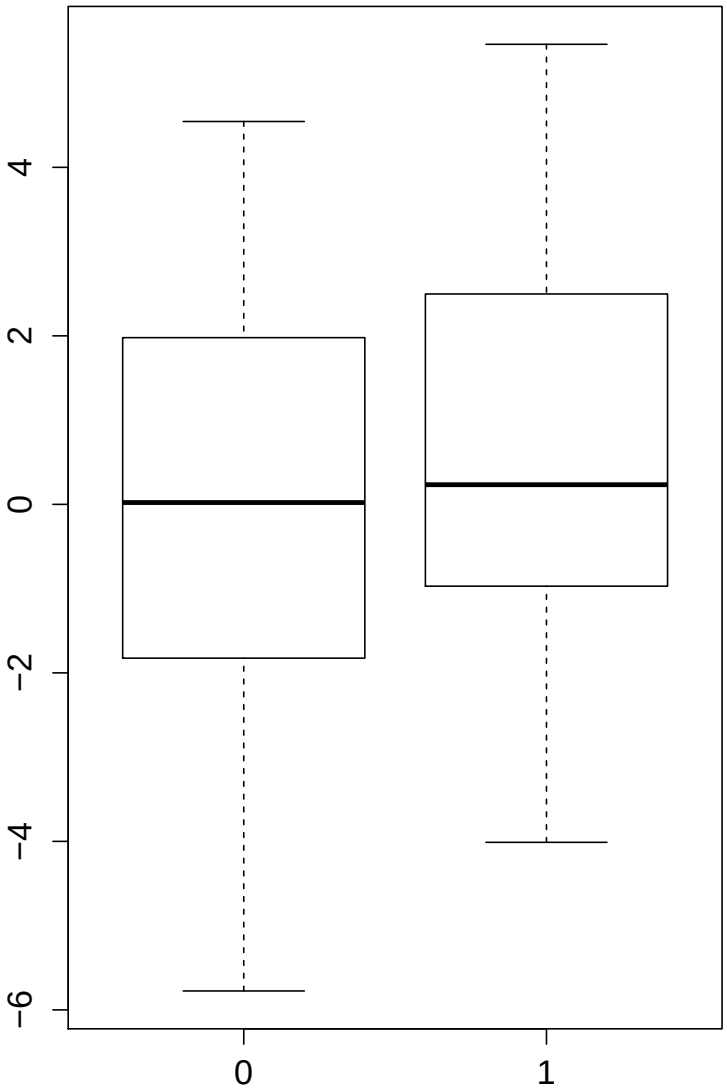
# Covariate adjustment in RCTs

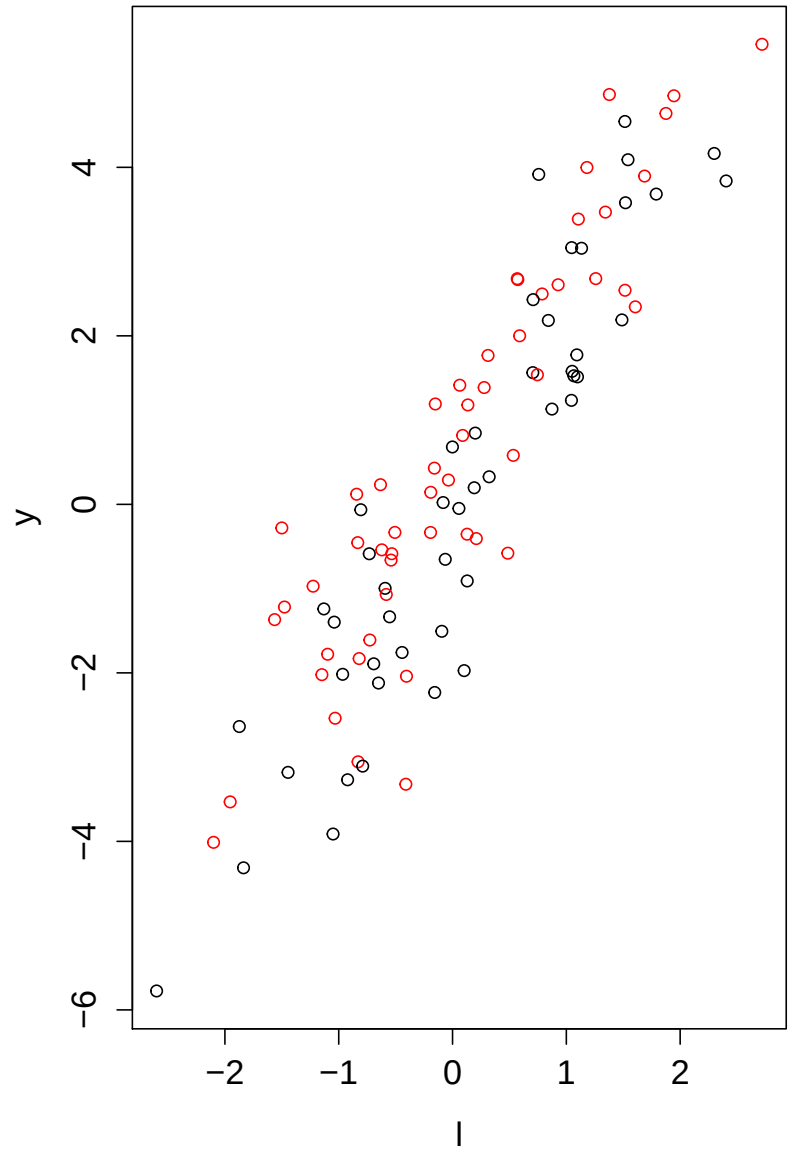
Pocock et al. (2002) surveyed 50 randomized clinical trial reports:

- 36 used covariate adjustment.
- 12 emphasised adjusted over unadjusted analysis.

*'The statistical emphasis on covariate adjustment is quite complex and often poorly understood,*
*and there remains confusion*
*as to what is an appropriate statistical strategy.'*

# Adjusted versus unadjusted analyses



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- Adjusted analysis relies on models;
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- Adjusted analysis makes fishing expeditions possible.
- Adjusted analysis may ignore uncertainty
  due to covariate selection,
  possibly causing inflated Type I errors.

# Non-collapsibility

(Greenland, Robins and Pearl, 1998)

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$$E(Y|A,L) = \text{expit}(\beta_0 + \beta_1 A + \beta_2 L).$$

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- Typical of the causal inference literature is to first be clear about the effect measure of interest, and then conceptualise an analysis strategy.

# Continuous outcomes

(Yang and Tsiatis, 2001)

- Focus on the population-averaged effect of treatment $A$ on $Y$:

$$E(Y|A=1) - E(Y|A=0)$$

- Fit linear regression model

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- What about other types of outcome?

# Dichotomous outcomes

(Tsiatis et al., 2009; Moore and van der Laan, 2009)

- Logistic regression is common,
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- We know that $P(A=1|L) = 0.5$ in a typical RCT,
  so let's use that knowledge.
- Infer all consistent estimators
  of along with the most precise estimator in the class.
- This leads to the following simple strategy.

# Dichotomous outcomes

(Tsiatis et al., 2009; Moore and van der Laan, 2009)

- Fit logistic regression model

$$E(Y|A,L) = \text{expit}(\beta_0 + \beta_1 A + \beta_2 L).$$

- Estimator of population-averaged effect of treatment is

$$\frac{1}{n}\sum_{i=1}^{n} \text{expit}(\hat{\beta}_0 + \hat{\beta}_1 + \hat{\beta}_2 L_i) - \text{expit}(\hat{\beta}_0 + \hat{\beta}_2 L_i).$$

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and estimate treatment effect as

$$\frac{1}{n(n-1)} \sum_{i=1}^{n} \sum_{j \neq i} \text{expit}\left\{\hat{\beta}_1 + \hat{\beta}_2(L_i - L_j)\right\}.$$

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# Power in Planning Aids CT group protocol 175

(Vermeulen. Thas and Vansteelandt. 2015)

**Table I.** Data analysis on 1000 random subsamples of the original ACTG 175 data set.

| TEST | POWER | RE | POWER | RE | POWER | RE |
|---|---|---|---|---|---|---|
| | $n_{sub} = 30$ | | $n_{sub} = 50$ | | $n_{sub} = 100$ | |
| MW | 9.7 | 1.00 | 15.3 | 1.00 | 25.8 | 1.00 |
| augMW probit0 BASE | 14.9 | 0.60 | 23.1 | 0.56 | 44.9 | 0.59 |
| augMW probit0 SIG | 14.0 | 0.54 | 22.9 | 0.51 | 44.3 | 0.56 |
| augMW logit0 BASE | 15.0 | 0.60 | 23.2 | 0.56 | 45.1 | 0.59 |
| augMW logit0 SIG | 14.1 | 0.55 | 23.6 | 0.51 | 44.8 | 0.56 |

NOTE: RE, empirical variance of the augmented test statistic $\widehat{T}(\boldsymbol{A}, \boldsymbol{Y}, \boldsymbol{X})$ divided by the empirical variance of $U/(N_1 N_0)$; BASE, adjustment for baseline CD4; SIG, adjustment for significant covariates in a univariate model; MW, Mann-Whitney $U$ test; augMW, augmented Mann-Whitney $U$ test; probit0, working probabilistic index model fitted under the null hypothesis using probit link; logit0, working probabilistic index model fitted under the null hypothesis using logit link.

The SIG procedure is designed to prevent Type I error inflation under covariate selection.

# Summary on covariate adjustment in RCTs

- There remains confusion as to whether covariate adjustment is appropriate in the analysis of RCTs.
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- There remains confusion as to whether covariate adjustment is appropriate in the analysis of RCTs.
- Adjustment allows to gain power,
  but comes with a number of drawbacks.
- The causal inference literature has offered
  simple proposals to gain power through covariate adjustment,
  which do not have these disadvantages.
- Power gain - but not Type I error rate -
  are dependent on correct specification of an outcome model.
- Recent extensions guarantee power gains
  regardless of correct specification.
- R packages: `speff2trial`, `iWeigReg`, `tmle`.

# Part II. Time-varying exposures


What is the effect of hospital-acquired infection on mortality?

# Nosocomial (= hospital-acquired) infections

- Nosocomial (= hospital-acquired) infections
  form a major public health problem in the Western world.
- They are believed to account for 50% of all major complications of hospitalization
  and to have a substantial impact
  on morbidity, mortality and medical costs.
- In Belgium, the estimated number of patients acquiring nosocomial infection is 103 000 to 116 000 per year.
- It is estimated that nosocomial infections contribute to the mortality of 2600 patients per year, to 700 000 extra hospital days and to a total annual cost of 400 million EUR.

  (Vrijens et al., 2009)

# Scientific results do not match bedside experience

Editorials

Ventilator-associated pneumonia and mortality:
The controversy continues*

*"Majority of the studies ignore the patients underlying severity of illness"*

*"The difficulty with assessing the influence of VAP on mortality stems from the fact that it is a complication of critical illness."*

*"Because observational data in regard to the attributable mortality of VAP are all that we will ever have,* ***studies of more methodological rigor are required*** *if we are going to answer this important question."*

*Crit Care Med. 2009 Oct;37(10)*

# Time-varying exposures and confounders

- The exposure and confounders are time-varying:
  - Patients acquire infections at different times.
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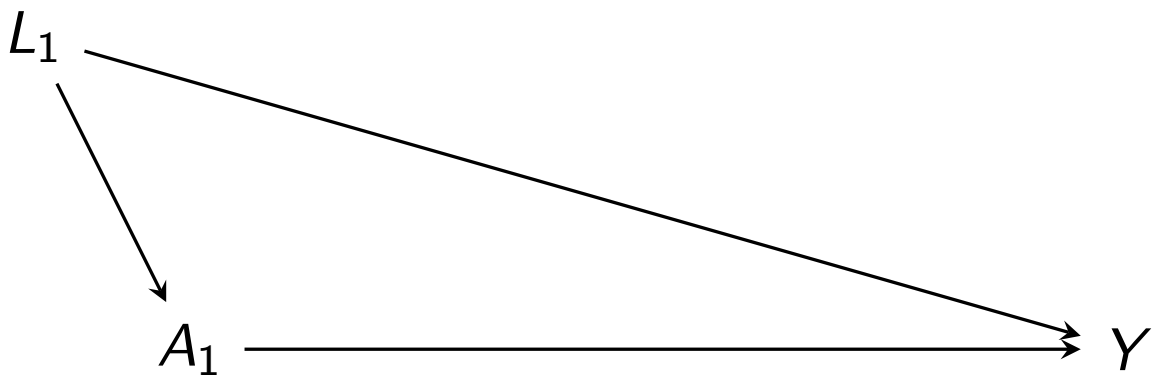
- This creates difficulties for analysis.
- Similar problems:
  - EPO dose for the treatment of anemia in hemodialysis patients is determined based on Hematocrit levels.
  - Retention in primary school is influenced by math scores and influences math scores.

# Conventional adjustment for confounding

$L_1$: disease severity at start of day 1
$A_1$: infection status at end of day 1
$Y$: 30-day mortality



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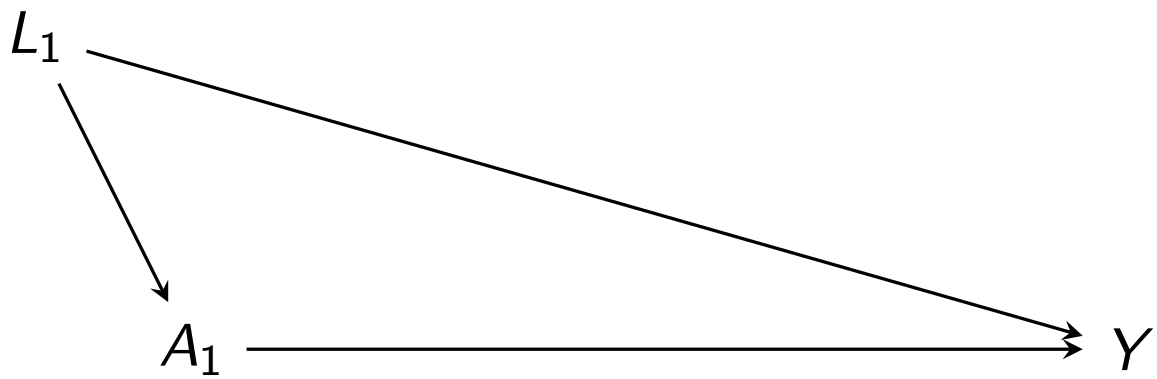
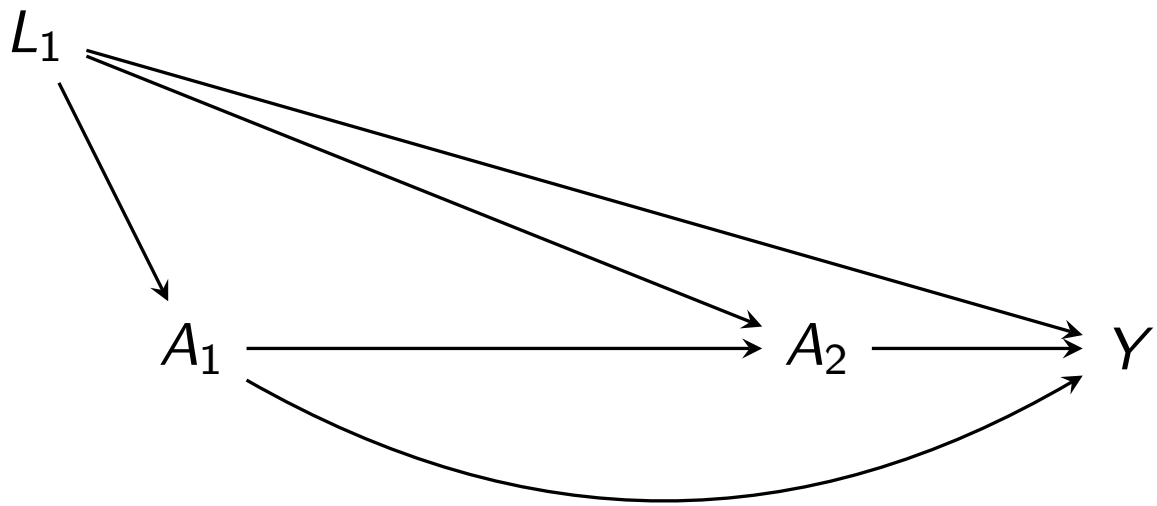



- To learn about the effect of infection on day 1, we would compare infected and uninfected on day 1 with the same disease severity at the start of day 1.
- This can be done through matching or regression.

# Conventional adjustment for confounding

$A_2$: infection status at end of day 2




Adjusting for disease severity on day 1 will usually not suffice...

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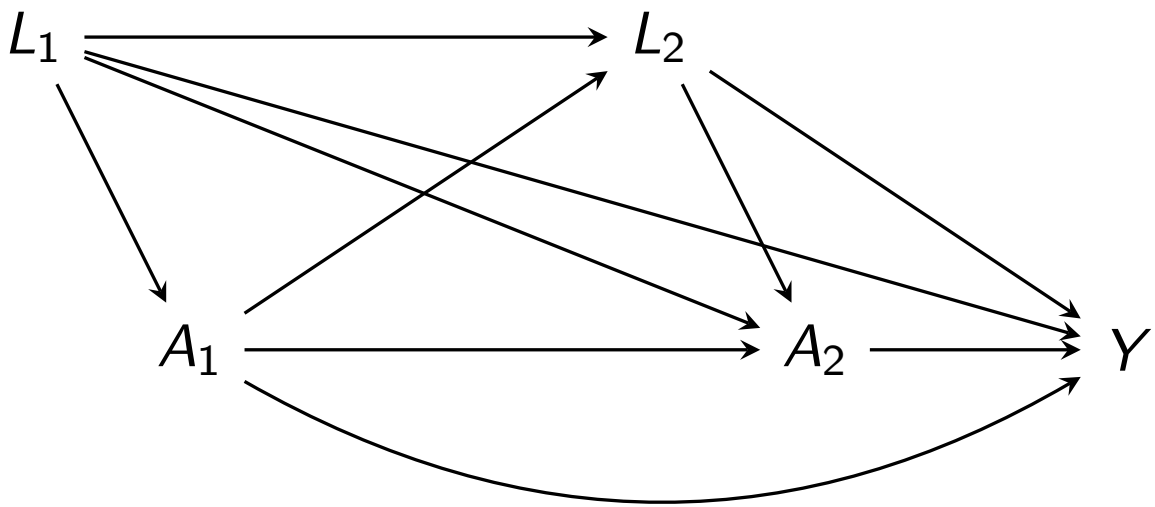

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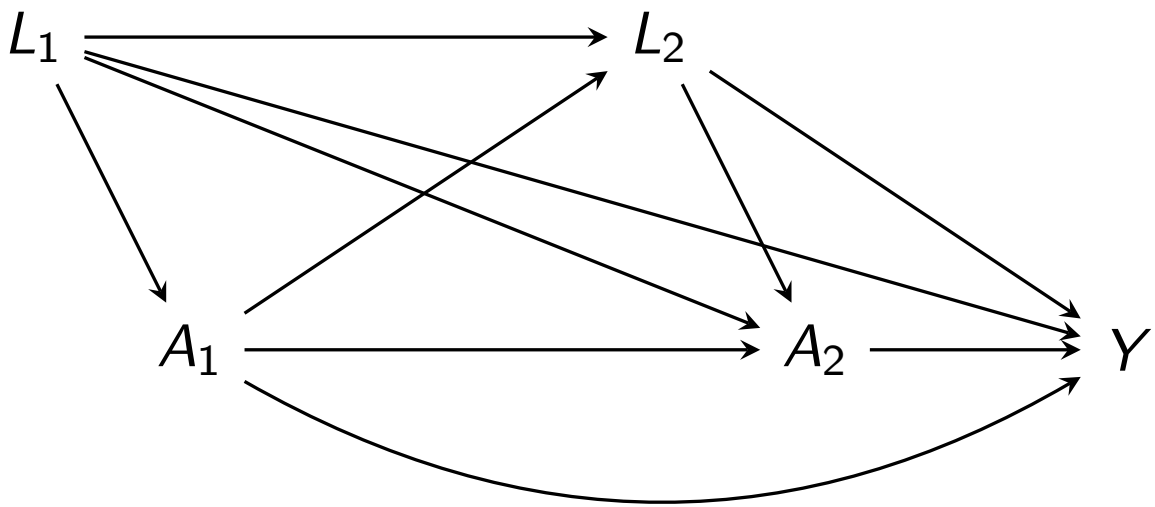


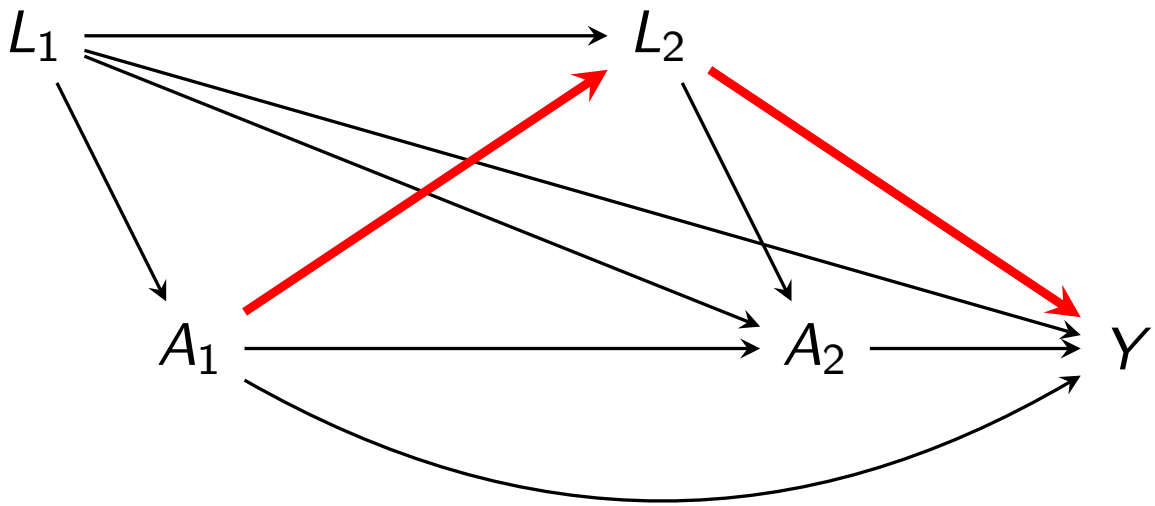

- Conventional approaches are based on matching or regressing on the history of disease severity on days 1 and 2.

  (e.g. regression models with time-varying covariates)

- This is problematic.

# Problem 1: Bias due to eliminating intermediate effects

Suppose that we compare patients who acquire infection
on day 1 versus day 2.




By insisting that they have the same disease severity on day 2,
we eliminate indirect effects
of early infection on later infection through disease severity.

# Problem 2: selection bias

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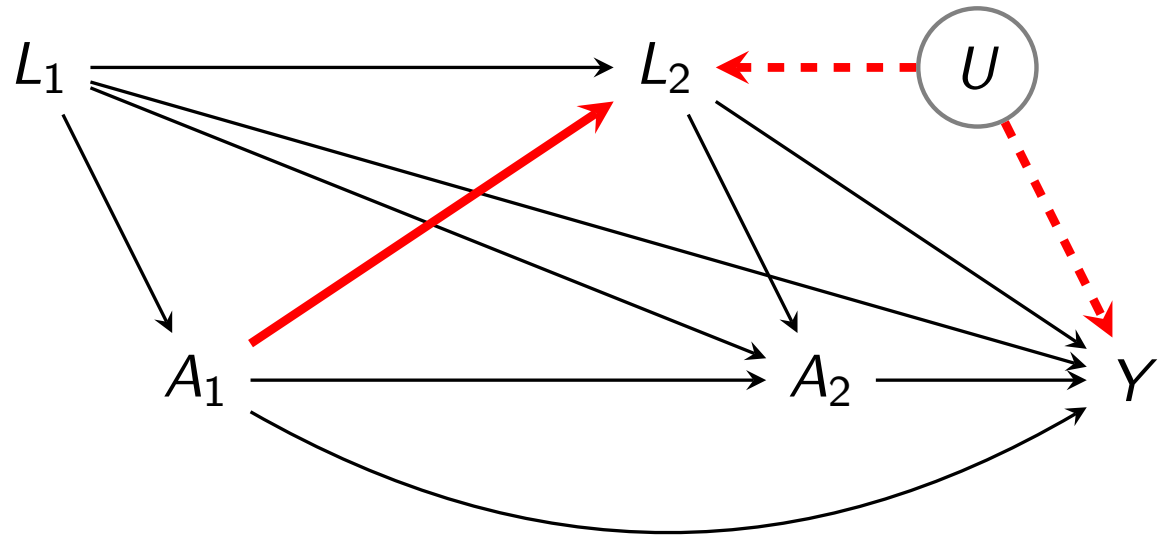
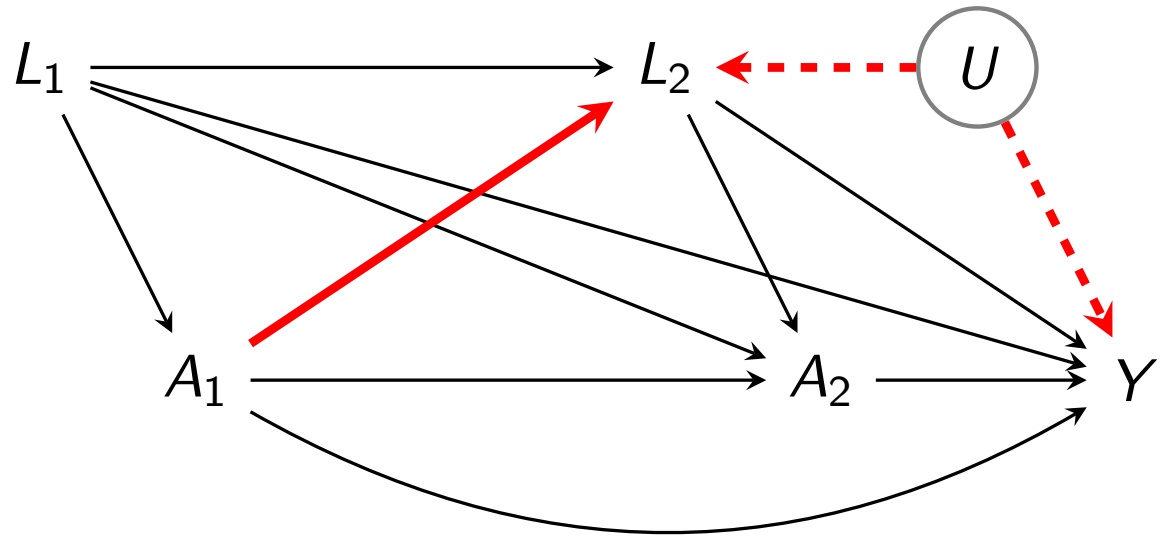


# Problem 2: selection bias

Suppose that we compare patients who acquire infection on day 1 versus day 2.




- By insisting that they have the same disease severity on day 2, we introduce selection bias.
- E.g., uninfected patients who are *as ill* as infected patients at the start of day 2, are likely 'not comparable'.

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- E.g., what would be the mortality risk
  - if all nosocomial infections could be avoided? (static regime)
  - if the EPO dose were 0 at Hct above 30%, were $d_1$ at Hct between 25% and 30%, and $d_2$ at Hct below 25%? (dynamic regime)

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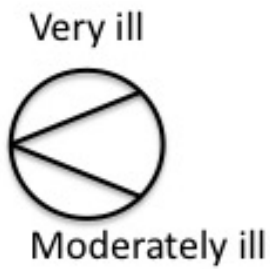
- Inverse probability weighting for Marginal Structural Models

  (Robins, Hernan and Brumback, 2000; Hernan, Robins and Brumback, 2001)

  - The key idea is to avoid the need for regression adjustment.

# Inverse probability weighting in a nutshell



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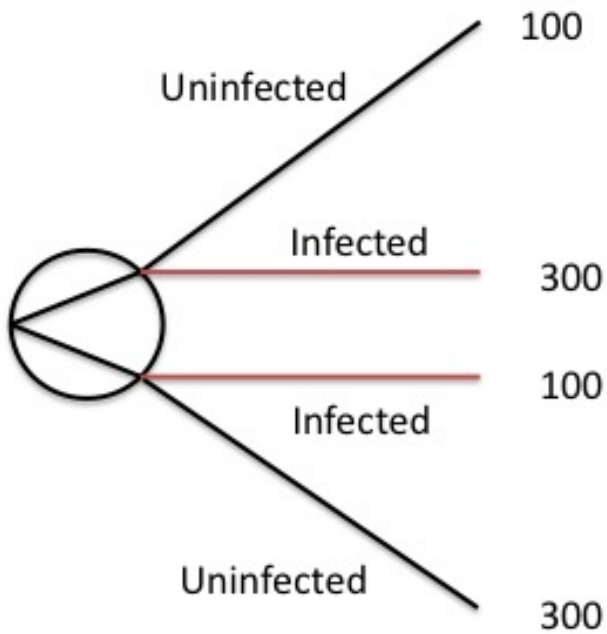

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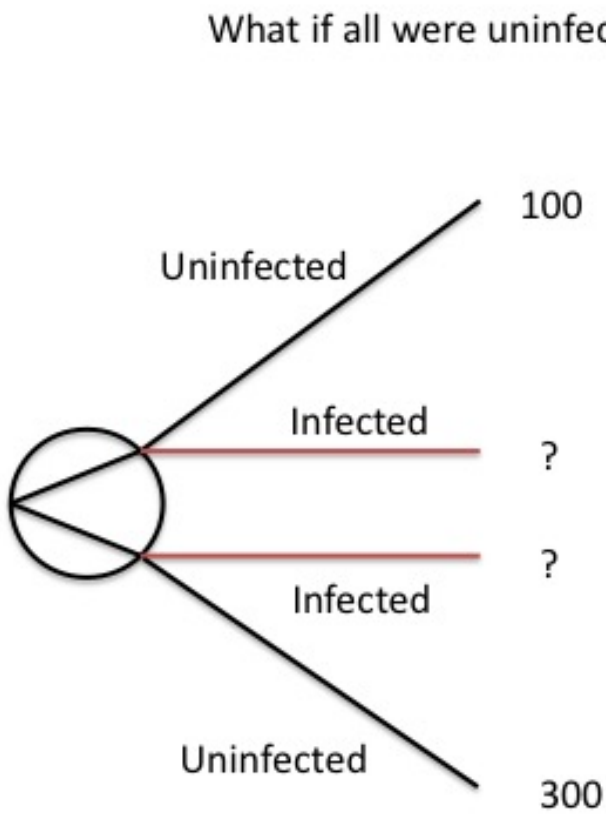

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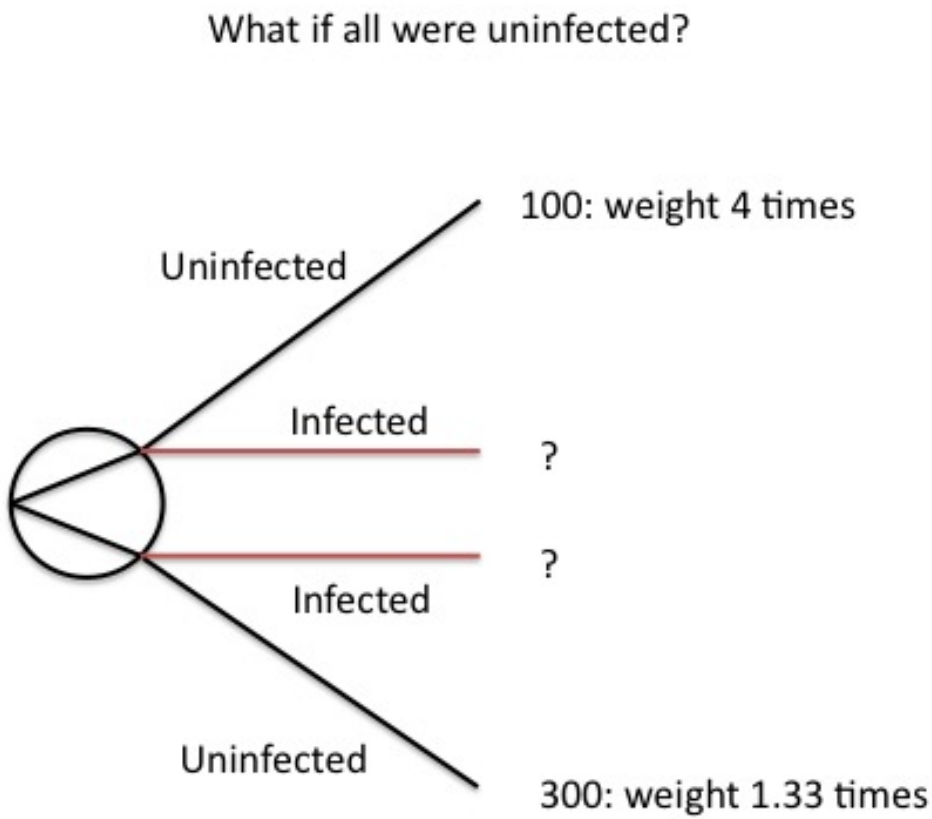

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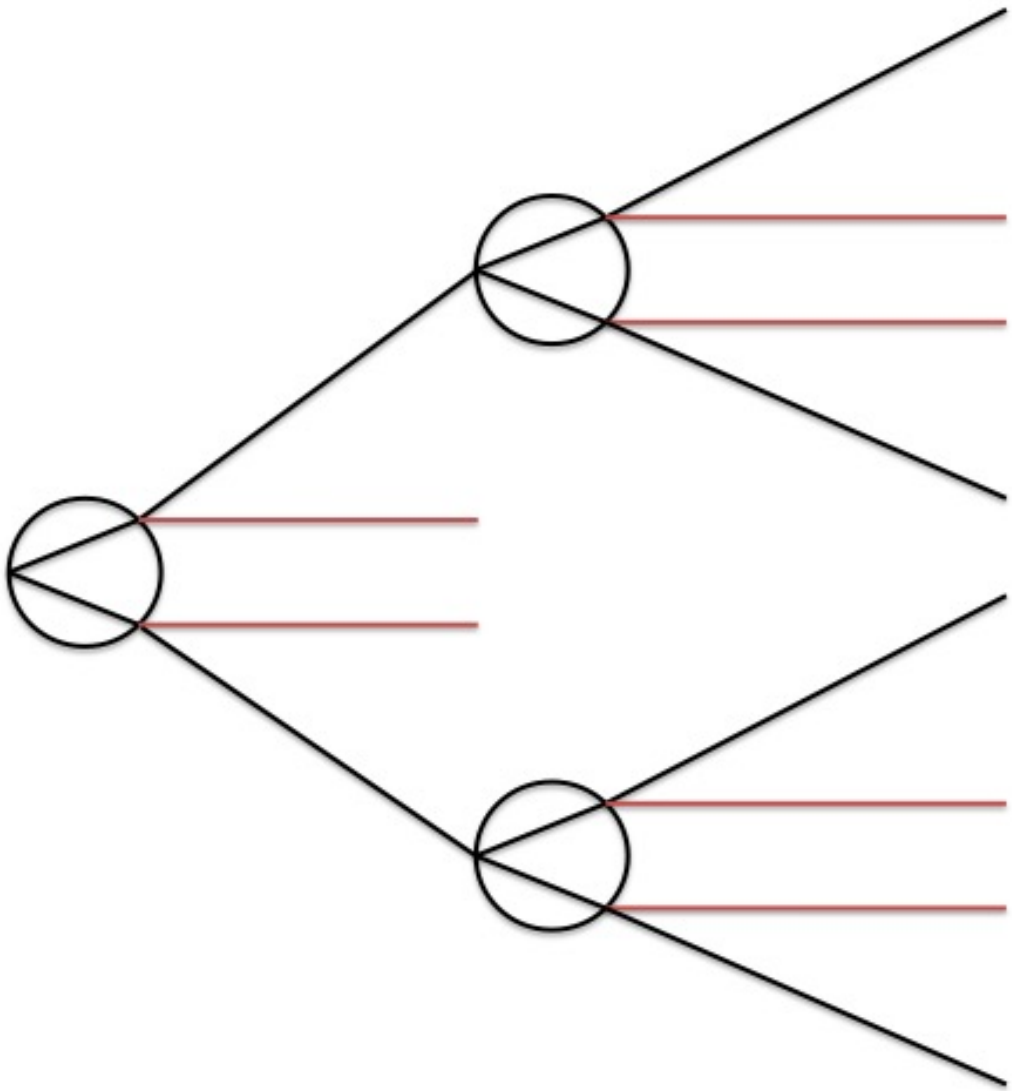

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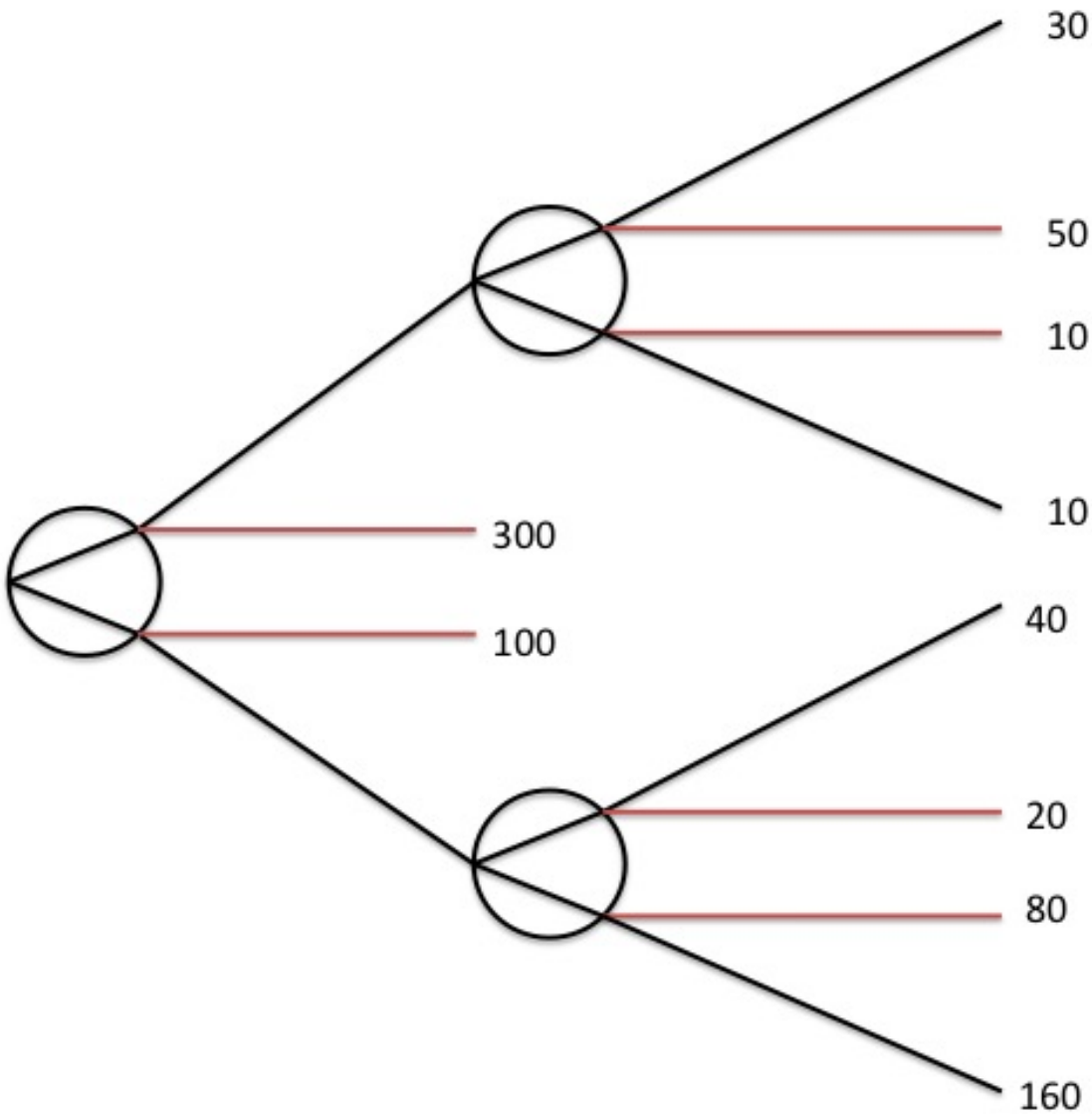

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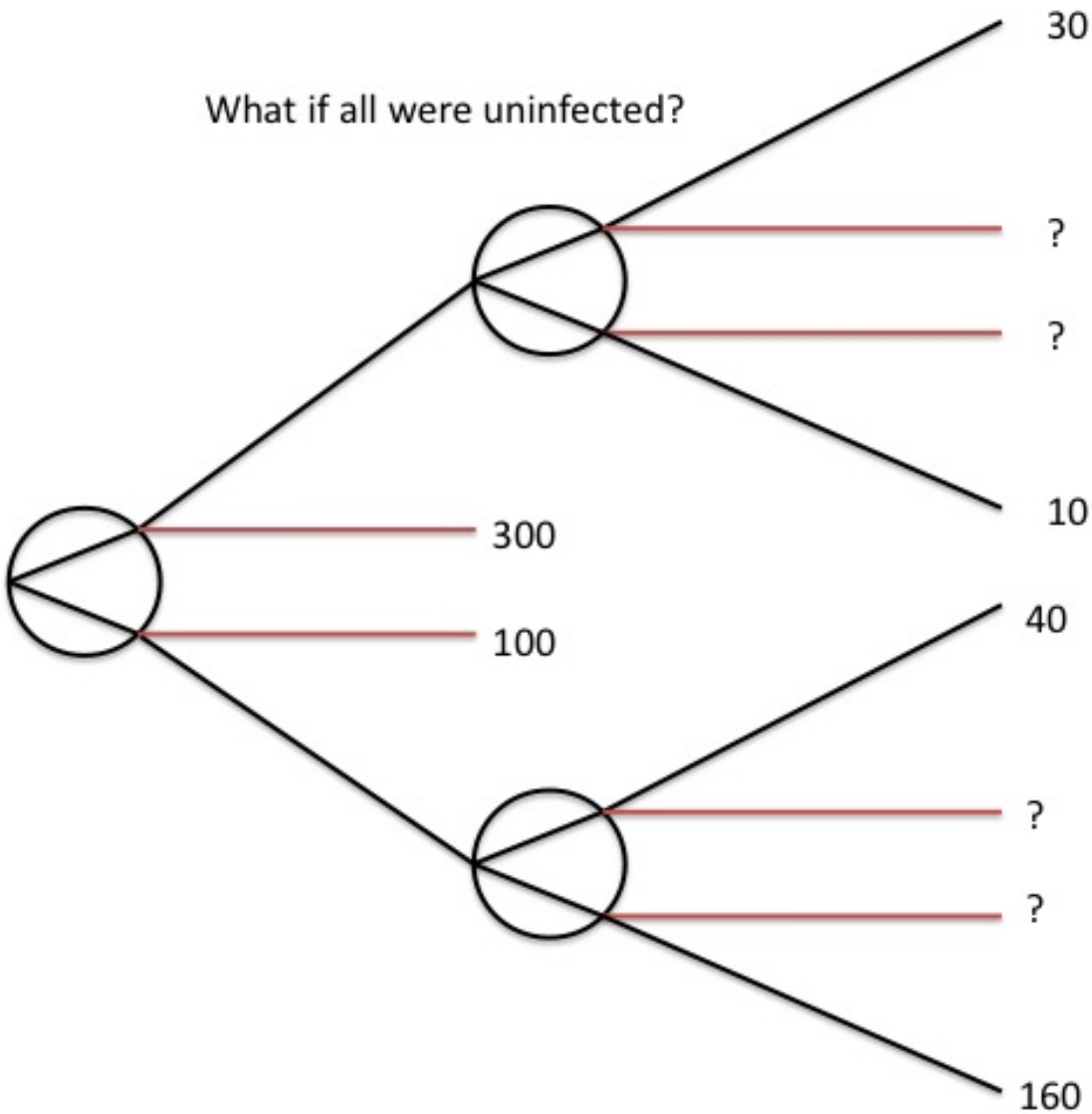

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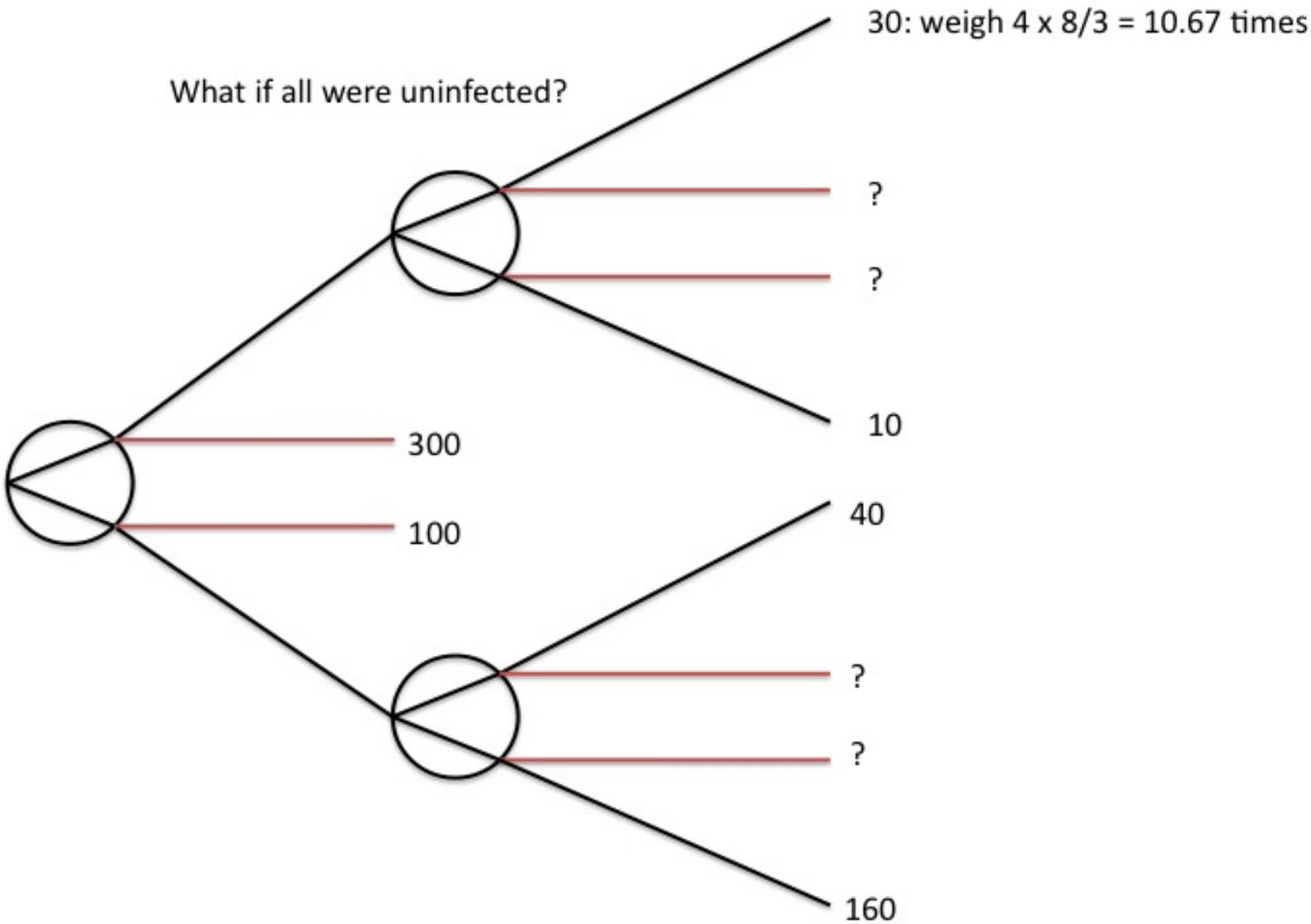

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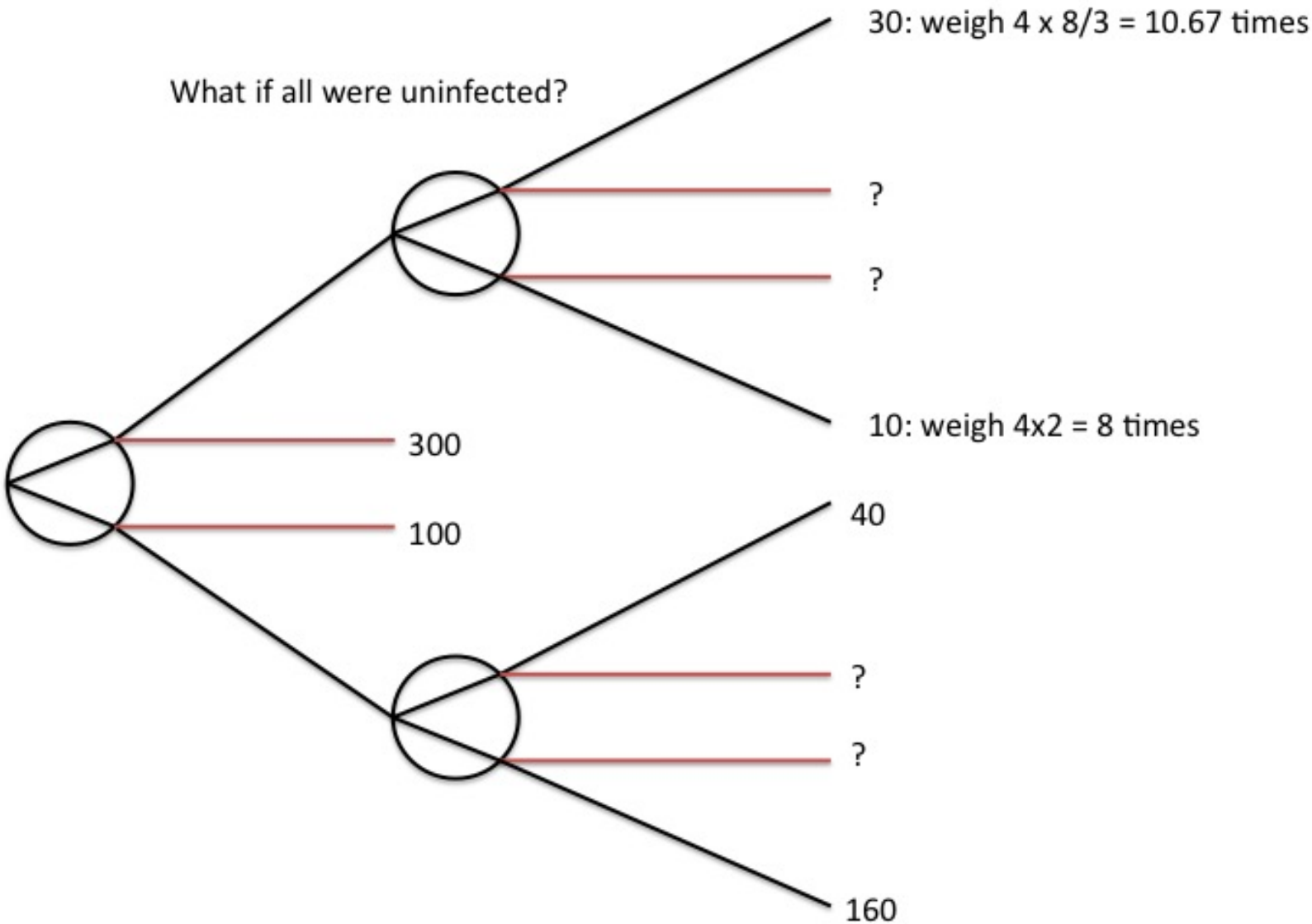

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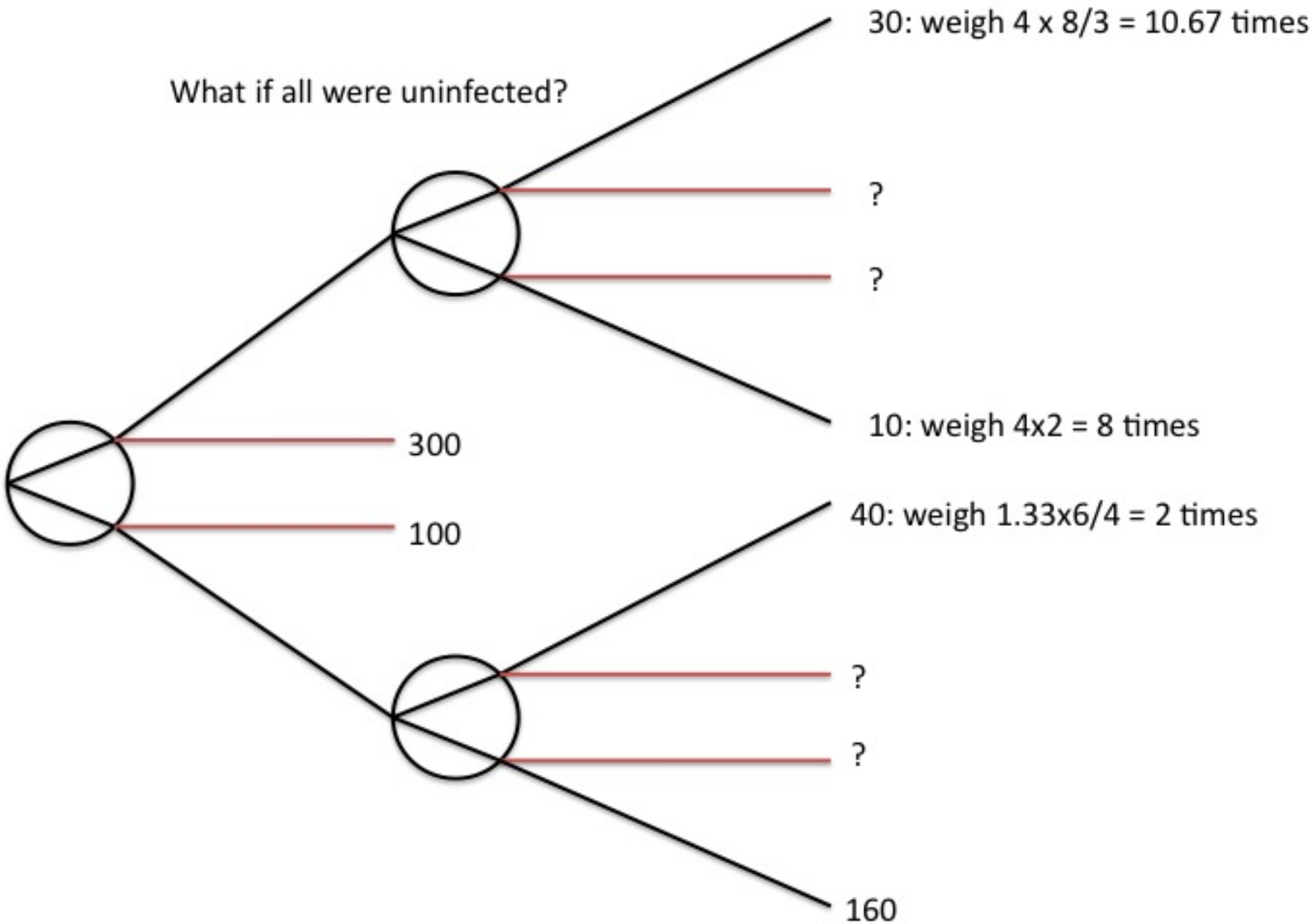

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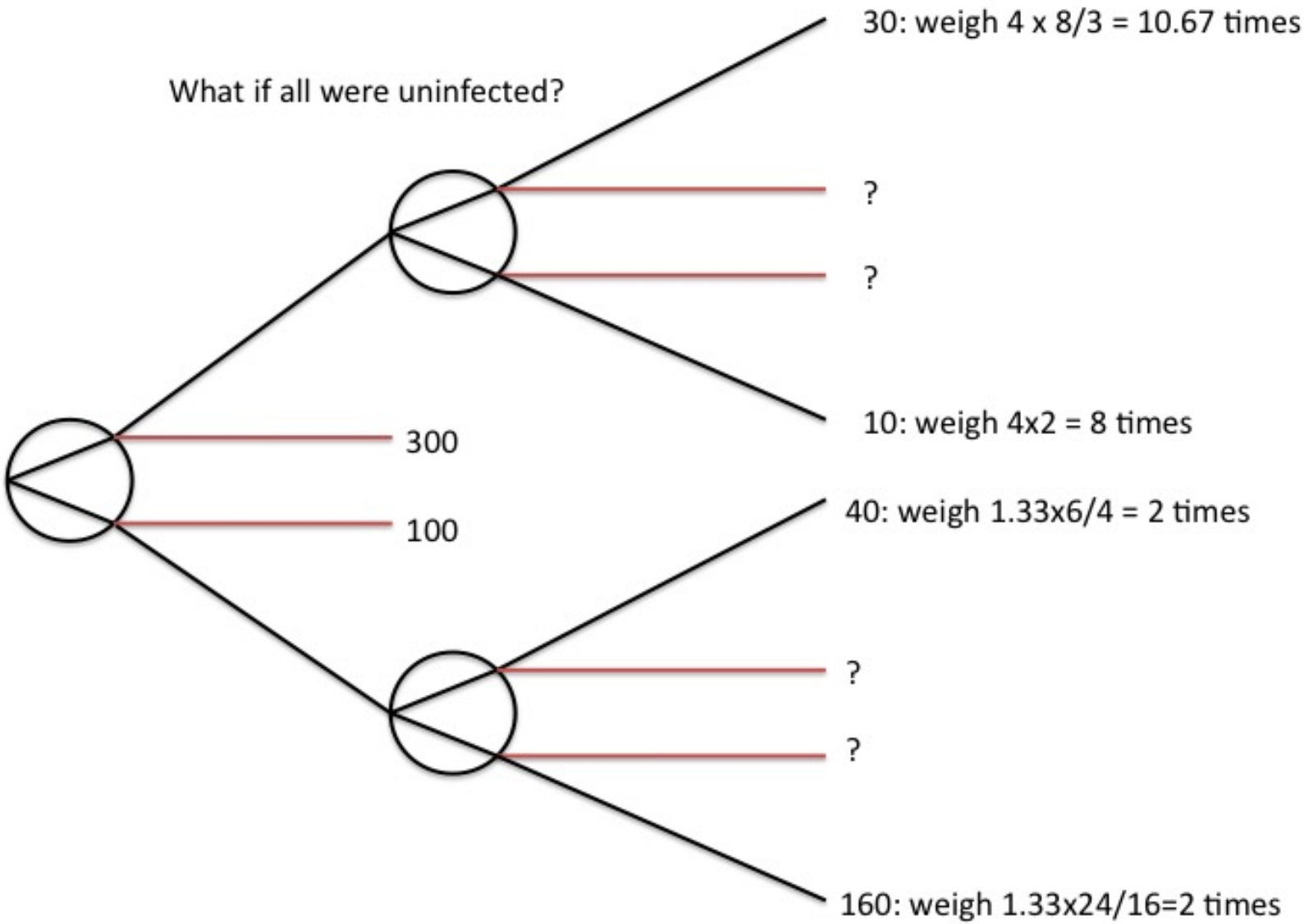
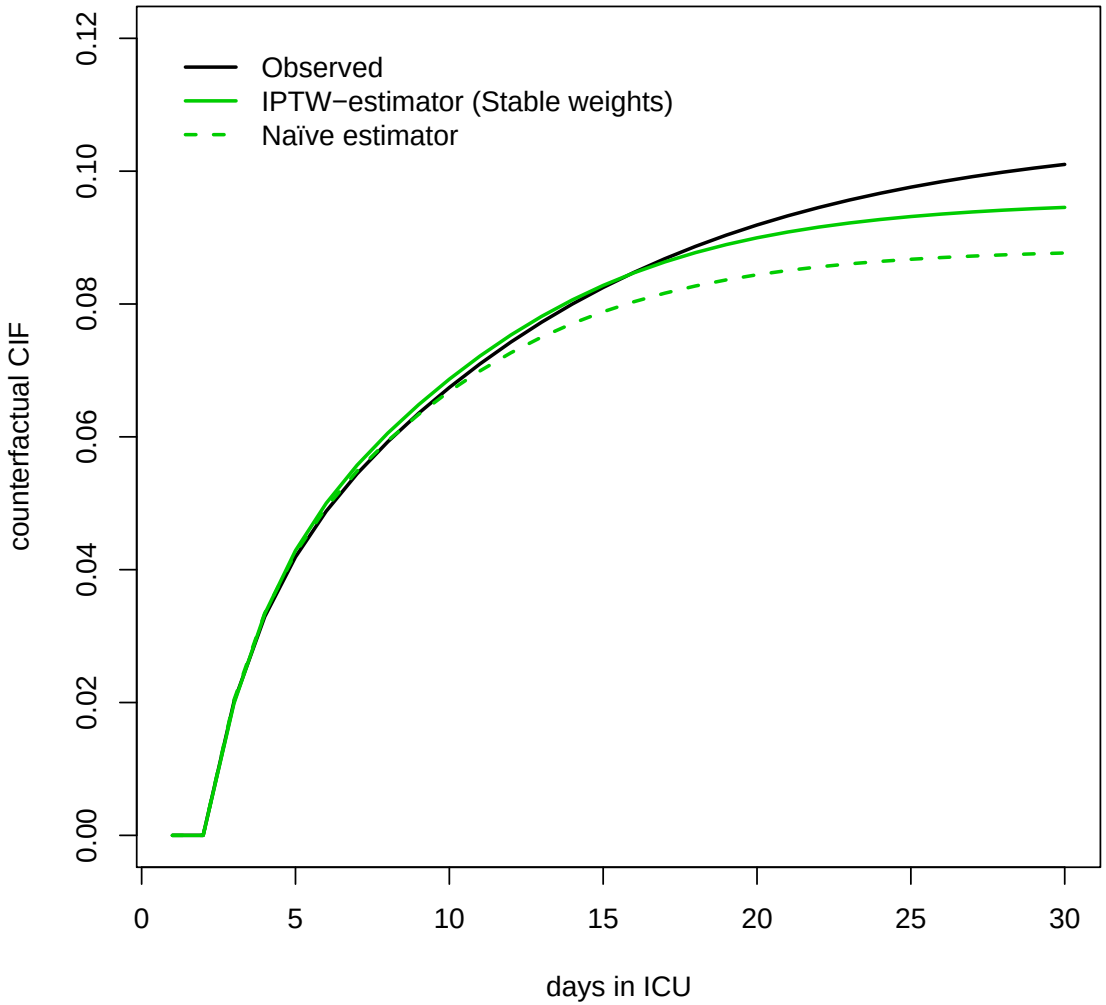
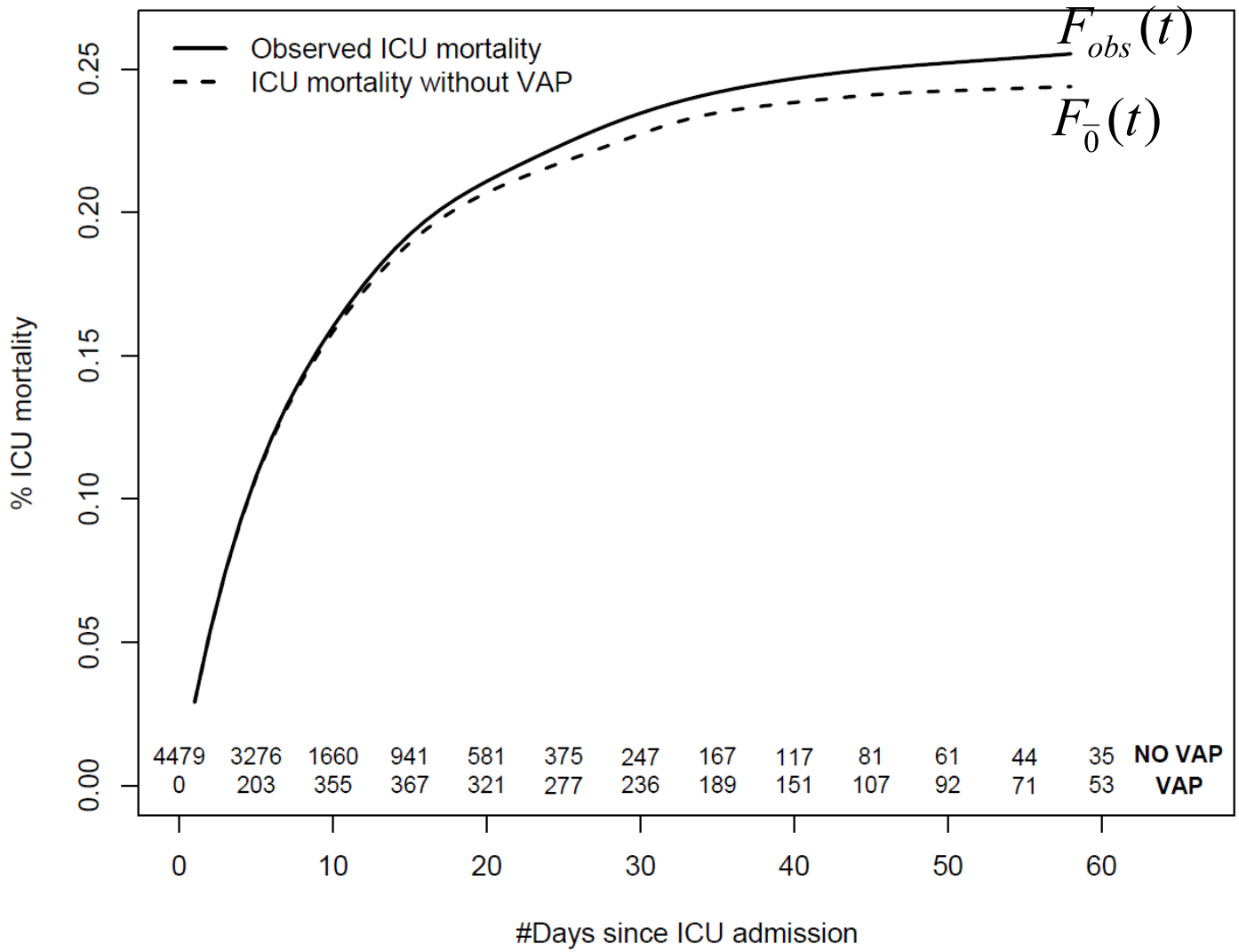


# The Belgian National Surveillance Study in ICU's

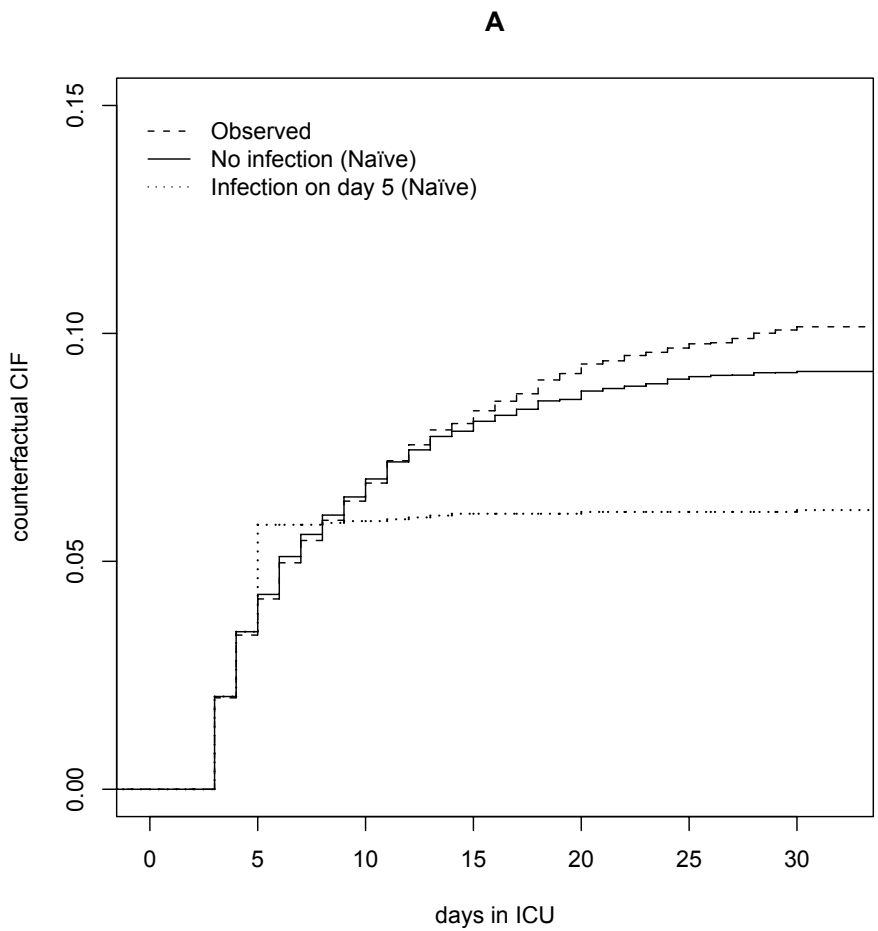


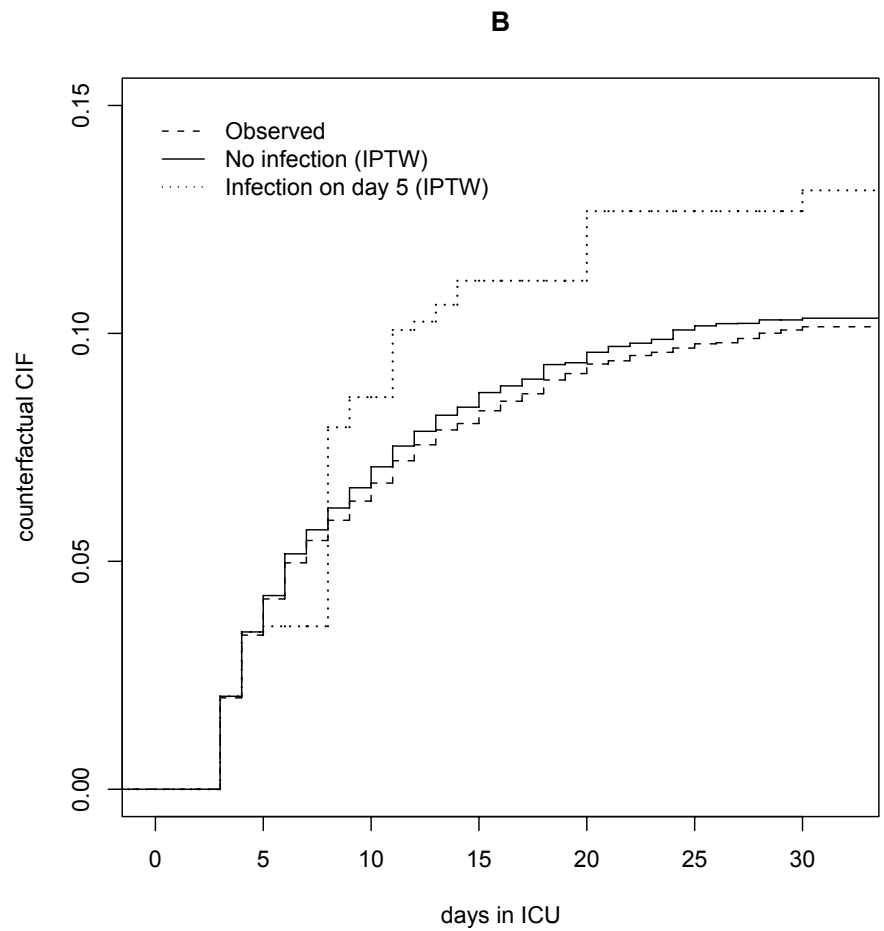
# Replication in the French Outcomerea study

(Bekaert et al., 2011)



# What if all acquire infection on day 5?



# Marginal structural models

- Inverse probability weighting is typically used in connection with marginal structural models.

  (Robins, Hernan and Brumback, 2000; Hernan, Robins and Brumback, 2001)

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- These enable one to analyse many exposure regimes in one go, which allows for borrowing of information between regimes.
- These models can be viewed as standard regression models for outcome given exposure, as if exposure was randomly assigned at each time.
- They allow to contrast how the entire population would fare if all individuals followed one versus another exposure regime.

# Summary

- Conventional statistical methods
  are not designed to answer causal questions.
- By statistical analyses that target causality, we can
  - better exploit a priori knowledge
    (e.g. randomisation, direction of causal effects)
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- The causal inference literature reconsiders standard statistical analyses that aim to answer causal questions
  and addresses new types of questions.
- There is lot's of exciting work
  for a wide variety of expertises...!