Assessing the impact of unmeasured confounding: confounding functions for causal inference

Jessica Kasza

jessica.kasza@monash.edu

Department of Epidemiology and Preventive Medicine,
Monash University
Victorian Centre for Biostatistics (ViCBiostat)

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Outline

1. What is causal inference?
2. How can the impact of unmeasured confounding be assessed?
3. An example: abciximab and death in percutaneous coronary intervention patients.

Causal inference: why and how?

There are many situations in which randomised trials cannot be conducted:

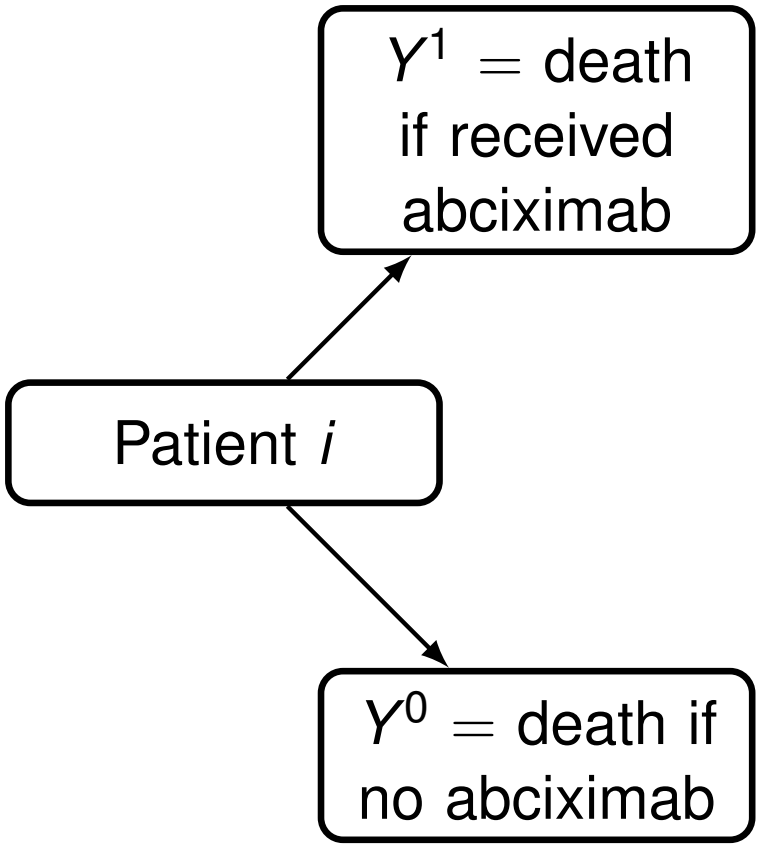
- Often difficult or unethical to randomise patients to treatments.
- But there may exist observational data containing treatments/exposures and outcomes of interest!

Causal inference permits causal interpretations of associations.

- Strict assumptions required:
  - The one I care about here is **no unmeasured confounding**.
  - Assume the others are satisfied. . .
- Use the potential outcomes framework. . .

Potential outcomes: abciximab and death

Each patient has two potential outcomes:



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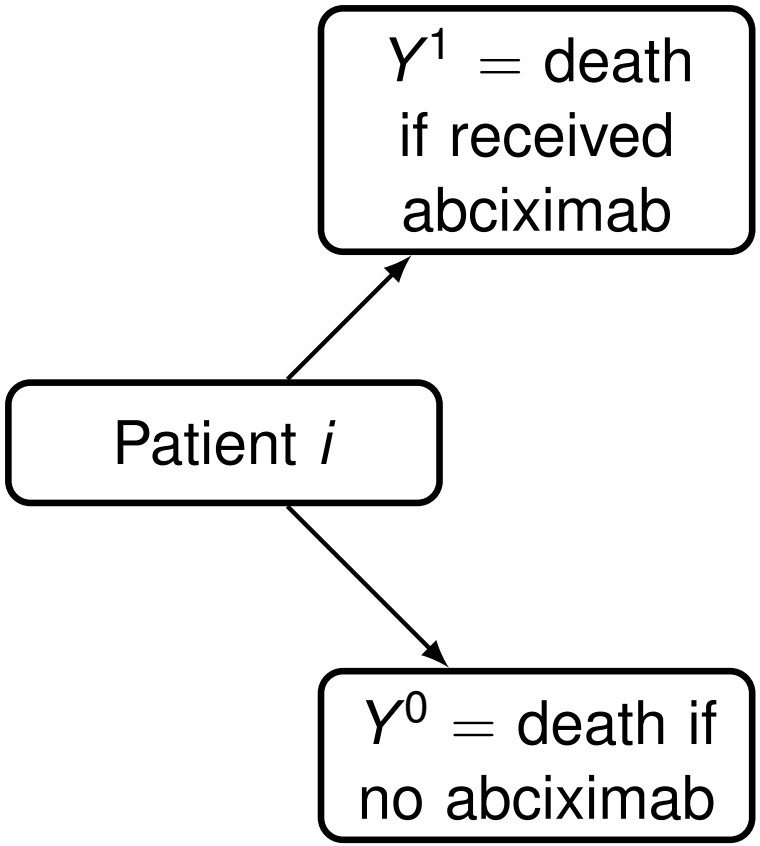
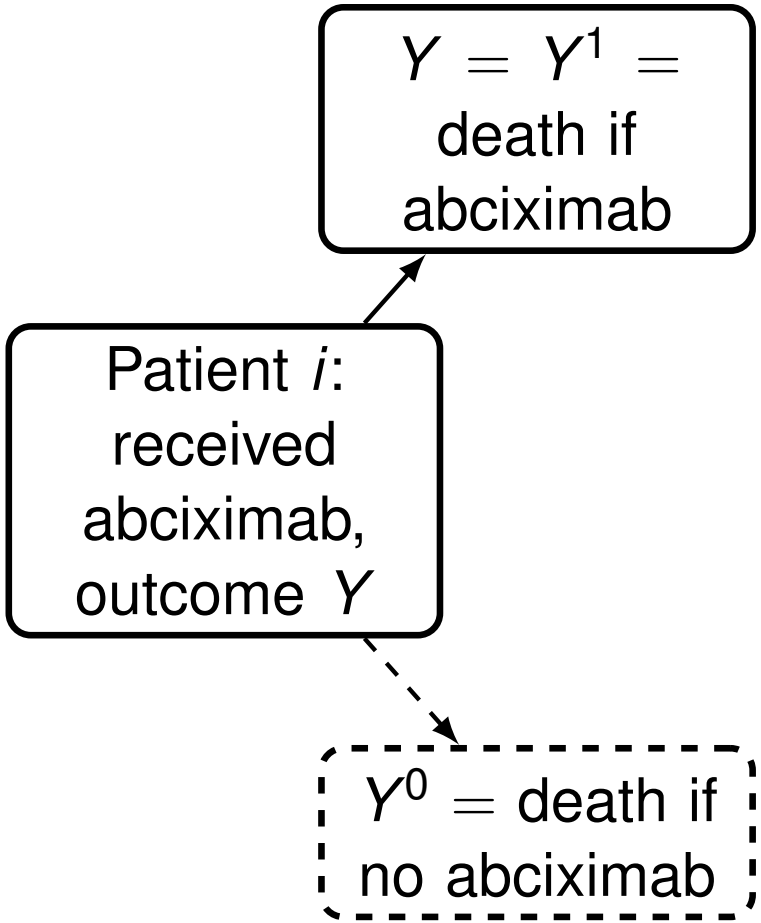


Of which only one is observed:



Potential outcomes and the causal odds ratio

$A = 0$ if patient did not receive treatment; $A = 1$ if received treatment.

- Causal odds ratio:

$$OR^c = \frac{P(Y^1 = 1)}{1 - P(Y^1 = 1)} \Big/ \frac{P(Y^0 = 1)}{1 - P(Y^0 = 1)}$$

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If causal inference assumptions are satisfied, $OR^c = OR$.

Differences between treatment groups

- If data are observational, likely to be differences between treatment groups.
  - **Measured confounders**:
    - e.g. treated subjects tend to be older & older patients more likely to experience the outcome.
  - **Unmeasured confounders**:
    - e.g. cognitive function; social connectedness; some measure of overall health.
- Adjusting for measured confounders:
  - Assume an inverse probability of treatment weighting approach used to estimate a marginal odds ratio.
  - Skip the details!

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How can we adjust for the unmeasured differences that we suspect are present?

Correcting for unmeasured confounding

- **Instrumental variables**: a variable related to treatment and only related to outcome through treatment.
  - Able to adjust for the entire impact of unmeasured confounding.
  - Problem: IVs may not be available if there is a limited set of recorded variables.
- **External adjustment**: assume the existence of one or more unmeasured (binary) confounders.
  - Useful if you have good expert knowledge on particular unmeasured confounders.
  - Problems:
    - difficult to assess the entire impact of unmeasured confounding;
    - assumptions may be as untenable as original assumption of no unmeasured confounding.

Confounding function approach[1]

Adjust estimates using a confounding function that describes the degree of unmeasured confounding

$$c(a) = \frac{P(Y^a = 1|A = 1)}{P(Y^a = 1|A = 0)}, \quad a = 0, 1$$

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- $c(0)$, $c(1)$ are a counterfactual quantities: values selected by investigators.
- Requires contextual knowledge to quantify the impact of unmeasured confounding, in terms of counterfactual outcomes.

What differences in the outcomes are due to unaccounted-for differences in the treatment groups, rather than due to the effect of treatment on the outcome?

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- No unmeasured confounding is present.

$c(0) > 1, c(1) > 1, c(0) = c(1) \Rightarrow$

- Risk of (both) potential outcomes higher among those actually treated.
- Some of the observed risk of the outcome for treated subjects is due to some unmeasured 'ill health';
- Effect of treatment the same in treated and untreated groups.

Adjusting for unmeasured confounding

$$OR^c = \frac{P(Y^1 = 1)}{1 - P(Y^1 = 1)} \Big/ \frac{P(Y^0 = 1)}{1 - P(Y^0 = 1)}$$

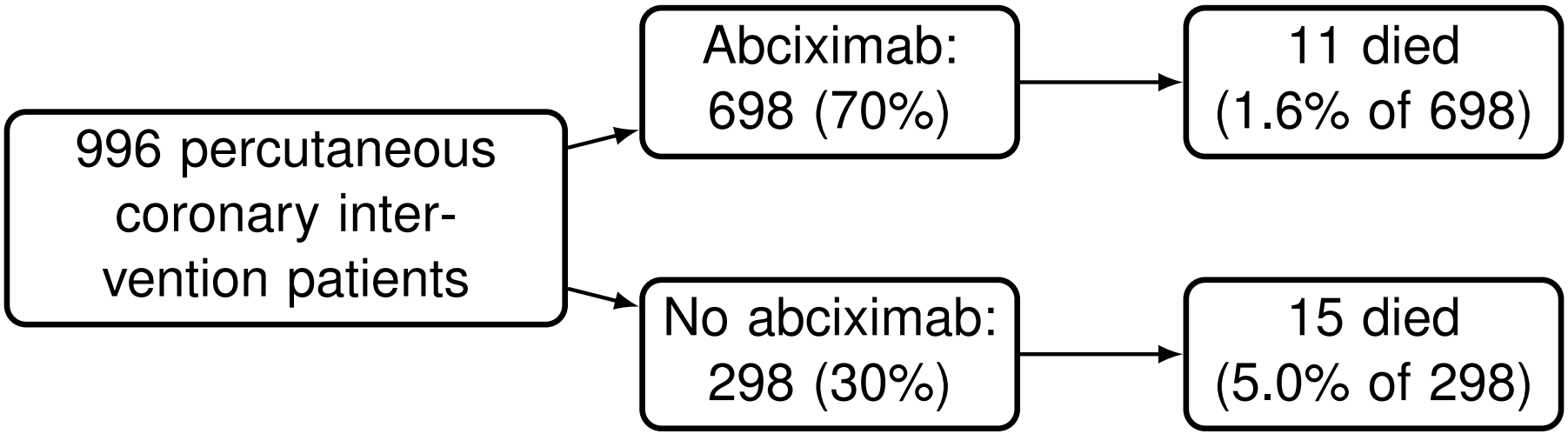
$$c(a) = \frac{P(Y^a = 1|A = 1)}{P(Y^a = 1|A = 0)}, \quad h(a) = P(A = 0) + c(a)P(A = 1)$$

The causal odds ratio can be written as:

$$OR^c = \frac{h(1)P(Y = 1|A = 1)/c(1)}{1 - h(1)P(Y = 1|A = 1)/c(1)} \Big/ \frac{h(0)P(Y = 1|A = 0)}{1 - h(0)P(Y = 1|A = 0)}$$

- Consider sensitivity of OR to range of values of $c(1)$ and $c(0)$.
  - Beware implicit assumptions if $c(1) \neq c(0)$: differential treatment effect in treated and untreated.

Application: Abciximab and death[2]



- Administration of abciximab at discretion of interventionist.
- Adjust for sex, height, diabetes, recent MI, left ventricle ejection fraction, number of vessels in PCI, insertion of coronary stent using inverse probability of treatment weighting.

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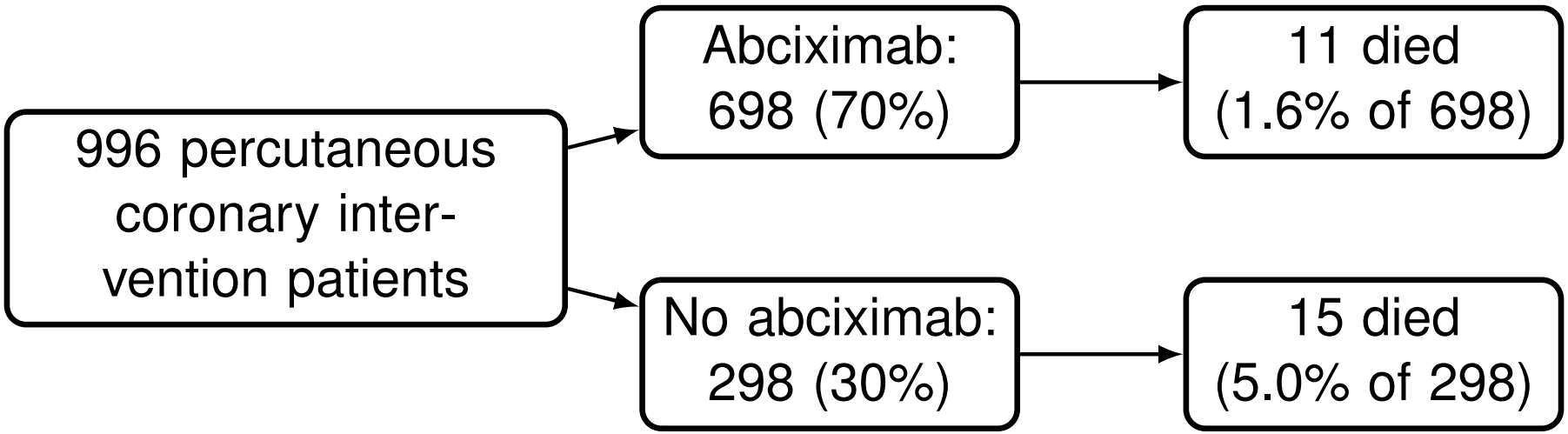

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$$\text{OR} = 0.17, 95\%\ \text{CI}\ (0.08, 0.46)$$

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Application: Abciximab and death

$$c(\text{Abciximab}) = \frac{P(Y^{\text{Abc}} = 1|\text{Abc})}{P(Y^{\text{Abc}} = 1|\text{No Abc})}$$

$$c(\text{No Abciximab}) = \frac{P(Y^{\text{No Abc}} = 1|\text{Abc})}{P(Y^{\text{No Abc}} = 1|\text{No Abc})}$$

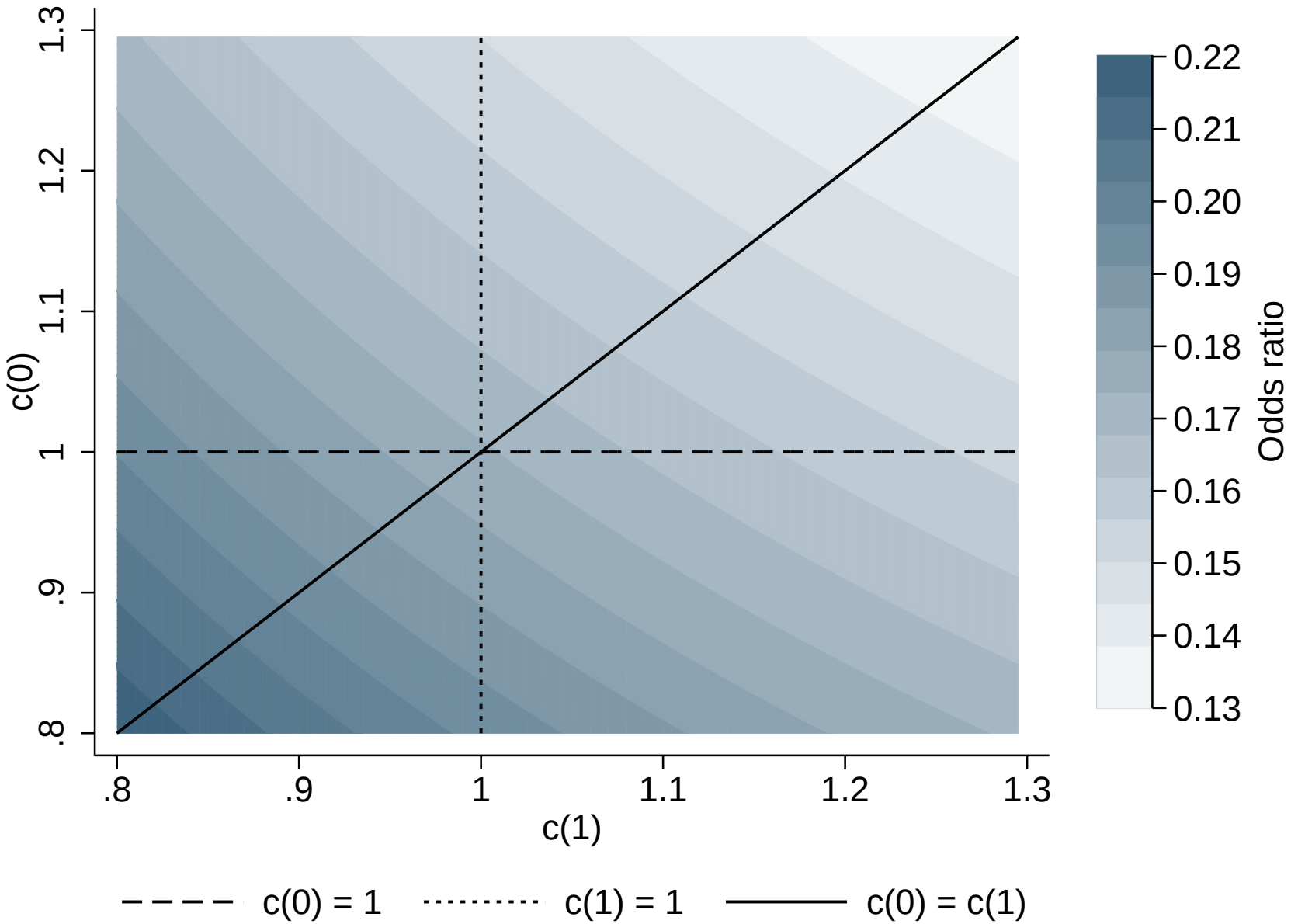
If both > 1, then

$$P(Y^{\text{Abc}} = 1|\text{Abc}) > P(Y^{\text{Abc}} = 1|\text{No Abc})$$

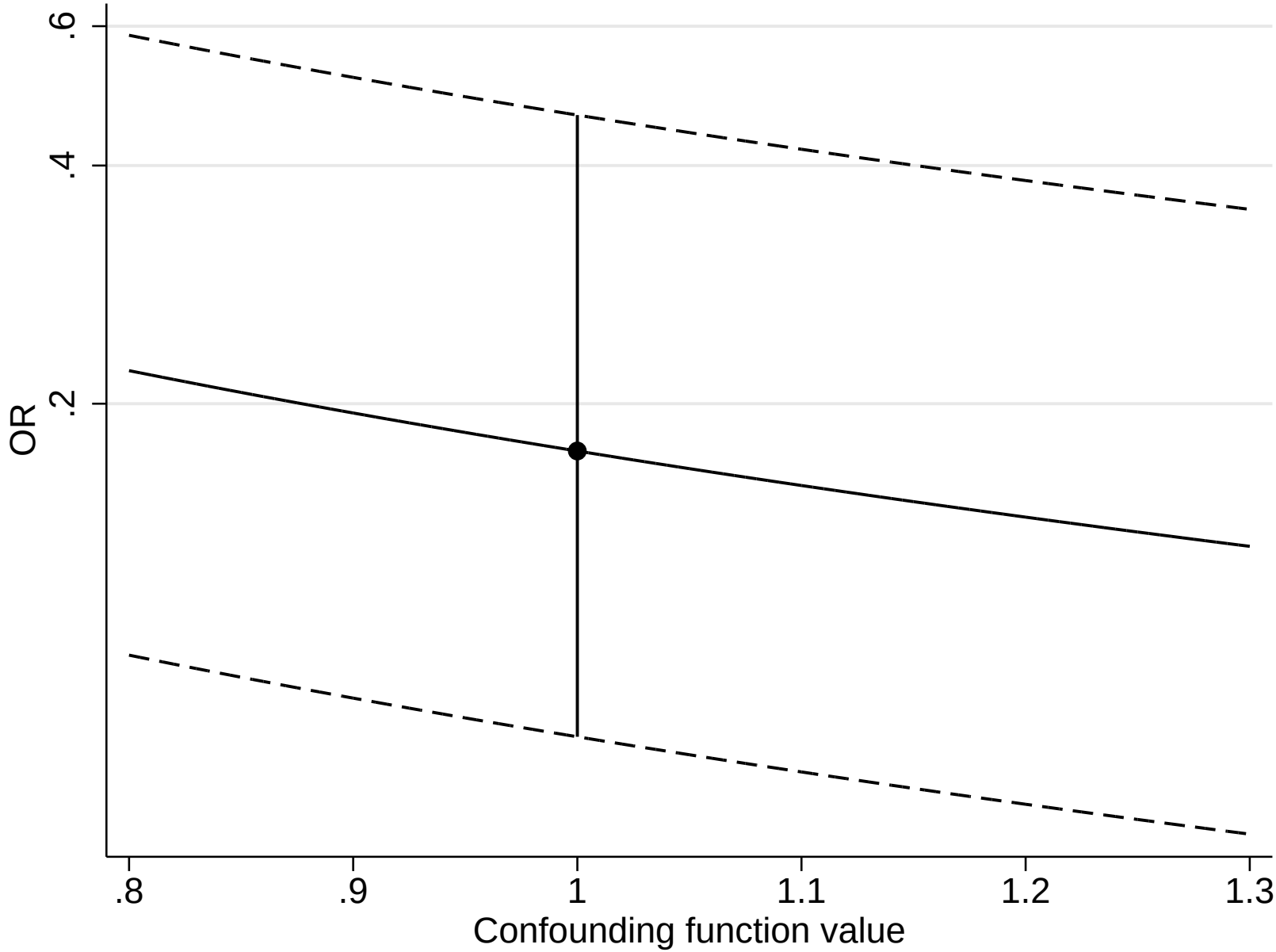
$$P(Y^{\text{No Abc}} = 1|\text{Abc}) > P(Y^{\text{No Abc}} = 1|\text{No Abc})$$

- Had they not received Abciximab, those who actually received Abciximab **more likely to die** than those who did not receive Abciximab.

Sensitivity analysis for the OR



Sensitivity analysis for the OR, $c(0) = c(1) = 1$



Take-home messages

- Causal inference is useful in situations when randomised trials can't be conducted
  - Strict assumptions, including no unmeasured confounding.
  - Problem: in most applications, the assumption of unmeasured confounders will not be satisfied!
- Turn to alternative approaches:
  - Instrumental variables; external adjustment; confounding functions.
- I've described the confounding function approach for binary outcomes.
  - Approach also available for continuous outcomes.
  - Provides a way to assess the sensitivity of estimates to the entire effect of unmeasured confounding.
  - Easy to apply.
  - Contact me for Stata code!

References

- VanderWeele TJ, Arah OA. (2011) Bias formulas for sensitivity analysis of unmeasured confounding for general outcomes, treatments, and confounders. *Epidemiology*, 22:42-52.
- Robins JM. (1999) Association, causation and marginal structural models. *Synthese*, 121:151-79.
- Brumback BA, Hernan MA, Haneuse SJPA, et al. (2004) Sensitivity analyses for unmeasured confounding assuming a marginal structural model for repeated measures. *Statistics in Medicine*, 23:749-767.

Propensity scores

- Propensity score for subject i, with observed covariates $X_i = x_i$, treatment $A_i = a_i$:

$$PS_i = P(A_i = 1 | X_i = x_i)$$

  Usually estimated using logistic regression models.
- Rosenbaum & Rubin (Biometrika, 1983): adjustment for PS sufficient to remove bias due to all X.
- Inverse probability of treatment weighting: Each subject's observation assigned a weight:

$$w_i = \frac{a_i}{PS_i} + \frac{1 - a_i}{1 - PS_i}$$

- Each subject's observation weighted by $1/w_i$.