Missing outcomes due to death: survivor average causal effects

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Overview

1. Why do outcomes missing due to death require careful consideration?
   - What's wrong with the usual approach?
2. What are survivor average causal effects?
   - How can they be estimated?
3. An example: pain outcomes and the ENIGMA study.

Outcomes missing due to death: crude approach

- Mortality is an important outcome in many clinical trials
  - Other outcomes are often also important: e.g. quality of life, post-surgical pain.
- Example: ENIGMA (and ENIGMA II) trials[1]
  - ENIGMA: ≈2000 surgical patients randomised to nitrous oxide(N_2O)-based anaesthesia, or N_2O-free anaesthesia.
- Pain substudies:

  The plan: assess the impact of N_2O on long-term pain outcomes:

$$Y = 1 \text{ if chronic pain at 1 year post-surgery,}$$

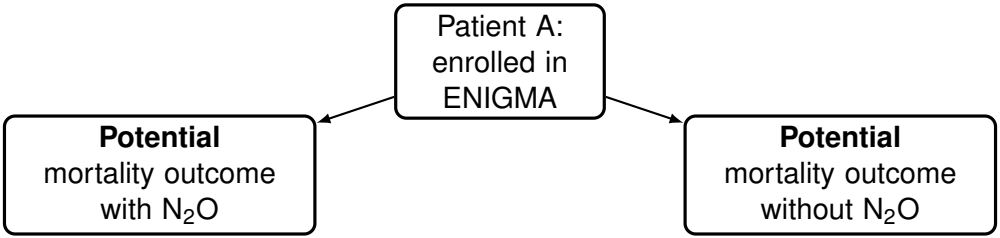
$$\text{Crude relative risk} = \frac{P(Y = 1|N_2O)}{P(Y = 1|N_2O\text{-free})}$$

  The problem: pain outcomes were 'truncated by death'.

[1] Myles et al. Anesthesiology, 2007; Myles et al. The Lancet, 2014.

Survival outcomes: potential, observed and counterfactual

- Y is defined only for those **who survived**.
- Rubin[2] noted that patients should be stratified on survival:
  - But not just on observed survival!
  - On *counterfactual survival*: what would have happened if...



[2] Rubin, Statistical Science, 2006

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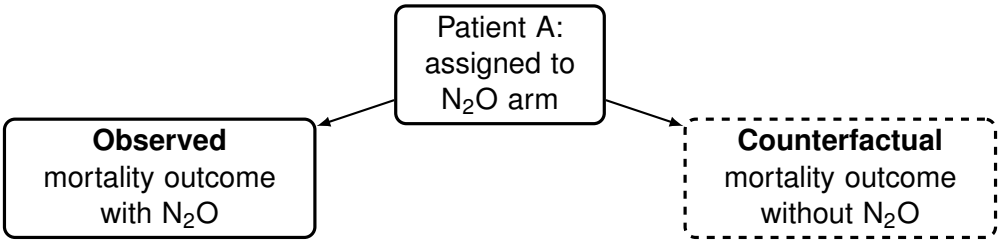

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Stratifying patients by potential outcomes

Patient classification	Survive on N_2O?	Survive w/o N_2O?
Always-survivors	Yes	Yes
N_2O-survivors	Yes	No
N_2O-free-survivors	No	Yes
Never-survivors	No	No

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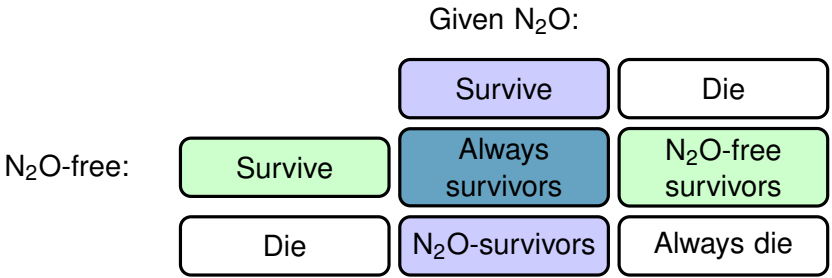
So what's wrong with considering

$$\text{Crude relative risk} = \frac{P(Y = 1|\text{N}_2\text{O})}{P(Y = 1|\text{N}_2\text{O-free})}?$$

What's wrong with being crude?



Probability of chronic pain calculated for two different groups!

- Only really makes sense to compare outcomes for always-survivors.

Survivor average causal effects (SACE)

$$\text{Crude relative risk} = \frac{P(Y = 1|\text{N}_2\text{O})}{P(Y = 1|\text{N}_2\text{O-free})}, \quad \text{SACE} = \frac{P(Y = 1|\text{N}_2\text{O}, \textbf{Always-survivor})}{P(Y = 1|\text{N}_2\text{O-free}, \textbf{Always-survivor})}$$

- A 'principal strata effect'.
- Estimate the effect of N_2O on pain among those patients who would have

survived under either treatment.

  - But who are they?
  - We have no way of knowing...

So how can the SACE be estimated?

Estimating the SACE: Monotonicity assumption

Patient classification	Survive on N_2O?	Survive w/o N_2O?
N_2O-survivors	Yes	No
N_2O-free-survivors	No	Yes

- Monotonicity: effect of N_2O on survival agrees in its direction for all patients.
- For ENIGMA, assume no N_2O-survivors!
  - No patients for whom N_2O protects against death: any potential benefits outweighed by risks.

Confounding function approach[3] to estimating the SACE

- Monotonicity not required (but simplifies things if assumed!)
- Can be used to re-analyse published results.
- Estimate the crude relative risk (or odds ratio), and adjust using a 'confounding function'.

Confounding function: how would the pain outcomes of the N_2O and no-N_2O groups differ if, instead of the treatment they actually received, no-one got N_2O?

[3] Described for continuous outcomes in Chiba & VanderWeele, Am. J. Epi., 2011.

Sensitivity analysis for the SACE

$Y^{\text{N}_2\text{O-free}}$ = Pain outcome that *would have* been observed had patient been assigned to N_2O-free arm.

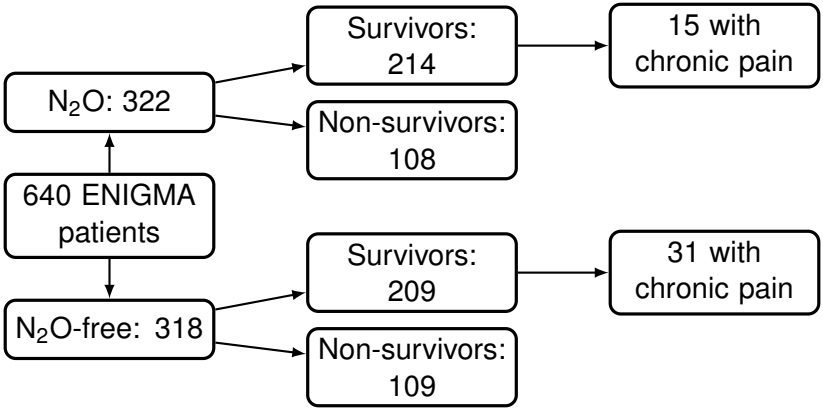
- Confounding function:

$$c = \frac{P(Y^{\text{N}_2\text{O-free}} = 1 | \text{N}_2\text{O-free}, \text{Survivor})}{P(Y^{\text{N}_2\text{O-free}} = 1 | \text{N}_2\text{O}, \text{Survivor})}$$

- Monotonicity: N_2O had a detrimental effect on health.
- Those who survived *even with* N_2O 'stronger/fitter' than those who survived without the extra challenge of N_2O
  - had they been assigned to no-N_2O, they would have had a lower probability of chronic pain than N_2O-free patients.
  - Fitting to assume $c > 1$.

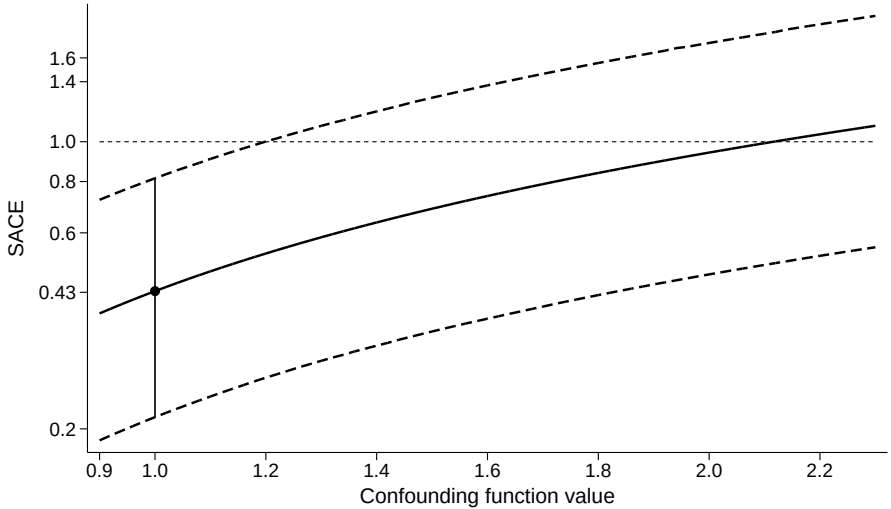
ENIGMA: Chan et al's pain substudy[4]

Odds ratio 0.43, **95% CI** (0.23, 0.83)



[4] Chan et al, Pain, 2011

Sensitivity analysis for chronic pain: ORs and bootstrapped 95% CIs



Take-home messages

- Comparing outcomes when there may be truncation by death requires careful thought...
  - It's easy to get it wrong!
  - Important when outcomes are only defined for survivors (e.g. QoL).
  - Conclusions obtained via SACEs and the crude approach should be compared.
- If treatment does not affect survival $\Rightarrow$ crude approach valid.
- Weighting approaches[5]:
  - Require monotonicity assumption be valid.
  - Not so useful for re-analysis of previously published results.
- Sensitivity analysis approaches are easy to apply.
  - Contact me for Stata code!
  - Monotonicity was assumed here, but is not required.

[5] Tchetgen Tchetgen, Statistics in Medicine, 2014

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