The Impact of Immortal Time Bias in Observational Studies

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What is Causal Inference

- Process of determining causal effect of exposure/intervention
- Goal: establish whether a causal effect exists, its direction, and strength
- Methods
  - Randomized experiments which control for confounding
  - Observational studies with assumptions and covariates
- Challenges:
  - Confounding variables can distort causal relationships in observational studies
  - Ethical and practical limitations can constrain the feasibility of conducting RCTs

What is the Target Trial Framework

- Methodological framework used to design and analyze studies aimed at mimicking the conditions of an idealized randomized trial using observational data

- Aims to estimate the effects of treatments or interventions as if they were assigned by randomization in real-world settings

What is the Target Trial Framework

- Implementation:
    - Design: Researchers define inclusion/exclusion criteria, treatment protocols, and outcome assessments that mirror an RCT
    - Analysis: Statistical methods adjust for biases inherent in observational data to approximate RCT-like conditions
- Applications:
    - Useful when RCTs are impractical or unethical
    - Provides insights into real-world effectiveness and safety of treatments

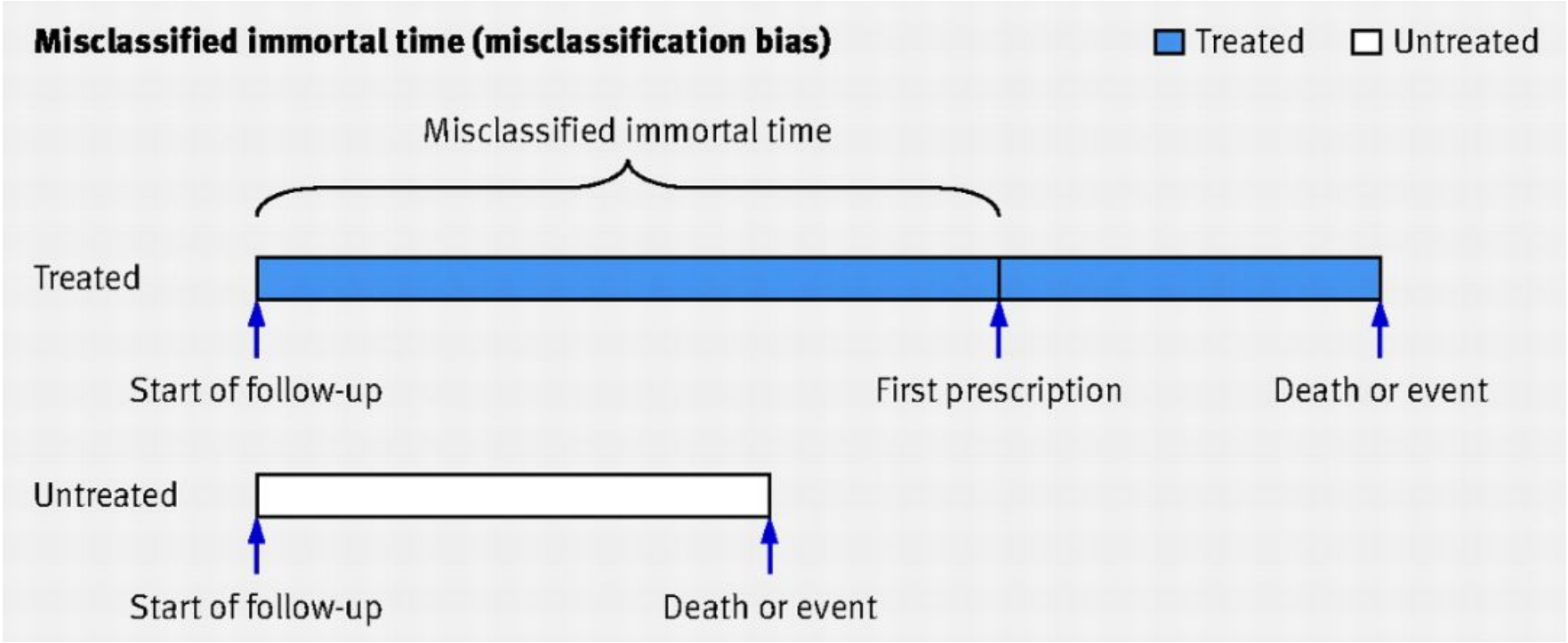
What is Time 0?

- The defined starting point for measuring events in a time-based analysis
- Medical Trial Example
  - Time 0 is the moment a patient first enters the trial.
  - Time elapsed until a measurable event (e.g., the patient achieves a specific health outcome, like a reduction in blood pressure) is measured from that point onwards

Immortal Time Bias

- When participants are counted as being risk for an outcome during a period of time where the outcome can’t happen
- In treatment groups this can happen if people are considered treated before the treatment, creating a time when the outcome is impossible
- Can create a false impression of improved outcomes or reduced risk in the exposed group

Immortal Time Bias



https://retractionwatch.com/2021/01/27/immortal-time-bias-fells-jama-journal-asthma-paper/

Simulation Overview

- The simulation demonstrates different methods at handling this bias
- We created hypothetical patient data with
  - Sample Size: 1000
  - Repetitions: 1000

Simulation Overview

- We created hypothetical patient data with
  - Event times (Y(0) and Y(1))
    - Time to event under no treatment (Y(0)) or treatment (Y(1))
    - Generated using an exponential distribution
  - Treatment assignment (A)
    - Patients receive treatment if they survive long enough to meet the cutoff time.
    - Generated using a uniform distribution
  - Follow up period - defines the time window for observing the outcomes
  - The true effect of the treatment is 0

Methods of estimating treatment events

- **Incorrect method (biased)**

- **Follow up method (Adjusted)**

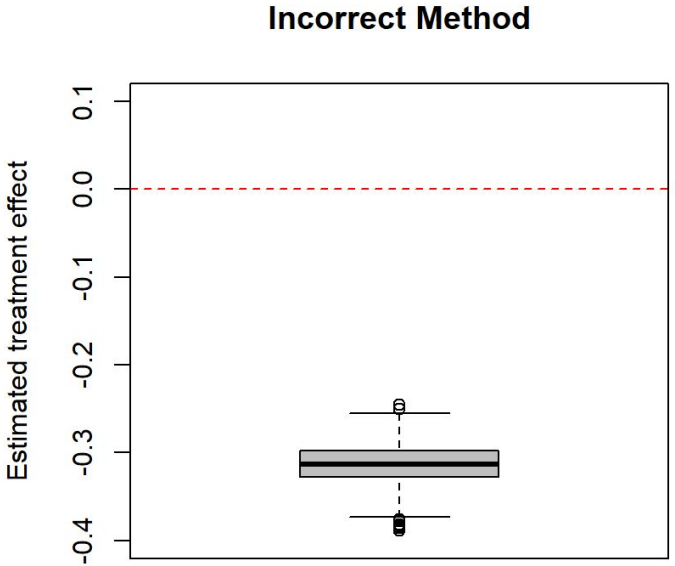
Incorrect method (biased)

- Compares the risk of the event by the cutoff between the treated (A=1) and untreated (A=0)
- It ignores the “immortal time” before the treatment leading to a false treatment benefit

Follow up method (Adjusted)

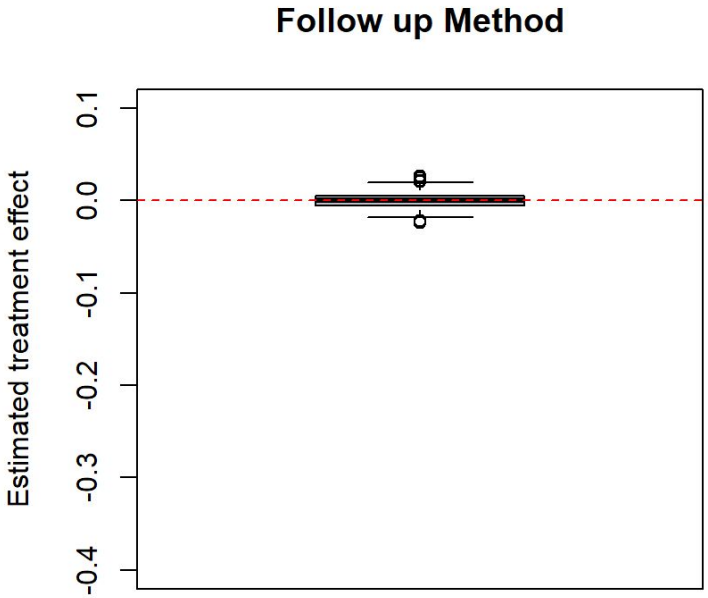
- Compares the event incidence rates per person-time
- Adjusts for treatment not starting at time 0 by calculating the event rates separately for the control and treatment periods, ensuring that only time at risk is considered for each group

Results and interpretation



Compares risk of the event by the cutoff

Min: -0.39 | Q1: -0.33 | Median: -0.31 | Q3: -0.3 | Max: -0.25



Compares event incidence per person-time

Min: -0.02 | Q1: -0.01 | Median: 0 | Q3: 0 | Max: 0.03

Conclusion

- The target trial framework helps clarify the design of a study by explicitly defining the treatment assignment, follow-up, and outcome measurement
- Immortal time bias can falsely suggest that treatment is beneficial.
- Simulations help reveal biases in observational studies and test correction methods.

Thank you