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Immortal Person-Time Bias in Observational Studies*

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Key Concepts

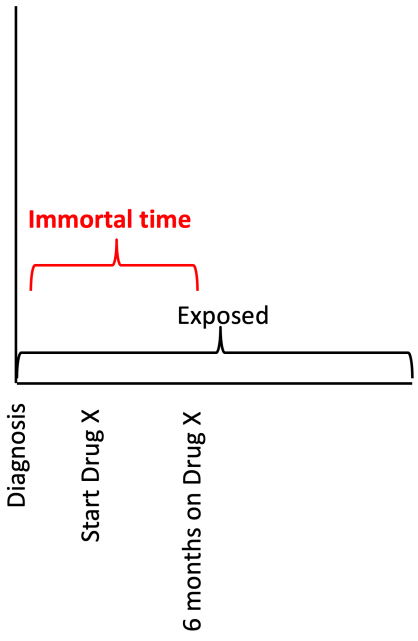
- Define immortal person-time bias in observational studies
- Recognize common study designs where this bias arises
- Review real-world examples from epidemiologic and clinical research
- Discuss design and analytic strategies to prevent or mitigate immortal time bias

Basic Idea: What Is "Immortal" Person-Time?

- "Immortal" person-time = a period during follow-up when, **by design**, the outcome cannot occur for a study participant (or group of participants) and they must survive to be classified as at a particular level of exposure
- Occurs when exposure is defined using **information that becomes available only after cohort entry**
- If this immortal time is **misclassified** (often as exposed time) or **excluded differently** between groups, effect estimates become biased

Simple Example

- Study question: "Does Drug X reduce mortality in patients with condition Y?"
- Design:
  - Cohort entry = date of diagnosis of Y
  - Exposure = "received Drug X for ≥6 months at any time during follow-up"
  - Compare mortality between "ever treated ≥6 months" vs "never treated or <6 months"
- To be in the "≥6 months Drug X" group, patients must
  - Survive long enough to start Drug X, **and**
  - Survive an additional 6 months
- That pre-treatment and early-treatment period is **immortal time** if counted as exposed person-time but during which death "cannot" occur for those ultimately classified as exposed.



Formal Definition in Time-to-Event Studies

- Immortal time bias arises when:
  - Follow-up starts at time t_0 (cohort entry), but
  - Exposure status is determined based on events **after** t_0 (e.g., "ever used drug," "received surgery within 6 months")
  - The period between t_0 and exposure assignment is misclassified as exposed or handled asymmetrically
- Consequence:
  - Artificially lowers the estimated hazard of the outcome in the "exposed" group (or perhaps the opposite, depending on the misclassification pattern)
- It is essentially a **time-related selection bias**: you are conditioning on survival until exposure.

Key Mechanisms That Generate Immortal Time Bias

- **Eligibility defined post-baseline**
  - Example: only patients who survive 90 days are eligible to be "treated"
- **Exposure defined by future information**
  - Example: "patients who ever receive transplant," "those who used a drug for at least 1 year"
- **Misaligned time zero**
  - Comparing treatment groups whose start of follow-up is at **different times (on the time scale of interest) or disease stages**
- **Improperly treating exposure as fixed**
  - Analyses that treat a time-varying treatment as a baseline covariate ("ever vs never")

Real-World Example
Statins and Mortality in Diabetes

- Large observational cohort of patients with diabetes, evaluating whether statin use reduces all-cause mortality
- Naïve design:
  - Cohort entry: first diabetes prescription
  - Exposure: "≥1 year of statin use anytime during follow-up" vs "no statins"
  - All follow-up between cohort entry and meeting the 1-year threshold was misclassified as **exposed**
- Findings (before correction):
  - ~43% of non-user person-time was incorrectly allocated to statin users, producing a large spurious survival benefit of statins
- When exposure was modeled correctly as **time-dependent**, the protective effect of statins on mortality was markedly attenuated

Real-World Example
Statins and Mortality in Rheumatic Disease

- Review of 8 cohort studies of statin use in rheumatic diseases
- All found lower mortality in statin users vs non-users (13–57%)
- Re-evaluation showed that several studies:
  - Started follow-up before statin initiation
  - Counted pre-statin survival time as exposed time
- Conclusion: Apparent survival benefits largely explained by immortal time bias; more rigorous "prevalent new-user" designs and time-varying exposure modeling are required for an unbiased estimates

Oncology Example:
Surgery / Radiation Timing in Cancer

- Common question: “Does receiving surgery or radiation improve survival in cancer patients?”
- Naïve design:
  - Time zero: date of cancer diagnosis
  - Exposure: “received surgery (or RT) during follow-up” vs “did not”
  - Patients must survive long enough to receive surgery/RT → **immortal time**
- Studies have shown:
  - Comparing ever-treated vs never-treated from diagnosis can greatly overestimate benefit of treatment
  - Time-dependent exposure models or target-trial designs give more modest or null effects
- Example: colon cancer survival differences between older and younger groups driven partly by immortal-time issues in treatment classification.

“Nobel Prize Winners Live Longer”

- Question: Do Nobel Prize winners live longer than non-winners?
- Naïve approach:
  - Compare lifespan of Nobel laureates vs other scientists from year of birth
- Immortal time problem:
  - To become a laureate, you must survive long enough to receive the prize → laureates are, by definition, **immortal** up to the award date
- Correct approach:
  - Treat “winning the prize” as a **time-varying exposure** and compare mortality from the date of prize (or from eligibility)

Conceptual Summary

- **The biased design effectively asks:**
  - "Among those who survive long enough to get treatment, how do outcomes compare with everyone else (including those who died early)?"
- **As a result:**
  - Exposed group is enriched with healthier survivors at baseline and during early follow-up
  - Unexposed group includes early deaths that could never have occurred in the exposed group under the way exposure is defined
- This is **not** the causal contrast we want (e.g., in a randomized trial we would compare "treat at time zero vs not treat at time zero" – corresponding to the sensible counterfactual contrast)

Direction and Magnitude of Bias

- **Most commonly:**
  - Bias favors **exposed group**, inflating apparent benefit (HR < 1 when true HR ~ 1)
- But bias can favor **unexposed group** when:
  - Long-duration or high-dose exposure categories inherit a lot of early unexposed person-time from people who must survive to "qualify" for that category
- **Magnitude can be large:**
  - Relative risks or hazard ratios can be greatly distorted (e.g., apparent 50% mortality reductions in the statin example)

How to Recognize Immortal Time Bias

- **Red flags** in the **methods** section of a publication:
  - Exposure defined using future information ("ever received," "received ≥X months," "received within 6 months")
  - **Time zero defined differently across exposure groups**
  - Survival curves start at diagnosis but exposure measured at later procedures/dispensing, beginning of treatment
- **Check:**
  - Is exposure treated as **fixed at baseline** when it clearly changes over time?
  - Did the authors account for time between cohort entry and exposure initiation?

Design Strategies to Prevent Immortal Time Bias

- **Align time zero with eligibility and treatment decision**
  - Define cohort entry at the moment the causal comparison is meaningful (e.g., first prescription, date of surgery decision)
- **New-user (incident-user) design**
  - Include only individuals at the time they initiate therapy vs appropriate comparators who are also at "decision time"
- **Active-comparator design can be helpful**
  - Compare initiators of Drug A vs Drug B at the same time, rather than Drug A vs "no treatment" with different entry times
- **Eligibility criteria fixed at baseline**
  - Avoid excluding patients post-baseline based on future survival (e.g., "survived 90 days to be included")

Analytic Strategies:
Time-Varying Exposure Models

- Consider treatment as a **time-dependent covariate** in survival models:
  - Before treatment starts → person-time counts as **unexposed**
  - After treatment starts → person-time counts as **exposed**
- Cox model with time-dependent exposure (and time-dependent confounders, if possible)
- Suitable when treatment can start at multiple times during follow-up and when other assumptions are reasonable

Analytic Strategies:
Landmark Analysis & Delayed Entry

- **Landmark analysis**
  - Choose a fixed "landmark" time (e.g., 6 months after diagnosis)
  - Include only patients alive and under observation at landmark
  - Classify exposure status at that landmark (e.g., "has surgery by 6 months" vs "no surgery by 6 months")
  - Analyze survival **from landmark onward**
- **Delayed entry (left truncation)**
  - Start follow-up at the time individuals become at risk under the exposure definition (e.g., date of treatment initiation)
- These approaches remove immortal time by **aligning at-risk time with exposure status**, though they may answer different causal questions

Target Trial Emulation
Clone-Censor-Weight Methods

- **Target trial emulation**:
  - Explicitly define the "hypothetical randomized trial" (eligibility, time zero, treatment strategies, follow-up, outcome)
  - Design the observational analysis to mimic this target trial

Potential Analytic Strategy in Target Trials
Clone-Censor-Weight Methods

- **Clone-censor-weight (CCW) methods** (often used with treatment initiation or surgical interventions):
  - "Clone" each patient into multiple treatment strategies at baseline
  - Censor each clone when they deviate from that strategy
  - Use inverse probability weights to adjust for informative censoring
- These approaches have been shown to substantially reduce immortal time bias in comparative effectiveness research

Practical Checklist for Your Own Studies

- Ask yourself:
- **When does follow-up start?**
  - Is this the same “time zero” you would use in a randomized trial?
- **How is exposure defined?**
  - Does it depend on events after time zero?
- **How is person-time classified?**
  - Is all time before treatment incorrectly counted as exposed?
- **Are exclusion criteria applied post-baseline based on survival or events?**
- **What analysis strategy is used?**
  - Fixed vs time-varying exposure; landmark; delayed entry; CCW; etc.

Summary

- Immortal person-time bias is a **time-related selection bias** that arises when exposure is defined using future information and immortal person-time is misallocated
- It can produce **substantial, biased estimates of treatment effects** in observational studies
- Prevention requires:
  - Careful alignment of **time zero**, eligibility, and exposure definition
  - Appropriate design (new-user, active comparator, if possible) and analysis (time-varying exposure, target-trial emulation)
- Recognizing and addressing immortal person-time bias is essential for valid causal inference in epidemiology

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