SESSION 4: SOME OBSERVATIONAL DATA BIASES AND HOW TO CORRECT THEM

Module 13: Survival Analysis for Observational Data

Summer Institute in Statistics for Clinical Research
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OUTLINE

- **Immortal-time bias**
  - **Examples: Oscar winners,** Valganciclovir Tx in Glioblastoma, Stanford Heart Transplant Program
  - Simulation
  - Correction using time-dependent covariates
- Index event bias
  - Examples: Regular aspirin use and MI in subjects with ACS, BMI and outcome in PCI-treated subjects
  - Correction using adjustment
- More on TDCs if time

EXAMPLE

- Does winning an Oscar confer a survival advantage?
- Redelmeier and Singh (2001) sampled 762 Oscar acting nominees from the beginning of the Oscars to 2001.
- **Background:** Social status is an important predictor of poor health. Most studies of this issue have focused on the lower echelons of society.
- **Objective:** To determine whether the increase in status from winning an academy award is associated with long-term mortality among actors and actresses.
- **Design:** Retrospective cohort analysis.
- **Setting:** Academy of Motion Picture Arts and Sciences.

Redelmeier DA, Singh SM. Annals of Internal Medicine. 2001 May 15;134(10):955.)

EXAMPLE

- **Participants:** All actors and actresses ever nominated for an academy award in a leading or a supporting role were identified (n=762). For each, another cast member of the same sex who was in the same film and was born in the same era was identified (n=887).
- **Measurements:** Life expectancy and all-cause mortality rates.
- Compared censored data on age at death between winners and non-winning nominees and winners and controls.
- Actors included only once, category based on highest achievement (winner, nominee, or control)

SURVIVAL OF OSCAR WINNERS

- **Results:** All 1649 performers were analyzed; the median duration of follow-up time from birth was 66 years, and 772 deaths occurred (primarily from ischemic heart disease and malignant disease). Life expectancy was 3.9 years longer for Academy Award winners than for other, less recognized performers (79.7 vs. 75.8 years; P = 0.003).
- This difference was equal to a 28% relative reduction in death rates (95% CI, 10% to 42%).
- Adjustment for birth year, sex, and ethnicity yielded similar results, as did adjustments for birth country, possible name change, age at release of first film, and total films in career.

SURVIVAL OF OSCAR WINNERS

- **Results (continued):** Additional wins were associated with a 22% relative reduction in death rates (CI, 5% to 35%), whereas additional films and additional nominations were not associated with a significant reduction in death rates.
- **Conclusion:** The association of high status with increased longevity that prevails in the public also extends to celebrities, contributes to a large survival advantage, and is partially explained by factors related to success.

RESULTS

- Setting time zero as birth, compared risk of death after adjustment in Cox models:
- Conclusion: winning may promote survival.
- Is there a bias?

RESULTS

- Setting time zero as birth, compared risk of death after adjustment in Cox models:
- Conclusion: winning may promote survival.
- Is there a bias?
- Yes! (There are two…)

IMMORTAL TIME BIAS

- Winners given credit for survival as winners before they won. Winning can't possibly have contributed to this portion of their survival.
- Reverse causality: Those who live longer have more chance to become winners.

IMMORTAL TIME BIAS

Bias that occurs when definition of cohort, or of comparison groups, depends on event that occurs after the start of follow-up

Subjects not “at risk” (of death) before group defining event occurs

It’s easy to fall in that trap once the data are available.

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RECENT CLINICAL EXAMPLE

- Survival in Patients with Glioblastoma Receiving Valganciclovir

  (Söderberg-Nauclér et al. (2013) NEJM 369(10):985–986.)
- Observational hazard ratios for death, controls to treated with Valganciclovir (anti-CMV) (all P < .0001):
  - Any treatment after diagnosis: HR = 2.59
  - At least 6 months treatment after diagnosis: HR = 3.20
  - At least 6 months treatment after diagnosis and then continuous treatment beyond diagnosis:HR = 5.52
- Problem: Glioblastoma raplidly lethal and subjects had to survive to be treated!

IMMORTAL TIME BIAS

- Suissa S. Immortal time bias in observational studies of drug effects. Pharmacoepidem Drug Safe. 2007 Mar 1;16(3):241–249.
- When exposed time is counted incorrectly as an exposed person or not counted as at risk, while surviving until exposure occurs.
  - Diabetics, use of statins and outcome of starting insulin therapy
  - Heart-failure hospital patients, prescription for beta-blockers, and outcome of readmission to hospital

OLDER EXAMPLES

- Survival of “responders” vs “non-responders” in Cancer clinical trials.
- Hormone use in cohort with Benign Breast Disease and Breast cancer risk
- Effectiveness of Heart Transplant in prolonging survival

DATA ANALYSIS EXAMPLE

- Early days of Stanford Heart Transplant program
  - Subjects admitted to program when heart condition was sufficiently severe
  - Donor heart was sought
  - Some patients received heart
  - Some died before a suitable heart could be found
- Question: did heart transplant prolong survival?

STANFORD

- Without covariables
- Naïve model examines survival as a function of whether subject received a heart transplant
- Subjects who lived long enough to receive a transplant lived longer:

	HR	2.5 %	97.5 %
Wrong: Fixed	0.27	0.17	0.43

STANFORD

- With correct model for time-dependent transplant status:

	HR	2.5 %	97.5 %
Correct: Time-dependent	1.14	0.63	2.05

- No evidence prior transplant influences mortality

OSCARS EXAMPLE

- I said there was another bias, in addition to immortal time bias. What was it?

IMMORTAL TIME BIAS

- Subject spends some time under observation for outcome before “exposure” occurs
- Subject is not given credit for survival as a non-exposed person until exposure occurs
  - In some bad analyses, the time prior to exposure is omitted (left entry at exposure time)
  - In others, the subject is counted as exposed before exposure occurs
- In both cases, bias is toward making exposure appear to be associated with longer survival

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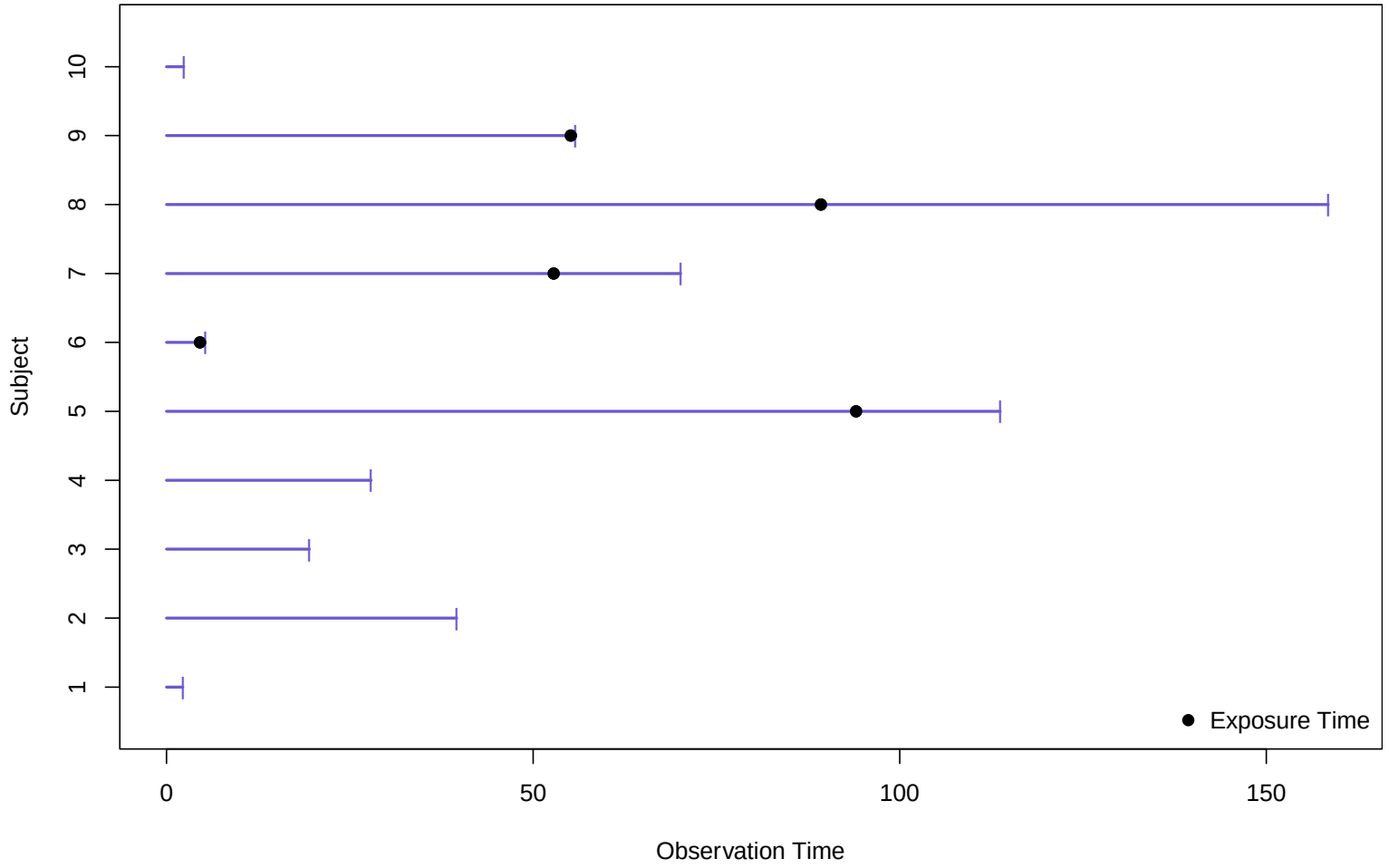
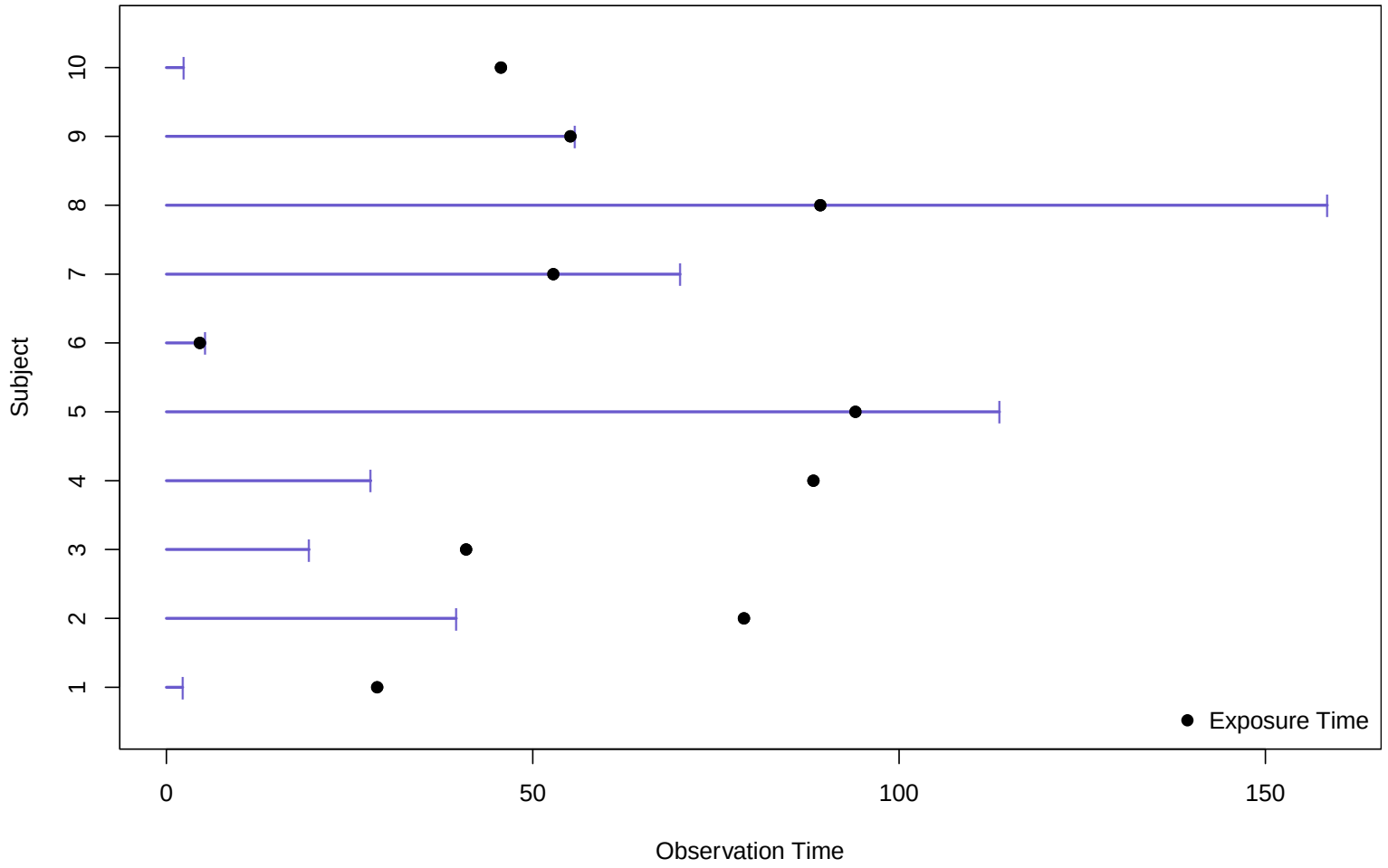
BIAS SIMULATION

- Exposure times and survival times generated independently (exposure HR = 1)
- Mean survival time for those who were exposed before death: 80.7
- Mean survival time for those who were not exposed before death: 18.3
- REASON: Those who lived long enough to be exposed, lived longer

OBSERVED DATA PICTURE



GENERATED DATA PICTURE



SIMULATION

- Previous plots were of a subset of one of the simulated data sets
- No association between exposure and survival (HR = 1)
- 1000 replications of sample size 100
- Compare three analysis strategies
  - Ordinary Cox model counting any subject exposed before death as exposed
  - Cox model left entering exposed subjects when they are exposed.
  - Cox model with appropriate TDC

SIMULATION

- Ordinary Cox model counting any subject exposed before death as exposed:
  - All coefficients negative, indicating protective effect of exposure.
- Cox model with left entry at exposure time for exposed observations:
  - All coefficients negative.

	mean coefficient (log HR)	Pr[Reject Ho]
ordinary	-1.8027810	1.000
left-enter	-0.9468022	0.939

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OPERATIONALIZING SOLUTION

- Time-dependent exposure variable!
- Let subject be categorized as not exposed at times before exposure occurs, and let exposure status change when exposure has occurred

TIME DEPENDENT EXPOSURE

Let the time-dependent binary prior exposure variable be:

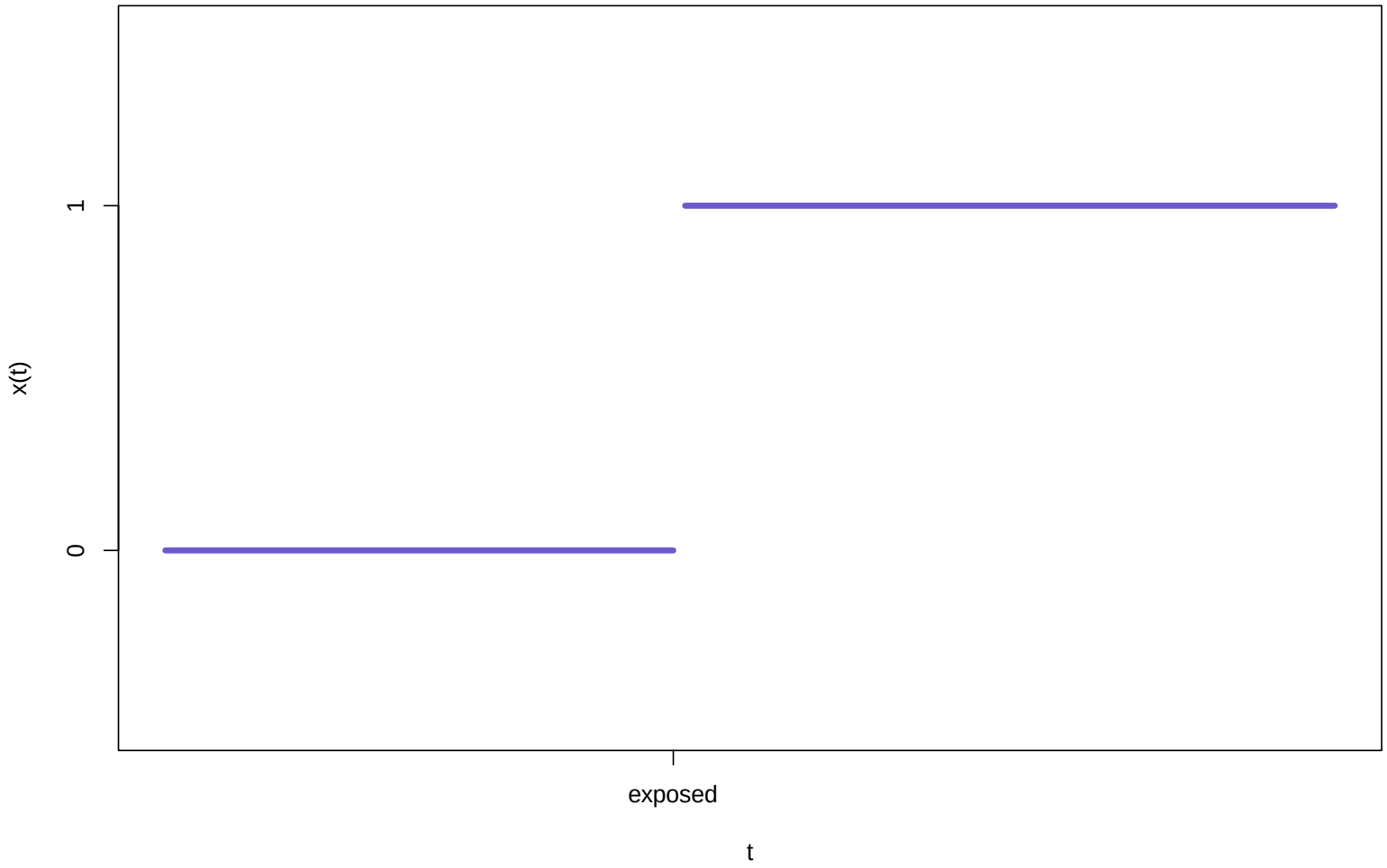
$$x(t) = \begin{cases} 1 & \text{exposed prior to time } t \\ 0 & \text{Otherwise} \end{cases} .$$

Then the model is

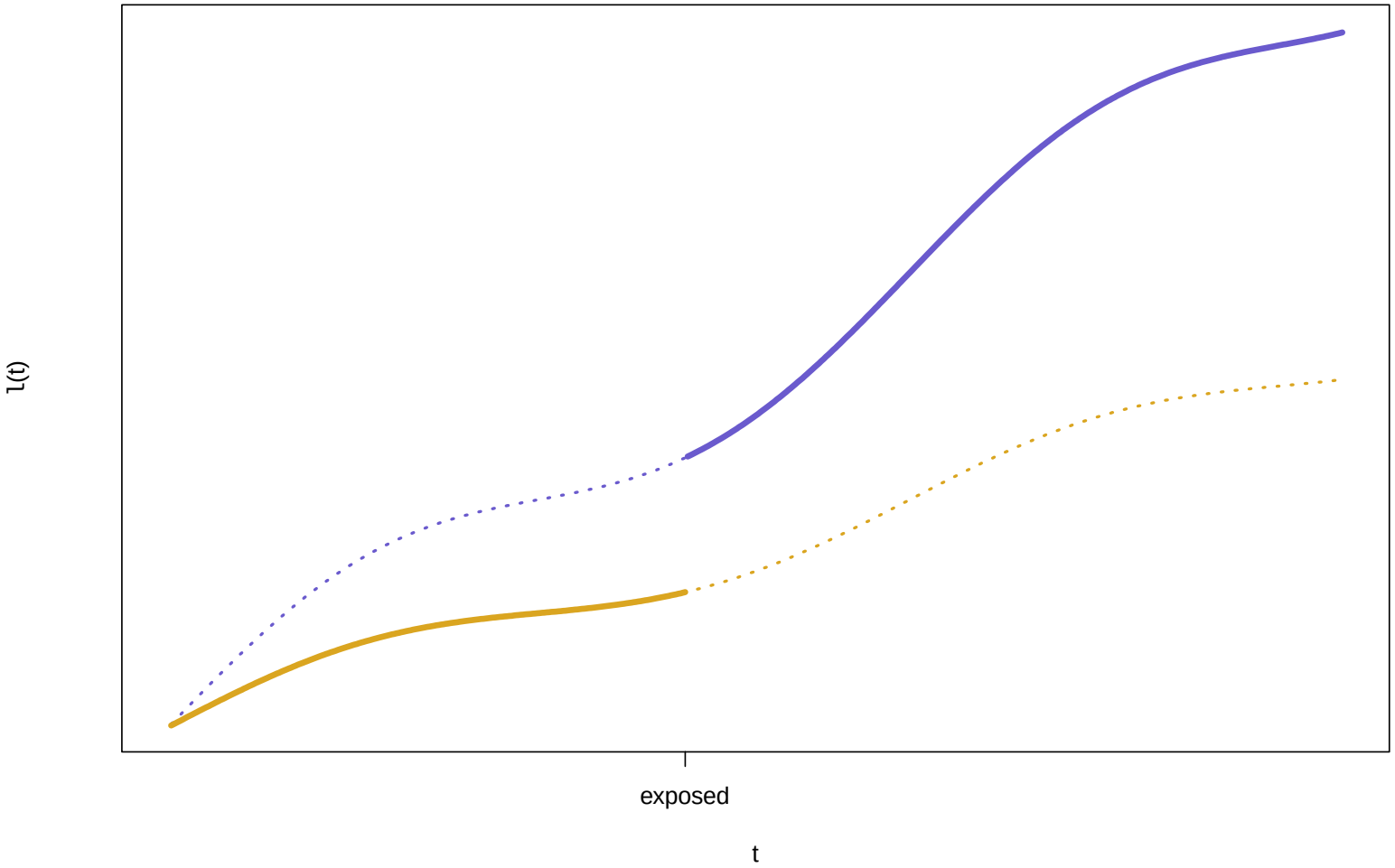
$$\lambda(t) = \lambda_0(t) e^{\beta x(t)}$$

e^{β} is the hazard ratio associated with **prior** exposure

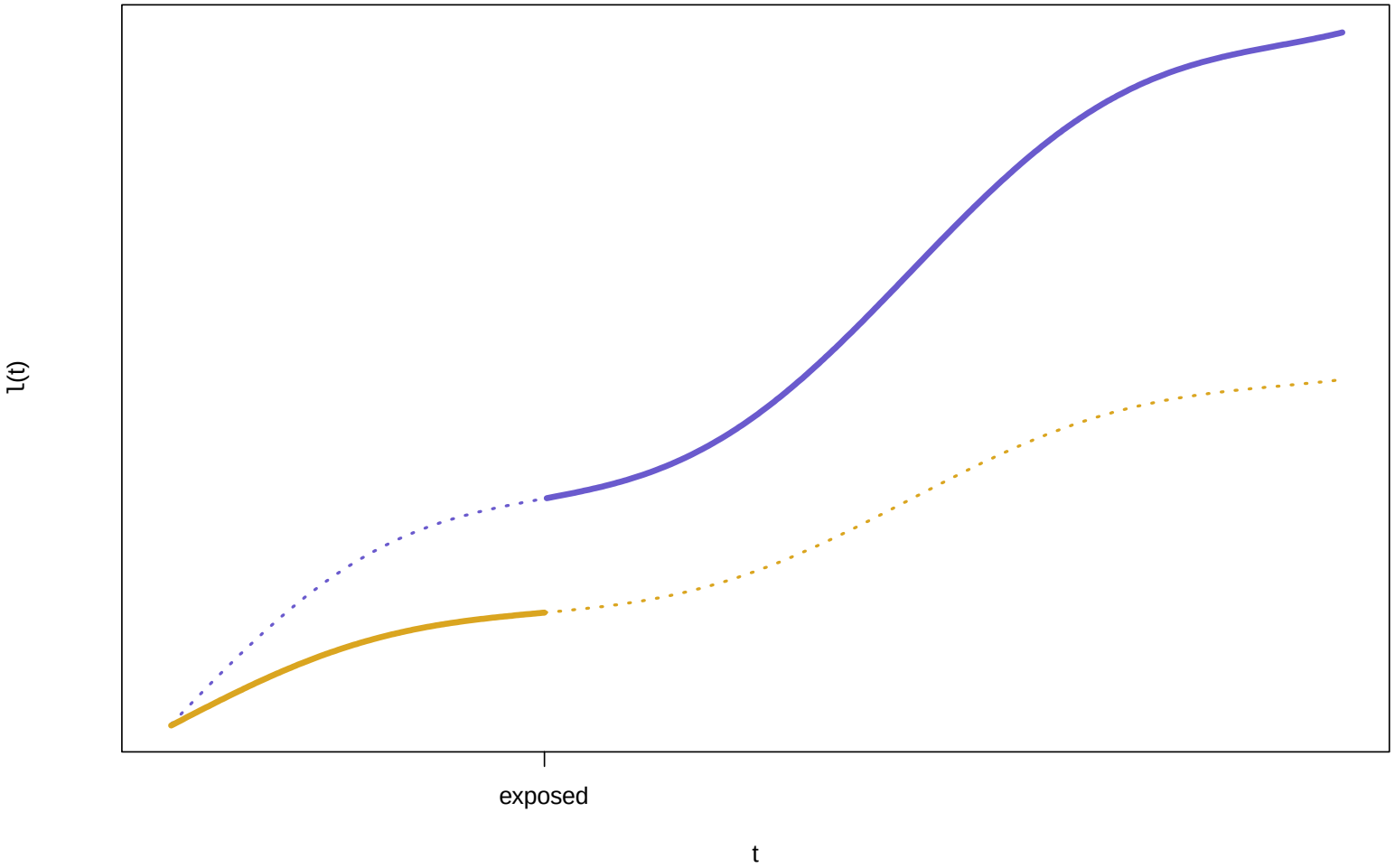
TIME-DEPENDENT EXPOSURE



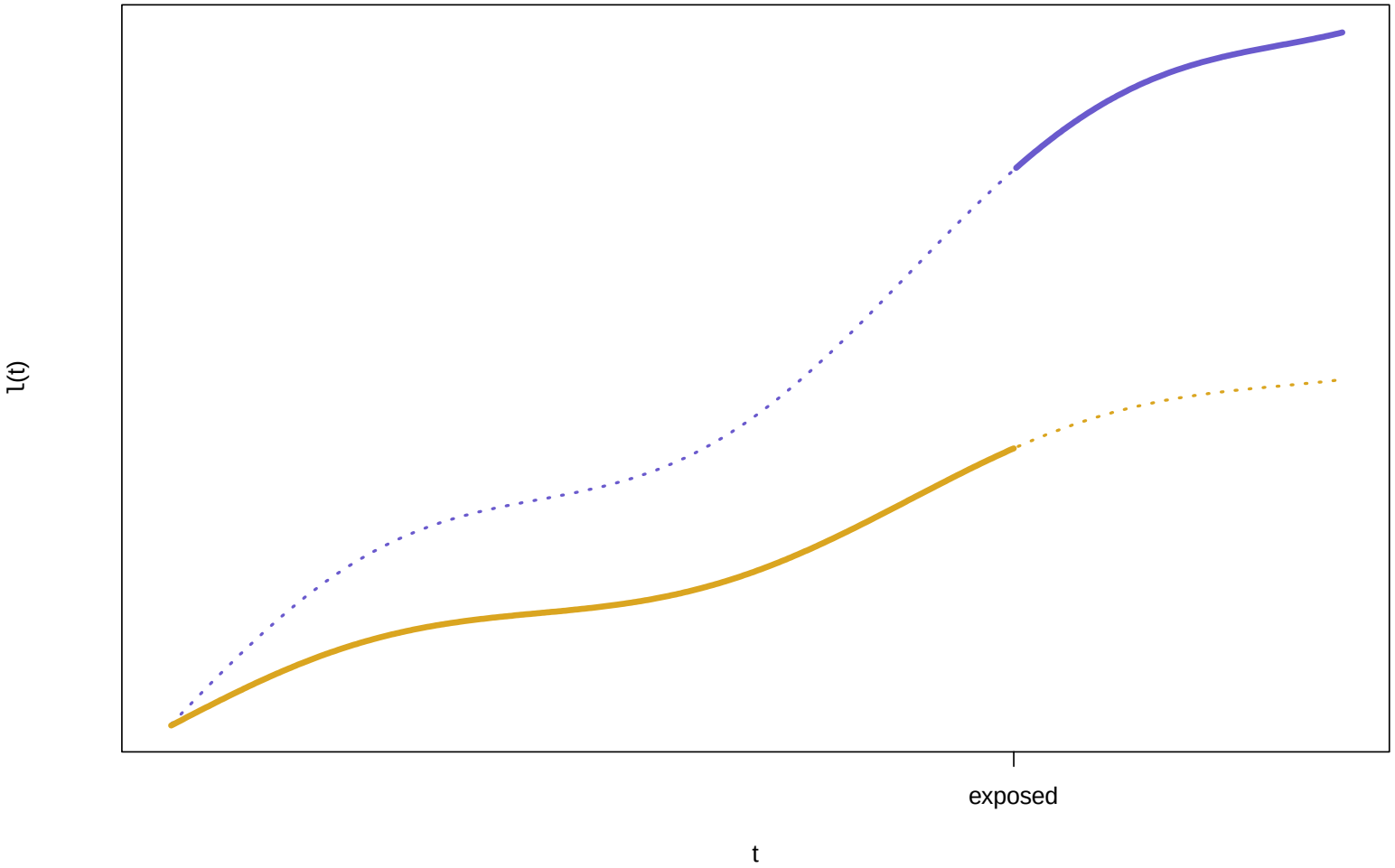
TIME-DEPENDENT EXPOSURE



EARLIER



LATER



WHY IT WORKS

- Exposed subject contributes survival to risk sets as unexposed before s/he is exposed
- Exposed subject contributes survival to risk sets as exposed after s/he is exposed until censoring or death
- Exposed subject contributes death to risk set as exposed when s/he dies

SIMULATION

Compare to correct time-dependent exposure model:

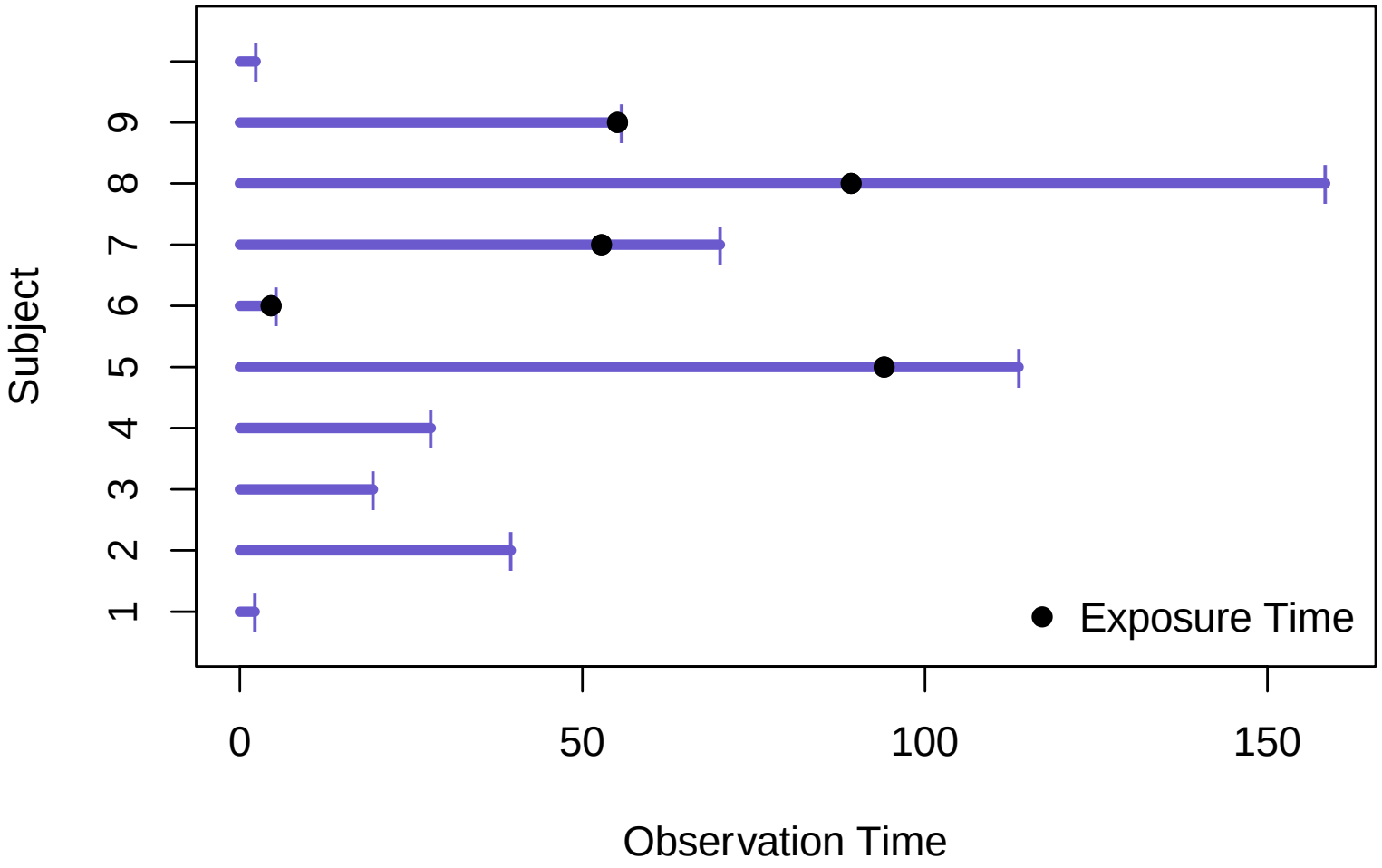
	mean coefficient (log HR)	Pr[Reject Ho]
ordinary	-1.8027810	1.000
left-enter	-0.9468022	0.939
correct	-0.0059659	0.048

TDC model correctly estimates HR near one (log HR near zero) and correctly rejects H_0 only 5% of the time.

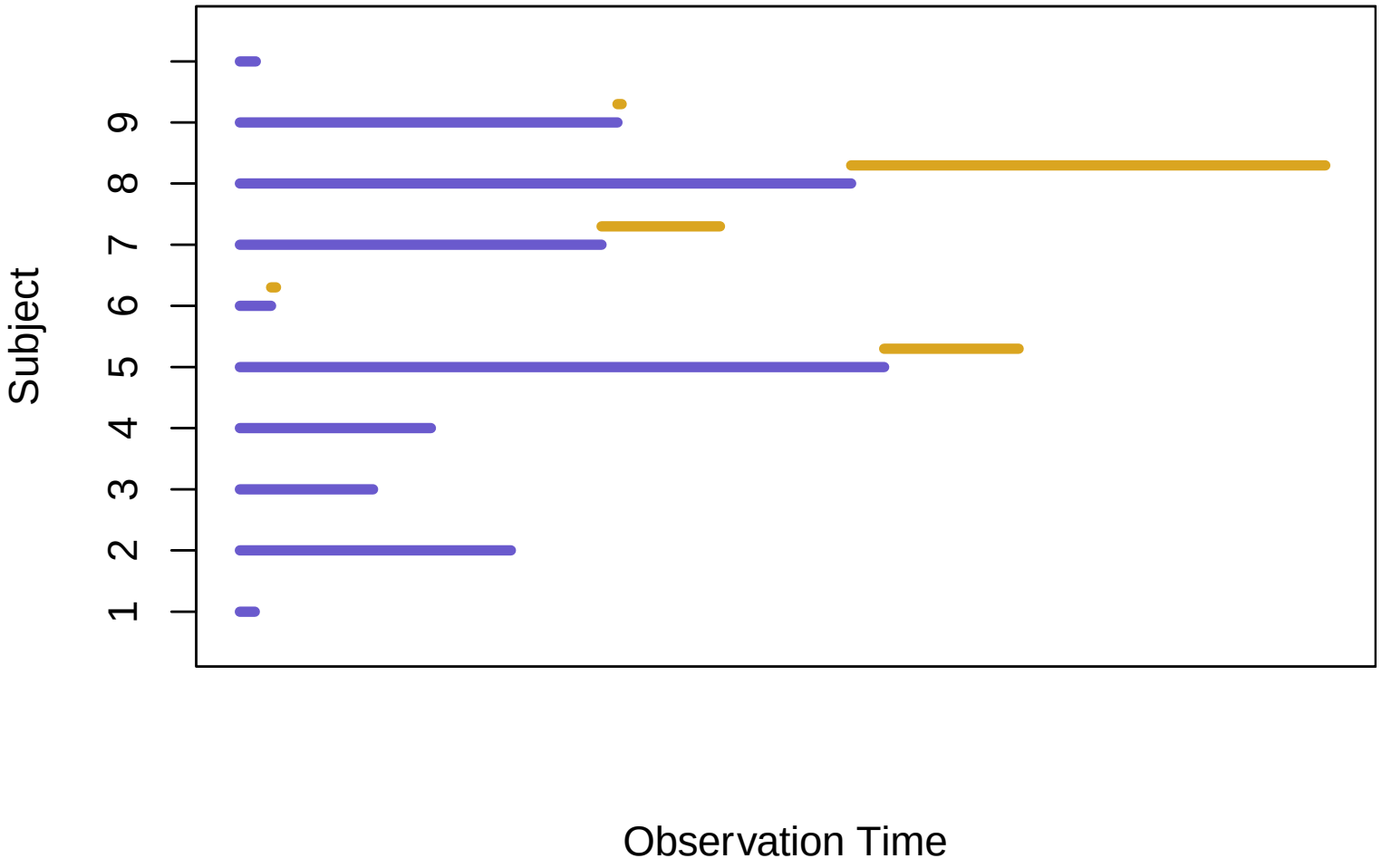
HOW TO DO IT

- Divide exposed subjects' information into two records:
- The first record starts at time zero (or entry into observation), has exposure coded as unexposed, and removes the subject from risk sets (as if censored) at the time of exposure.
- The second record left enters at the time of exposure, has exposure coded as exposed, and follows subjects until s/he dies or is truly censored.

PICTURE


Subject
1
2
3
4
5
6
7
8
9
0
50
100
150
Observation Time
Exposure Time

PICTURE



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INDEX EVENT BIAS

- Example: Rich et al (2010) studied 66,443 Acute Coronary Syndrome (ACS) patients who participated in thrombolysis or MI RCTs
- Baseline trial information about prior “regular” aspirin use at least one week before presentation was available
- Recall there is strong evidence that regular aspirin use prevents ischemic events, but in this population the opposite was true.

Rich JD, Cannon CP, Murphy SA, Qin J, Giugliano RP, Braunwald E. Journal of the American College of Cardiology (2010) Oct 19; 56(17):1376–1385.

EXAMPLE

- In this population, prior regular aspirin use was positively associated with:
  - Recurrent MI: adjusted HR = 1.24 (95% CI: 1.12 – 1.37)
  - Composite ACS event of MI, ischemia requiring hospitalization, urgent revascularization, or stroke: Adjusted HR = 1.08, (95% CI: 1.03-1.13)

OBESITY EXAMPLE

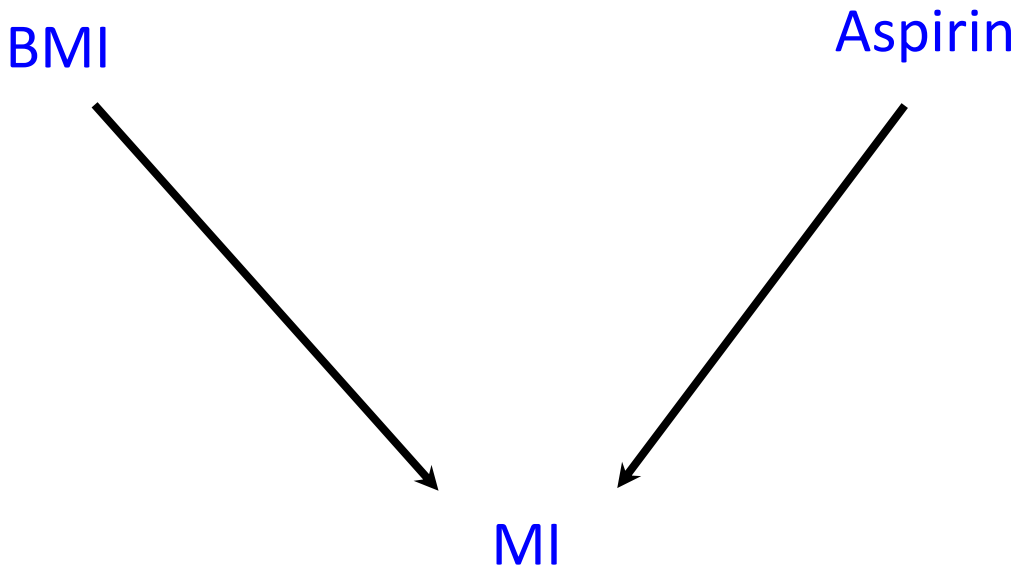
- Gruberg et al (2002) studied BMI category and subsequent MI in a case series of 9633 patients who underwent percutaneous coronary intervention.
- Overweight and obesity are known to be related to the risk of MI
- In this population, adjusted comparison of overweight and obese patients to normal weight patients: HR = .96, (95% CI: .94 - .98)

Gruberg L. et al Journal of the American College of Cardiology. (2002) 20;39(4):578–584.

INDEX EVENT BIAS

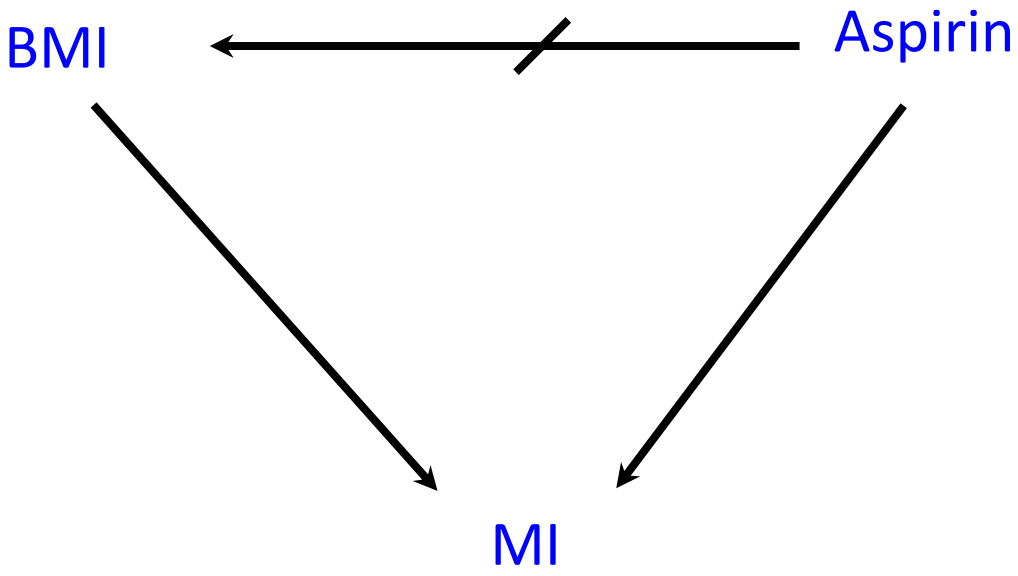
- Why?
- Subjects with a prior (“Index”) clinical event are not representative of the population.
- Risk factors for the outcome that may be independent of exposure in the general population are much less likely to be independent in a population who have experienced the index event.
- All risk factors for both the index event and the outcome are potential confounders.

COLLIDER BIAS



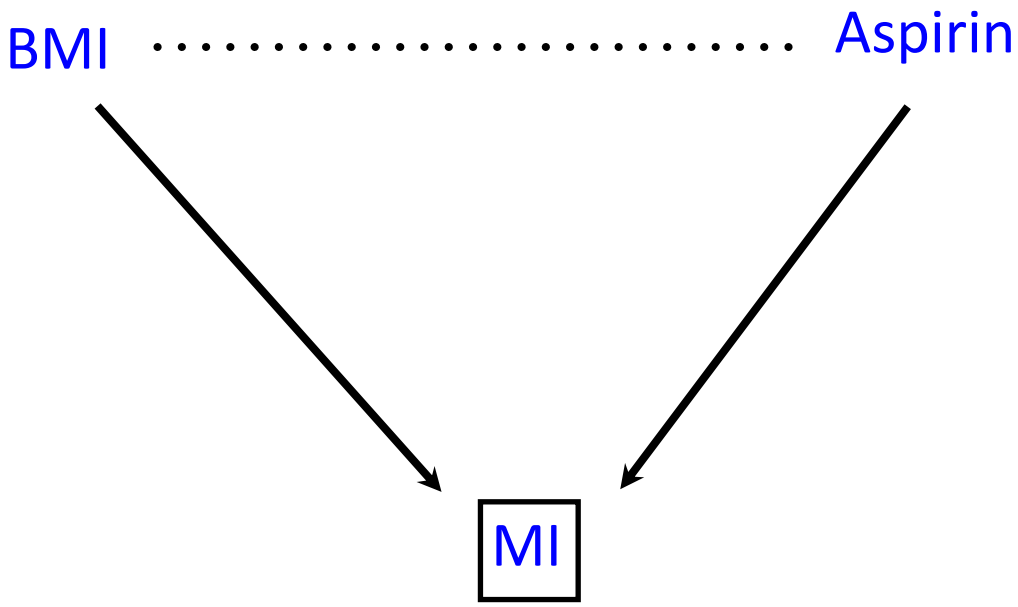
Both low/normal BMI and Aspirin use reduce the risk of MI.

COLLIDER BIAS



There is no reason to expect that aspirin use influences BMI, so a study of BMI and MI would likely refrain from adjusting for aspirin use.

COLLIDER BIAS



Because BMI and aspirin use are both causally related to MI, they will often not be independent of each other in those who have suffered an MI.

SUFFICIENT CAUSE MODEL

Population distribution (independent)

	Overweight	Normal weight
No aspirin	.4	.4
Aspirin	.1	.1

Probability of MI during time period

	Overweight	Normal weight
No aspirin	.005	.005
Aspirin	.005	.001

SUFFICIENT CAUSE MODEL

Distribution among cases

	Overweight	Normal weight
No aspirin	.43	.43
Aspirin	.11	.02

OR = 0.2

Expected among cases if independent

	Overweight	Normal weight
No aspirin	.47	.40
Aspirin	.07	.06

INDEPENDENT CAUSE MODEL

Population distribution (independent)

	Overweight	Normal weight
No aspirin	.4	.4
Aspirin	.1	.1

Probability of MI during time period

	Overweight (.04)	Normal weight (.01)
No aspirin (.1)	.004	.001
Aspirin (.05)	.002	.0005

INDEPENDENT CAUSE MODEL

Distribution among cases

	Overweight	Normal weight
No aspirin	.71	.18
Aspirin	.09	.02

OR = 1.0

Expected among cases if independent

	Overweight	Normal weight
No aspirin	.71	.18
Aspirin	.09	.02

SYNERGY MODEL

Population distribution (independent)

	Overweight	Normal weight
No aspirin	.4	.4
Aspirin	.1	.1

Probability of MI during time period

	Overweight (.04)	Normal weight (.01)
No aspirin (.1)	.006	.001
Aspirin (.05)	.002	.0005

SYNERGY MODEL

Distribution among cases

	Overweight	Normal weight
No aspirin	.79	.13
Aspirin	.07	.02

OR = 1.25

Expected among cases if independent

	Overweight	Normal weight
No aspirin	.78	.14
Aspirin	.07	.01

ANTAGONISM MODEL

Population distribution (independent)

	Overweight	Normal weight
No aspirin	.4	.4
Aspirin	.1	.1

Probability of MI during time period

	Overweight (.04)	Normal weight (.01)
No aspirin (.1)	.0025	.001
Aspirin (.05)	.002	.0005

ANTAGONISM MODEL

Distribution among cases

	Overweight	Normal weight
No aspirin	.60	.24
Aspirin	.12	.03

OR = 0.62

Expected among cases if independent

	Overweight	Normal weight
No aspirin	.62	.23
Aspirin	.11	.04

IMPLICATION FOR ANALYSIS

- When evaluating a risk factor for the index event for its association with outcome, need to consider all risk factors for the index event for adjustment, even if they are independent of the risk factor under study in the population.
- In the example, Gruberg et al. adjusted for age, gender, diabetes, hypertension, previous PCI, smoking, saphenous vein graft intervention, and left ventricular ejection fraction (LVEF), but neglected other CVD risk factors (not thought to be associated with BMI) such as LDL cholesterol levels .

INDEX EVENT BIAS REFERENCES

- Cole SR, Platt RW, Schisterman EF, Chu H, Westreich D, Richardson D, Poole C. Illustrating bias due to conditioning on a collider. Int J Epidemiol. 2010 Apr 1;39(2):417–420.
- Dahabreh IJ, Kent DM. Index Event Bias as an Explanation for the Paradoxes of Recurrence Risk Research. JAMA. 2011 Feb 23;305(8):822–823.
- Flanders WD, Eldridge RC, McClellan W. A Nearly Unavoidable Mechanism for Collider Bias with Index-Event Studies: Epidemiology. 2014 Sep;25(5):762–764.
- Smits LJM, van Kuijk SMJ, Leffers P, Peeters LL, Prins MH, Sep SJS. Index event bias—a numerical example. Journal of Clinical Epidemiology. 2013 Feb;66(2):192–196.

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OTHER TDC POSSIBILITIES (IF TIME)

More than one change in status:

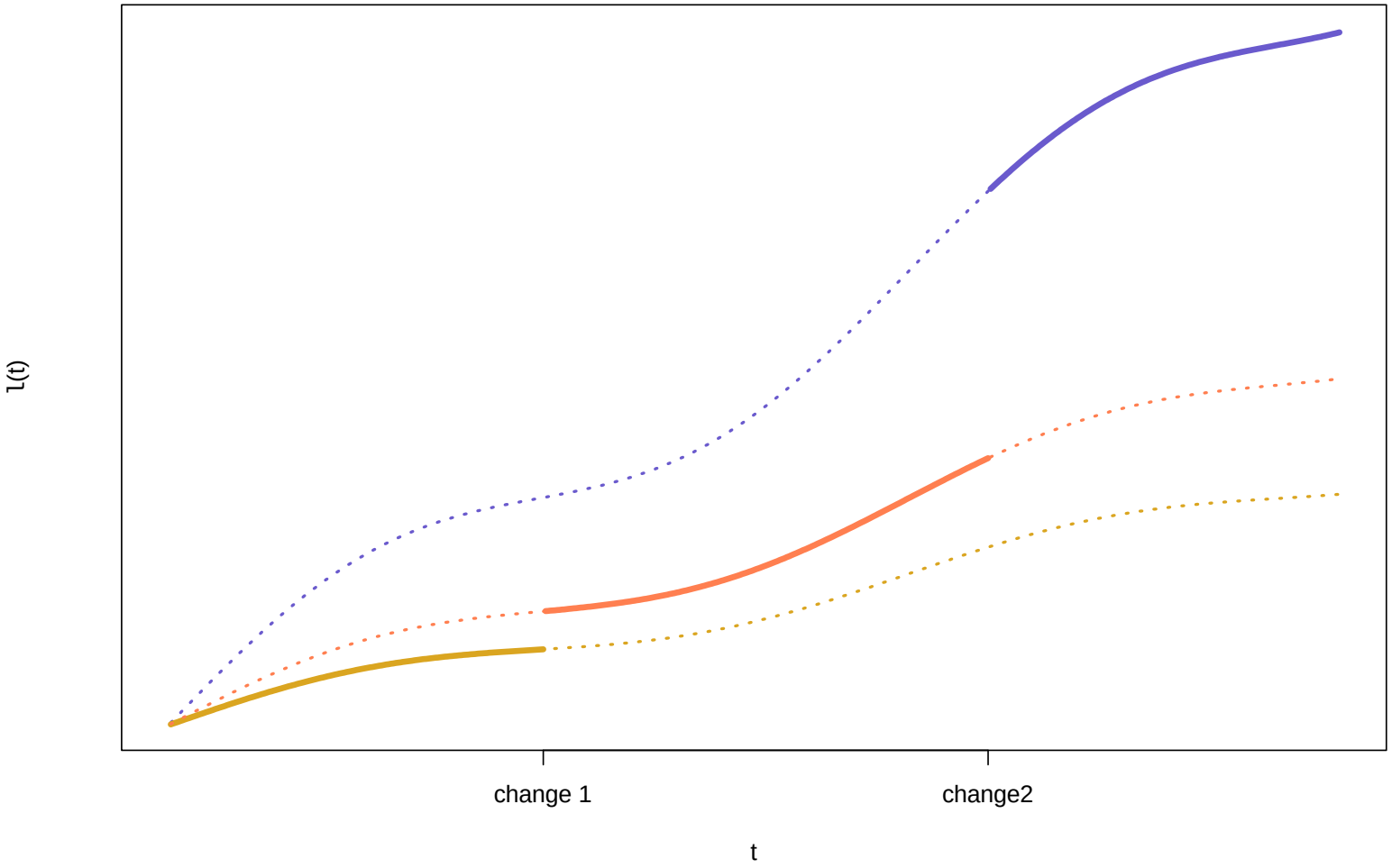
Let $\lambda(t)$ be the hazard for stroke:

$$x_{AF1}(t) = \begin{cases} 1 & \text{First Episode Atrial Fibrillation by } t \\ 0 & \text{Otherwise} \end{cases}$$

$$x_{AF2}(t) = \begin{cases} 1 & \text{Second Episode Atrial Fibrillation by } t \\ 0 & \text{Otherwise} \end{cases}$$

$$\lambda(t) = \lambda_0(t) e^{\beta_1 x_{AF1}(t) + \beta_2 x_{AF2}(t)}$$

TWO CHANGES



OTHER POSSIBILITIES

A change in numerical value of a continuous variable.

Examples:

$x(t)$ = most recently recorded value of fasting insulin at time t.

$x(t)$ = cumulative recorded exposure to radon at time t.

$$\lambda(t) = \lambda_0(t)e^{\beta x(t)}$$

PRIMARY BILIARY CIRRHOSIS

- 312 patients in RCT of d-penacillamine
- Some biomarkers were measured repeatedly over time
- Compare influence of baseline measures on survival (non-time-dependent model) to influence of most recent measure (time-dependent model) on survival.

PRIMARY BILIARY CIRRHOSIS

x = bilirubin (mg/dl) measured at baseline

$x(t)$ = most recently measured bilirubin (mg/dl) at day t.

Baseline model:

$$\lambda(t) = \lambda_0(t)e^{\beta x}$$

Time-dependent model:

$$\lambda(t) = \lambda_0(t)e^{\beta x(t)}$$

PRIMARY BILIARY CIRRHOSIS

Baseline model:

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
log(bili)	0.9890831	2.688768	0.0783597	12.62235	0

Time-dependent model:

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
log(bili)	1.370255	3.936355	0.0949917	14.425	0

OTHER POSSIBILITIES

- Time-interaction with time-dependent exposure variable like prior heart transplant

TO WATCH OUT FOR

- Make sure subjects give credit to the appropriate group (covariate value) if exposure changes over time using time-dependent covariates
- In index event studies, adjust for all available risk factors for the index event if you believe they influence outcome, even if you don't think they are associated with exposure.