SESSION 1:
REVIEW AND COX MODEL
FOR ADJUSTMENT AND INTERACTION

Module 17: Survival Analysis for Observational Data
Summer Institute in Statistics for Clinical Research
University of Washington
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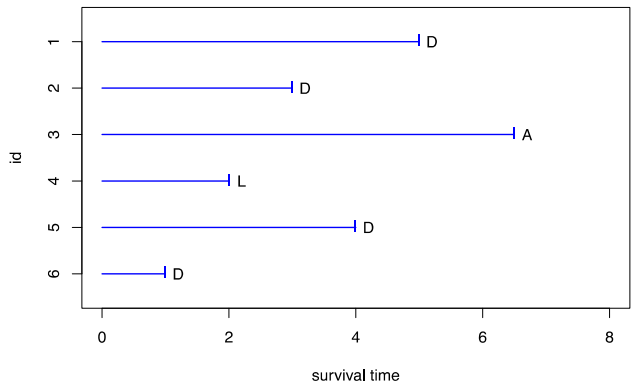
OVERVIEW

- Session 1
  - Quick review of introductory material
  - Adjustment in the Cox model: confounding and precision
  - Effect modification in the Cox model
- Session 2
  - Nonparametric hazard function estimation
  - Competing risks
  - Cumulative Incidence estimation
- Session 3
  - Left entry and left truncation
  - Choice of the time variable
  - Interactions with functions of time
- Session 4
  - Immortal time bias
  - Time-dependent covariates

OUTLINE

- Review of censored data, KM estimation, logrank test and Cox model basics
- Covariate adjustment in Cox model
- Stratification adjustment in Cox model
- Interaction (Effect Modification) in Cox Model
- Precision in Cox model

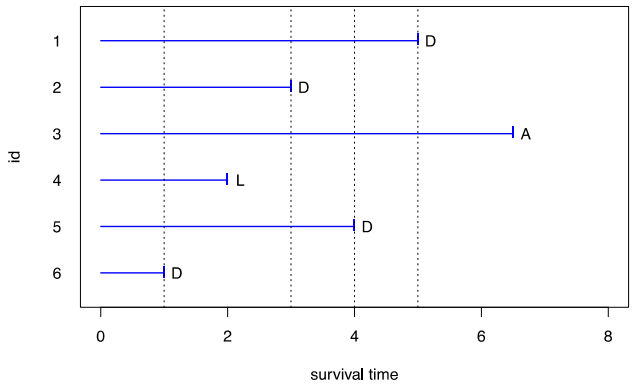
CENSORED DATA



id	Y	δ
1	5	1
2	3	1
3	6.5	0
4	2	0
5	4	1
6	1	1

"Censored" observations give some information about their survival time.

RISK SETS

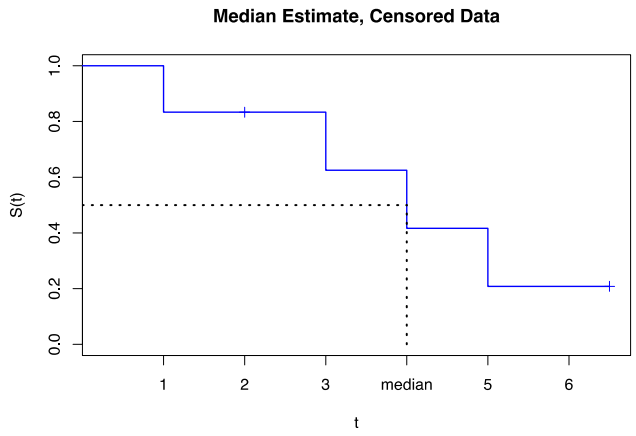


R_1 {1,2,3,4,5,6} R_2 {1,2,3,5} R_3 {1,3,5} R_4 {1,3}

CENSORED DATA ASSUMPTION

- Important assumption: subjects who are censored at time t are at the same risk of dying at t as those at risk but not censored at time t.

MEDIAN & SURVIVAL CENSORED DATA



EQUIVALENT CHARACTERIZATIONS

- Any <u>one</u> of the density function(f(t)), the survival function(S(t)) or the hazard function(λ(t)) is enough to determine the survival distribution.
- They are each functions of each other:
  - $S(t) = \int_t^\infty f(s)ds = e^{-\int_0^t \lambda(s)ds}$
  - $f(t) = -\frac{d}{dt}S(t) = \lambda(t)e^{-\int_0^t \lambda(s)ds}$
  - $\lambda(t) = \frac{f(t)}{S(t)}$

LOGRANK TEST

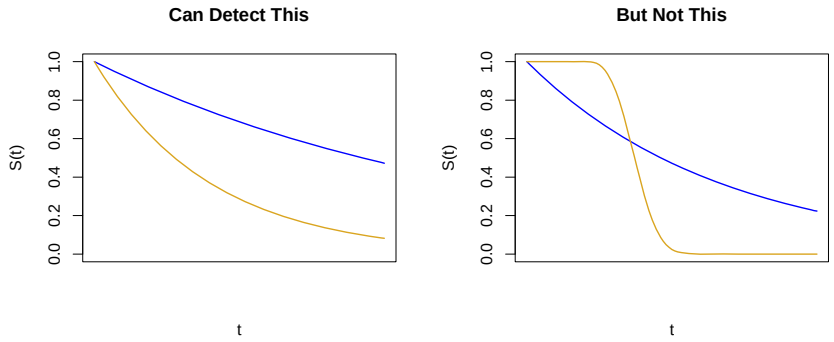
- The test is based on a 2x2 table of group by current status at each observed failure time (ie for each risk set)
- $T_{(j)}$, $j=1,\ldots m$, as shown in the Table below.

Event/Group	1	2	Total
Die	$d_{1(j)}$	$d_{2(j)}$	$D_{(j)}$
Survive	$n_{1(j)}-d_{1(j)}= s_{1(j)}$	$n_{2(j)}-d_{2(j)} = s_{2(j)}$	$N_{(j)}-D_{(j)} = S_{(j)}$
At Risk	$n_{1(j)}$	$n_{2(j)}$	$N_{(j)}$

LOGRANK TEST

- Detects consistent differences between survival curves over time.
- Best power when:
  - H_0: $S_1(t) = S_2(t)$ for all t vs H_A: $S_1(t) = [S_2(t)]^c$, or
  - H_0: $\lambda_1(t) = \lambda_2(t)$ for all t vs H_A: $\lambda_1(t) = c\,\lambda_2(t)$
- Good power whenever survival curve difference is in consistent direction

LOGRANK TEST



Other tests (generalized Wilcoxon and others) can give more weight to early or late differences.

COX REGRESSION MODEL

- Usually written in terms of the hazard function
- As a function of independent variables $x_1, x_2, \ldots x_k$,

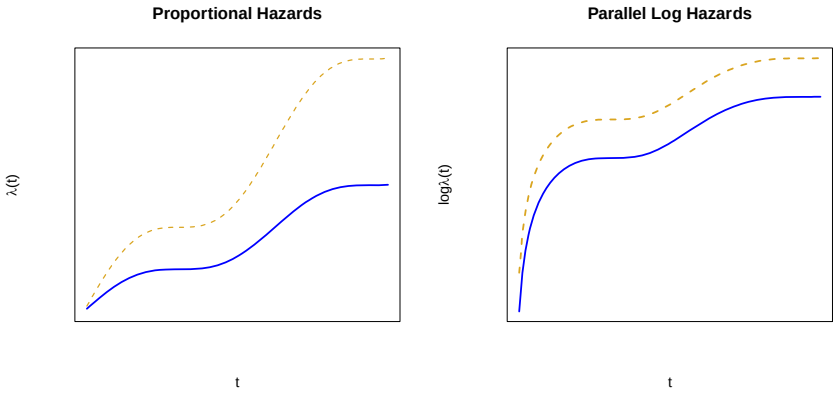
$$\lambda(t) = \lambda_0(t)e^{\beta_1 x_1 + \cdots + \beta_k x_k}$$

↑ relative risk / hazard ratio

$$\log\lambda(t) = \log\lambda_0(t) + \beta_1 x_1 + \cdots + \beta_k x_k$$

↑ intercept

EXAMPLE



RELATIONSHIP TO SURVIVAL FUNCTION

Single binary x:

$$x = \begin{cases} 1 & \text{Test treatment} \\ 0 & \text{Standard treatment} \end{cases}$$

$$\lambda(t) = \lambda_0(t)e^{\beta x} \implies S(t) = [S_0(t)]^{e^{\beta x}}$$

In terms of $S_0(t)$:

$S(t)$ for $x = 1$: $[S_0(t)]^{e^{\beta \cdot 1}} = [S_0(t)]^{e^{\beta}}$

$S(t)$ for $x = 0$: $[S_0(t)]^{e^{\beta \cdot 0}} = [S_0(t)]^1 = S_0(t)$

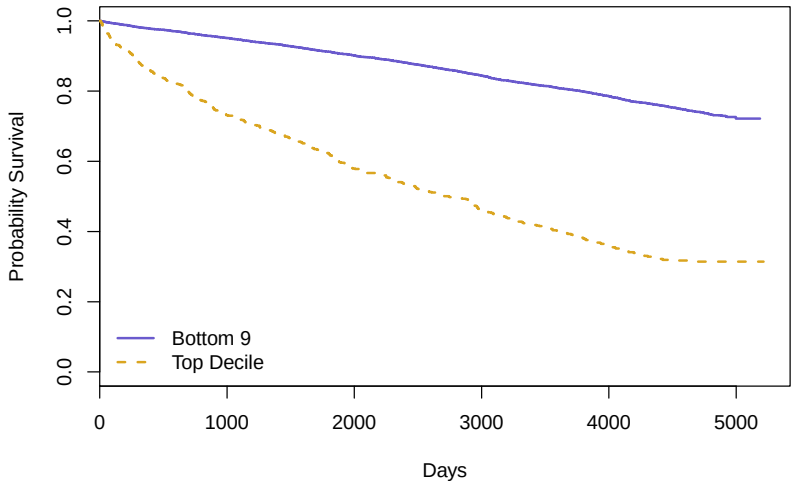
CONFOUNDING

- Observational data: sometimes observed associations between an explanatory variable and outcome can be due to their joint association with another variable.
  - Age related to both sex and risk of death.
  - Age related to immunoglobulin levels and risk of death (example next)

SURVIVAL AND IG

- Random subset of the data from A. Dispenzieri, J. Katzmann, R. Kyle, D. Larson, T. Therneau, C. Colby, R. Clark, G. Mead, S. Kumar, L.J. Melton III, and S.V. Rajkumar. Use of monoclonal serum immunoglobulin (ig) free light chains (flc) to predict overall survival in the general population. Mayo Clinic Proc, 87:512–523, 2012.
- Are high free-chain ig levels associated with survival?
  - Population-based Olmstead County example
  - Men and women 50+ years of age

TOP DECILE FLC



COX REGRESSION

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
topdecileTRUE	1.452639	4.274378	0.0523126	27.7684	0

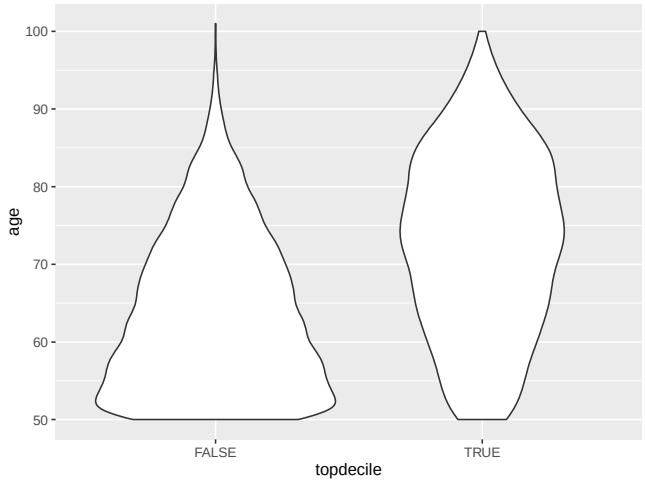
	2.5 %	97.5 %
topdecileTRUE	3.857841	4.735889

ADJUSTED COX REGRESSION

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
topdecileTRUE	0.8012613	2.228350	0.0543721	14.73663	0
age	0.1018649	1.107234	0.0022780	44.71700	0

	2.5 %	97.5 %
topdecileTRUE	2.003096	2.478934
age	1.102301	1.112189

WHY?



ADJUSTMENT MODEL

One binary variable, x_1, with continuous adjustment variable x_2:

$$x_1 = \begin{cases} 1 & \text{Top decile FLC} \\ 0 & \text{Otherwise} \end{cases}$$

x_2 = Age in years

$$\lambda(t) = \lambda_0(t)e^{\beta_1 x_1 + \beta_2 x_2}$$

Interpretation of e^{β_1}:

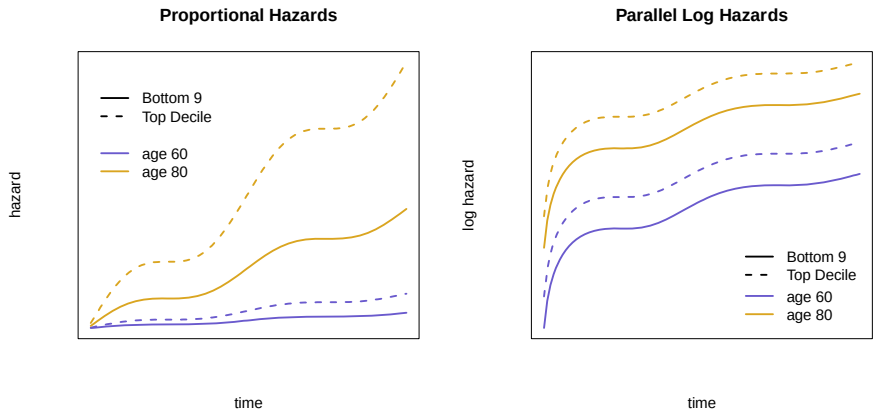
"Relative risk (or hazard ratio) comparing top decile FLC to the rest, among those of the same age".

$\lambda(t)$ for $x_1 = 1$ and x_2: $\lambda_0(t)e^{\beta_1 \cdot 1 + \beta_2 x_2}$

$\lambda(t)$ for $x_1 = 0$ and x_2: $\lambda_0(t)e^{\beta_1 \cdot 0 + \beta_2 x_2}$

ratio: $e^{\beta_1(1-0)+\beta_2(x_2-x_2)} = e^{\beta_1}$

ADJUSTMENT



RESULTS

- "We found strong evidence that adjusted for age, free light chain(FLC) values in the top decile were associated with the risk of death (P < .0001). Among individuals of the same age, we estimate that having an FLC value in the top decile is associated with 2.23 times the hazard of death (95% CI: 2.00, 2.48)."

STRATIFICATION ADJUSTMENT

One binary variable, x_1, with grouped adjustment variable x_2:

$$x_1 = \begin{cases} 1 & \text{Top decile FLC} \\ 0 & \text{Otherwise} \end{cases}$$

$$x_2 = \begin{cases} 0 & \text{age 50-59} \\ 1 & \text{age 60-69} \\ 2 & \text{age 70-79} \\ 3 & \text{age 80-89} \\ 4 & \text{age 90+} \end{cases}$$

$$\lambda(t) = \lambda_{0x_2}(t)e^{\beta_1 x_1}$$

STRATIFICATION ADJUSTMENT

$$\lambda(t) = \lambda_{0x_2}(t)e^{\beta_1 x_1}$$

Interpretation of e^{β_1}:

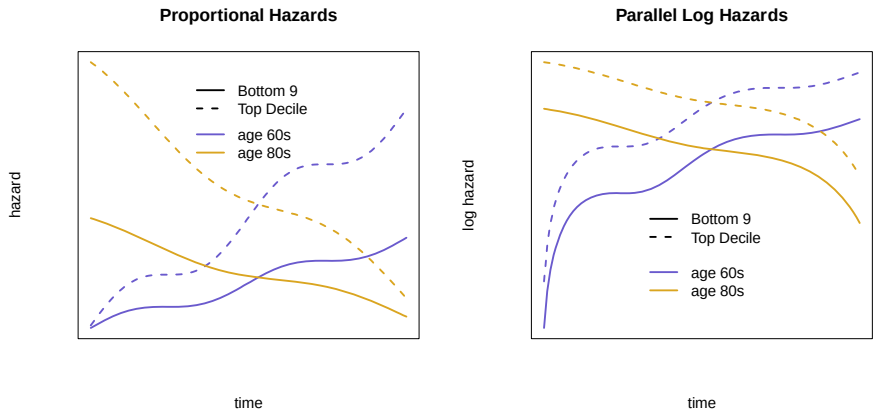
"Relative risk (or hazard ratio) comparing top decile FLC to the rest, among those in the same age group".

$\lambda(t)$ for $x_1 = 1$ and x_2: $\lambda_{0x_2}(t)e^{\beta_1 \cdot 1}$

$\lambda(t)$ for $x_1 = 0$ and x_2: $\lambda_{0x_2}(t)e^{\beta_1 \cdot 0}$

ratio: $\frac{\lambda_{0x_2}(t)}{\lambda_{0x_2}(t)}e^{\beta_1(1-0)} = e^{\beta_1}$

STRATIFICATION ADJUSTMENT



INTERACTION

One binary variable with continuous linear interaction, x_1 and x_2

$x_1 = \begin{cases} 1 & \text{Top Decile FLC} \\ 0 & \text{Otherwise} \end{cases}$

$x_2 =$ Age in years

$$\lambda(t) = \lambda_0(t)e^{\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1 x_2}$$

Interpretation of e^{β_1}:

"Relative risk (or hazard ratio) comparing top decile FLC to the rest among those with age (= x_2) = zero".

Interpretation of $e^{\beta_1 + x_2\beta_3}$:

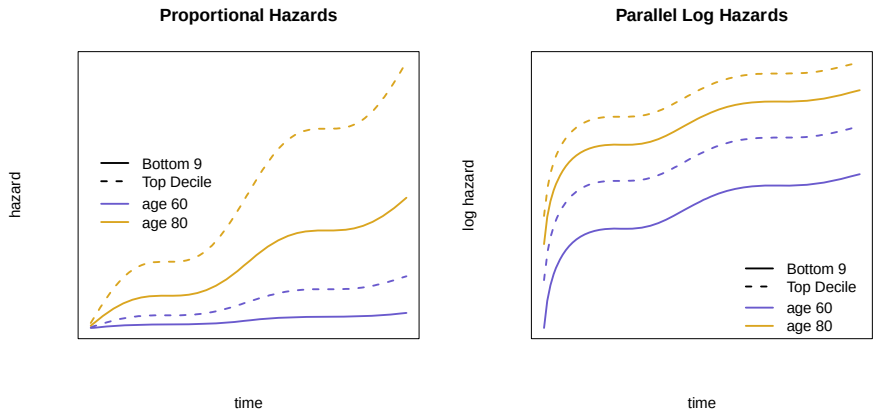
"Relative risk (or hazard ratio) comparing top decile FLC to the rest among those with age = x_2".

$\lambda(t)$ for $x_1 = 1$ and $x_2 = 0$: $\lambda_0(t)e^{\beta_1 \cdot 1}$ $\lambda(t)$ for $x_1 = 1$ and $x_2 \neq 0$: $\lambda_0(t)e^{\beta_1 \cdot 1 + \beta_2 \cdot x_2 + \beta_3 \cdot 1 \cdot x_2}$

$\lambda(t)$ for $x_1 = 0$ and $x_2 = 0$: $\lambda_0(t)e^{\beta_1 \cdot 0}$ $\lambda(t)$ for $x_1 = 0$ and $x_2 \neq 0$: $\lambda_0(t)e^{\beta_1 \cdot 0 + \beta_2 \cdot x_2 + \beta_3 \cdot 0}$

ratio: $e^{\beta_1(1-0)} = e^{\beta_1}$ ratio: $e^{\beta_1(1-0)+\beta_3(x_2-0)} = e^{\beta_1 + x_2\beta_3}$

INTERACTION



INTERACTION

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
topdecileTRUE	2.7312322	15.3517922	0.4154009	6.574930	0.0e+00
age	0.1067648	1.1126726	0.0025185	42.392311	0.0e+00
topdecileTRUE:age	-0.0252304	0.9750852	0.0054342	-4.642936	3.4e-06

	2.5 %	97.5 %
topdecileTRUE	6.8009436	34.6536508
age	1.1071938	1.1181785
topdecileTRUE:age	0.9647549	0.9855261

TOP DECILE HR BY AGE

age	exp(coef)	z	Pr(>|z|)	2.5 %	97.5 %
50	3.897886	8.499784	0.00e+00	2.848328	5.334189
60	3.077554	10.309487	0.00e+00	2.485373	3.810831
70	2.429865	13.162515	0.00e+00	2.128957	2.773302
80	1.918486	10.861243	0.00e+00	1.705679	2.157843
90	1.514729	4.368336	1.25e-05	1.257254	1.824932

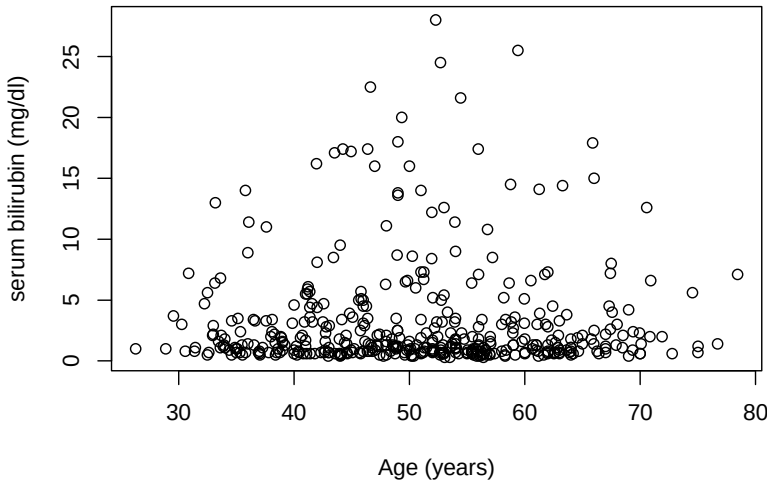
ADJUSTMENT AND PRECISION

- In Cox regression, addition of variables to a model that are associated only with the outcome can improve power.
- There is little effect on the coefficient estimate for other variables (eg treatment) or their standard errors, except when the association between outcome and the added variable is very strong.
- When there is an effect of adding a predictive variable, this is what happens to inference for the treatment variable or other variable of interest:
  - The standard error of its coefficient increases
  - The estimate of the coefficient moves farther from zero
  - The test of whether the coefficient is zero has more power.

PRIMARY BILIARY CIRRHOSIS

- Clinical trial with virtually no treatment effect
- Conducted before widespread use of immune suppressive therapies
- Good data for examining prognostic factors in PBC
- Some patients received liver transplant—treated as censored here
- Serum bilirubin associated with survival
- Treating age as a "precision variable"

AGE-BILIRUBIN ASSOCIATION



PRECISION

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
bili	0.1418533	1.152408	0.0115685	12.26201	0

	2.5 %	97.5 %
bili	1.126572	1.178836

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
bili	0.1436238	1.154450	0.0114189	12.577714	0e+00
age	0.0431303	1.044074	0.0080554	5.354198	1e-07

	2.5 %	97.5 %
bili	1.128899	1.180578
age	1.027719	1.060689

TO WATCH OUT FOR:

- Coefficients in Cox regression are positively associated with risk, not survival.
  - Positive β means large values of x are associated with shorter survival.
- Without certain types of time-dependent covariates (more later), Cox regression does not depend on the actual times, just their order.
  - Can add a constant to all times to remove zeros (which are removed by some software) without changing inference
- For LRT, nested models must be compared based on same subjects.
  - If some values of variables in larger model are missing, these subjects must be removed from fit of smaller model.
- Coefficient interpretation depends on what other variables are in the model and how they are coded (ie. interaction terms, 0/1 vs 1/-1 etc.)

SESSION 2: COMPETING RISKS, CAUSE-SPECIFIC HAZARDS, CUMULATIVE INCIDENCE AND FINE-GRAY MODELS

Module 17: Survival Analysis for Observational Data

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OUTLINE

- Definition of competing risks
- Identifiability issues
- Estimating cumulative incidence
- Interpretation under independent competing risks
  - Cumulative incidence
  - Fine-Gray regression
  - Cox regression
  - Cause-specific hazards
- Interpretation under dependent competing risks
  - Cox regression and cause-specific hazards
  - Cumulative incidence and Fine-Gray regression
- Composite outcomes
- Examples

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- **Definition of competing risks**
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COMPETING RISKS

- When there is more than one cause of failure:
  - Cancer recurrence or death before recurrence
  - MI, stroke, PE or death from other causes
- The different types of failure are called “competing risks”.
  - They “compete” to be the first to make subjects experience an event

MONOCLONAL GAMMOPATHY

- 241 Mayo Clinic Patients (Monoclonal Gammopathy of Undetermined Significance)
- 20-40 years of follow-up after diagnosis
- 64 developed plasma cell malignancy (PCM), 163 died without it.
- PCM and death without PCM are competing risks

R Kyle, Benign monoclonal gammopathy – after 20 to 35 years of follow-up, Mayo Clinic Proc 1993; 68:26-36

DATA

- In the monoclonal gammopathy data, there are k = 2 competing risks
- Data for the i^{th} subject are T_i and c_i, where
  - T_i = time to first of PCM or death
  - c_i = 1 if PCM; c_i = 2 if death

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CENSORING?

- Let c = k, k = 1, …, K indicate the "cause" of failure out of K competing risks. Here K = 2 (PCM and death no PCM).
- Suppose we are interested in risk factors for the development of PCM
- How do we treat the subjects who die without having experienced PCM? Can we treat them as censored?
  - Censoring assumptions:
  - Are they met?

IDENTIFIABILITY AND COMPETING RISKS

- Tsiatis (1975) showed that we cannot identify from ($T, c = k$) data whether subjects who fail from one cause would have been more or less susceptible later to failure from another cause, had they survived.
  - Cannot tell whether those who die from heart disease would have been more or less likely to develop cancer had they lived.
  - Cannot tell whether those who die w/o PCM would have been more or less likely to develop PCM had they lived.
- Dependence between the competing risks is not identifiable from (T, c) data.

OUTLINE

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- Identifiability issues
- **Estimating cumulative incidence**
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  - Cumulative incidence
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TREATING DEATHS AS CENSORING

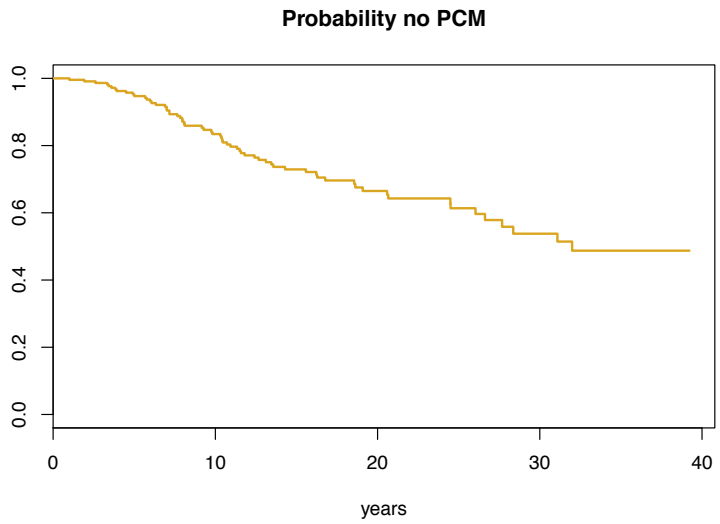
- What could be the effect on the KM estimate of S(t)?

- What could be the effect on Cox regression for the association of risk factors with PCM?

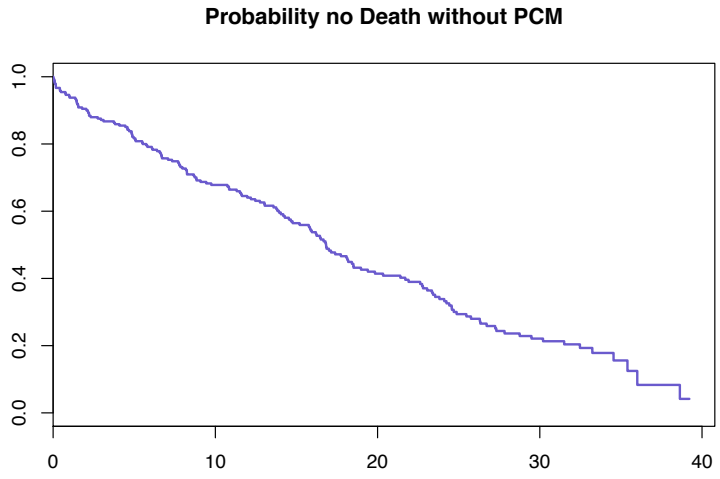
KAPLAN MEIER

- In situations like this, it was once common practice to apply the KM method to estimate "survival" functions:
  - Probability of avoiding PCM over time
  - Probability of avoiding death w/o PCM
- For PCM curve, treat deaths w/o PCM as censored
- For death w/o PCM, treat PCMs as censored

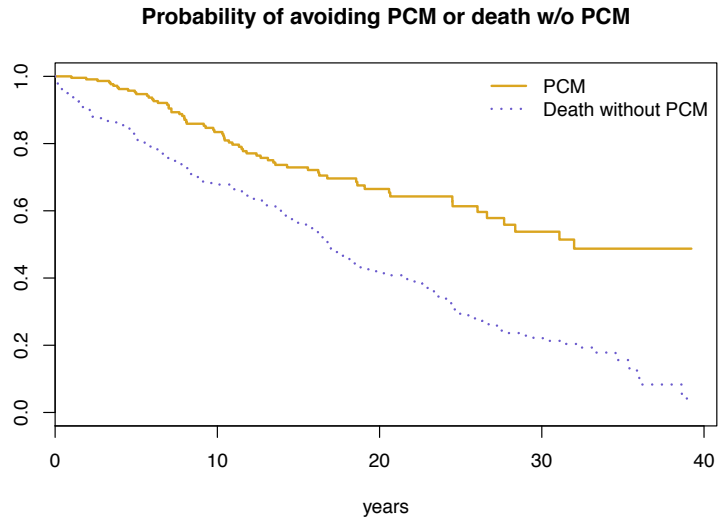
KM FOR NO PCM



KM FOR DEATH NO PCM



BOTH KM SURVIVAL FUNCTIONS



What is wrong with this picture?

KM ESTIMATE OF S(t)

- Recall that the Kaplan-Meier estimate of the survival function S(t) = Pr[T > t] = the probability of surviving beyond time t is given by:

$$\hat{S}(t) = \prod_{j:t_{(j)} \le t} \frac{S_{(j)}}{N_{(j)}}$$

- Where $t_{(j)}$ is the j^{th} smallest failure time, $S_{(j)}$ is the number known to survive beyond $t_{(j)}$, and $N_{(j)}$ is the number at risk of being observed to fail at $t_{(j)}$.

ESTIMATING 1 – S(t) FOR KTH TYPE

- We can write

$$1 - \hat{S}^{(k)}(t) = \sum_{j:t_{(j)} \le t} \frac{D_{(j)}^{(k)}}{N_{(j)}} \hat{S}^{(k)}(t_{(j-1)})$$

- At the second failure time of type k,

$$1 - \hat{S}^{(k)}(t_{(2)}) = 1 - \frac{N_{(1)} - D_{(1)}^{(k)}}{N_{(1)}} \cdot \frac{N_{(2)} - D_{(2)}^{(k)}}{N_{(2)}} = \frac{D_{(1)}^{(k)}}{N_{(1)}} + \frac{D_{(2)}^{(k)}}{N_{(2)}} \cdot \frac{N_{(1)} - D_{(1)}^{(k)}}{N_{(1)}}$$

- If any failures of another type have occurred between $t_{(1)}$ and $t_{(2)}$, *the* $\frac{N_{(1)} - D_{(1)}^{(k)}}{N_{(1)}}$ term is too big.
- This bias will accumulate and get larger, as we move to larger and larger $t_{(j)}$.

ESTIMATING CUMULATIVE INCIDENCE

- Letting $D_{(j)}^{(\bar{k})}$ = the number of failures of types other than k at $t_{(j)}$, an unbiased estimate of $F^{(k)}(t)$ is given by

$$\sum_{j:t_{(j)} \le t} \frac{D_{(j)}^{(k)}}{N_{(j)}} \prod_{i=1}^{j-1} \frac{N_{(i)} - D_{(i)}^{(k)} - D_{(i)}^{(\bar{k})}}{N_{(i)}} = \sum_{j:t_{(j)} \le t} \frac{D_{(j)}^{(k)}}{N_{(j)}} \prod_{i=1}^{j-1} \frac{N_{(i)} - D_{(i)}^{(k)}}{N_{(i)}} \cdot \frac{N_{(i)} - D_{(i)}^{(\bar{k})}}{N_{(i)}}$$

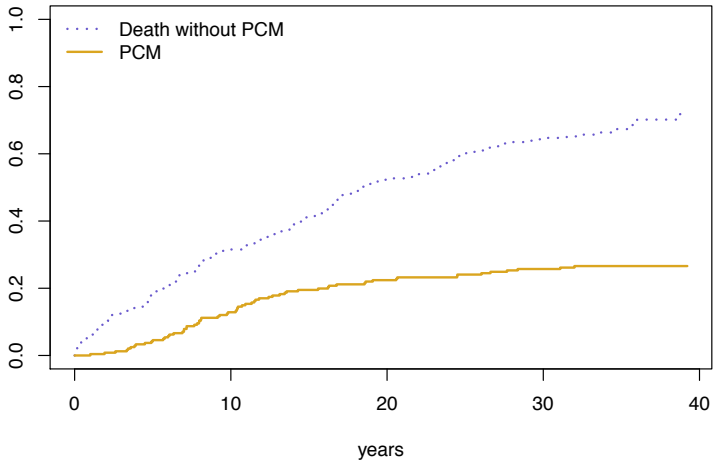
↑
no ties between failures of different types

- Compare to biased upward

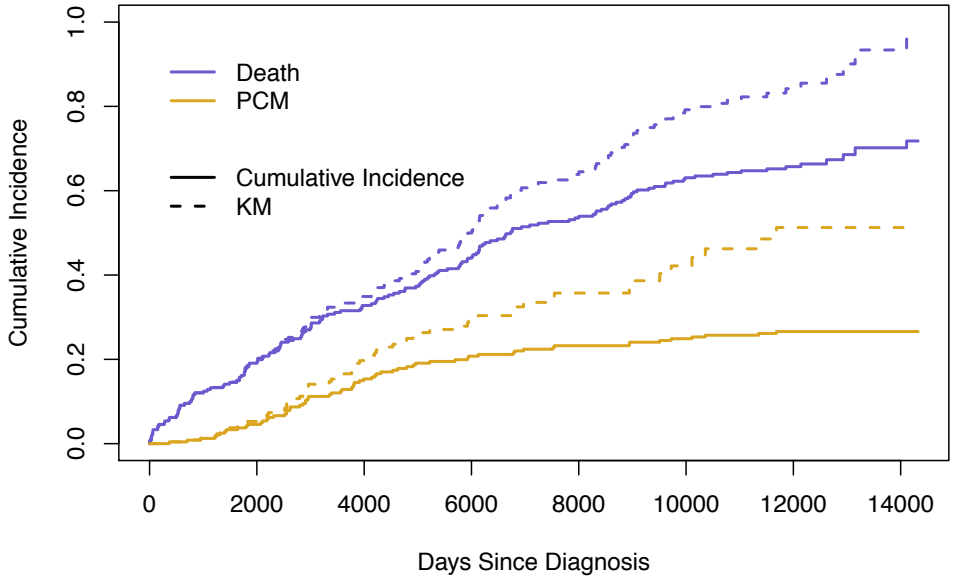
$$1 - \hat{S}^{(k)}(t) = \sum_{j:t_{(j)} \le t} \frac{D_{(j)}^{(k)}}{N_{(j)}} \hat{S}^{(k)}(t_{(j-1)}) = \sum_{j:t_{(j)} \le t} = \frac{D_{(j)}^{(k)}}{N_{(j)}} \prod_{i=1}^{j-1} \frac{N_{(i)} - D_{(i)}^{(k)}}{N_{(i)}}$$

.

CUMULATIVE INCIDENCE



CUMULATIVE INCIDENCE



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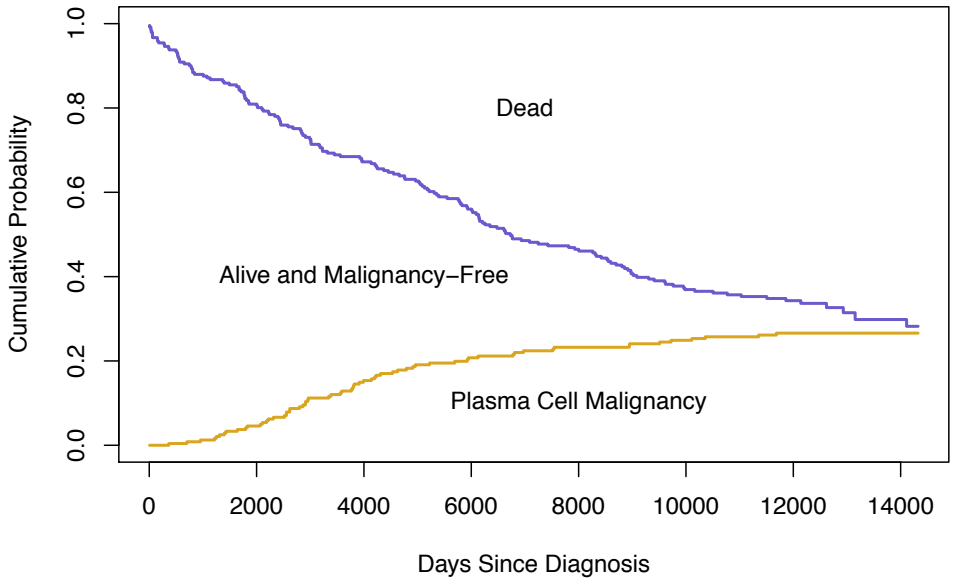


OUTLINE

- Definition of competing risks
- Identifiability issues
- Estimating cumulative incidence
- **Interpretation under independent competing risks**
  - **Cumulative incidence**
  - **Fine-Gray regression**
  - **Cox regression**
  - **Cause-specific hazards**
- Interpretation under dependent competing risks
  - Cox regression and cause-specific hazards
  - Cumulative incidence and Fine-Gray regression
- Composite outcomes
- Examples

START BY ASSUMING INDEPENDENCE

- To understand the strengths and weaknesses of estimating cumulative incidence and various regression models for competing risks data, it is helpful to begin by assuming the two risks are independent (unverifiable assumption)
  - Subjects who fail of one cause at t would have the same risk as those who do not fail of going on to experience the other event
  - In example: participants who die without PCM at t would be just as likely as those who do not to go on to develop PCM after t.

INDEPENDENT COMPETING RISKS AND CUMULATIVE INCIDENCE

- How might an intervention that increased the rate of the competing risk (death w/o PCM) influence the cumulative incidence of the event of interest (PCM)?

INDEPENDENT COMPETING RISKS AND CUMULATIVE INCIDENCE

- How might an intervention that increased the rate of the competing risk (death w/o PCM) influence the cumulative incidence of the event of interest (PCM)?
  - Higher death w/o PCM rate could mean fewer subjects develop PCM: ie. lower PCM incidence

SOME SUBTLETIES

- Cumulative incidence: the probability that an event of type *k* has occurred by time *t:*
  - Makes sense without requiring that a time to the k^{th} type of event be defined for all subjects
  - Depends on the portion of the population still at risk at each time, so its value will depend not only on the risk of the event of interest, but also on the risk of all the other causes of failure.
  - Is a population-specific quantity that depends on what other risks are operating in the population and how they are related to the risk of the event of interest.

INDEPENDENT COMPETING RISKS AND CUMULATIVE INCIDENCE

- How might an intervention that increased the rate of the competing risk (death w/o PCM) influence the cumulative incidence of the event of interest (PCM)?
  - Higher death w/o PCM rate could mean fewer subjects develop PCM: ie. lower PCM incidence
  - Would we think this is wrong we were interested mainly in what influenced overall cost or prognosis?

INDEPENDENT COMPETING RISKS AND CUMULATIVE INCIDENCE

- How might an intervention that increased the rate of the competing risk (death w/o PCM) influence the cumulative incidence of the event of interest (PCM)?
  - Higher death w/o PCM rate could mean fewer subjects develop PCM: ie. lower PCM incidence
  - Would we think this is wrong we were interested mainly in what influenced cost or prognosis?
  - If cost, no. If prognosis, probably, though would want to look at association with all competing risks. This argues for a different (combined) definition of the event of interest. More on this later.

INDEPENDENT COMPETING RISKS AND CUMULATIVE INCIDENCE

- How might an intervention that increased the rate of the competing risk (death w/o PCM) influence the cumulative incidence of the event of interest (PCM)?
  - Higher death w/o PCM rate could mean fewer subjects develop PCM: ie. lower PCM incidence
- For understanding causal associations, how useful would it be to look at how risk factors are associated with the cumulative incidence?

INDEPENDENT COMPETING RISKS AND CUMULATIVE INCIDENCE

- How might an intervention that increased the rate of the competing risk (death w/o PCM) influence the cumulative incidence of the event of interest (PCM)?
  - Higher death w/o PCM rate could mean fewer subjects develop PCM: ie. lower PCM incidence
- For understanding causal associations, how useful would it be to look at how risk factors are associated with the cumulative incidence.
  - Not very. Apparent associations could be due to causal association only with the competing risk.

CUMULATIVE INCIDENCE: WHEN TO USE

- Q: For what types of questions would we be interested in cumulative incidence, and determining what variables associated with cumulative incidence?
- A:

CUMULATIVE INCIDENCE: WHEN TO USE

- Q: For what types of questions would we be interested in cumulative incidence, and variables associated with cumulative incidence?
- A: In studying prognosis, and variables related to prognosis like total cost, population disease burden.

INDEPENDENCE: WHEN TO USE

Q: When would we want to estimate the cumulative incidence?

"Independent" competing risks		
	Prognosis/Cost	**Causality**
Estimating distribution of T	Cumulative Incidence (Not KM)	
Regression		

ASSOCIATIONS WITH PROGNOSIS

- To see if a risk factor is associated with prognosis/ cost, best to see how it is related to cumulative incidence.
- Fine-Gray regression models are the analogue of Cox regression for the cumulative incidence function.

FINE-GRAY HAZARD

$$\lambda^{FG(k)}(t) = \lim_{\Delta t \to 0} \Pr[T \in [t, t+\Delta t), c = k | T \geq t \text{ or both } T < t \text{ and } c \neq k]/\Delta t$$

- The risk of failure of type k among those still event free at *t* and those who have experienced any event other than a type k event by time *t*. (Note if type k is not death, this would include subjects who had already died.)
- The hazard function associated with the sub-distribution function which is the cumulative incidence of a type-k failure.

FINE-GRAY MODEL

- Fine-Gray hazard

$$\lambda^{FG(k)}(t) = \lim_{\Delta t \to 0} \Pr[T \in [t, t+\Delta t), c = k | T \geq t \text{ or both } T < t \text{ and } c \neq k]/\Delta t$$

- Fine-Gray regression model

$$\lambda^{FG(k)}(t|\mathbf{x}) = \lambda^{FG(k)}(t|\mathbf{0})e^{\beta \mathbf{x}}$$

INTERPRETATION

- When is Fine-Gray model appropriate?
- When concern is about associations with population burden of Type k events (ie PCM), total cost of type k events, or patient prognosis

FINE-GRAY RISK SETS

- All those who have not yet failed of any cause PLUS all those who have previously failed of all causes other than the cause of interest
- In monoclonal gammopathy example, assuming interest is in association with PCM, at time t, the risk sets is composed of:
  - All those alive and at risk of developing PCM AND
  - All those who died earlier without PCM

INDEPENDENCE: WHEN TO USE

Q: What regression model to use when interested in prognosis or total cost?

"Independent" competing risks		
	Prognosis/Cost	**Causality**
Estimating distribution of T	Cumulative Incidence (Not KM)	
Regression	Fine/Gray regression	

CAUSALITY AND INDEPENDENT COMPETING RISKS

- Q: So if we are interested in what is causally related to one of our competing risks and we think the different risks are independent, what can we do?
- A:

CAUSALITY AND INDEPENDENT COMPETING RISKS

- Q: So if we are interested in what is causally related to one of our competing risks and we think the different risks are independent, what can we do?
- A: Cox regression.
  - When we treat failures of the other types like we treat censoring, we are estimating the association with the "cause-specific hazard function" (Prentice et al., 1978)

$$\lambda^{(k)}(t) = \lim_{\Delta t \to 0} \Pr[T \in [t, t+\Delta t), c = k | T \geq t] / \Delta t$$

PROPERTIES

T = time to first "failure" of any type

$$\lambda^{(k)}(t) = \lim_{\Delta t \to 0} \Pr[T \in [t, t+\Delta t), c = k | T \geq t] / \Delta t$$

- The different events defined by c must be mutually exclusive
- The different events defined by c must be exhaustive
- The hazard function for the distribution of T is given by :

$$\lambda(t) = \sum_{k=1}^{K} \lambda^{(k)}(t)$$

COX MODEL RISK SETS

- All those who have not yet failed of any cause
- In monoclonal gammopathy example, assuming interest is in association with PCM, at time t, the risk sets is composed of:
  - All those alive, PCM free, and at risk of developing PCM
- Under independent competing risks, this will not be affected by variables that cause differences in the risk of failure due to other causes (death no PCM).
  - If more people die sooner without PCM, there are fewer PCM events in the population, but there are also fewer subjects in the risk set (denominator).
  - If the risks are independent, the cause-specific hazard function should be unaffected.

COX MODEL

- Cause-specific hazard

$$\lambda^{(k)}(t) = \lim_{\Delta t \to 0} \Pr[T \in [t, t+\Delta t), c = k | T \geq t]/\Delta t$$

- Cox model

$$\lambda^{(k)}(t|\mathbf{x}) = \lambda^{(k)}(t|\mathbf{0})e^{\beta \mathbf{x}}$$

INDEPENDENCE: WHEN TO USE

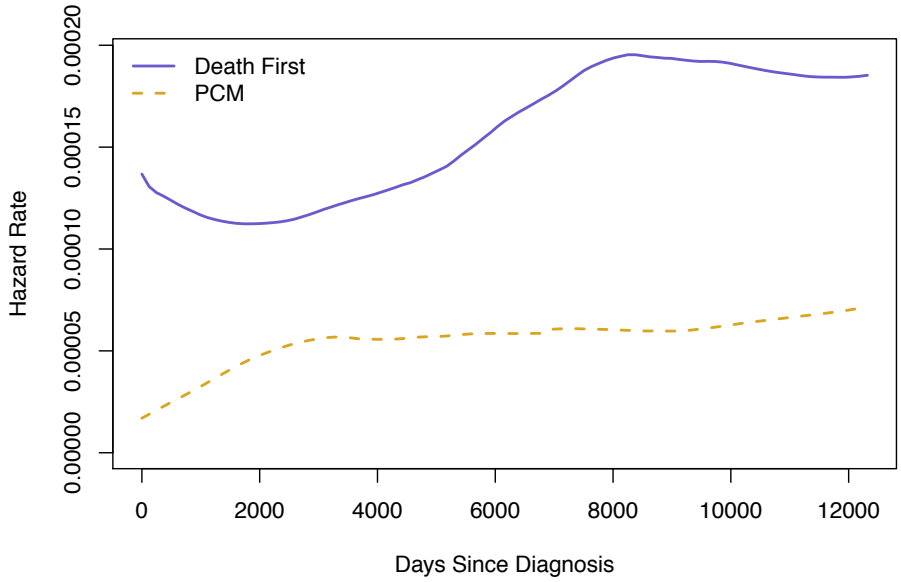
Q: What to plot when interested in causality?

"Independent" competing risks		
	Prognosis/Cost	**Causality**
Estimating distribution of T	Cumulative Incidence (Not KM)	
Regression	Fine/Gray regression	Cox regression

INDEPENDENCE: DISTRIBUTION ESTIMATION FOR CAUSALITY

- Can estimate the cause-specific hazard function for a subgroup (or the whole sample) using kernel – smoothing methods (not covered).
- Allows visual comparison of the cause-specific hazard functions

MG DATA : HAZARDS



INDEPENDENCE: WHEN TO USE

Q: What to plot when interested in causality?

"Independent" competing risks		
	Prognosis/Cost	**Causality**
Estimating distribution of T	Cumulative Incidence (Not KM)	Kernel-smoothed cause-specific hazards
Regression	Fine/Gray regression	Cox regression

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DEPENDENT COMPETING RISKS

- How do these interpretations and recommendations change when we think the competing risks might be dependent?
  - As <u>one</u> example: What if subjects who died with without PCM were also less likely to go on to develop PCM, had they lived? (ie. Pretend population is a mix of susceptibles to PCM and susceptibles to death from other causes.) How would this affect interpretation of:
    - Cumulative incidence?
    - Cause-specific hazard?

DEPENDENT COMPETING RISKS

- In addition, suppose there is a potential risk factor that raises the risk of death with no PCM among susceptibles (and that susceptibles who die without PCM would be unlikely to go on to develop PCM)
- How might this risk factor affect the cause-specific hazard function for PCM?

DEPENDENT COMPETING RISKS

- In addition, suppose there is a potential risk factor that raises the risk of death with no PCM among susceptibles (and that susceptibles who die without PCM would be unlikely to go on to develop PCM)
- How might this risk factor affect the cause-specific hazard function for PCM?
  - It could raise it (fewer alive and at risk at any time, but a higher proportion of them develop PCM)
- Do we care?

DEPENDENT COMPETING RISKS

- In addition, suppose there is a potential risk factor that raises the risk of death with no PCM among susceptibles (and that susceptibles who die without PCM would be unlikely to go on to develop PCM)
- How might this risk factor affect the cause-specific hazard function for PCM?
  - It could raise it (fewer alive and at risk at any time, but a higher proportion of them develop PCM)
- Do we care?
  - Yes if interested in causality for PCM. Risk factor associated with PCM cause-specific hazard, but not biologically/causally related to the PCM disease process.
  - Perhaps not if interested in predicting annual per-person cost.

INTERPRETATION

- Prentice et al (1978) argued that the cause-specific hazard function (Cox model) was the best basis for causal inference in the population as it is constituted, but cannot extend interpretation to another population where competing risks are not operating.
  - Cannot say how x might be related to cancer risk in a population where there are no deaths from MI

DEPENDENT COMPETING RISKS

- Still suppose there is a potential risk factor that raises the risk of death with no PCM among susceptibles (and that susceptibles who die without PCM would be unlikely to go on to develop PCM)
- How might this risk factor affect the cumulative incidence of PCM?

DEPENDENT COMPETING RISKS

- Still suppose there is a potential risk factor that raises the risk of death with no PCM among susceptibles (and that susceptibles who die without PCM would be unlikely to go on to develop PCM)
- How might this risk factor affect the cumulative incidence of PCM?
  - Might not affect it much if the two sub-populations of susceptibles are entirely distinct.
- Do we care?

DEPENDENT COMPETING RISKS

- Still suppose there is a potential risk factor that raises the risk of death with no PCM among susceptibles (and that susceptibles who die without PCM would be unlikely to go on to develop PCM)
- How might this risk factor affect the cumulative incidence of PCM?
  - Might not affect it much if the two sub-populations of susceptibles are entirely distinct.
- Do we care?
  - No. Fine-Gray regression gives valid estimate of association with prognosis and total cost in population as currently constituted.

DEPENDENT COMPETING RISKS

- As another example: What if subjects who died with without PCM were more likely to go on to develop PCM, had they lived? (ie. Pretend some members of the population are frail and susceptible to both PCM and other causes of death.) How would this affect interpretation of:
  - Cumulative incidence?
  - Cause-specific hazard?

DEPENDENT COMPETING RISKS

- Pretend some members of the population are frail and susceptible to both PCM and other causes of death, so those who die without PCM would have been more likely to develop it, had they lived.
- How might a risk factor that increases the risk of death without PCM affect the cause-specific hazard function for PCM?

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DEPENDENT COMPETING RISKS

- Pretend some members of the population are frail and susceptible to both PCM and other causes of death, so those who die without PCM would have been more likely to develop it, had they lived.
- How might a risk factor that increases the risk of death without PCM affect the cause-specific hazard function for PCM?
  - It could lower it (presence of risk factor is depleting the population of susceptibles)
- Do we care?

DEPENDENT COMPETING RISKS

- Pretend some members of the population are frail and susceptible to both PCM and other causes of death, so those who die without PCM would have been more likely to develop it, had they lived.
- How might a risk factor that increases the risk of death without PCM affect the cause-specific hazard function for PCM?
  - It could lower it (presence of risk factor is depleting the population of susceptibles)
- Do we care?
  - Perhaps, if interested in biologic causality for PCM.
  - Perhaps not, if interested in predicting annual per-person cost.

DEPENDENT COMPETING RISKS

- Pretend some members of the population are frail and susceptible to both PCM and other causes of death, so those who die without PCM would have been more likely to develop it, had they lived.
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DEPENDENT COMPETING RISKS

- Pretend some members of the population are frail and susceptible to both PCM and other causes of death, so those who die without PCM would have been more likely to develop it, had they lived.
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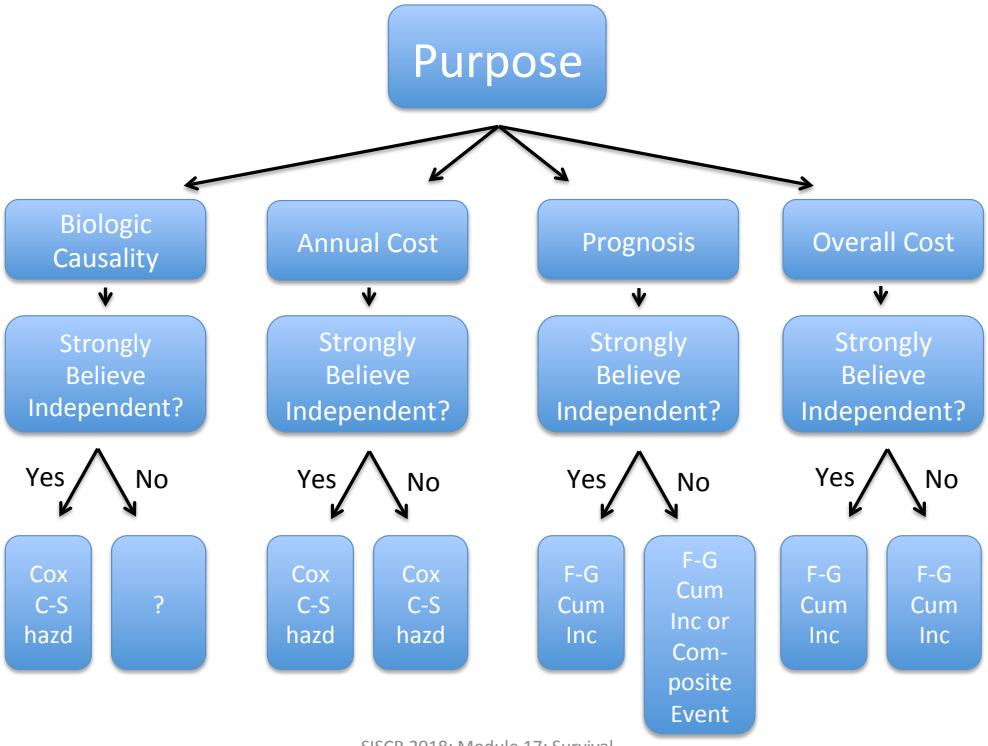
DEPENDENT COMPETING RISKS

- Pretend some members of the population are frail and susceptible to both PCM and other causes of death, so those who die without PCM would have been more likely to develop it, had they lived.
- How might this risk factor affect the cumulative incidence of PCM?
  - Might lower it. (presence of risk factor depletes the population of susceptibles)
- Do we care?
  - No. Accurate estimate of association with prognosis and total cost in population as currently constituted.

DEPENDENT COMPETING RISKS

"Dependent" competing risks		
	Prognosis/Cost	**Causality**
Estimating distribution of T	Cumulative Incidence (Not KM)	? Interpreting cause-specific hazard estimates may require knowledge/ assumption about mechanism
Regression	Fine/Gray regression	? Interpreting Cox regression may require knowledge/ assumption about mechanism



COMPETING RISKS: IMPORTANT POINTS

- Because we cannot tell whether competing risks are dependent, we cannot estimate hazard or incidence or anything else about the distribution of the event (time) of interest if there were no competing risks.
- All we can estimate and relate exposures to is the cumulative incidence and cause-specific hazard of the event of interest in the population as it is constituted (with potentially dependent competing risks).

COMPETING RISKS: IMPORTANT POINTS

- Biologic causality inferences from Cox regression must depend not only on the data, but also on biologic knowledge/assumptions that cannot be verified in the data.
- Cumulative incidence estimation and Fine-Gray regression are OK for inferences about prognosis or total cost even in the face of dependent competing risks, but these are not the same as inferences about biologic causality and may not be what we are interested in.

ADJUSTED FOR COMPETING RISKS

- Some people think of the results of Fine-Gray regression as the regression method that is "adjusted for competing risks"
- This is incorrect!
  - Fine-Gray regression gives us valid inferences about how variables are related to the cumulative incidence function.
  - It does not give us valid inferences about biologically causal associations between and exposure and the event of interest
  - Cox regression for cause-specific hazard functions can give valid inferences about biologically causal associations between exposure and the event of inference if the competing risks are independent, but we have no way of telling if they are.
  - If competing risks are not independent, all it tells us is how disease incidence rates in the population as it is constituted are related to exposure.

OUTLINE

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- Examples

PROGNOSIS

- If both competing risks are events we hope to avoid, Fine-Gray regression of risk factor's association with cumulative incidence of a single one of the risks may not be the most useful for estimating association with prognosis.
- Another option: composite events:
  - Death or PCM
  - Cancer relapse or death ("progression-free survival")
  - Death from any cause
- In clinical studies, combined event often of most interest to a patient

CUMULATIVE FUNCTIONS

Event-free Survival:

Estimating the probability a subject is alive and event-of-interest-free at time t is easy:

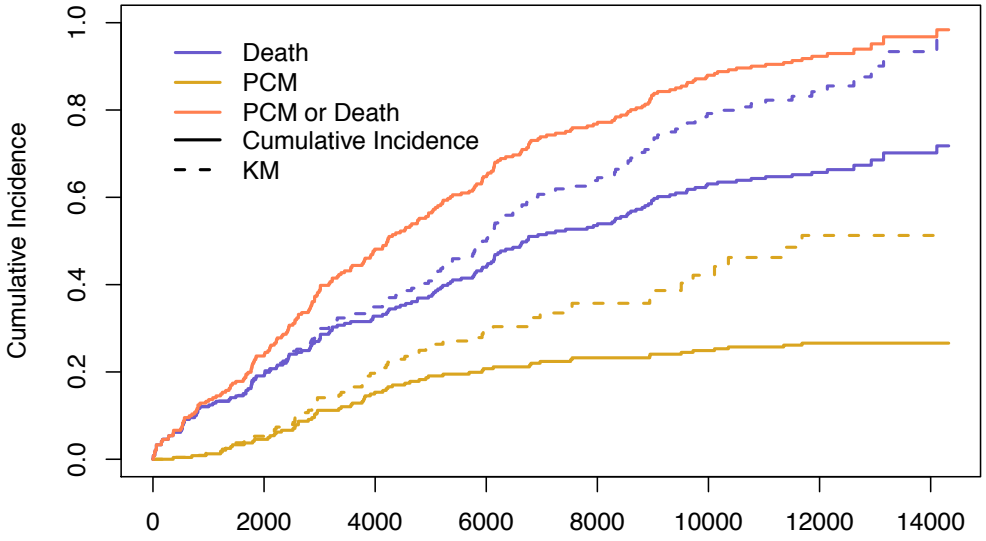
1. Redefine the event of interest to be either the original event of interest or death

$$\delta_i = \begin{cases} 1 & \text{event of interest or death from any cause} \\ 0 & \text{censored} \end{cases}$$

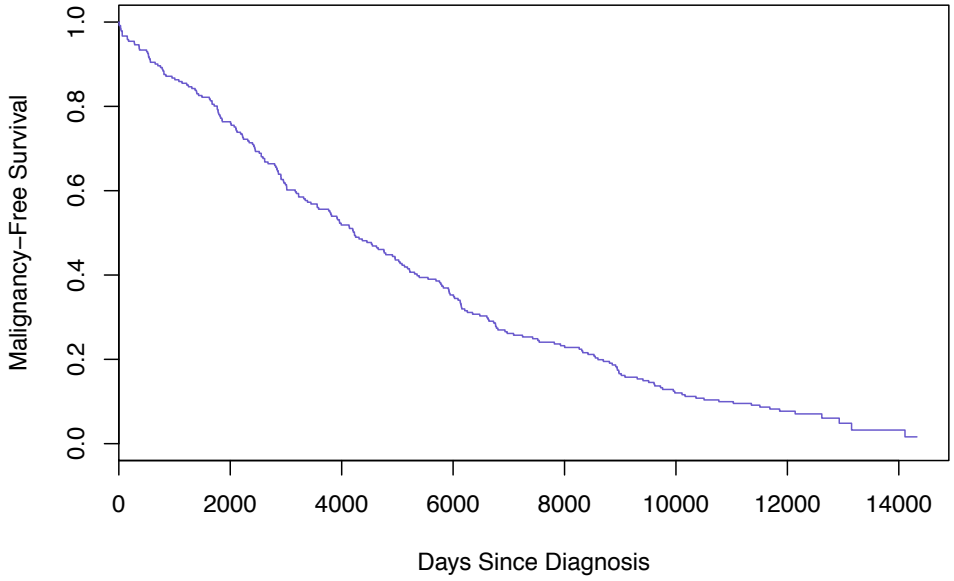
$$T_i = \text{ time to event of interest, death or censoring}$$

2. Compute the KM estimate of $S(t)$ in the usual way with (T_i, δ_i) data.

CUMULATIVE INCIDENCE



MALIGNANCY-FREE SURVIVAL



EXAMPLE

Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D, Davidson NE. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. New England Journal of Medicine. 2007;357(26):2666–2676.

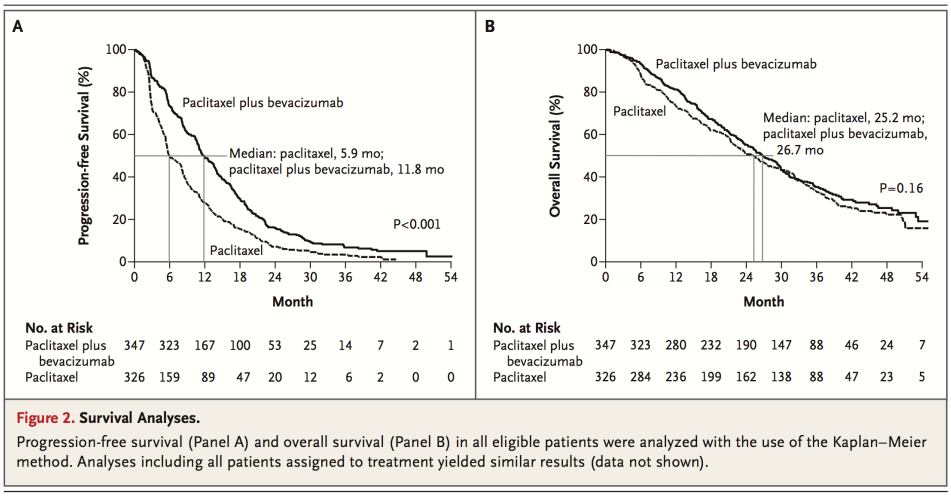


Figure 2. Survival Analyses.
Progression-free survival (Panel A) and overall survival (Panel B) in all eligible patients were analyzed with the use of the Kaplan–Meier method. Analyses including all patients assigned to treatment yielded similar results (data not shown).

FINE POINT

- When there are competing risks, functions that describe the probability distribution of the time to one of the events do not make sense.
- Cannot talk about $P[T > t]$ or $P[T \leq t]$ for a time to PCM T, since T does not exist for everyone
- Instead, need to interpret these functions as "Event has happened by time t" (cumulative incidence at t) and "Event has not happened by time t" (1 – cumulative incidence at t).

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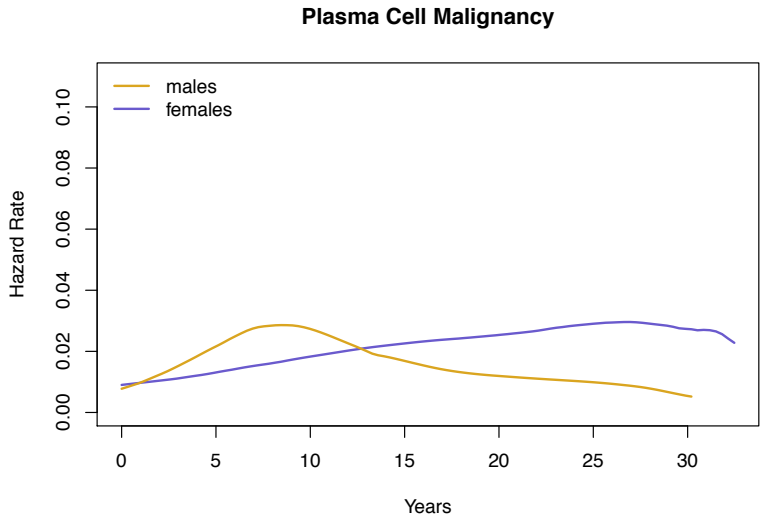
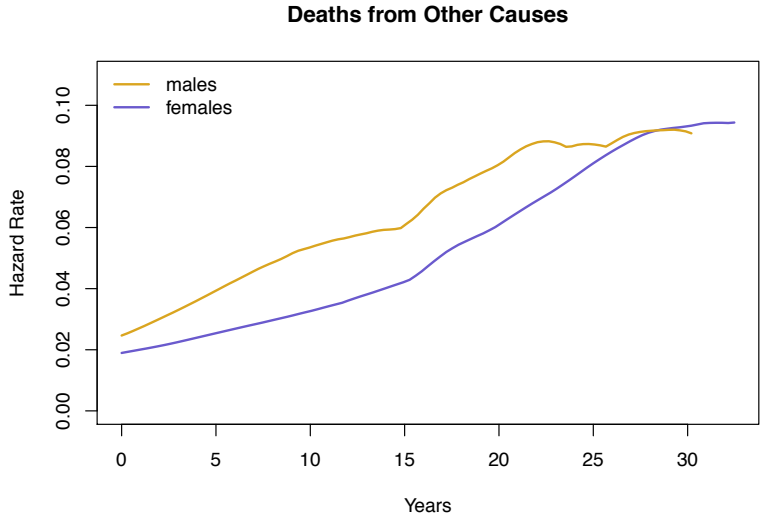
MGUS REGRESSION EXAMPLE

- Cox and Fine-Gray models for the association of sex with PCM and Death before PCM in the Monoclonal Gammopathy data.
- Will show
  - Cause-specific hazard functions by sex and cause
  - Cumulative incidence functions by sex and cause
  - Estimated Hazard ratios (male to female) by cause under both models

CAUSE-SPECIFIC HAZARD ESTIMATES



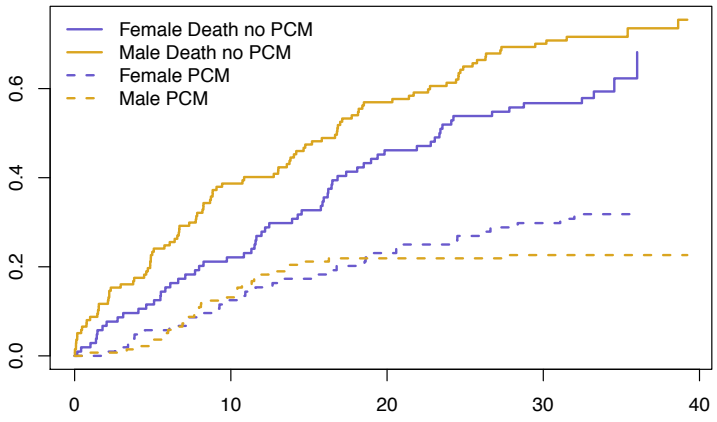
CAUSE-SPECIFIC HAZARD ESTIMATES



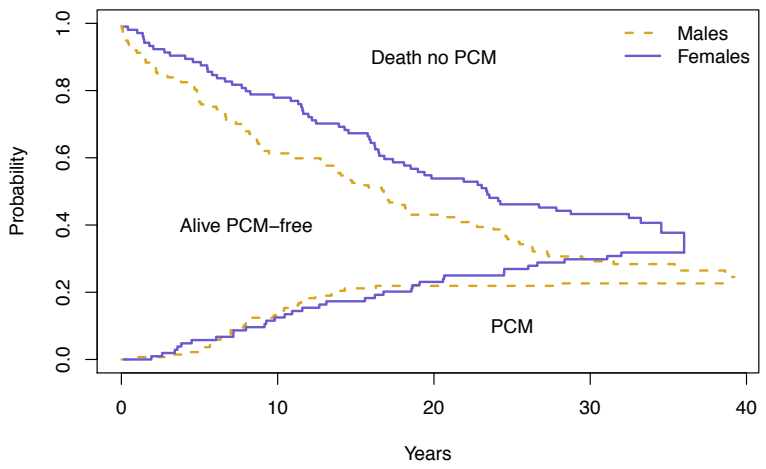
COX MODELS

Outcome Type	M/F Hazard Ratio	95% CI	P-value
Plasma Cell Malignancy	0.95	(0.58, 1.56)	0.8441
Death from Other Causes	1.55	(1.13, 2.14)	0.0064

CUMULATIVE INCIDENCE



CUMULATIVE INCIDENCE



FINE-GRAY MODELS

Outcome Type	M/F Hazard Ratio	95% CI	P-value
Plasma Cell Malignancy	0.71	(0.44, 1.16)	0.17
Death from Other Causes	1.45	(1.06, 1.97)	0.02

PCM hazard ratio farther from one here because men are more likely to die from other causes and not survive to develop PCM.

EXAMPLE

- Ashburner et al (2017) studied a cohort of 13,559 subjects diagnosed with atrial fibrillation (AF) at Kaiser Northern California
  - 1092 thromboembolism events (1017 ischemic strokes)
  - 4414 experienced death without thromboembolism event
  - Thromboembolism-free Death rate was 5.5/100 PY among warfarin takers and 8.1/100 PY among non-takers
  - Non-takers were older had higher stroke-risk scores
- They compared Cox and F-G regression with time-dependent current warfarin use as the exposure

EXAMPLE

Event	Model	Adjusted Hazard Ratio	95% CI
Thromboembolism	Cox	0.57	(0.50, 0.65)
	Fine-Gray	0.87	(0.77, 0.99)

- They concluded that the Fine-Gray model that "accounted for" competing risks gave a better "real-world" assessment of the benefit of warfarin.
- What are your thoughts?

Ashburner JM, Go AS, Chang Y, Fang MC, Fredman L, Applebaum KM, Singer DE. J Am Geriatr Soc. 2017 Jan 1;65(1):35–41.

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TO WATCH OUT FOR

- Interpretation in the presence of competing risks can be tricky and requires extra care.
  - Cannot interpret cumulative incidence or cause-specific hazard as applying in a population without competing risks present.
  - 1 – KM estimator can give upward biased estimate of cumulative incidence.
  - Fine-Gray model is not THE way to account for competing risks. It tells us only what variables are associated with cumulative incidence, and this may not be what you are interested in.

SESSION 3a: CHOICE OF THE TIME SCALE AND INTERACTIONS WITH TIME

Module 17: Survival Analysis for Observational Data

Summer Institute in Statistics for Clinical Research
University of Washington
July, 2018

Barbara McKnight, Ph.D.

OUTLINE

- Choice of the time scale for analysis
- Left entry into observation (left truncation)
- Cox models including interaction with time variables/ time-dependent coefficients

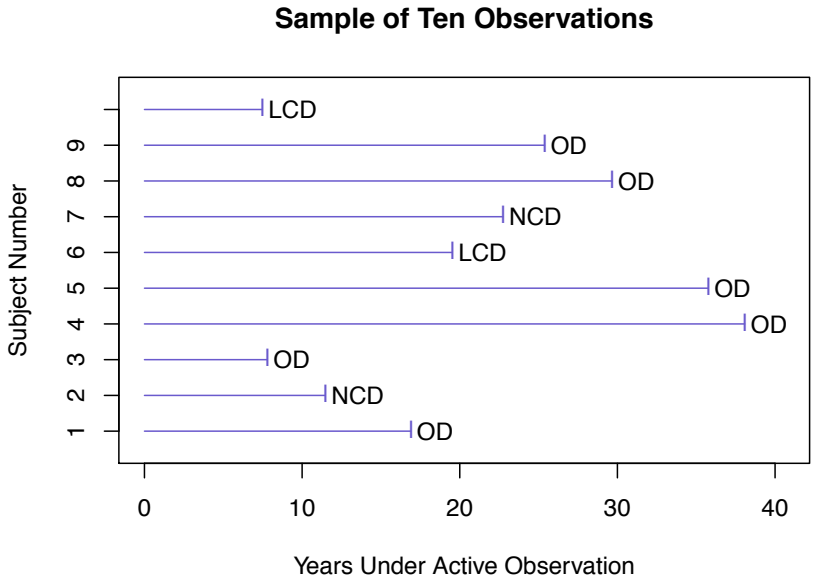
OUTLINE

- **Choice of the time scale for analysis**
- Left entry into observation (left truncation)
- Cox models including interaction with time variables/ time-dependent coefficients

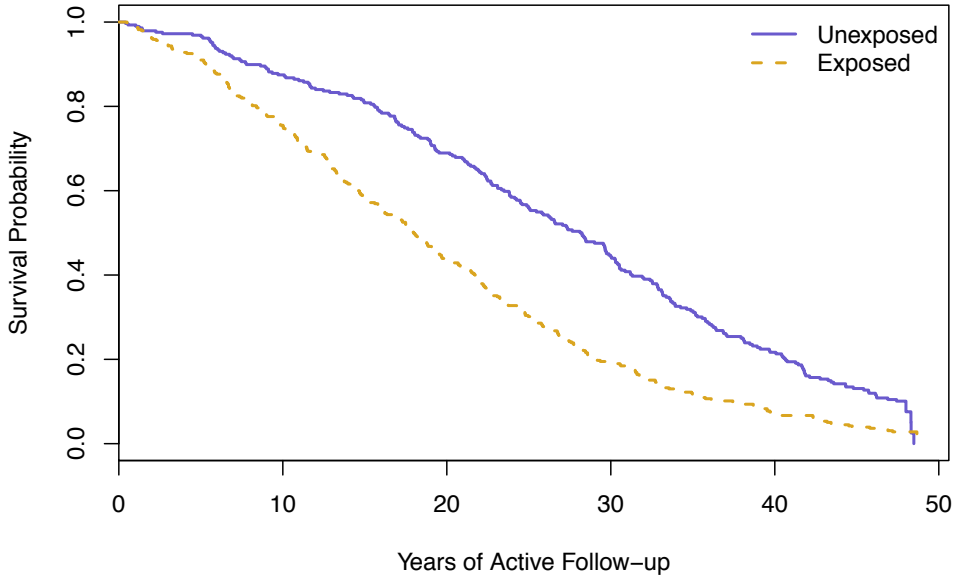
WELSH NICKEL REFINERS STUDY

- 679 nickel refinery workers identified twice on paysheets April 1929, 1934, 1939, 1944, 1949
- Follow-up until 1981
- Refinery cleaned up by various means 1922-1932, so all important exposure occurred before beginning of follow-up
- Interest in whether duration of employment in high-exposure areas, and age at first exposure, were related to lung and nasal sinus cancer mortality risk.

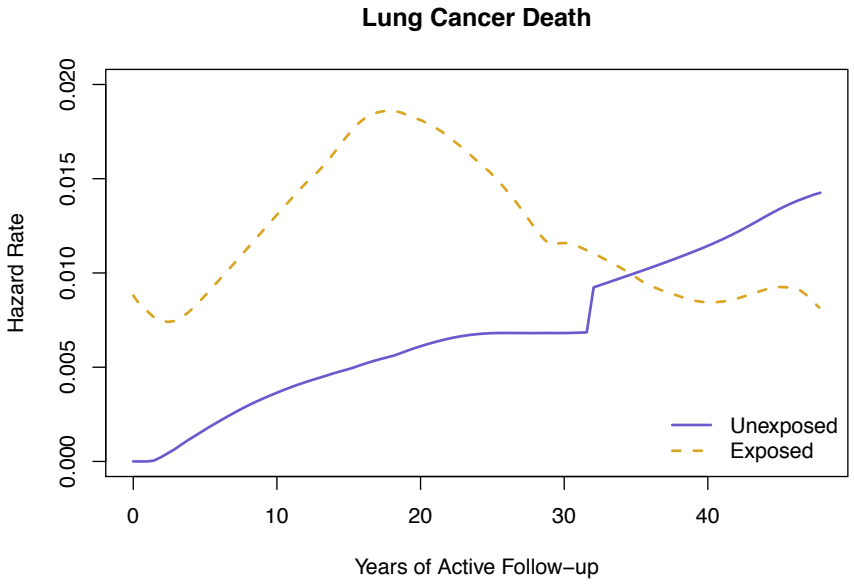
WELSH NICKEL REFINERS



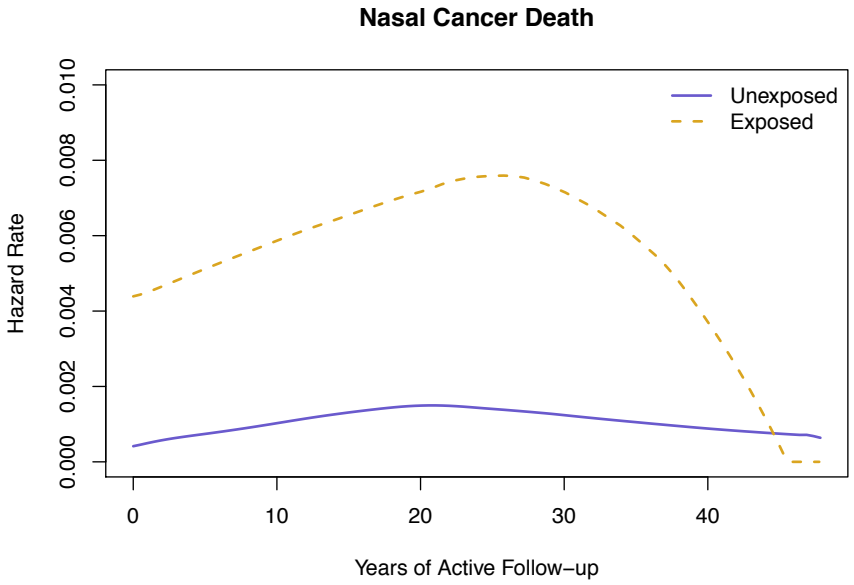
ALL-CAUSE MORTALITY



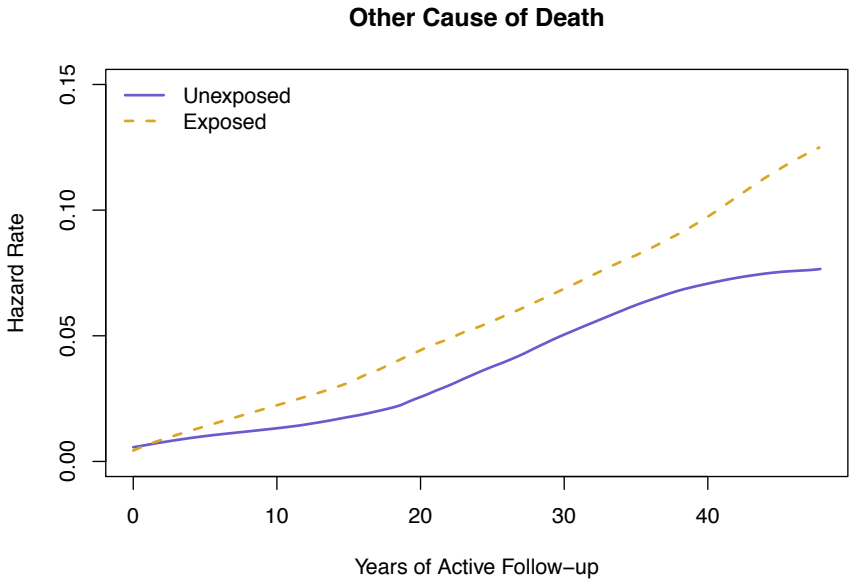
WELSH NICKEL REFINERS



WELSH NICKEL REFINERS



WELSH NICKEL REFINERS



LUNG CANCER FU TIME

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
exposedTRUE	0.9200182	2.509336	0.1869493	4.921217	9e-07

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
exp0.5 - 4.0	0.6030012	1.8275955	0.2121299	2.8426041	0.0044747
exp4.5 - 8.0	1.0862839	2.9632419	0.2828485	3.8405146	0.0001228
exp8.5-12.0	1.2772969	3.5869307	0.3742268	3.4131628	0.0006421
exp12.5+	1.4873597	4.4253955	0.4798472	3.0996524	0.0019375
afe20-27.5	0.8103938	2.2487934	0.3079688	2.6314149	0.0085030
afe27.5 - 35	0.9149895	2.4967489	0.3291081	2.7802097	0.0054324
afe35+	0.8068991	2.2409482	0.4237839	1.9040342	0.0569057
yfe1910-1914	0.3342204	1.3968510	0.2695145	1.2400835	0.2149445
yfe1915-1919	-0.1340505	0.8745459	0.3749097	-0.3575540	0.7206771
yfe1920-1925	0.0744977	1.0773429	0.2966621	0.2511197	0.8017216

NASAL CANCER FU TIME

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
exposedTRUE	1.614074	5.023236	0.3516507	4.589994	4.4e-06

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
exp0.5 - 4.0	0.8356274	2.3062606	0.4032111	2.072432	0.0382252
exp4.5 - 8.0	1.1366437	3.1162916	0.4706657	2.414970	0.0157365
exp8.5-12.0	2.2945326	9.9197981	0.5117936	4.483316	0.0000073
exp12.5+	2.8713357	17.6605917	0.5697217	5.039892	0.0000005
afe20-27.5	1.4686105	4.3431963	0.7518514	1.953326	0.0507810
afe27.5 - 35	2.1598639	8.6699580	0.7588726	2.846148	0.0044252
afe35+	3.4767227	32.3535148	0.7843101	4.432842	0.0000093
yfe1910-1914	0.7130093	2.0401213	0.3728470	1.912338	0.0558329
yfe1915-1919	0.5040978	1.6554913	0.5034466	1.001294	0.3166849
yfe1920-1925	-0.9304088	0.3943924	0.5152666	-1.805684	0.0709677

OTHER CAUSES FU TIME

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
exposedTRUE	0.3962896	1.4863	0.0972056	4.076818	4.57e-05

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
exp0.5 - 4.0	0.1318081	1.1408894	0.1105672	1.1921083	0.2332188
exp4.5 - 8.0	0.1308735	1.1398236	0.1603797	0.8160231	0.4144869
exp8.5-12.0	0.0324914	1.0330250	0.2563862	0.1267282	0.8991555
exp12.5+	-0.0774111	0.9255093	0.3964677	-0.1952520	0.8451957
afe20-27.5	0.5275548	1.6947832	0.1539622	3.4265217	0.0006114
afe27.5 - 35	1.1070376	3.0253827	0.1653356	6.6956992	0.0000000
afe35+	1.9740626	7.1998671	0.1942464	10.1626701	0.0000000
yfe1910-1914	-0.2148112	0.8066937	0.1515491	-1.4174361	0.1563555
yfe1915-1919	-0.5297679	0.5887416	0.1766843	-2.9983870	0.0027141
yfe1920-1925	-1.1456390	0.3180206	0.1502442	-7.6251795	0.0000000

COX REGRESSION MODEL

$$\lambda(t) = \lambda_0(t)e^{\beta_1 x_1 + \cdots + \beta_k x_k}$$

Interpretation of e^{β_1} in general:

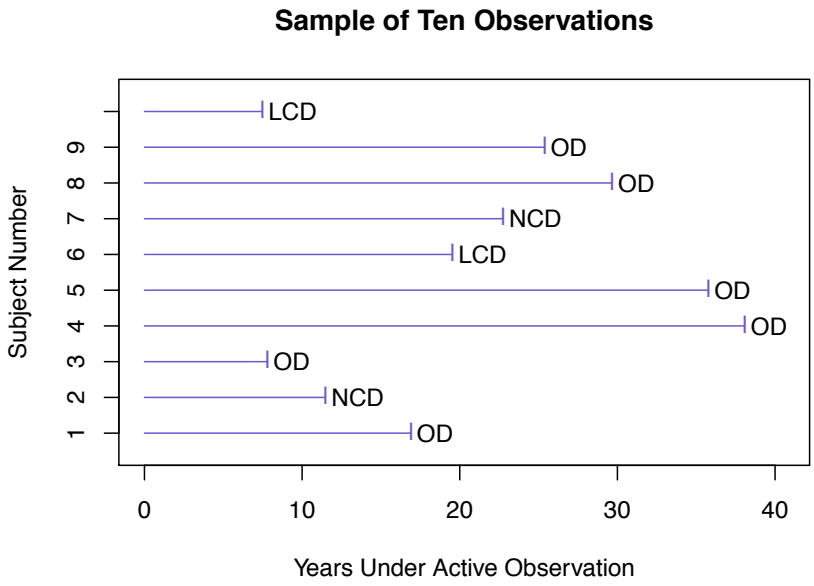
"Relative risk (or hazard ratio) associated with a one unit higher value of x_1, holding $x_2, \ldots, x_k$ constant".

$$\begin{aligned} \lambda(t) \text{ for } x_1 + 1: &\quad \lambda_0(t)e^{\beta_1(x_1+1)+\cdots+\beta_k x_k} \\ \lambda(t) \text{ for } x_1: &\quad \lambda_0(t)e^{\beta_1 x_1+\cdots+\beta_k x_k} \\ \text{ratio:} &\quad e^{\beta_1(x_1+1-x_1)} = e^{\beta_1} \end{aligned}$$

COX REGRESSION MODEL

- $e^{\beta 1}$ is the RR associated with a one-unit difference of x_1, holding other x's and t constant.
- Some functional form is required for how the hazard function at each t depends on $x_2 \ldots x_k$.
- No functional form is required for how the hazard at each $x_2 \ldots x_k$ depends on t, since $\lambda_0(t)$ can be any function.
- The time scale for t is the variable that is adjusted for the most finely/thoroughly.

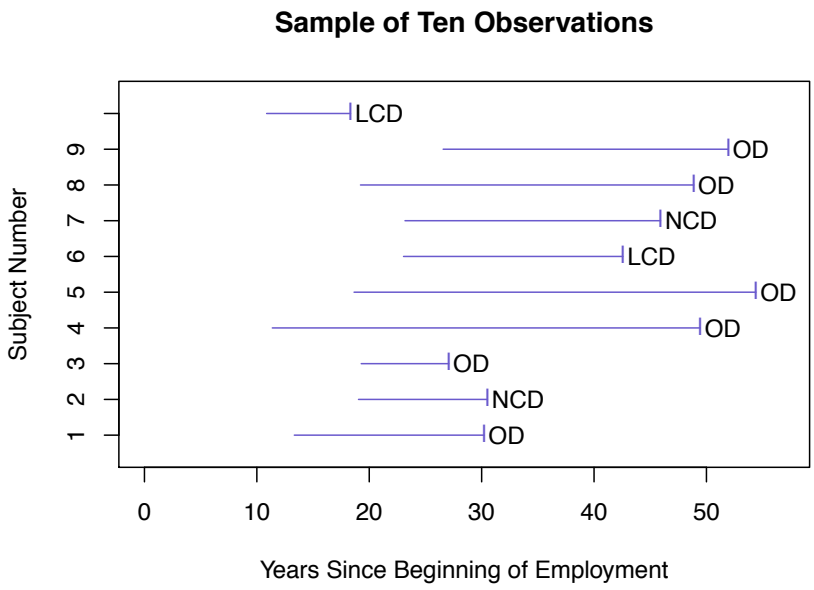
WELSH NICKEL REFINERS



OUTLINE

- **Choice of the time scale for analysis**
- **Left entry into observation (left truncation)**
- Cox models including interaction with time variables/ time-dependent coefficients

WELSH NICKEL REFINERS



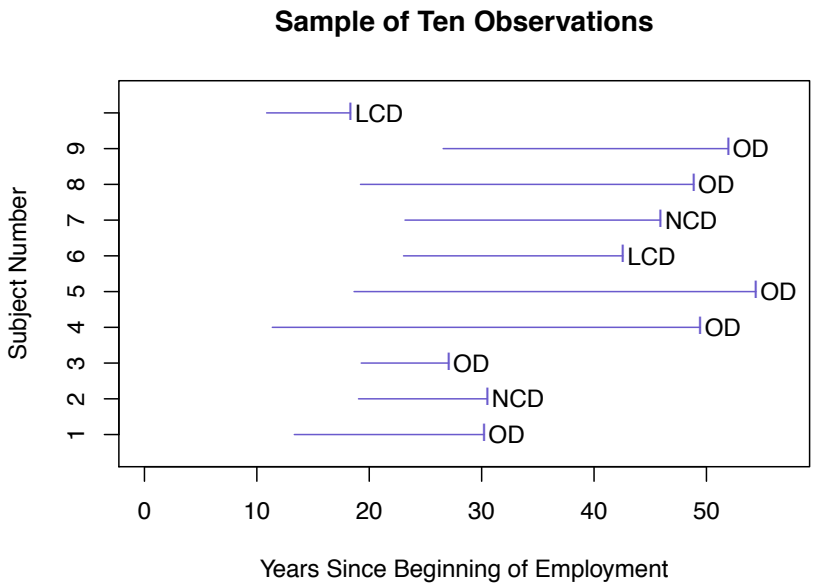
OBSERVATION STARTING LATE

- Should not include subjects in risk sets before they are under observation:
  - Other subjects "just like" them who died before their entry time are not observed
  - Falsely inflates the numbers at risk in early risk sets
  - Biases cause-specific hazard estimation
  - Can bias Cox model estimation

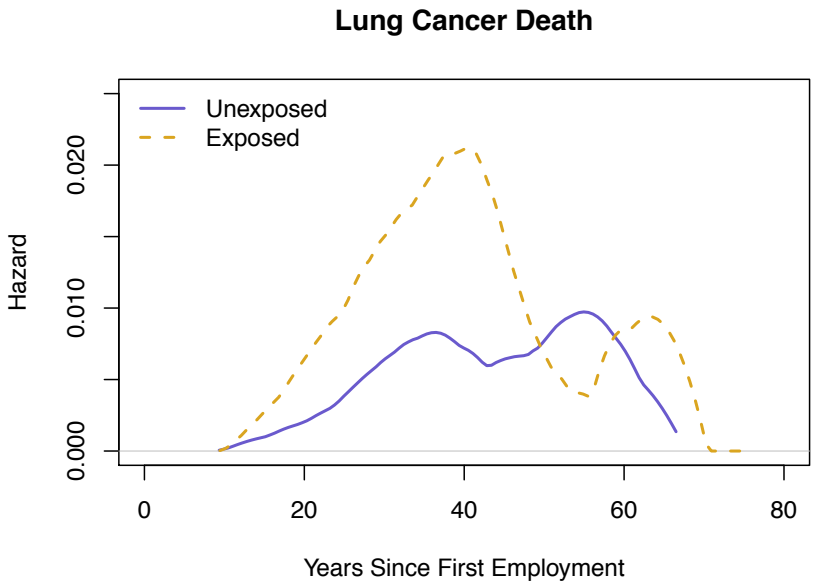
OBSERVATION STARTING LATE

- Solution: “Left enter” subjects at time when active follow-up starts
  - Subjects only contribute to risk sets where their event could have been observed
  - They are only in the denominator if we could have seen them in the numerator

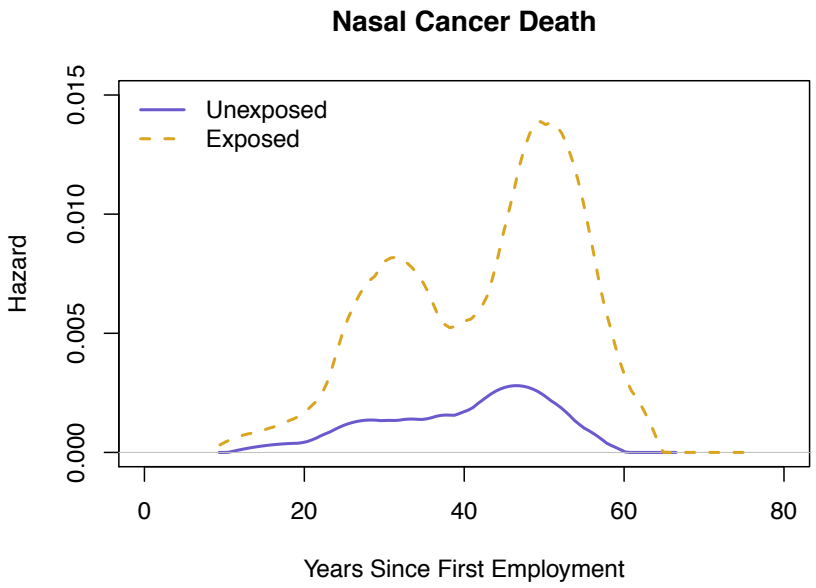
WELSH NICKEL REFINERS



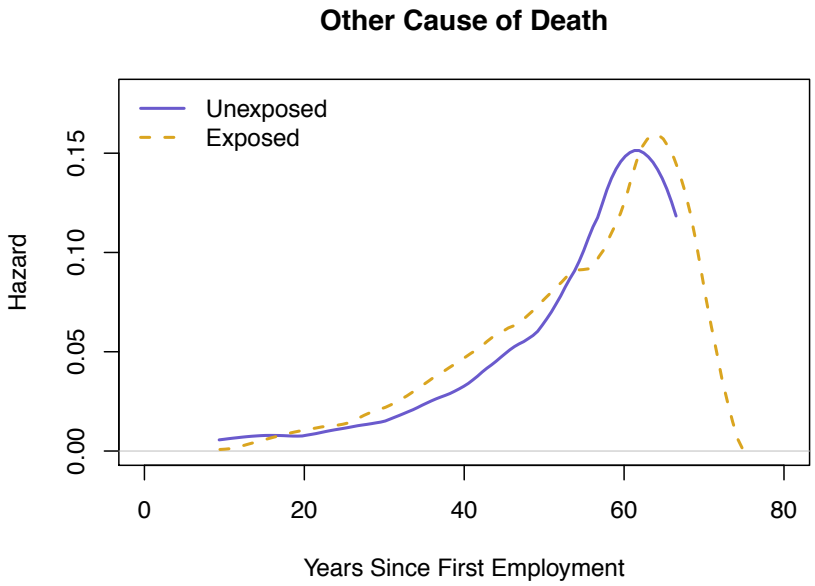
LUNG CANCER



NASAL CANCER



OTHER CAUSES



LUNG CANCER TFE

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
exposedTRUE	0.8000334	2.225615	0.1860041	4.301159	1.7e-05

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
exp0.5 - 4.0	0.6111674	1.842581	0.2123734	2.877796	0.0040046
exp4.5 - 8.0	1.0952795	2.990018	0.2838639	3.858467	0.0001141
exp8.5-12.0	1.2880174	3.625591	0.3739070	3.444754	0.0005716
exp12.5+	1.4327121	4.190048	0.4791166	2.990321	0.0027868
afe20-27.5	0.7604881	2.139320	0.3081636	2.467806	0.0135944
afe27.5 - 35	0.8670846	2.379962	0.3281099	2.642665	0.0082256
afe35+	0.7982183	2.221579	0.4224336	1.889571	0.0588154
yfe1910-1914	0.4358460	1.546271	0.2724801	1.599552	0.1096981
yfe1915-1919	0.1753274	1.191636	0.3775109	0.464430	0.6423397
yfe1920-1925	0.6547157	1.924595	0.2991155	2.188839	0.0286086

NASAL CANCER TFE

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
exposedTRUE	1.540408	4.666495	0.3503185	4.397165	1.1e-05

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
exp0.5 - 4.0	0.8958359	2.449382	0.4044464	2.2149680	0.0267623
exp4.5 - 8.0	1.1991717	3.317368	0.4727052	2.5368277	0.0111862
exp8.5-12.0	2.3214816	10.190761	0.5173928	4.4868842	0.0000072
exp12.5+	2.8655920	17.559445	0.5727364	5.0033346	0.0000006
afe20-27.5	1.4721869	4.358757	0.7527320	1.9557917	0.0504897
afe27.5 - 35	2.1770312	8.820082	0.7601145	2.8640834	0.0041822
afe35+	3.6025888	36.693104	0.7886401	4.5681026	0.0000049
yfe1910-1914	1.0373701	2.821786	0.3798834	2.7307593	0.0063189
yfe1915-1919	1.1291520	3.093033	0.5130845	2.2007137	0.0277563
yfe1920-1925	0.0166965	1.016837	0.5257787	0.0317558	0.9746668

OTHER CAUSE OF DEATH TFE

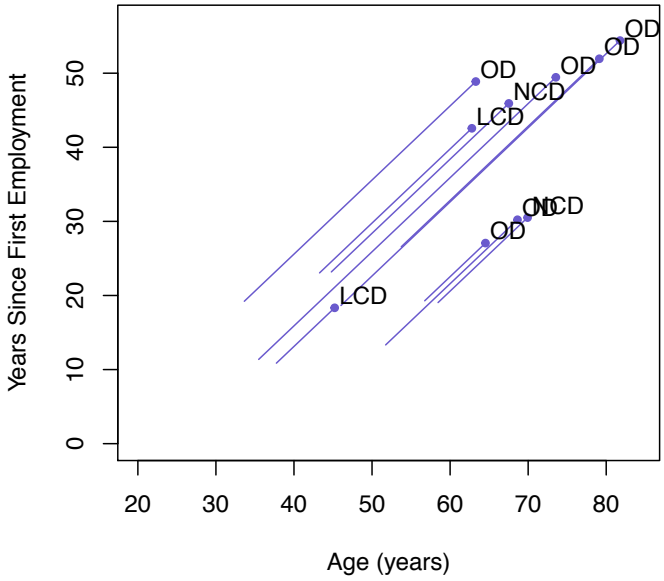
	coef	exp(coef)	se(coef)	z	Pr(>|z|)
exposedTRUE	0.2164895	1.24171	0.0966131	2.240788	0.0250398

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
exp0.5 - 4.0	0.1685250	1.183558	0.1106070	1.5236376	0.1275993
exp4.5 - 8.0	0.2360561	1.266245	0.1602288	1.4732445	0.1406851
exp8.5-12.0	0.0585201	1.060266	0.2564181	0.2282213	0.8194742
exp12.5+	0.0245456	1.024849	0.3964995	0.0619059	0.9506378
afe20-27.5	0.5704774	1.769111	0.1545876	3.6903186	0.0002240
afe27.5 - 35	1.1656136	3.207891	0.1665088	7.0003136	0.0000000
afe35+	2.0835886	8.033245	0.1957375	10.6448086	0.0000000
yfe1910-1914	0.2087081	1.232085	0.1540413	1.3548842	0.1754544
yfe1915-1919	0.2329453	1.262312	0.1788233	1.3026563	0.1926921
yfe1920-1925	0.1024386	1.107869	0.1529133	0.6699127	0.5029135

CHOOSING A TIME SCALE

- What time scale makes the most sense for the Welsh Nickel Refiners study?

TWO TIME SCALES



CHOOSING A TIME SCALE

- Cardiovascular Health Study
  - NHLBI cohort of older Americans (65+)
  - Many baseline demographic and health measures.
  - Follow-up for more than 20 years for a large number of health conditions.
- What is the best time scale: age or time since baseline?

OUTLINE

- Choice of the time scale for analysis
- Left entry into observation (left truncation)
- **Cox models including interaction with time variables/time-dependent coefficients**

TIME INTERACTIONS

- So far, most of our Cox models have assumed that the hazard ratio is constant over time
- It's possible to incorporate interaction terms with functions of time to allow the HR to depend on time.
- Requires a hypothesized functional form for f(t).

TIME INTERACTIONS

- One way the hazard ratio can depend on time: interaction with a function of time

$$\lambda(t|x) = \lambda_0(t)e^{\beta_1 x + \beta_2 x * f(t)}$$

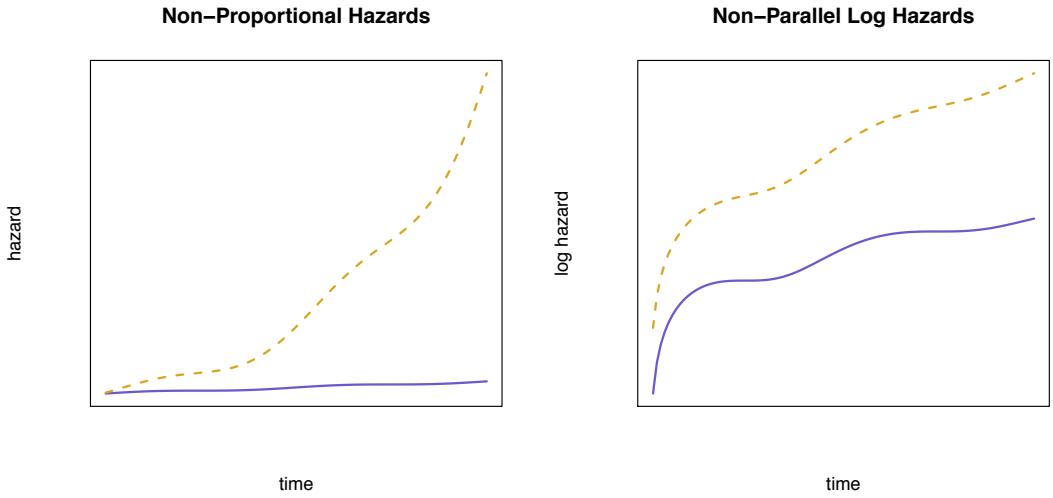
- Here the hazard ratio depends on time through the interaction term

$$\begin{aligned} \lambda(t|x+1) &= \lambda_0(t)e^{\beta_1(x+1)+\beta_2(x+1)*f(t)} \\ \lambda(t|x) &= \lambda_0(t)e^{\beta_1(x)+\beta_2(x)*f(t)} \\ \text{HR}(t) &= e^{\beta_1+\beta_2 f(t)} \end{aligned}$$

- Commonly used functions are:

$$f(t) = t,\ f(t) = \log(t),\ \text{and}\ f(t) = \hat{S}(t).$$

TIME INTERACTIONS

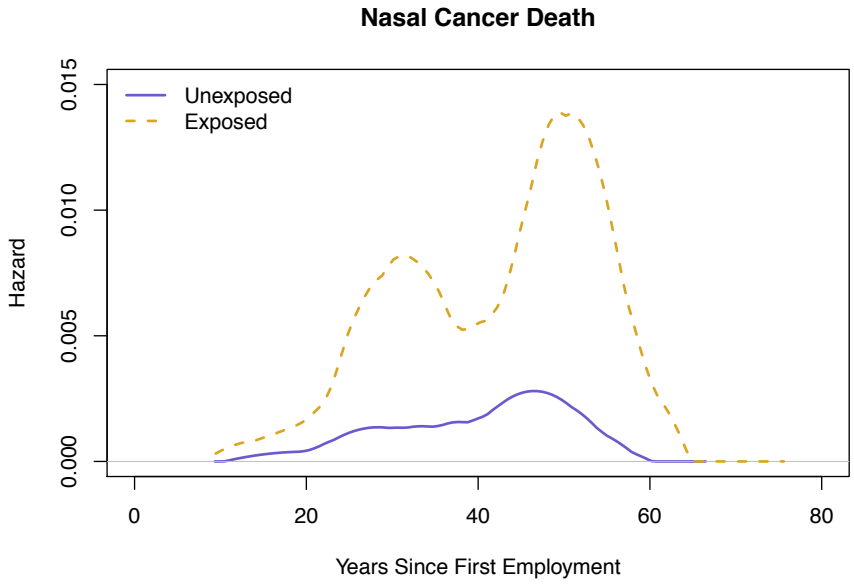


NASAL CANCER TIME INTERACTION

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
exposedTRUE	1.540408	4.666495	0.3503185	4.397165	1.1e-05

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
exposedTRUE	1.0613334	2.890222	5.161871	0.2056102	0.8370954
tt(exposed)	0.1290554	1.137753	1.388229	0.0929641	0.9259321

NASAL CANCER



ESTIMATING THE HR AS A FUNCTION OF TIME

- In exploratory analyses, may be of interest to estimate how the hazard ratio varies over time
- Estimate based on ratio of kernel-smoothed hazard estimates can be very variable
- Better choice is based on smoothed Schoenfeld residuals
- Can be thought of as an estimate of a time-dependent coefficient of a fixed variable

ESTIMATING THE HR AS A FUNCTION OF TIME

Another way for the hazard ratio to depend on time: time-dependent coefficients.

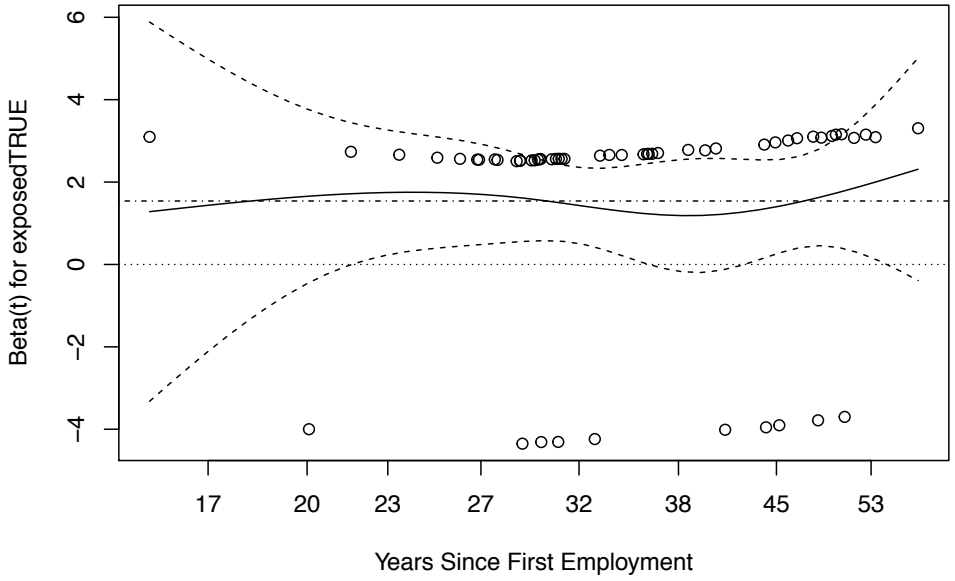
$$\lambda(t) = \lambda_0(t)e^{\beta(t)x}$$

Here the hazard ratio depends on time through the time-dependent coefficient $\beta(t)$

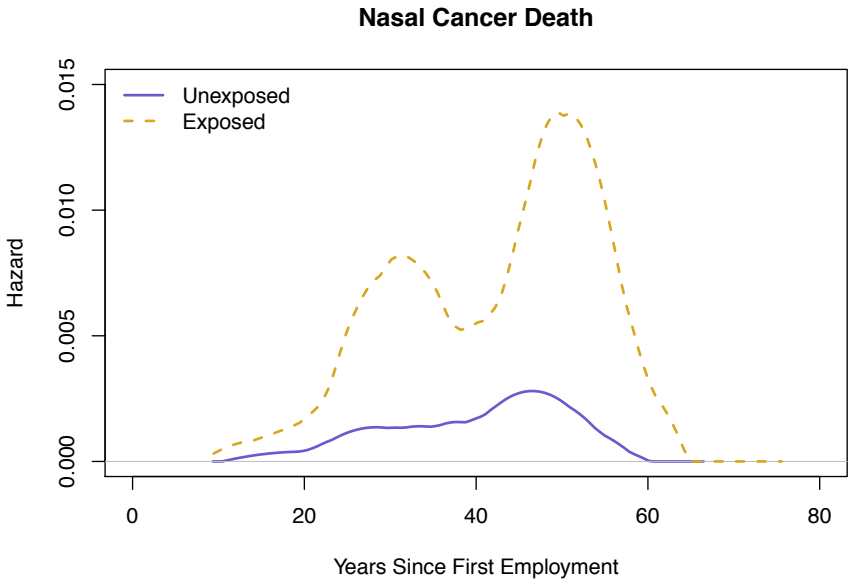
$$\begin{aligned} \lambda(t|x+1) &= \lambda_0(t)e^{\beta(t)(x+1)} \\ \lambda(t|x) &= \lambda_0(t)e^{\beta(t)(x)} \\ \text{hazard ratio} &= e^{\beta(t)(x+1)-\beta(t)x} = e^{\beta(t)} \end{aligned}$$

Estimated hazard ratio can be an arbitrary function of time $e^{\beta(t)}$.

NASAL HR ESTIMATE



NASAL CANCER



EXAMPLE

- Real et al. 2016, "Survival Predictors in Liver Transplantation: Time-Varying Effect of Red blood Cell Transfusion", Transplantation Proceedings, 48, 3303.
- 543 consecutive patients, 2006-2014, retrospectively
- Preoperative
  - Age, sex, Model for End-Stage Liver Disease score, primary diagnosis, cold ischemia time, international normalized ratio, serum albumin, hemoglobin levels
- Intraoperative
  - Norepinephrine, blood loss, red blood cell transfusions surgical time

RESULTS

- Only significant independent predictors:
- Red blood cell transfusion, HR=1.16 (1.04-1.29)
- Sex, HR=1.71 (1.10-2.65)
- Non-proportionality
  - "multivariate Cox regression model was subsequently upgraded by adding a time-varying interaction between red blood cell transfusion and time since liver transplantation"

RESULTS

Table 3. Multivariate Cox Regression (Time-Varying Interaction With RBC Transfusion Not Included)

Variable	HR	95% CI	*P* Value
Age (y)	1.02	1.00–1.04	.061
Female sex*	1.71	1.10–2.65	.016
Intraoperative RBC (units)	1.16	1.04–1.29	.005
Intraoperative blood loss (L)	0.90	0.79–1.03	.135
Intraoperative norepinephrine (mg)	1.02	0.97–1.07	.508
Surgical time (h)	1.19	0.95–1.48	.125

Abbreviations as in Tables 1 and 2.
*$P < .05$.

RESULTS

Table 4. Multivariate Cox Regression Including the Time-Varying Interaction With RBC Transfusion

Variable	HR	95% CI	*P* Value
Age (y)	1.02	1.00–1.04	.077
Female sex	1.66	1.07–2.56	.024
Intraoperative RBC (units)	1.25	1.12–1.40	.000
Intraoperative blood loss (L)	0.91	0.80–1.03	.147
Intraoperative norepinephrine (mg)	1.01	0.96–1.06	.803
Surgical time (h)	1.20	0.96–1.49	.105
Time-varying interaction with intraoperative RBC transfusion	0.98	0.97–0.99	.001

Abbreviations: as in Tables 1 and 2.

RESULTS

Table 5. Time-Varying Effect of RBC Transfusion on Patient Survival

Time Since LT	HR	95% CI	*P* Value
3 mo	1.14	1.020–1.257	.015
6 mo	1.12	1.003–1.240	.033
1 y	1.11	0.986–1.225	.070
2 y	1.09	0.968–1.210	.132
3 y	1.08	0.958–1.202	.183

Abbreviations: LT, liver transplantation; others as in Tables 1 and 2.

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

Module 17: Survival Analysis for Observational Data

Summer Institute in Statistics for Clinical Research
University of Washington
July, 2018

Susanne May, Ph.D.

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.

SURVIVAL OF OSCAR WINNERS

- Acknowledgement in the original article
- The authors thank Susan Campbell for data entry; Robert Tibshirani and Jerry Lawless for statistical insights; and Peter Austin, Ahmed Bayoumi, Chaim Bell, Victor Fuchs, David Juurlink, David Naylor, Miriam Shuchman, Leonard Syme, and John-Paul Szalai for commenting on drafts of this manuscript.

- Note on Acknowledgements….

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

Module 17: Survival Analysis for Observational Data

Summer Institute in Statistics for Clinical Research
University of Washington
July, 2018

Barbara McKnight, Ph.D.

OUTLINE

- Immortal-time bias
  - Examples: 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

OUTLINE

- **Immortal-time bias**
  - **Examples: Valganciclovir Tx in Glioblastoma, Stanford Heart Transplant Program**
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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

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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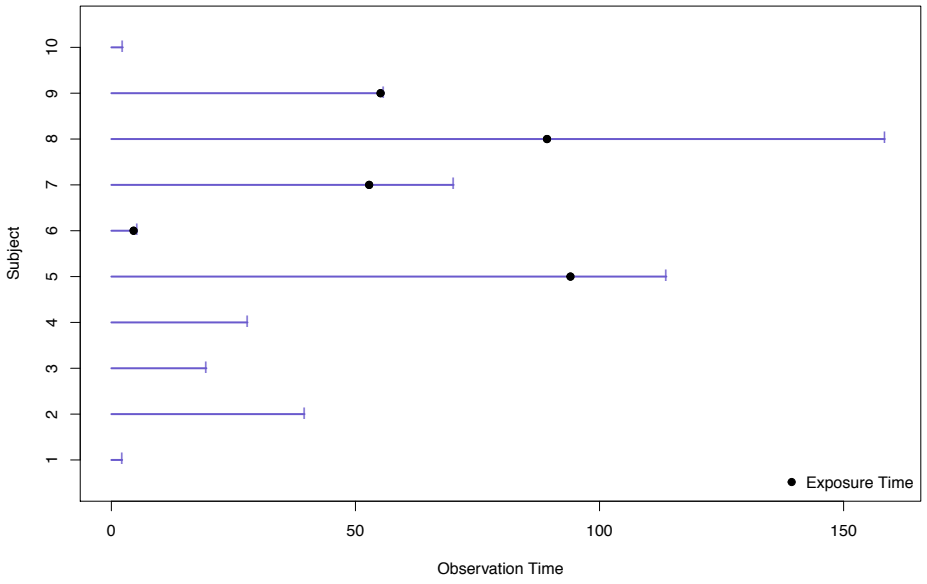
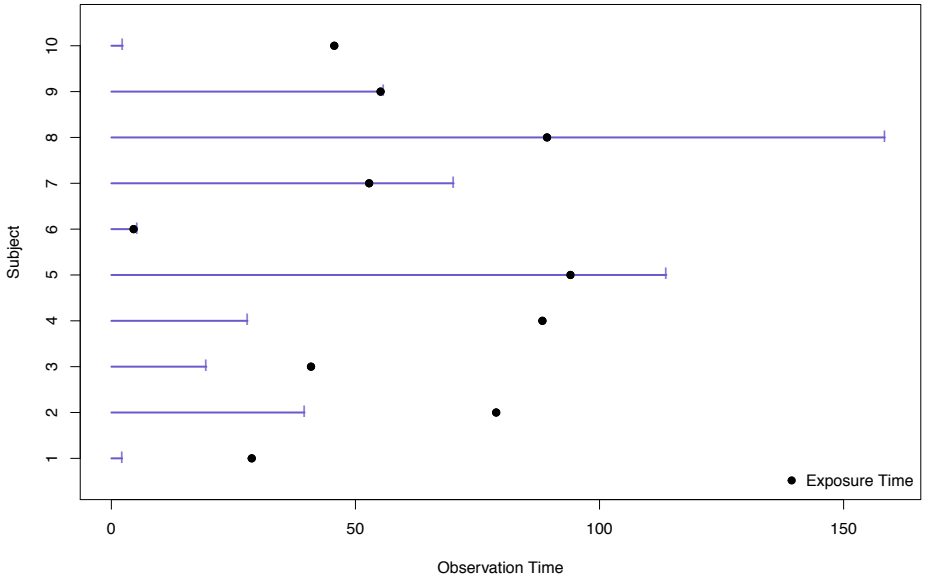
BIAS SIMULATION

- 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

OUTLINE

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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:

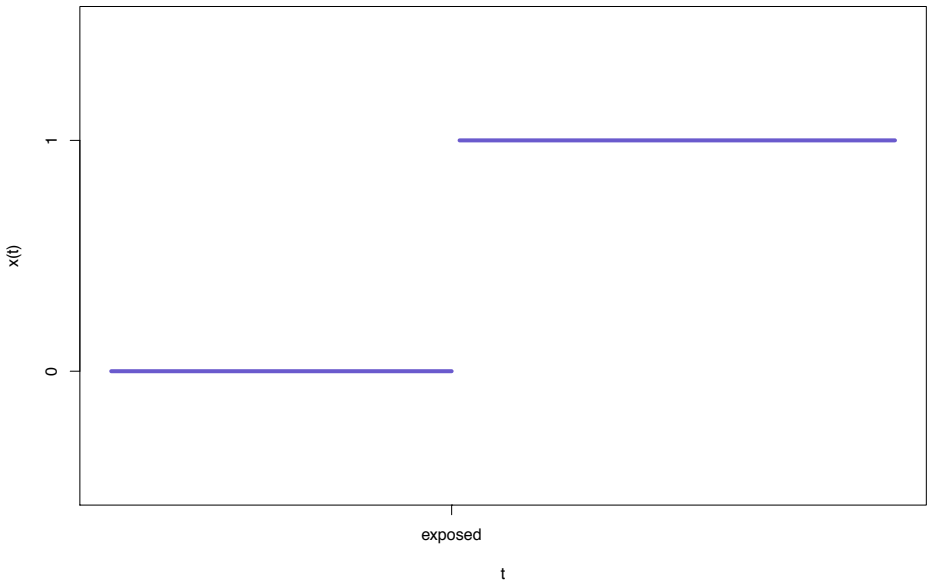
$$x(t) = \begin{cases} 1 & \text{exposed prior to time } t \\ 0 & \text{Otherwise} \end{cases} .$$

Then the model is

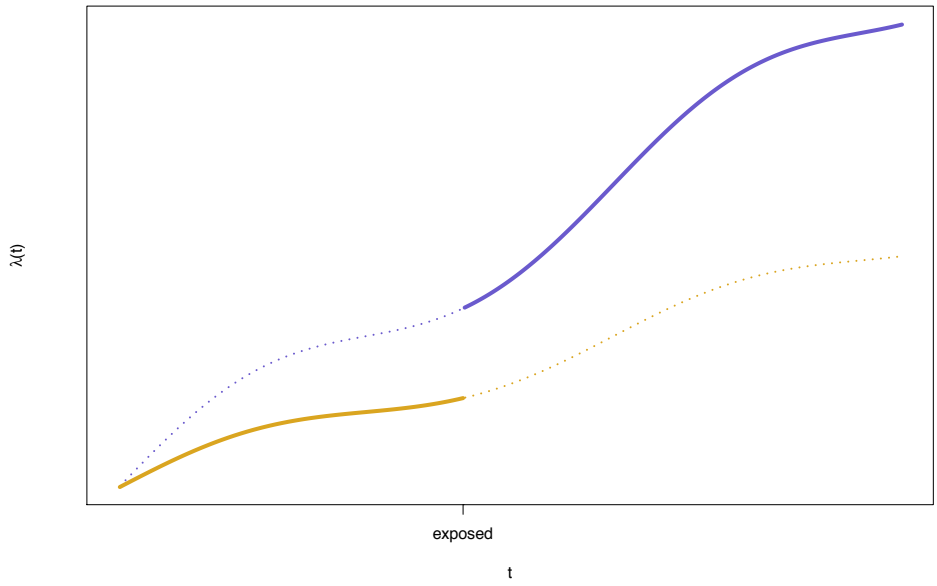
$$\lambda(t) = \lambda_0(t)e^{\beta x(t)}$$

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

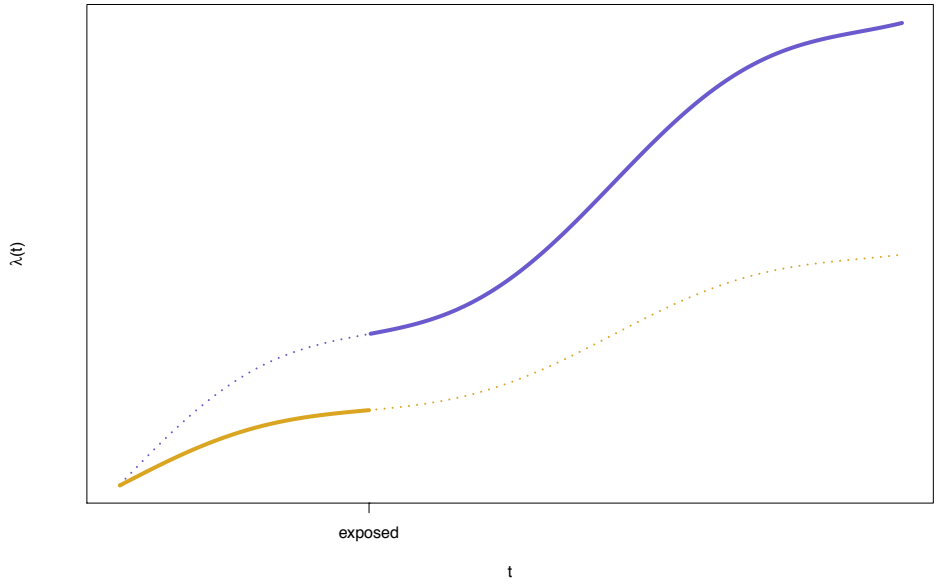
TIME-DEPENDENT EXPOSURE



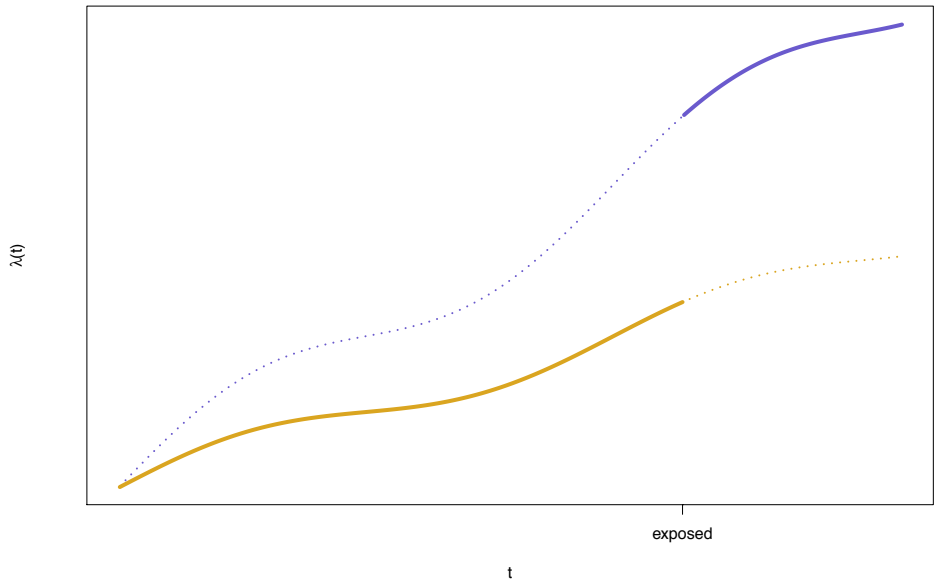
TIME-DEPENDENT EXPOSURE



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:

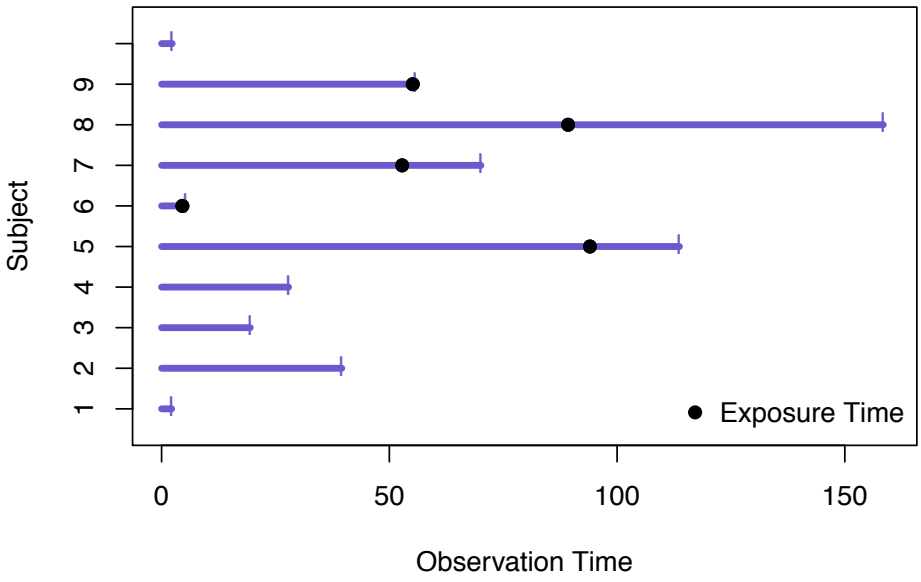
	mean coefficient (log HR)	Pr[Reject Ho]
ordinary	-1.8027810	1.000
left-enter	-0.9468022	0.939
correct	-0.0059659	0.048

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

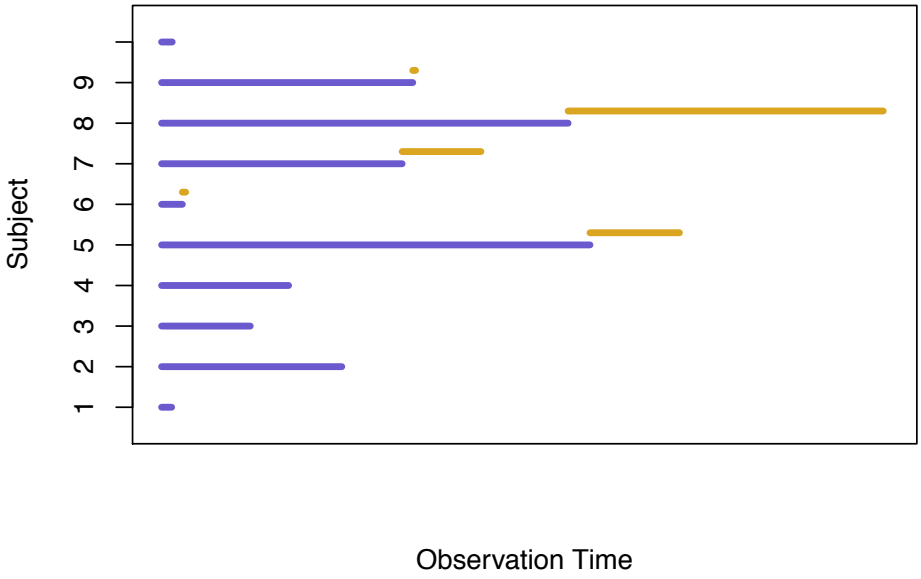
HOW TO DO IT

- 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



PICTURE



OUTLINE

- Immortal-time bias
  - Examples: Valganciclovir Tx in Glioblastoma, Stanford Heart Transplant Program
  - Simulation
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- More on TDCs if time

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

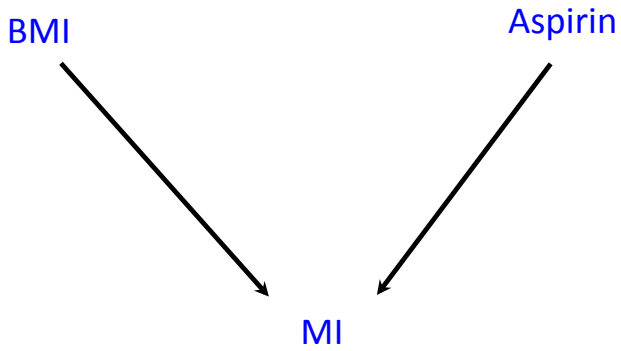
- Gruberg et al (2002) studied BMI category and subsequent MI in a case series of 9633 patients who underwent percutaneous coronary intervention.
- Overweight and obesity are known to be related to the risk of MI
- In this population, adjusted comparison of overweight and obese patients to normal weight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

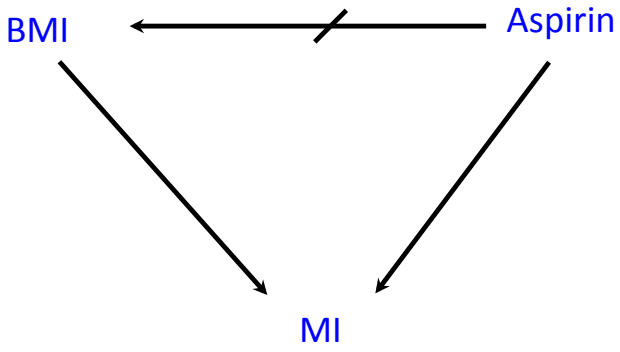
- Why?
- Subjects with a prior ("Index") clinical event are not representative of the population.
- Risk factors for the outcome that may be independent of exposure in the general population are much less likely to be independent in a population who have experienced the index event.
- All risk factors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

COLLIDER BIAS



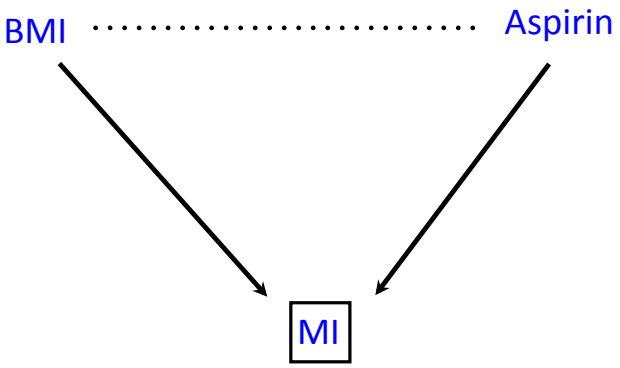
Both low/normal BMI and Aspirin use reduce the risk of MI.

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.
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- 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.

OUTLINE

- Immortal-time bias
  - Examples: Oscar winners, Valganciclovir Tx in Glioblastoma, Stanford Heart Transplant Program
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- **More on TDCs if time**

OTHER TDC POSSIBILITIES (IF TIME)

More than one change in status:

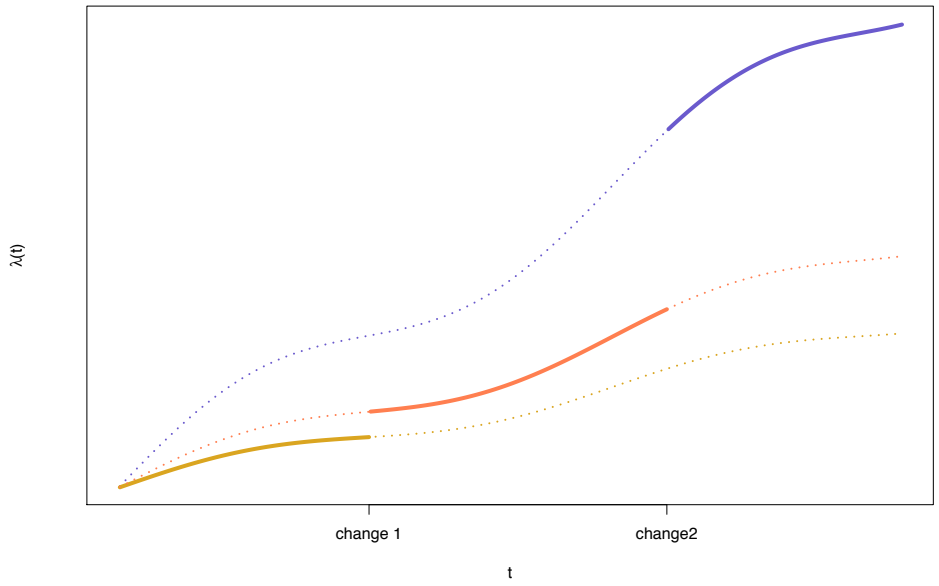
Let $\lambda(t)$ be the hazard for stroke:

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

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

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

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.