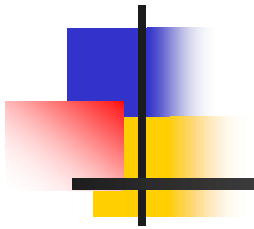

Introduction to Cox Regression

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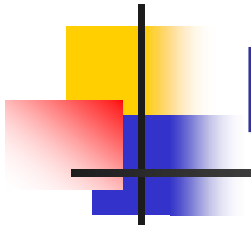
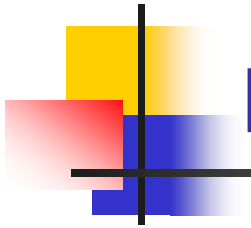


History

- "Regression Models and Life-Tables" by D.R. Cox, published in 1972, is one of the most frequently cited journal articles in statistics and medicine
- Introduced "maximum partial likelihood"

Cox regression vs.logistic regression



Distinction between rate and proportion:

- Incidence (hazard) rate: number of new cases of disease per population at-risk per unit time (or mortality rate, if outcome is death)
- Cumulative incidence: proportion of new cases that develop in a given time period

Cox regression vs.logistic regression

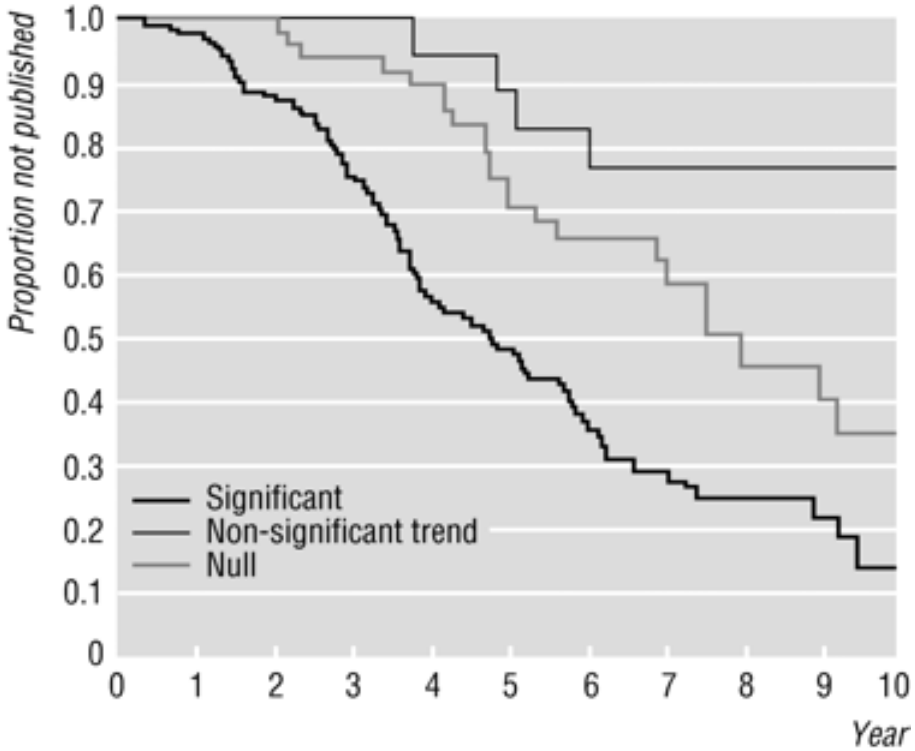
<u>Distinction between hazard/rate ratio and odds ratio/risk ratio:</u>

- Hazard/rate ratio: ratio of incidence rates
- Odds/risk ratio: ratio of proportions

Logistic regression aims to estimate the odds ratio; Cox regression aims to estimate the hazard ratio
Gain power/precision.

Example 1: Study of publication bias

By Kaplan-Meier methods



No at risk						
Significant	144	127	77	36	15	2
Non-significant trend	20	20	19	14	4	3
Null	52	52	46	24	10	7

From: Publication bias: evidence of delayed publication in a cohort study of clinical research projects BMJ 1997;315:640-645 (13 September)

Univariate Cox regression

Table 4 Risk factors for time to publication using univariate Cox regression analysis

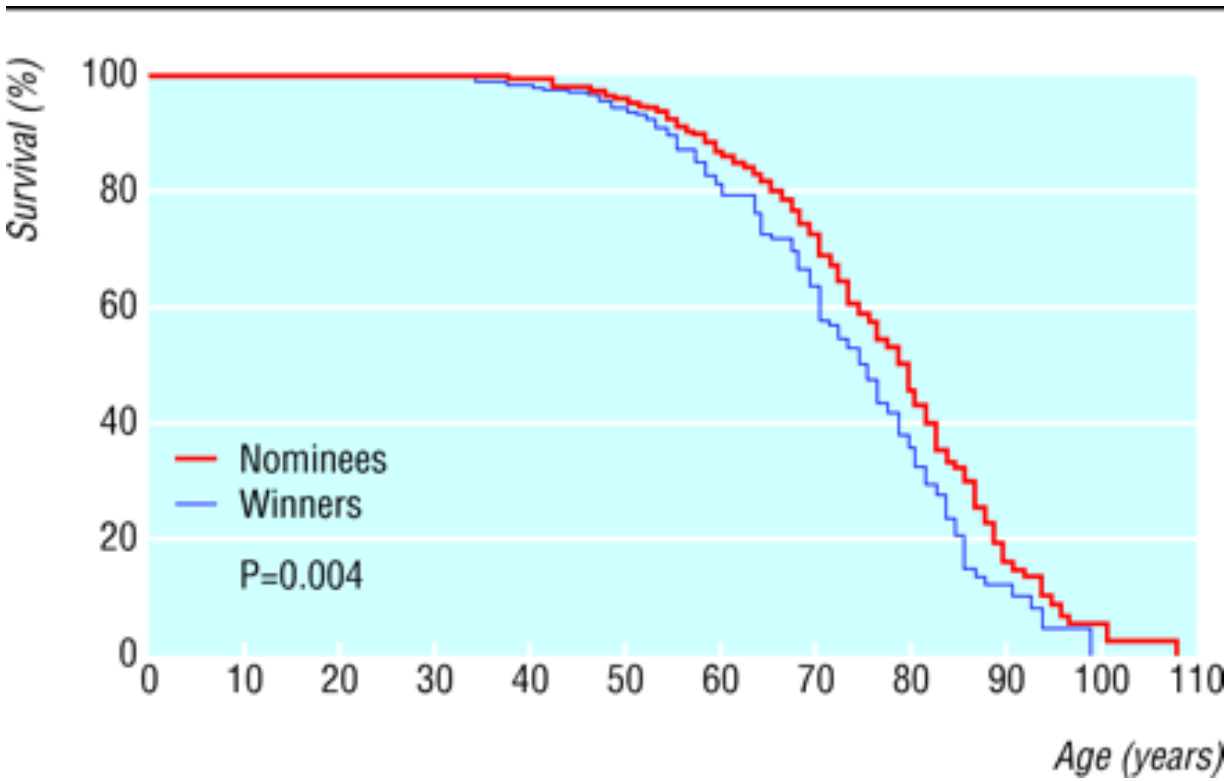
Characteristic	# not published	# published	Hazard ratio (95% CI)
Null	29	23	1.00
Non-significant trend	16	4	0.39 (0.13 to 1.12)
Significant	47	99	2.32 (1.47 to 3.66)

From: Publication bias: evidence of delayed publication in a cohort study of clinical research projects BMJ 1997;315:640-645 (13 September)

Interpretation: Significant results have a 2-fold higher incidence of publication compared to null results.

Example 2: Study of mortality in academy award winners for screenwriting

Kaplan-Meier methods



From: **Longevity of screenwriters who win an academy award: longitudinal study** *BMJ* 2001;323:1491-1496 (22-29 December)

Table 2. Death rates for screenwriters who have won an academy award.* Values are percentages (95% confidence intervals) and are adjusted for the factor indicated

	Relative increase in death rate for winners
Basic analysis	37 (10 to 70)
Adjusted analysis	
Demographic:	
Year of birth	32 (6 to 64)
Sex	36 (10 to 69)
Documented education	39 (12 to 73)
All three factors	33 (7 to 65)
Professional:	
Film genre	37 (10 to 70)
Total films	39 (12 to 73)
Total four star films	40 (13 to 75)
Total nominations	43 (14 to 79)
Age at first film	36 (9 to 68)
Age at first nomination	32 (6 to 64)
All six factors	40 (11 to 76)
All nine factors	35 (7 to 70)

HR=1.37; interpretation: 37% higher incidence of death for winners compared with nominees

HR=1.35; interpretation: 35% higher incidence of death for winners compared with nominees even after adjusting for potential confounders

Characteristics of Cox Regression

- Does not require that you choose some particular probability model to represent survival times, and is therefore more robust than parametric methods discussed last week.
- *Semi*-parametric

  (recall: Kaplan-Meier is *non-parametric*; exponential and Weibull are *parametric*)
- Can accommodate both discrete and continuous measures of event times
- Easy to incorporate time-dependent covariates—covariates that may change in value over the course of the observation period

Continuous predictors

E.g.: hmohiv dataset from the lab (higher age-group predicted worse outcome, but couldn't be treated as continuous in KM, and magnitude not quantified):

Using Cox Regression→

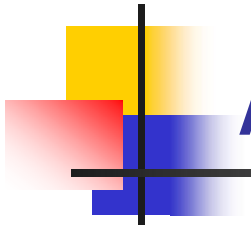
The estimated coefficient for Age in the HMOHIV dataset: β=.092

$HR=e^{.092}=1.096$

Interpretation: 9.6% increase in mortality rate for every 1-year older in age.

Characteristics of Cox Regression, continued

- Cox models the effect of covariates on the hazard rate but leaves the baseline hazard rate unspecified.
- Does NOT assume knowledge of absolute risk.
- Estimates *relative* rather than *absolute* risk.



Assumptions of Cox Regression

- Proportional hazards assumption: the hazard for any individual is a fixed proportion of the hazard for any other individual
- Multiplicative risk

Recall: The Hazard function

$$h(t) = \lim_{\Delta t \longrightarrow 0} \frac{P(t \le T < t + \Delta t / T \ge t)}{\Delta t}$$

In words: the probability that ***if you survive to t***, you will succumb to the event in the next instant.

$$\text{Hazard from density and survival}: h(\text{t}) = \frac{f(t)}{S(t)}$$

The model

Components:

•A baseline hazard function that is left unspecified but must be positive (=the hazard when all covariates are 0)

•A linear function of a set of k fixed covariates that is exponentiated. (=the relative risk)

$$h_i(t) = \lambda_0(t) e^{\beta_1 x_{i1} + \ldots + \beta_k x_{ik}}$$

Can take on any form!

$$\log h_i(t) = \log \lambda_0(t) + \beta_1 x_{i1} + \ldots + \beta_k x_{ik}$$

The model

Proportional hazards:

Hazard for person i (eg a smoker)

Hazard ratio

$$HR_{i,j} = \frac{h_i(t)}{h_j(t)} = \frac{\lambda_0(t)e^{\beta_1 x_{i1}+\ldots+\beta_k x_{ik}}}{\lambda_0(t)e^{\beta_1 x_{j1}+\ldots+\beta_k x_{jk}}} = e^{\beta_1(x_{i1}-x_{j1})+\ldots+\beta_1(x_{ik}-x_{jk})}$$

Hazard for person j (eg a non-smoker)

Hazard functions should be strictly parallel!

Produces covariate-adjusted hazard ratios!

The model: binary predictor

$$HR_{lung\ cancer/smoking} = \frac{h_i(t)}{h_j(t)} = \frac{\cancel{\lambda_0(t)}e^{\beta_{smoking}(1)+\cancel{\beta_{age}(60)}}}{\cancel{\lambda_0(t)}e^{\beta_{smoking}(0)+\cancel{\beta_{age}(60)}}} = e^{\beta_{smoking}(1-0)}$$

$$HR_{lung\ cancer/smoking} = e^{\beta_{smoking}}$$

This is the hazard ratio for smoking adjusted for age.

The model:continuous predictor

$$HR_{lung\ cancer/10-years\ \text{increase in age}} = \frac{h_i(t)}{h_j(t)} = \frac{\lambda_0(t)e^{\beta_{smoking}(0)+\beta_{age}(70)}}{\lambda_0(t)e^{\beta_{smoking}(0)+\beta_{age}(60)}} = e^{\beta_{age}(70-60)}$$

$$HR_{lung\ cancer/10-years\ \text{increase in age}} = e^{\beta_{age}(10)}$$

This is the hazard ratio for a 10-year increase in age, adjusted for smoking.

Exponentiating a continuous predictor gives you the hazard ratio for a 1-unit increase in the predictor.

The "Partial Likelihood" (PL)

Where there are *m* event times (as in Kaplan-Meier methods!) and L_i is the partial likelihood for the i^{th} event time:

$$L_p(\boldsymbol{\beta}) = \prod_{i=1}^{m} L_i$$

The Likelihood for each event

Consider the following data:

Males: 1, 3, 4, 10+, 12, 18

(call them subjects j=1-6)

Note: there is a term in the likelihood for each event, *NOT* each individual—note similarity to likelihood for conditional logistic regression…

$$L_p(\beta) = \prod_{i=1}^{m} L_i = \left(\frac{h_1(1)}{h_1(1)+h_2(1)+h_3(1)+h_4(1)+h_5(1)+h_6(1)}\right)x$$

$$\left(\frac{h_2(3)}{h_2(3)+h_3(3)+h_4(3)+h_5(3)+h_6(3)}\right)x\left(\frac{h_3(4)}{h_3(4)+....+h_6(4)}\right)$$

$$x\left(\frac{h_5(12)}{h_5(12)+h_6(12)}\right)x\left(\frac{h_6(18)}{h_6(18)}\right)$$

The "risk set"

Given … rred at time=3, this i… t it happened to subject 2 rather than to one of the other subjects at risk.

The PL

$$L_p(\boldsymbol{\beta}) = \prod_{i=1}^{m} L_i =$$

$$\left(\frac{\cancel{\lambda_0(t=1)}e^{\boldsymbol{\beta}\mathbf{x}_1}}{\cancel{\lambda_0(1)}e^{\boldsymbol{\beta}\mathbf{x}_1} + \cancel{\lambda_0(1)}e^{\boldsymbol{\beta}\mathbf{x}_2} + \cancel{\lambda_0(1)}e^{\boldsymbol{\beta}\mathbf{x}_3} + \cancel{\lambda_0(1)}e^{\boldsymbol{\beta}\mathbf{x}_4} + \cancel{\lambda_0(1)}e^{\boldsymbol{\beta}\mathbf{x}_5} + \cancel{\lambda_0(1)}^{\boldsymbol{\beta}\mathbf{x}_6}}\right)x$$

....

$$x\left(\frac{\cancel{\lambda_0(18)}e^{\boldsymbol{\beta}\mathbf{x}_6}}{\cancel{\lambda_0(18)}e^{\boldsymbol{\beta}\mathbf{x}_6}}\right)$$

$$\therefore L_p(\boldsymbol{\beta}) = \prod_{i=1}^{m} L_i = \left(\frac{e^{\boldsymbol{\beta}\mathbf{x}_1}}{e^{\boldsymbol{\beta}\mathbf{x}_1} + e^{\boldsymbol{\beta}\mathbf{x}_2} + e^{\boldsymbol{\beta}\mathbf{x}_3} + e^{\boldsymbol{\beta}\mathbf{x}_4} + e^{\boldsymbol{\beta}\mathbf{x}_5} + ^{\boldsymbol{\beta}\mathbf{x}_6}}\right)x....x\,1$$

The PL

$$\therefore L_p(\boldsymbol{\beta}) = \prod_{i=1}^{m} \left(\frac{e^{\boldsymbol{\beta}\mathbf{x}_j}}{\sum_{j \in R(t_i)} e^{\boldsymbol{\beta}\mathbf{x}_j}} \right)^{\delta_j}$$

Where, δ_j is the censoring variable (1=if event, 0 if censored) and $R(t_i)$ is the risk set at time t_i

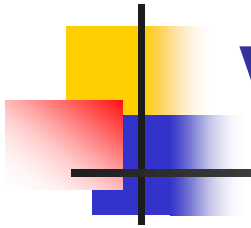
Note: we haven't yet specified how to account for ties (later)

$$\therefore \log L_p(\boldsymbol{\beta}) = \sum_{i=1}^{m} \delta_j [\boldsymbol{\beta}\mathbf{x}_j - \log(\sum_{j \in R(t_i)} e^{\boldsymbol{\beta}\mathbf{x}_j})]$$

Maximum likelihood estimation…

$$\therefore \log L_p(\boldsymbol{\beta}) = \sum_{i=1}^{m} \delta_j [\boldsymbol{\beta}\mathbf{x}_j - \log(\sum_{j \in R(t_i)} e^{\boldsymbol{\beta}\mathbf{x}_j})]$$

- Once you've written out log of the PL, then maximize the function→
  - Take the derivative of the function
  - Set derivative equal to 0
  - Solve for the most likely values of beta (values that make the data most likely!).
  - These are your ML estimates!



Variance of β

- Standard maximum likelihood methods for variance:
- Variance is the inverse of the observed information evaluated at MPLE estimate of β:

$$Var(\hat{\beta}) = \mathbf{I}(\hat{\beta})^{-1}$$

Hypothesis Testing
H_0: $\beta=0$

- 1. The Wald test:

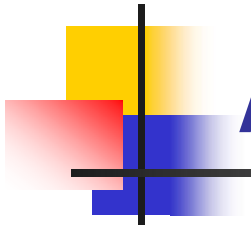
$$Z = \frac{\hat{\beta} - 0}{\text{asymptotic standard error}\,(\hat{\beta})}$$

2. The Likelihood Ratio test:

Reduced=reduced model with k parameters; Full=full model with k+r parameters

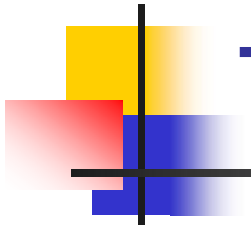
$$-2\ln\frac{L_p(reduced)}{L(full)} =$$

$$-2\ln(L_p(reduced)) - [-2\ln(L_p(full))] \sim \chi^2_r$$



A quick note on ties…

- The PL assumed no tied values among the observed survival times
- Not often the case with real data



Ties

- **Exact method** (time is continuous; ties are a result of imprecise measurement of time)
- **Breslow approximation** (SAS default)
- **Efron approximation**
- **Discrete method** (treats time as discrete; ties are real)

In SAS:

option on the model statement:

ties=exact/efron/breslow/discrete

Ties: Exact method

- Assumes ties result from imprecise measurement of time.
- Assumes there is a true unknown order of events in time.
- Mathematically, the exact method calculates the exact probability of all possible orderings of events.
- For example, in the hmohiv data, there were 15 events at time=1 month. (We can assume that all patients did not die at the precise same moment but that time is measured imprecisely.) ID's= 13, 16, 28, 32, 52, 54, 69, 72, 78, 79, 82, 83, 93, 96, 100
- With 15 events, there are 15! (1.3×10^{12})different orderings.

- Instead of 15 terms in the partial likelihood for 15 events, get 1 term that equals:

$$L = \sum_{i=1}^{15!} P(O_i)$$

Where O_i is the i^{th} possible ordering; for example, here, $15!^{th}$ ordering is: 100, 96, 93, 83, 82, 79, 78, 72, 69, 54, 52, 32, 28, 16, 13

Exact, continued

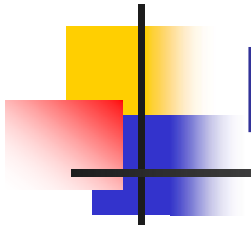
$$L = \sum_{i=1}^{15!} P(O_i)$$

$$eg: P(O_{15!}) = \left(\frac{e^{\beta x_{100}}}{e^{\beta x_1} + e^{\beta x_2} + \ldots e^{\beta x_{100}}}\right)\left(\frac{e^{\beta x_{96}}}{e^{\beta x_1} + e^{\beta x_2} + \ldots e^{\beta x_{99}}}\right)$$

$$\left(\frac{e^{\beta x_{93}}}{e^{\beta x_1} + e^{\beta x_2} + \ldots e^{\beta x_{95}} + e^{\beta x_{97}} + e^{\beta x_{98}} + e^{\beta x_{99}}}\right)\ldots.$$

Each $P(O_i)$ has 15 terms; sum 15! $P(O_i)$'s…

Hugely complex computation!…so need approximations…



Breslow and Efron methods

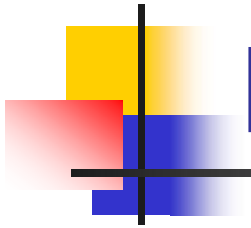
- Breslow (1974)
- Efron (1977)
- Both are approximations to the exact method.

→both have much faster calculation times

→Breslow is SAS default.

→Breslow does not do well when the number of ties at a particular time point is a large proportion of the number of cases at risk.

→Prefer Efron to Breslow



Discrete method

- Assumes time is truly discrete.
- When would time be discrete?

When events are only periodic, such as:

--Winning an Olympic medal (can only happen every 4 years)

--Missing a class (can only happen on Mondays or Wednesdays at 3:15pm)

--Voting for President (can only happen every 4 years)

Discrete method

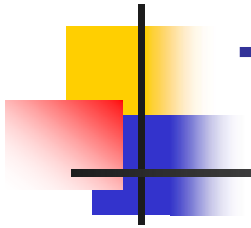
- Models proportional odds: coefficients represent odds ratios, not hazard ratios.
- For example, at time= 1 month in the hmohiv data, we could ask the question: given that 15 events occurred, what is the probability that they happened to this particular set of 15 people out of the 98 at risk at 1 month?

$$L_1 = \frac{\prod_{i=1}^{15} Odds_i}{\prod_{j \in P(1)}^{15} Odds_j + \prod_{j \in P(2)}^{15} Odds_j + \ldots.}$$

All possible sets of 15 out of 98!

Odds are a function of an individual's covariates.

Recursive algorithm makes it possible to calculate.



Ties: conclusion

→We'll see how to implement in SAS and compare methods (often doesn't matter much!).

Evaluation of Proportional Hazards assumption:

Recall proportional hazards concept:

Hazard for person i (eg a smoker)

Hazard ratio for smoking

$$HR = \frac{h_i(t)}{h_j(t)} = \frac{\lambda_0(t)e^{\beta x_i}}{\lambda_0(t)e^{\beta x_j}} = e^{\beta_1(x_i - x_j)}$$

Hazard for person j (eg a non-smoker)

implies: $h_i(t) = HRh_j(t)$; where hazard ratio HR is constant

Recall relationship between survival function and hazard function…

$$\text{Survival from hazard}: S(t) = e^{(-\int_0^t h(u)du)}$$

$$h_i(t) = \lambda_0(t)e^{\beta x_i}$$

$$P_i(X > t) = S_i(t) = e^{(-\int_0^t \lambda_0(u)e^{\beta x}du)}$$

Evaluation of Proportional Hazards assumption:

$$h_i(t) = HRh_j(t)$$

$$S_j(t) = e^{-\int_0^t h_j(u)du} \quad \text{and} \quad S_i(t) = e^{-\int_0^t HRh_j(u)du}$$

Multiply both sides by a negative and take logs again

$$\therefore S_i(t) = e^{HR(-\int_0^t h(u)du)}$$

$$S_i(t) = (e^{(-\int_0^t h(u)du)})^{HR} \rightarrow S_i(t) = S_j(t)^{HR}$$

Take log of both sides

$$\log S_i(t) = \log S_j(t)^{HR} \rightarrow \log S_i(t) = HR \log S_j(t)$$

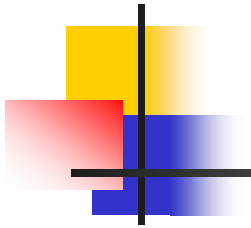
$$\log(-\log S_i(t)) = \log(-HR \log S_j(t))$$

$$\log(-\log S_i(t)) = \log HR + \log(-\log S_j(t))$$

$$\therefore Y(t) = K + X(t)$$

i.e., log(-log) survival curves are parallel, and different by log(HR)

Evaluation of Proportional Hazards assumption:



e.g., graph we'll produce in lab…

Cox models with Non-Proportional Hazards

Violation of the PH assumption for a given covariate is equivalent to that covariate having a significant interaction with time.

$$\log h(t) = \log \lambda_0(t) + \beta_x x + \beta_{xt} xt \rightarrow$$

Time-interaction coefficient

The covariate multiplied by time

$$\log h(t) = \log \lambda_0(t) + (\beta_x + \beta_{xt} t)x$$

If Interaction coefficient is significant→ indicates non-proportionality, and at the same time its inclusion in the model corrects for non-proportionality!

Negative value indicates that effect of x decreases linearly with time.

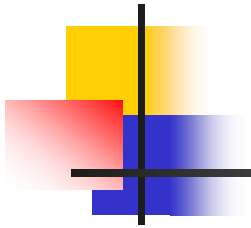
Positive value indicates that effect of x increases linearly with time.

This introduces the concept of a time-dependent covariate…

Time-dependent covariates

- Covariate values for an individual may change over time
- For example, if you are evaluating the effect of taking the drug raloxifene on breast cancer risk in an observational study, women may start and stop the drug at will. Subject A may be taking raloxifene at the time of the first event, but may have stopped taking it by the time the 15th case of breast cancer happens.
- If you are evaluating the effect of weight on diabetes risk over a long study period, subjects may gain and lose large amounts of weight, making their baseline weight a less than ideal predictor.
- If you are evaluating the effects of smoking on the risk of pancreatic cancer, study participants may change their smoking habits throughout the study.
- Cox regression can handle these time-dependent covariates!

Time-dependent covariates



- For example, evaluating the effect of taking oral contraceptives (OCs) on stress fracture risk in women athletes over two years—many women switch on or off OCs .
- If you just examine risk by a woman's OC-status at baseline, can't see much effect for OCs. But, you can incorporate times of starting and stopping OCs.

Time-dependent covariates

- Ways to look at OC use:
- Not time-dependent
  - Ever/never during the study
  - Yes/no use at baseline
  - Total months use during the study
- Time-dependent
  - Using OCs at event time t (yes/no)
  - Months of OC use up to time t

Time-dependent covariates: Example data

4 events

ID	Time	Fracture	StartOC	StopOC
2	11	0	10	11
4	24	0	0	24
5	19	0	0	11

1. Time independent predictor…

- Baseline use (yes/no)

Time-dependent covariates

Order by Time…

ID	Time	Fracture	StartOC	StopOC
6	6	1	.	.
2	11	0	10	11
1	12	1	0	12
7	17	1	1	7
5	19	0	0	11
3	20	1	.	.
4	24	0	0	24

Time-dependent covariates

3 OC users at baseline

ID	Time	Fracture	StartOC	StopOC
6	6	1	.	.
2	11	0	10	11
1	12	1		12
7	17	1	1	7
5	19	0		11
3	20	1	.	.
4	24	0		24

Time-dependent covariates

4 non-users at baseline

ID	Time	Fracture	StartOC	StopOC
6	6	1		.
2	11	0		11
1	12	1	0	12
7	17	1		7
5	19	0	0	11
3	20	1		.
4	24	0	0	24

Time-dependent covariates

ID	Time	Frac	
6	6		
2	11		
1	12		
7	17		
5	19		11
3	20		.
4	24		24

First event is in a non-OC user at baseline. (risk set: 3 users/4 non)

Second event is in a baseline

s in a non-user at

Next is a censoring (baseline

Fourth and last event is in a non-

Censoring.

The PL using baseline value of OC use

$$L_p(\beta_{oc}) = \frac{e^{\beta(0)}}{3e^{\beta(1)} + 4e^{\beta(0)}} x \frac{e^{\beta(1)}}{3e^{\beta(1)} + 2e^{\beta(0)}} x \frac{e^{\beta(0)}}{2e^{\beta(1)} + 2e^{\beta(0)}} x \frac{e^{\beta(0)}}{e^{\beta(1)} + e^{\beta(0)}}$$

The PL using ever/never value of OC use

A second time-independent option would be to use the variable “ever took OCs” during the study period…

Time-dependent covariates

First event is in a never-user. (risk set: 5 ever users/2 never)

Second event is in an ever-user.

Next is a censoring (ever user).

Fourth and last event is in a never-

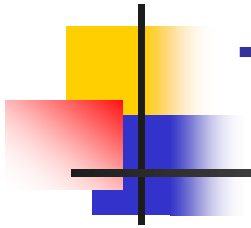
Censoring.

ID	Time	Frac		
6	6			
2	11			
1	12			
7	17			
5	19			11
3	20			.
4	24			24

The PL using ever/never value of OC use

"Ever took OCs" during the study period

$$L_p(\beta_{oc}) = \frac{e^{\beta(0)}}{5e^{\beta(1)} + 2e^{\beta(0)}} x \frac{e^{\beta(1)}}{4e^{\beta(1)} + e^{\beta(0)}} x \frac{e^{\beta(1)}}{3e^{\beta(1)} + e^{\beta(0)}} x \frac{e^{\beta(0)}}{e^{\beta(1)} + e^{\beta(0)}}$$



Time-dependent...

Time-dependent covariates

First event at time 6

ID	Time	Fracture	StartOC	StopOC
2	11	0	10	11
1	12	1	0	12
7	17	1	1	7
5	19	0	0	11
3	20	1	.	.
4	24	0	0	24

The PL at t=6

$$L_p(\beta_{oc}) = \frac{e^{\beta x_6(t=6)}}{e^{\beta x_1(6)} + e^{\beta x_2(6)} + e^{\beta x_3(6)} + e^{\beta x_4(6)} + e^{\beta x_5(6)} + e^{\beta x_6(6)} + e^{\beta x_7(6)}}$$

X is time-dependent

Time-dependent covariates

At the first event-time (6), there are 4 not on OCs and 3 on OCs.

ID	Time	Fractur

The PL at t=6

$$L_p(\beta_{oc}) = \frac{e^{\beta x_6(t=6)}}{e^{\beta x_1(6)} + e^{\beta x_2(6)} + e^{\beta x_3(6)} + e^{\beta x_4(6)} + e^{\beta x_5(6)} + e^{\beta x_6(6)} + e^{\beta x_7(6)}}$$

$$= \frac{e^{\beta(0)}}{3e^{\beta(0)} + 4e^{\beta(1)}}$$

Time-dependent covariates

Second event at time 12

ID	Time	Fracture	StartOC	StopOC

The PL at t=12

$$L_p(\beta_{oc}) = \frac{e^{\beta(0)}}{3e^{\beta(0)} + 4e^{\beta(1)}} x \frac{e^{\beta(1)}}{2e^{\beta(1)} + 3e^{\beta(0)}}$$

Time-dependent covariates

Third event at time 17

ID	Time	Fracture	StartOC	StopOC

The PL at t=17

$$L_p(\beta_{oc}) = \frac{e^{\beta(0)}}{3e^{\beta(0)} + 4e^{\beta(1)}} x \frac{e^{\beta(1)}}{2e^{\beta(1)} + 3e^{\beta(0)}} x \frac{e^{\beta(0)}}{e^{\beta(1)} + 3e^{\beta(0)}}$$

Time-dependent covariates

Fourth event at time 20

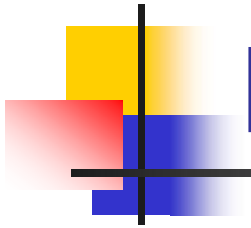
ID	Time	Fracture	StartOC	StopOC

The PL at t=20

$$L_p(\beta_{oc}) = \frac{e^{\beta(0)}}{3e^{\beta(0)} + 4e^{\beta(1)}} x \frac{e^{\beta(1)}}{2e^{\beta(1)} + 3e^{\beta(0)}} x \frac{e^{\beta(0)}}{e^{\beta(1)} + 3e^{\beta(0)}} x \frac{e^{\beta(0)}}{e^{\beta(1)} + e^{\beta(0)}}$$

vs. PL for OC-status at baseline (from before):

$$L_p(\beta_{oc}) = \frac{e^{\beta(0)}}{4e^{\beta(0)} + 3e^{\beta(1)}} x \frac{e^{\beta(1)}}{3e^{\beta(1)} + 2e^{\beta(0)}} x \frac{e^{\beta(0)}}{2e^{\beta(1)} + 2e^{\beta(0)}} x \frac{e^{\beta(0)}}{e^{\beta(1)} + e^{\beta(0)}}$$



References

Paul Allison. *Survival Analysis Using SAS*. SAS Institute Inc., Cary, NC: 2003.