Lecture 8

Thursday, November 9, 2023 17:46

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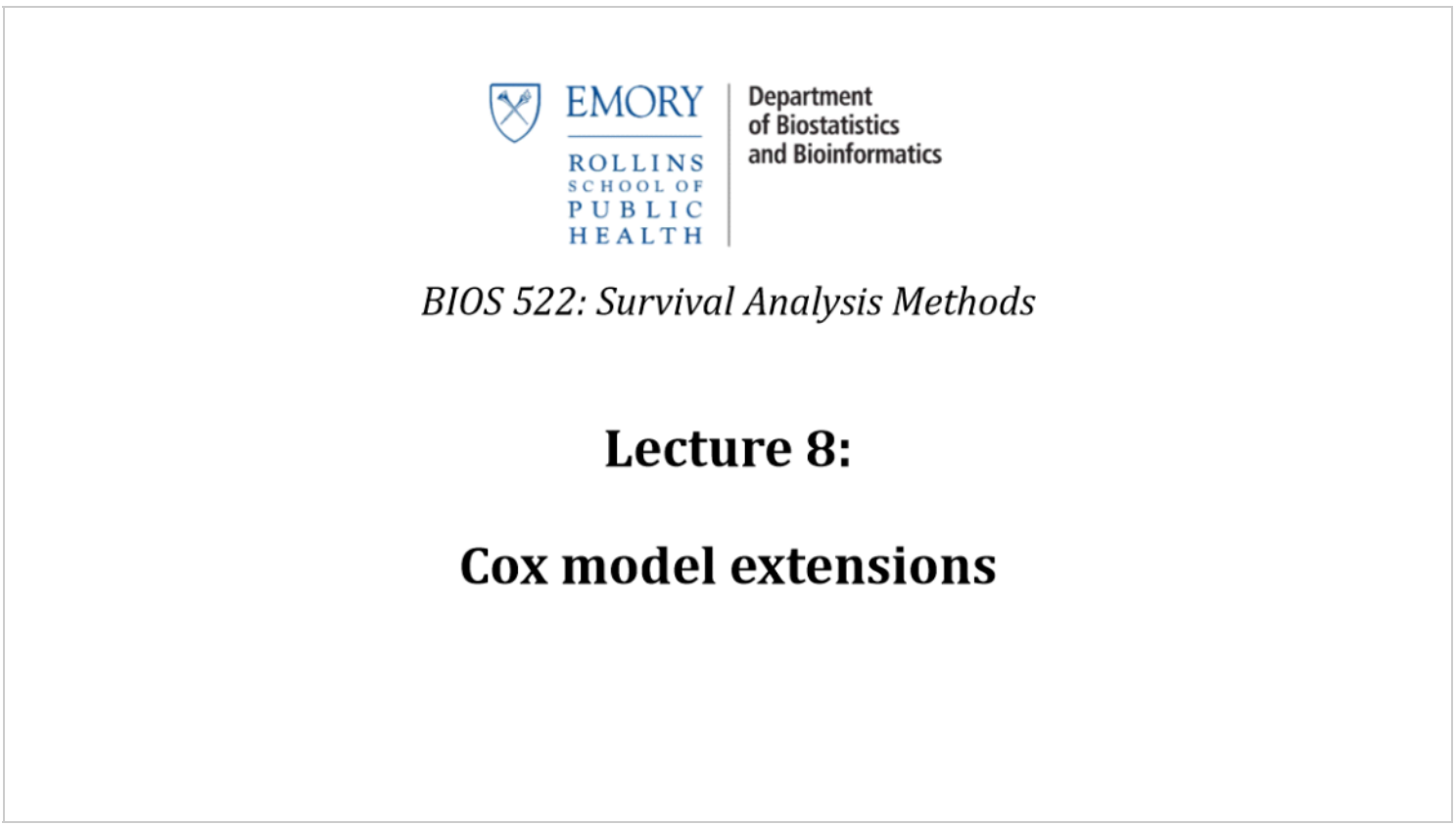


Previously

- *Diagnostics for the Cox model*
- *Assessing the functional form of covariates*
- *Plots and hypothesis tests to detect violations of the proportional hazards assumption*

Extending the basic Cox model

$h_i(t) = h_0(t)\exp(\beta X_i)$ basic model

$h_{si}(t) = h_{s0}(t)\exp(\beta X_i)$ stratified Cox model

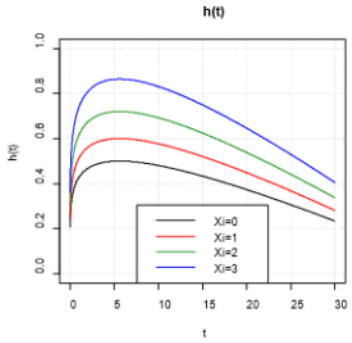
$h_i(t) = h_0(t)\exp\left(\beta X_i(t)\right)$ time-dependent covariates

$h_i(t) = h_0(t)\exp(\beta(t) X_i)$ time-varying effects

Stratified Cox model

- In a traditional Cox model, we assume that the *shape* of the hazard function is the same for all groups

$$h_i(t) = h_0(t)\exp(\beta X_i)$$



- This is a very restrictive assumption that we way wish to relax for certain covariates
  - Especially for covariates that we are not interested in studying/measuring, but only want to adjust for in the analysis

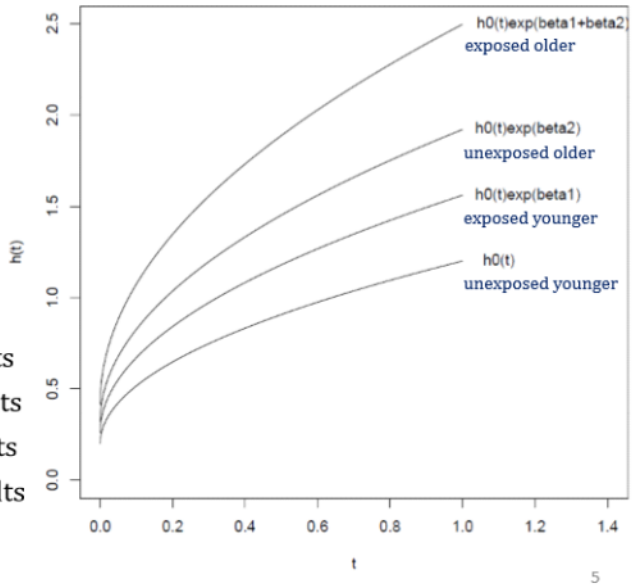
An example without stratification

- Say we have two covariates
  - $X_{i1} = 1$ if exposed, 0 if unexposed
  - $X_{i2} = 1$ if older, 0 if younger

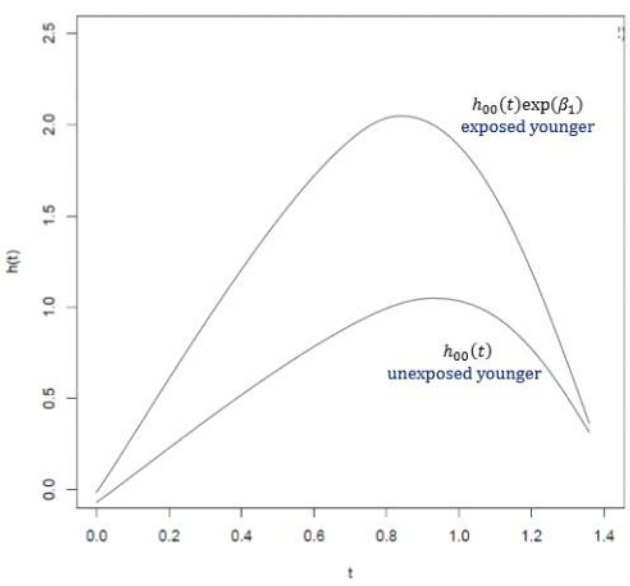
- Fit a Cox model

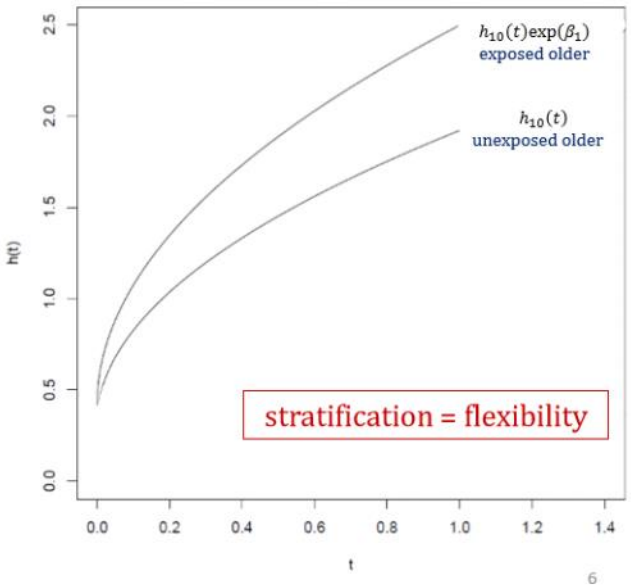
$$h_i(t) = h_0(t)\exp(\beta_1 X_{i1} + \beta_2 X_{i2})$$

$h_i(t) = h_0(t)$ for unexposed younger adults
$h_i(t) = h_0(t)e^{\beta_1}$ for exposed younger adults
$h_i(t) = h_0(t)e^{\beta_2}$ for unexposed older adults
$h_i(t) = h_0(t)e^{\beta_1+\beta_2}$ for exposed older adults



Now with stratification





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Stratified Cox model

- Important to note that now we can no longer measure the effect of the stratifying variable (here, age) on survival

- Standard Cox model:

$$h_i(t) = h_0(t)\exp(\beta_1 X_{i1} + \beta_2 X_{i2})$$

  - β_2 measures the hazard ratio for older vs. younger

- Stratified Cox model:

$$h_{si}(t) = h_{s0}(t)\exp(\beta_1 X_{i1})$$

  - *No easy way to compare* $h_{00}(t)$ *and* $h_{10}(t)$

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Stratified Cox partial likelihood

- Partial likelihood:

$$L(\beta) = \prod_{s=1}^{S} \prod_{i=1}^{m_s} \frac{\exp(\beta X_{si})}{\sum_{j \in R(T_{si})} \exp(\beta X_{sj})}$$

- $s = 1, \ldots, S$ strata, each with m_s unique failure times. $R(T_{si})$ is the risk set at failure time T_{si}.

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Stratified Cox model examples

- Stratify on cancer stage
- Stratify on study center for a multi-center trial
- Simultaneously stratify on sex and age (<40 vs. ≥40 years)
  - Fit four separate baseline hazard functions

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Example: Aspirin and cancer

Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials

Peter M Rothwell, Michelle Wilson, Jacqueline F Price, Jill F F Belch, Tom W Meade, Ziyah Mehta

Goal: Researchers sought to examine the impact of daily aspirin use on the growth or metastasis of cancers.

Population: The researchers analyzed data from **five large randomized trials** of daily aspirin (≥75 mg daily) versus control for the prevention of vascular events in the UK. Electronic and paper records were reviewed for all participants with incident cancer. The analysis included data from 17,285 trial participants followed for a mean of 6.5 years.

Example: Aspirin and cancer

Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials

Peter M Rothwell, Michelle Wilson, Jacqueline F Price, Jill F F Belch, Tom W Meade, Ziyah Mehta

Outcome variable: The main endpoint was **time from randomization to diagnosis of metastasis** (site of metastasis specified). The researchers further considered time from randomization to diagnosis of metastasis including metastatic cancers in which the site of the metastasis was not specified.

Predictor variables: The primary predictor of interest was **allocation to aspirin or placebo**. All analyses followed the intention-to-treat principle, meaning that individuals were analyzed per their randomization group, regardless of actual compliance. Researchers were **not interested in differences across the five trials**.

Example: Aspirin and cancer

Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials

Peter M Rothwell, Michelle Wilson, Jacqueline F Price, Jill F F Belch, Tom W Meade, Ziyah Mehta

Statistical analysis: The researchers fit a Cox proportional hazards regression model with randomization as the sole predictor, stratified by trial. Thus, five strata are defined, but the model returns a single estimate of the treatment effect.

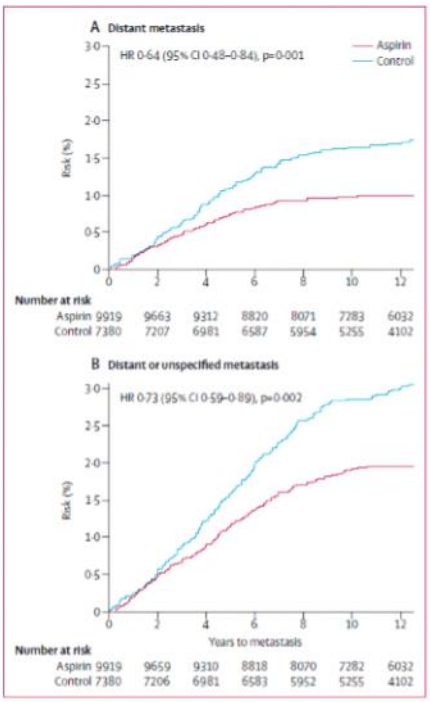


Figure 1: **The effect of aspirin on risk of metastasis due to any incident cancer diagnosed during five trials of aspirin versus control**
Analysis is based on time from randomisation to diagnosis of metastasis during or after the trials. Part A shows definite site-specific distant metastasis and part B also includes metastatic cancers in which the site of the metastasis was not specified. HR=hazard ratio from a Cox regression stratified by trial.

Results: Figure 1 plots the estimated **cumulative incidence** of time from randomization until distant metastasis (Panel A) and time from randomization until distant or unspecified metastasis (Panel B).

These are Kaplan-Meier curves (although plotted as cumulative incidence instead of survival) for the combined data.

The Cox model is fit stratifying on trial. In Panel A, the **hazard ratio** is 0.64 (95% CI 0.48 to 0.84), p = 0.001, indicating a protective effect of aspirin.

What would the KM plots look like if they wanted to stratify on trial?

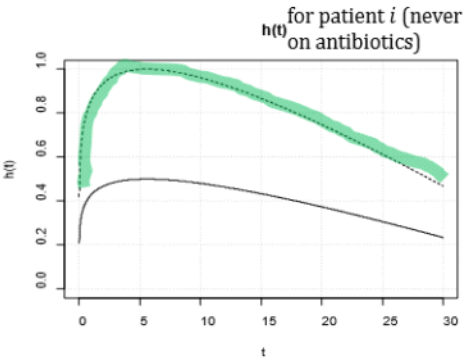
Time-dependent covariates

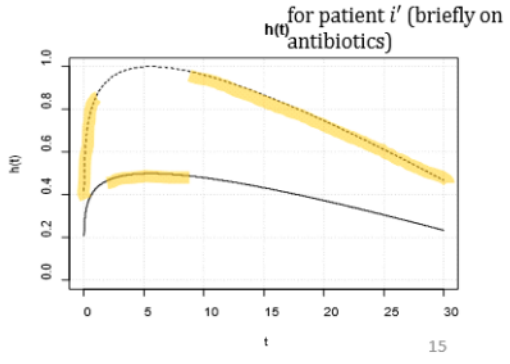
- Allow covariate values to change during the course of the study
- Allow an individual's hazard to change over time as their covariates change

$$h_i(t) = h_0(t)\exp\left(\beta X_i(t)\right)$$

Hospital-acquired infection

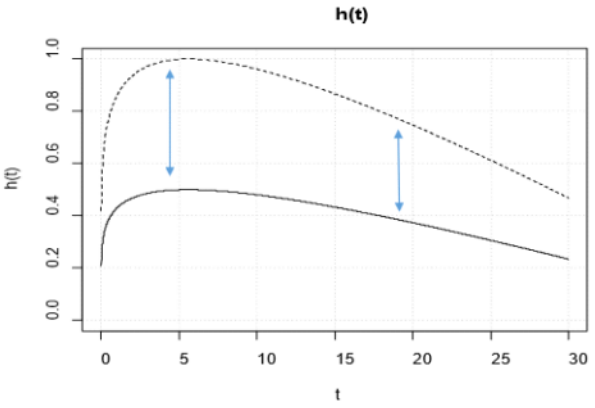
- Modeling time from hospital admission until hospital-acquired infection
  - $X_i(t) = 1$ if patient is currently receiving antibiotics
  - $X_i(t) = 0$ otherwise





Time-dependent covariates

- $\exp(\beta)$ is still interpreted as the hazard ratio for a one-unit change in X_i



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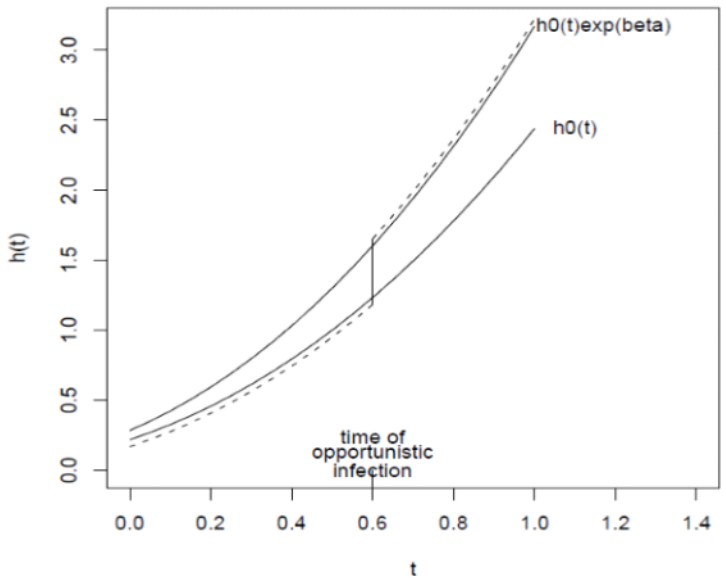
Time-dependent covariates



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Cox partial likelihood

- Partial likelihood:

$$L(\beta) = \prod_{i=1}^{m} \frac{\exp\left(\beta X_i(T_i)\right)}{\sum_{j \in R(T_i)} \exp\left(\beta X_j(T_i)\right)}$$

- Individuals contribute their value of the covariate at each time T_i when the partial likelihood is calculated

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Time-dependent covariates

Examples:

- Vaccination status
  - 0 if never vaccinated
  - 1 if previously vaccinated
- Current smoking status
  - 0 if not currently smoking
  - 1 if currently smoking
- Accumulated smoking status
  - Number of pack-years smoked
- Blood pressure
  - Changes value each time it is measured

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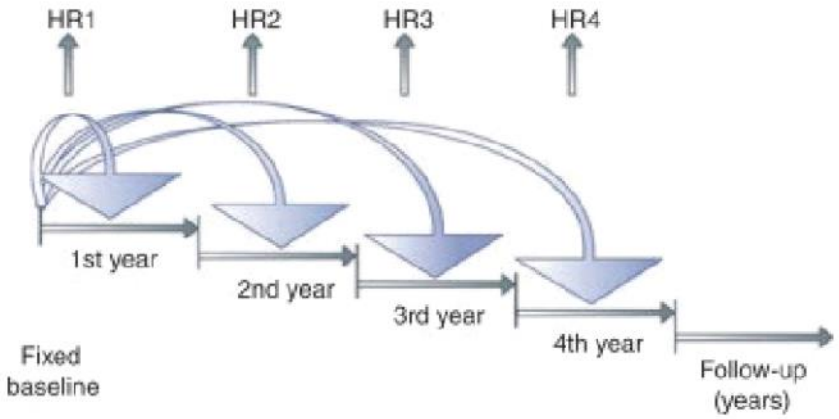
Time-varying effects

- Allow the effect of a covariate to change over time

$$h_i(t) = h_0(t)\exp(\beta(t)X_i)$$

- Can be used to model *waning* of an effect over time
- Can be used to model *build-up* of an effect over time

Time-varying effects



- *Relaxes the proportional hazards assumption*

Dekker et al. (2008) https://www.sciencedirect.com/science/article/pii/S0085253815534704

Time-varying effects

Examples:

- Vaccine effectiveness wanes over time
- Breastfeeding protects against infant mortality
  - This effect may be strongest for newborns but weaken as the baby ages
- Mortality in dialysis patients
  - Being underweight is a strong risk factor for mortality in the short term
  - Being overweight is a strong risk factor for mortality in the long term

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Time-varying effects

- One common approach to modeling time-varying effects is to break time up into *non-overlapping intervals* and assume that the *hazard ratio is constant within each interval* (**piecewise constant**)

$$h_i(t) = h_0(t)\exp(\beta_1 I[0 \le t < t_1]X_i + \beta_2 I[t_1 \le t < t_2]X_i \dots)$$

$$h_i(t) = h_0(t)\exp(\beta_1 I[0 \le t < t_1]X_i + \beta_2 I[t_1 \le t < t_2]X_i \dots)$$

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Example: Tdap Waning

Waning Tdap Effectiveness in Adolescents

Nicola P. Klein, MD, PhD, Joan Bartlett, MPH, MPP, Bruce Fireman, MA, Roger Baxter, MD

Goal: Researchers investigated the effectiveness of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) for protection against pertussis. The researchers were interested in waning of vaccine effectiveness over time.

Population: The researchers used routinely collected data from adolescents within the Kaiser Permanente Northern California health care network. The study population included network members starting at age 10 years.

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Example: Tdap Waning

Waning Tdap Effectiveness in Adolescents

Nicola P. Klein, MD, PhD, Joan Bartlett, MPH, MPP, Bruce Fireman, MA, Roger Baxter, MD

Outcome variable: The primary outcome was time until first occurrence of testing positive by polymerase chain reaction (PCR) for pertussis. The time origin was the child's 10th birthday. Children were censored at time of receipt of a second Tdap vaccine (booster), disenrollment from the health care network, or end of follow-up.

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Example: Tdap Waning

Waning Tdap Effectiveness in Adolescents

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Predictor variables: The predictor variable of greatest interest was Tdap vaccination status. Tdap vaccination status was coded using a set of indicator variables to allow the effect of vaccine to vary over time. Individuals in the population were:

- Unvaccinated
- Too-recently-vaccinated-to-benefit (within 1-7 days of vaccination)
- Vaccinated in the previous 8 days to <1 year ("year 1")
- Vaccinated in the previous 1 to <2 years ("year 2")
- Vaccinated in the previous 2 to <3 years ("year 3")
- Vaccinated ≥ 3 years ago ("year 4+")

Example: Tdap Waning

Waning Tdap Effectiveness in Adolescents

Nicola P. Klein, MD, PhD, Joan Bartlett, MPH, MPP, Bruce Fireman, MA, Roger Baxter, MD

Statistical analysis: Researchers fit a Cox regression model to estimate the hazard ratio of pertussis for each Tdap time interval compared with the unvaccinated reference period. The regression was adjusted for birth year, gender, race, and facility.

$$h_i(t) = h_0(t)\exp\begin{pmatrix}\beta_1 I[\text{time since vax between 8 days to 1 year}]\\ +\beta_2 I[\text{time since vax between 1 to 2 years}]\\ +\beta_3 I[\text{time since vax between 2 to 3 years}]\\ +\beta_4 I[\text{time since vax 3 or more years ago}]\end{pmatrix}$$

TABLE 3 Tdap VE by Year After Tdap Vaccination

Year After Tdap (Time Since Tdap)	HR (95% CI)	Tdap VE (95% CI)
Year 1 (8 d to <1 y)	$\exp(\hat{\beta}_1)$ 0.31 (0.24 to 0.40)	68.8 (59.7 to 75.9)
Year 2 (1 to <2 y)	$\exp(\hat{\beta}_2)$ 0.43 (0.32 to 0.59)	56.9 (41.3 to 68.4)
Year 3 (2 to <3 y)	$\exp(\hat{\beta}_3)$ 0.75 (0.54 to 1.04)	25.2 (−4.3 to 46.4)
Year 4+ (≥3 y)	$\exp(\hat{\beta}_4)$ 0.91 (0.64 to 1.31)	8.9 (−30.6 to 36.4)

Concepts are highly related

- **Time-dependent covariates**, also called time-varying covariates
  - Covariate $X_i(t)$ is a function of time, but hazard ratio $\exp(\beta)$ is not
- **Time-varying effects**, also called time-dependent effects
  - Hazard ratios $\exp\big(\beta(t)\big)$ are functions of time, but covariates X_i are not
- *In practice, you can have both!*

$$h_i(t) = h_0(t)\exp\big(\beta(t)X_i(t)\big)$$

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Test your understanding

Example:

- Cohort study using electronic health records
- Outcome is time to influenza hospitalization
- Time zero is the start of the influenza season (October 15)
- Individuals are vaccinated throughout the season
- The effect of vaccination is assumed to be constant over time

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Test your understanding

Example:

- Trial randomizing participants to flu vaccine or placebo
- Outcome is time to influenza hospitalization
- Time zero is the time of vaccination
- The effect of vaccination is estimated in monthly intervals since vaccination date

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Test your understanding

Example:

- Cohort study using electronic health records
- Outcome is time to influenza hospitalization
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- Individuals are vaccinated throughout the season
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