Choice of time-scale in the Cox model for epidemiologic cohort studies where entry has no direct biological relevance

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Time-varying exposure in epidemiological cohort studies

- Study 1: We wish to examine the association between exposure to radioactive iodine and incidence of thyroid cancer among survivors of the Chornobyl accident. From a biological perspective it is important to consider
  - age at exposure
  - time since exposure
  - (attained age)
- Time since exposure is a 'time-varying' explanatory variable (the value changes with time) whereas age at exposure is fixed for each individual.
- Study 2: Invite women from the general population to participate in a cohort study; follow-up to assess the association between diet and incidence of breast cancer.
- From a biological perspective it is important to consider age at time of follow-up (attained age), a 'time-varying' explanatory variable.

- Time since entry is not of direct biological interest.
- The choice of variables to adjust for in a statistical model should be based, first and foremost, on biological and clinical considerations; we should only adjust for time-since entry if it has direct biological relevance.
- How do we, technically, adjust for the fact that a single exposure variable can assume multiple values for a single individual?
- One approach is to 'split' the person-time for each individual into bands, creating a data set containing multiple observations for each individual.
- This is what we do with Poisson regression; can adjust for two (but not three) time-varying explanatory variable.

- Estimates from the Cox model are always adjusted for one time-varying variable (the underlying time-scale) automatically.
- We get to adjust for one time-varying confounder 'for free'.
- It is therefore sensible to choose the most important time-varying confounder as the underlying time-scale.
- For many epidemiological cohort studies this is attained age.
- Can adjust for a second time-varying variable by splitting the data.

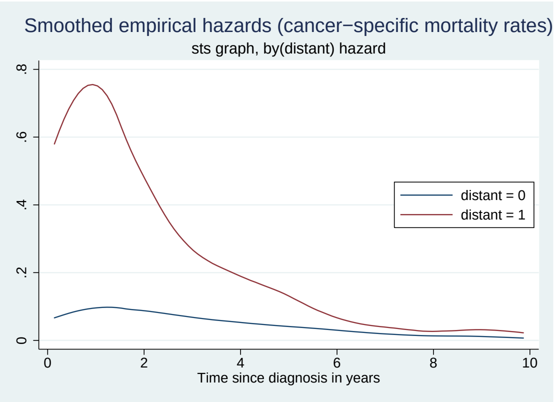
The Cox proportional hazards model

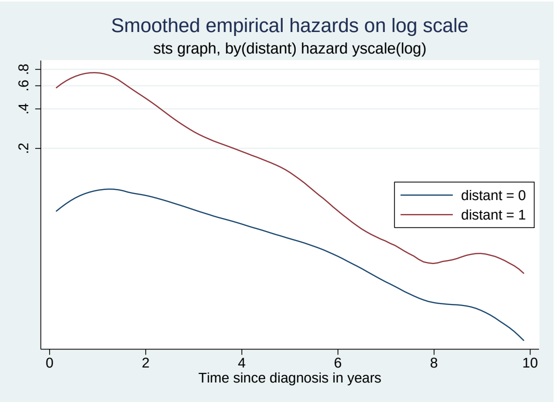
- The 'intercept' in the Cox model, the hazard (event rate) for individuals with all covariates z at the reference level, is an arbitrary function of time[1], often called the baseline hazard and denoted by $\lambda_0(t)$.
- The hazard at time t for individual with other covariate values is a multiple of the baseline
$$\lambda(t|z) = \lambda_0(t)\exp(\beta' z).$$
- Can extend the model to a 'stratified Cox model' which has separate baseline hazards for each level of some factor $j = 1, \ldots, J$
$$\lambda(t|j, z) = \lambda_{0j}(t)\exp(\beta' z).$$

[1] time t can be defined in many ways, e.g., attained age, time-on-study, calendar time, etc.

Example: survival of patients diagnosed with colon carcinoma

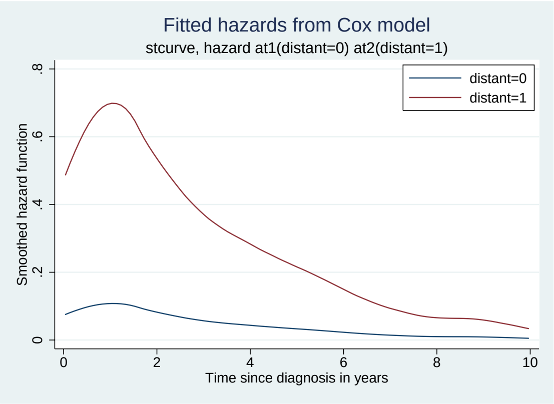
- Patients diagnosed with colon carcinoma in Finland 1984–95. Potential follow-up to end of 1995; censored after 10 years.
- Outcome is death due to colon carcinoma.
- Time-scale t is time-since-diagnosis in years.
- Interested in the effect of clinical stage at diagnosis (distant metastases vs no distant metastases).


Smoothed empirical hazards (cancer−specific mortality rates)
sts graph, by(distant) hazard

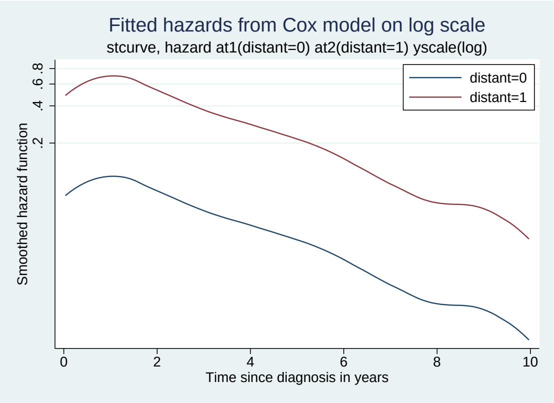

Smoothed empirical hazards on log scale
sts graph, by(distant) hazard yscale(log)

Fit a Cox model

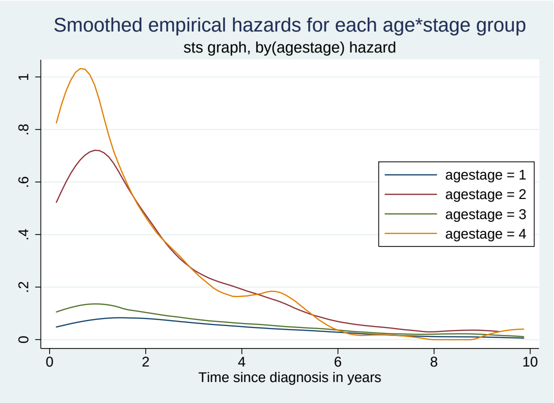
```
. stcox distant, basehc(base)

         failure _d:  status == 1
   analysis time _t:  (exit-origin)/365.25
             origin:  time dx

No. of subjects =        14648          Number of obs   =      14648
No. of failures =         7186
Time at risk    =  64134.28611
                                        LR chi2(1)      =    6164.83
Log likelihood  =   -62951.506          Prob > chi2     =     0.0000

--------------------------------------------------------------------
     _t | Haz. Ratio   Std. Err.    z    P>|z|   [95% Conf. Interval]
--------+-----------------------------------------------------------
distant |   7.190404   .1833347  77.37   0.000   6.839905    7.558863
--------------------------------------------------------------------
```


Fitted hazards from Cox model

stcurve, hazard at1(distant=0) at2(distant=1)


Fitted hazards from Cox model on log scale

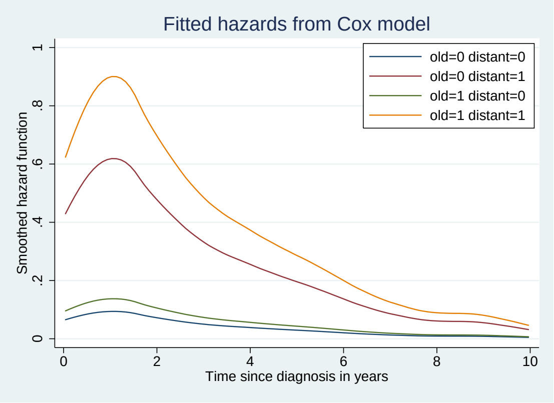
stcurve, hazard at1(distant=0) at2(distant=1) yscale(log)


Smoothed empirical hazards for each age*stage group

sts graph, by(agestage) hazard

Fit a Cox model adjusted for age at diagnosis

```
. stcox distant old, basehc(base)

         failure _d:  status == 1
   analysis time _t:  (exit-origin)/365.25
             origin:  time dx

No. of subjects =        14648         Number of obs   =      14648
No. of failures =         7186
Time at risk    =  64134.28611
                                       LR chi2(2)      =    6496.87
Log likelihood  =   -62785.488         Prob > chi2     =     0.0000

--------------------------------------------------------------------
     _t | Haz. Ratio   Std. Err.    z    P>|z|   [95% Conf. Interval]
--------+-----------------------------------------------------------
distant |   7.252431    .185139  77.61   0.000   6.898494    7.624528
    old |    1.57537   .0384735  18.61   0.000    1.50174    1.652611
--------------------------------------------------------------------
```


Fitted hazards from Cox model

Possible models

- Let a_0 be the age at entry and t the time-on-study.
- Using time-on-study as the time scale and adjusting for age at entry we have

$$\lambda(t|a_0, z) = \lambda_0(t)\exp(\xi a_0 + \gamma' z) \qquad \text{(Korn model 4).}$$

- Using attained age as the time scale we have

$$\lambda(a|a_0, z) = \lambda_0(a)\exp(\beta' z) \qquad \text{(Korn model 5).}$$

- Model (4) is appropriate for the cancer survival data but not for epidemiological cohort studies where time-on-study has no direct relevance.

- Nevertheless, this model is commonly applied in epidemiology.
- Model (5) is appropriate for epidemiological cohort studies (provided there are no cohort or period effects).
- Korn et al. [1] argue for the model with age as the time-scale and stratified on birth cohorts B_j

$$\lambda(a|b_0 \in B_j, z) = \lambda_{0j}(a)\exp(\beta' z) \qquad \text{(Korn model 3)}$$

that is, separate baseline hazards for each birth cohort.

- We will focus on a comparison of models (4) and (5), those most commonly applied in epidemiology.
- In particular, we will study conditions under which model (5) is correct but model (4) provides estimates without large bias.

Similarity of models (4) and (5)

- Assume model (5) is appropriate (hazard depends on attained age and there are no period or birth cohort effects).
- We also assume, for the moment, that the exposure of interest does not vary over time.
- Korn et al. suggested two conditions under which the γ's estimated from model (4) are similar to the β's estimated from model (5) is
  1. the baseline hazard $\lambda_0(a) = c\exp(\psi a)$ for some $c > 0$ and ψ; or
  2. the baseline ages, a_0, are independent of the covariates z.
- Thiébaut and Bénichou (2004) [2] performed simulations and observed bias even when the second condition was met.
- First condition can be written as $\ln[\lambda_0(a)] = \ln(c) + \psi a$;
  – we require the log hazard to be a linear function of (attained) age.

Example 1 from Korn et al.; condition 1 is satisfied

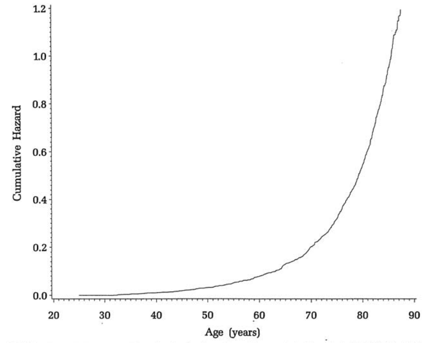


FIGURE 1. Cumulative hazard for mortality as a function of age (age ≥25 years) for women being followed in the NHANES I Epidemiologic Followup Study.

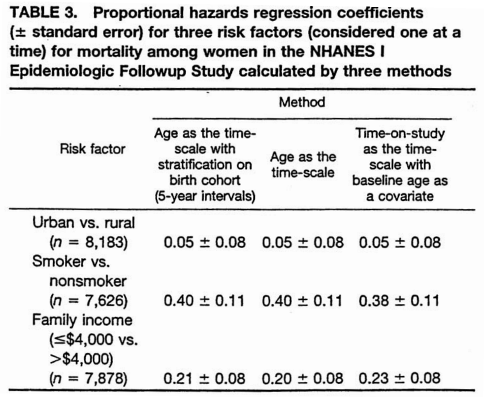


TABLE 3. Proportional hazards regression coefficients (± standard error) for three risk factors (considered one at a time) for mortality among women in the NHANES I Epidemiologic Followup Study calculated by three methods

Risk factor	Method		
	Age as the time-scale with stratification on birth cohort (5-year intervals)	Age as the time-scale	Time-on-study as the time-scale with baseline age as a covariate
Urban vs. rural (n = 8,183)	0.05 ± 0.08	0.05 ± 0.08	0.05 ± 0.08
Smoker vs. nonsmoker (n = 7,626)	0.40 ± 0.11	0.40 ± 0.11	0.38 ± 0.11
Family income (≤$4,000 vs. >$4,000) (n = 7,878)	0.21 ± 0.08	0.20 ± 0.08	0.23 ± 0.08

Example 2 from Korn et al.; condition 1 is not satisfied

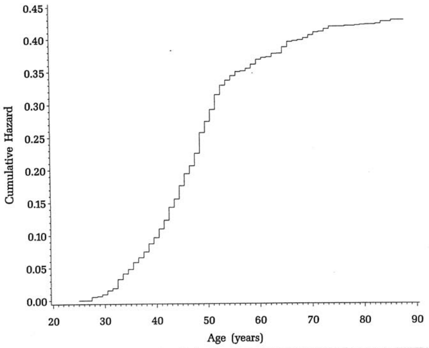


FIGURE 2. Cumulative hazard for ovary removal as a function of age (age ≥25 years) for women being followed in the NHANES I Epidemiologic Followup Study.

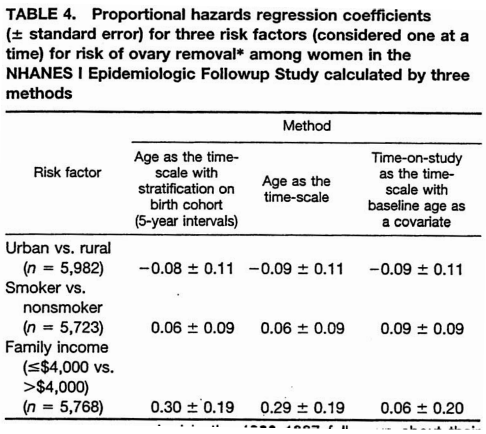


TABLE 4. Proportional hazards regression coefficients (± standard error) for three risk factors (considered one at a time) for risk of ovary removal* among women in the NHANES I Epidemiologic Followup Study calculated by three methods

Risk factor	Method		
	Age as the time-scale with stratification on birth cohort (5-year intervals)	Age as the time-scale	Time-on-study as the time-scale with baseline age as a covariate
Urban vs. rural (n = 5,982)	−0.08 ± 0.11	−0.09 ± 0.11	−0.09 ± 0.11
Smoker vs. nonsmoker (n = 5,723)	0.06 ± 0.09	0.06 ± 0.09	0.09 ± 0.09
Family income (≤$4,000 vs. >$4,000) (n = 5,768)	0.30 ± 0.19	0.29 ± 0.19	0.06 ± 0.20

Simulation study of Thiébaut and Bénichou (2004)

- Designed to simulate risk of breast cancer in the E3N cohort, 100k French women aged 40–65 years at recruitment (1989/90).
- Exposure of interest is menopausal status at recruitment (time-fixed) and menopausal status (time-varying).
- Table I: Covariate independent of age at entry
- Table II: Covariate dependent on age at entry; $\beta = 0$
- Table III: Covariate dependent on age at entry; $\beta = \ln(5)$

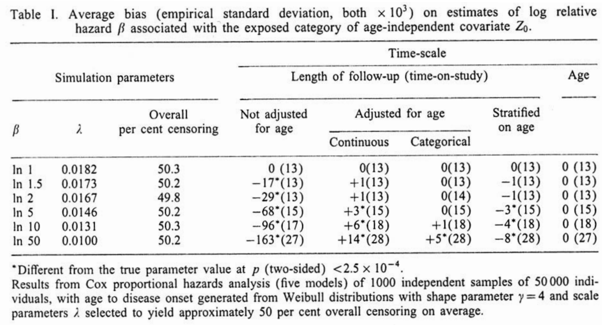


Table I. Average bias (empirical standard deviation, both $\times 10^3$) on estimates of log relative hazard β associated with the exposed category of age-independent covariate Z_0.

Simulation parameters			Time-scale				
			Length of follow-up (time-on-study)				Age
			Not adjusted for age	Adjusted for age		Stratified on age	
β	λ	Overall per cent censoring		Continuous	Categorical		
ln 1	0.0182	50.3	0 (13)	0(13)	0(13)	0(13)	0 (13)
ln 1.5	0.0173	50.2	−17*(13)	+1(13)	0(13)	−1(13)	0 (13)
ln 2	0.0167	49.8	−29*(13)	+1(13)	0(14)	−1(13)	0 (13)
ln 5	0.0146	50.2	−68*(15)	+3*(15)	0(15)	−3*(15)	0 (15)
ln 10	0.0131	50.3	−96*(17)	+6*(18)	+1(18)	−4*(18)	0 (18)
ln 50	0.0100	50.2	−163*(27)	+14*(28)	+5*(28)	−8*(28)	0 (27)

*Different from the true parameter value at p (two-sided) $<2.5 \times 10^{-4}$.
Results from Cox proportional hazards analysis (five models) of 1000 independent samples of 50 000 individuals, with age to disease onset generated from Weibull distributions with shape parameter $\gamma = 4$ and scale parameters λ selected to yield approximately 50 per cent overall censoring on average.

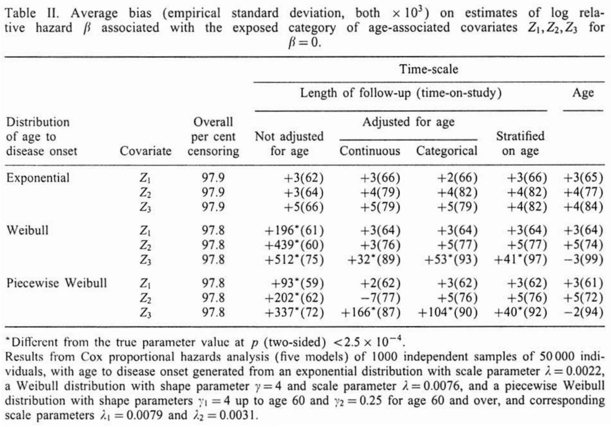


Table II. Average bias (empirical standard deviation, both $\times 10^3$) on estimates of log relative hazard β associated with the exposed category of age-associated covariates Z_1, Z_2, Z_3 for $\beta = 0$.

			Time-scale				
			Length of follow-up (time-on-study)				Age
Distribution of age to disease onset	Covariate	Overall per cent censoring	Not adjusted for age	Adjusted for age		Stratified on age	
				Continuous	Categorical		
Exponential	Z_1	97.9	+3(62)	+3(66)	+2(66)	+3(66)	+3(65)
	Z_2	97.9	+3(64)	+4(79)	+4(82)	+4(82)	+4(77)
	Z_3	97.9	+5(66)	+5(79)	+5(79)	+4(82)	+4(84)
Weibull	Z_1	97.8	+196*(61)	+3(64)	+3(64)	+3(64)	+3(64)
	Z_2	97.8	+439*(60)	+3(76)	+5(77)	+5(77)	+5(74)
	Z_3	97.8	+512*(75)	+32*(89)	+53*(93)	+41*(97)	−3(99)
Piecewise Weibull	Z_1	97.8	+93*(59)	+2(62)	+3(62)	+3(62)	+3(61)
	Z_2	97.8	+202*(62)	−7(77)	+5(76)	+5(76)	+5(72)
	Z_3	97.8	+337*(72)	+166*(87)	+104*(90)	+40*(92)	−2(94)

*Different from the true parameter value at p (two-sided) $<2.5 \times 10^{-4}$.
Results from Cox proportional hazards analysis (five models) of 1000 independent samples of 50 000 individuals, with age to disease onset generated from an exponential distribution with scale parameter $\lambda = 0.0022$, a Weibull distribution with shape parameter $\gamma = 4$ and scale parameter $\lambda = 0.0076$, and a piecewise Weibull distribution with shape parameters $\gamma_1 = 4$ up to age 60 and $\gamma_2 = 0.25$ for age 60 and over, and corresponding scale parameters $\lambda_1 = 0.0079$ and $\lambda_2 = 0.0031$.

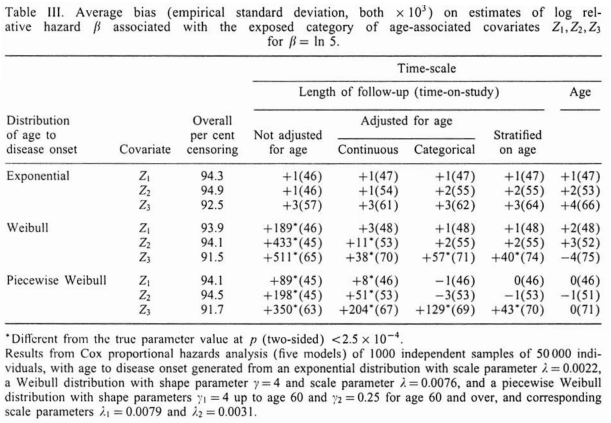


Table III. Average bias (empirical standard deviation, both $\times 10^3$) on estimates of log relative hazard β associated with the exposed category of age-associated covariates Z_1, Z_2, Z_3 for $\beta = \ln 5$.

			Time-scale				
			Length of follow-up (time-on-study)				Age
				Adjusted for age			
Distribution of age to disease onset	Covariate	Overall per cent censoring	Not adjusted for age	Continuous	Categorical	Stratified on age	
Exponential	Z_1	94.3	+1(46)	+1(47)	+1(47)	+1(47)	+1(47)
	Z_2	94.9	+1(46)	+1(54)	+2(55)	+2(55)	+2(53)
	Z_3	92.5	+3(57)	+3(61)	+3(62)	+3(64)	+4(66)
Weibull	Z_1	93.9	+189*(46)	+3(48)	+1(48)	+1(48)	+2(48)
	Z_2	94.1	+433*(45)	+11*(53)	+2(55)	+2(55)	+3(52)
	Z_3	91.5	+511*(65)	+38*(70)	+57*(71)	+40*(74)	−4(75)
Piecewise Weibull	Z_1	94.1	+89*(45)	+8*(46)	−1(46)	0(46)	0(46)
	Z_2	94.5	+198*(45)	+51*(53)	−3(53)	−1(53)	−1(51)
	Z_3	91.7	+350*(63)	+204*(67)	+129*(69)	+43*(70)	0(71)

*Different from the true parameter value at p (two-sided) $<2.5 \times 10^{-4}$.

Results from Cox proportional hazards analysis (five models) of 1000 independent samples of 50 000 individuals, with age to disease onset generated from an exponential distribution with scale parameter $\lambda = 0.0022$, a Weibull distribution with shape parameter $\gamma = 4$ and scale parameter $\lambda = 0.0076$, and a piecewise Weibull distribution with shape parameters $\gamma_1 = 4$ up to age 60 and $\gamma_2 = 0.25$ for age 60 and over, and corresponding scale parameters $\lambda_1 = 0.0079$ and $\lambda_2 = 0.0031$.

Mortality in relation to snus use; a cohort of Swedish men

- Randomly selected men (n=9976) aged 14–99 (at entry) living in Uppsala county 1973
- Participants were:
  - Invited to oral examination (at dentist)
  - Questionnaire on snus use (plus tobacco use & life-style factors)
  - Followed-up for cancer and death 1973-2002 via population registers
- 1427 (14%) were snus users; 8408 (84%) non-users at baseline
- If cumulative dose is the underlying exposure of interest and we model exposure (hours/day) at baseline as a fixed covariate then age-at-entry may approximate cumulative dose at entry and time-since entry may approximate cumulative dose during follow-up.

Results from fitting various models (outcome is death)

	time-on-study as time-scale			attained age as time-scale		
		adj. for age entry	adj. for att age		adj. for time-on-st	stratified age entry
	1	2 (4)	3	4 (5)	5	6
snus hrs/day						
0	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
1–6	1.1 (1.0-1.2)	1.0 (0.9-1.1)	1.1 (1.0-1.3)	1.0 (0.9-1.1)	1.1 (1.0-1.2)	1.0 (0.9-1.1)
7–15	1.5 (1.3-1.8)	1.0 (0.9-1.2)	1.2 (1.0-1.4)	1.0 (0.9-1.2)	1.1 (0.9-1.3)	1.0 (0.9-1.2)
16–24	2.5 (1.6-3.7)	1.3 (0.9-2.0)	1.8 (1.2-2.7)	1.3 (0.9-2.0)	1.6 (1.0-2.3)	1.3 (0.8-1.9)
time	1.5 sec	1.3 sec	14 sec	5 min	55 min	15 sec

- Which model is appropriate?
  - Model 1 is not appropriate but suggests the heavy users are older.
  - Age-specific mortality is exponential so we expect models 2 & 4 to be similar.
  - Model 6 extends 2 & 4 by controlling for cohort & period effects (suggests there are no such effects)
  - Models 3 & 5 both adjust for two time-scales. Why is time-on study a confounder given adjustment for attained age? Cumulative dose effect?

Categories used

- Age-at-entry: 0-19, 20-24, 25-29, 30-34, . . . , 90-94, 95+ yrs
- Attained age: 0-19, 20-24, 25-29, 30-34, . . . , 90-94, 95+ yrs
- Attained follow-up: 0-4, 5-9, 10-14, 15-19, 20-24, 25-29 yrs
- Results are preliminary and not adjusted for potential confounders (smoking, alcohol, etc.). Such adjustment will be performed after data have been cleaned.

SAS processing times for model 4

obs	time (seconds)
100	0.3
1000	1.3
5000	17
10000	300
20000	?

References

[1] Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am J Epidemiol* 1997; **145**:72–80.

[2] Thiébaut ACM, Bénichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Stat Med* 2004; **23**:3803–3820.