A Multi-State Model for Joint Modeling of Terminal and Non-Terminal Events with Application to Whitehall II

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The Whitehall II Study

- The Whitehall II study was initiated between 1985 and 1988.
- In that period 10308 civil servants (CS), aged 35–55, were registered in the study.
- After that starting point, called phase 1, the CS were contacted approximately every 3 years (phases 2–5) where they were asked to fill in a questionnaire and have a screening exam. An attempt was made to identify potential non–fatal CHD events retrospectively from the last phase attended.
- Phase 5 (last one) was scheduled for all CS sometime between 1997 and 1999.
- Mortality follow–up was available until 31 December 1999.

Scope of the this analysis:

To examine the incidence of coronary heart disease (CHD), fatal (F) and non–fatal (NF) amongst the CS. Features:

- Data can be regarded as semi-competing risks (a relatively new concept, Fine et al, 2001)
- Two events of interest, a terminal one and a non-terminal one.
- The terminal event can censor the non-terminal one, but not vice-versa.
- Interest in explanatory variables, notably the grade or employment 'level' of CS
- There is the possibility of informative censoring.

The Data

- From the 10308 CS registered in phase 1, 70 were excluded from the analysis since they had experienced a non–fatal CHD event before entering the study. Fifteen had missing information.
- From the 10238 CS in the study we have

		CHD events	Non-fatal events	Fatal events	All Deaths	Both NF and F events	LTF*
Male	n=6825 (66.8%)	255 (80.4%)	202 (78.9%)	58 (87.9%)	236 (68.2%)	5 (100%)	1280 (57.2%)
Female	n=3398 (33.2%)	62 (19.6%)	54 (21.1%)	8 (12.1%)	110 (31.8%)	0 (0%)	958 (42.8%)
Total	n=10223	317	256	66	346	5	2238

* LTF represents the CS who were lost-to-follow-up before experiencing any of the two events.

Table 1: Counts of observed events.

Two processes

Since we observe two expressions of CHD we assume that we have two processes operating at the same time.
$\Longrightarrow$ The NF–process.

- CS are considered to be under follow–up only if they have attended the last scheduled phase.

- We assume that CS are under continuous follow–up.

- They are considered to be lost to follow–up (LTF) only when they miss one phase, and the time of last phase attended (or the mid point between the two phases) is considered to be their censoring time (we have to wait for approx 3 years to find out whether a CS is LTF).

$\Longrightarrow$ The F–process.

- All CS were flagged at the National Health Service Central Registry (NHSCR), who provided date and cause of death (until 31/12/99).

- Because of the nature of the follow–up of this process we have complete records of almost all the CS until 31/12/99.

- We consider only CHD related deaths.

- Those who died during the study from causes other than CHD are considered to be censored for estimation purposes as in standard competing risk analyses. For the calculation of cumulative incidence curves a separate non-CHD cause-specific Weibull mortality hazard is estimated.

Joint Modelling of both processes

- A way of modelling the two processes simultaneously is needed. Assumptions, likely untestable, will be required.
- An approach to this problem is to consider a multi-state model with five possible states, where all the possible combinations of events are presented.
- Although we have complete information for the F–process, we are not able to observe NF events for CS after they are LTF.
- We can only allow for the possibility of such an event happening by introducing an unobserved (hidden) state.
- Therefore, we consider the multi-state model...

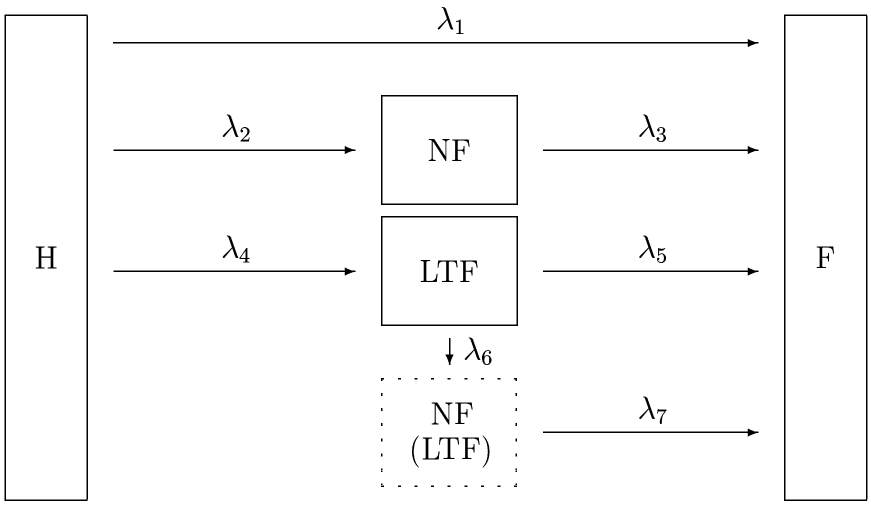


Figure 1: Whitehall II Multi–state Model

...where:

- the 'Fatal' state is an absorbing state.
- the 'NF(LTF)' state represents the NF event that might be experienced after the CS is lost-to-follow-up
- λ_m's are the transition rates between states

However, based on the available data, this model is non–identifiable, since we have no observations to estimate the transition rates λ_6 and λ_7. Hence, reasonable assumptions that involve these transition rates need to be made.

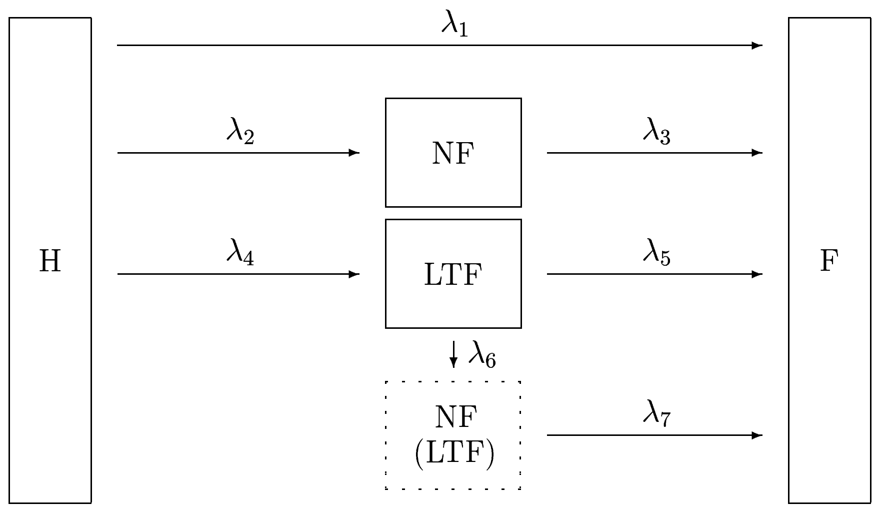


Figure 2: Whitehall II Multi–state Model

- While under observation, each CS can experience none, one or both of the events.
- NF events can occur after a CS is lost to follow-up (LTF) for the NF-process. In this case, it is unobserved.
- No loss to follow-up is possible for the F-process.
- An F event terminates both processes.

CENSORING:

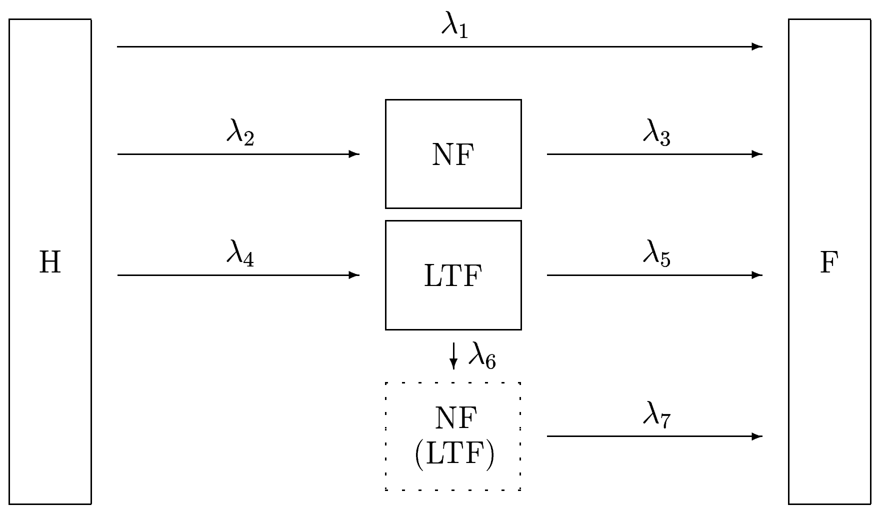
- For the two processes, we observed two separate censoring times.
- NF censoring happens throughout the study.
- F censoring, which is (mainly) the end of the observation period and serves as end-of-study (administrative) censoring for the F-process.
- Censoring for the NF-process is potentially informative.

We assume:

- The usual Markov like assumption that the transition rates at time t depend only on the state occupied at time t and not on the history of transitions up to time t.
- Weibull transition rates between states

$$\lambda_m(t) = \alpha_m e^{\beta'_m x}(t)^{\alpha_m - 1},$$

  where x is a vector of explanatory variabels and t is time from start of study.
- the CS are under continuous follow–up from the date they enter the study until the $31^s t$ of December 1999.
- The main issue is what happens if someone is LTF for the NF process. In this case, we assume the LTF time is the mid–point of the time period between their last observed stage and their first missed stage. An alternative is to take the time of the last observed stage.



Possible routes for a subject to take while under observation are: (1) $H \Rightarrow F$, (2) $H \Rightarrow NF$, (3) $H \Rightarrow NF \Rightarrow F$, (4) $H \Rightarrow LTF$, (5) $H \Rightarrow LTF \Rightarrow F$ and (6) $H \Rightarrow H$ (ie. no event).

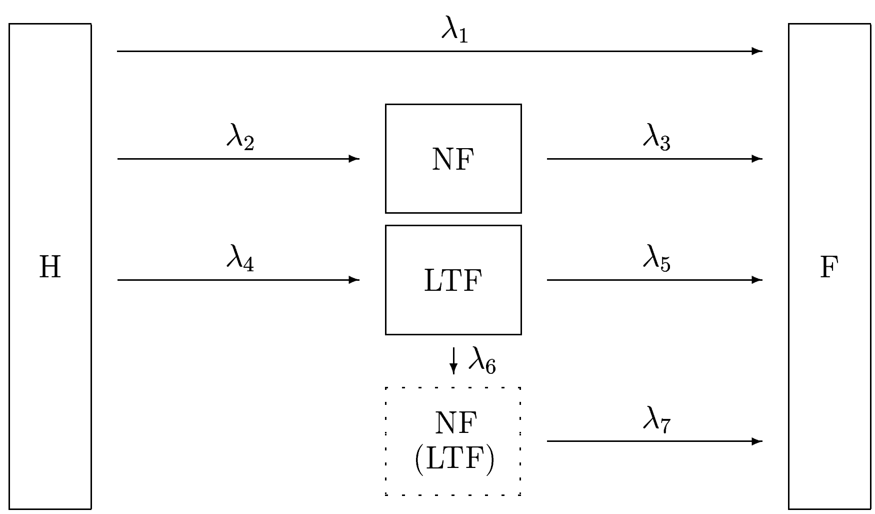
For the estimation, the likelihood takes the form

$$l(t) = \prod_{i=1}^{n} Q_{1i}(t_i)^{I_{1i}} Q_{2i}(s_i,t_i)^{I_{2i}} Q_{3i}(s_i,t_i)^{I_{3i}} Q_{4i}(s_i,t_i)^{I_{4i}} Q_{5i}(s_i,t_i)^{I_{5i}} Q_{6i}(t_i)^{1-\sum_{j=1}^{5} I_{ji}}$$

where $Q_{ki}()$, $k = 1,\dots,6$ are the probabilities for each one of the 6 possible 'routes' that subject i might take during the time that is under observation.

The times s_i and t_i denote relevant observations times associated with the routes.

Furthermore, the binary variables $I_{ji}, j = 1,\dots,5$, indicate whether the observation i follows the j^{th} route.



Identifiability Issue

In order to deal with the identifiability issue, we need some further assumptions. It is reasonable to assume that being censored with respect to the NF–process (i.e. LTF) may affect the subsequent rates of occurrence of the events (ie. λ_5 and λ_6). However, we could reasonably expect that:

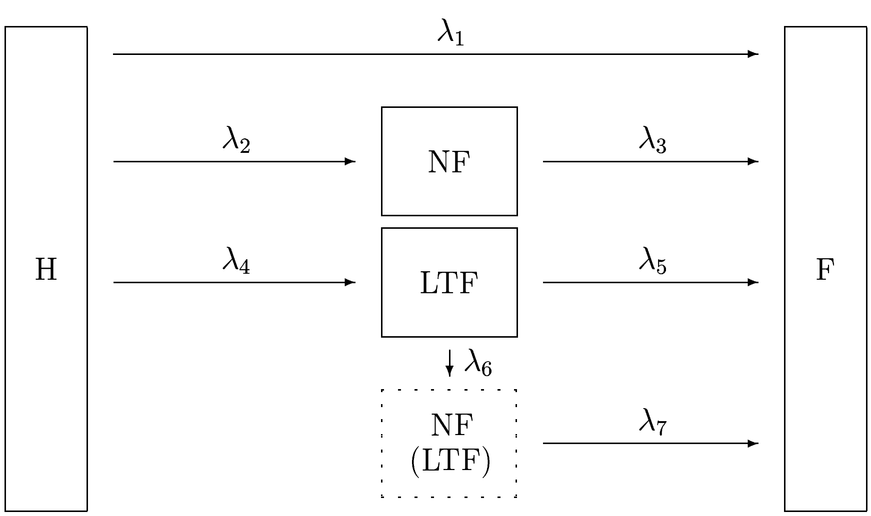
1. this would not affect λ_7, the rate of experiencing F event, after having an NF event. Hence,

$$\lambda_3 = \lambda_7.$$

2. although λ_5 and λ_6 would be different than λ_1 and λ_2 respectively, we may assume that the ratio of these hazards satisfies the relationship

$$\frac{\lambda_1}{\lambda_2} = k \, \frac{\lambda_5}{\lambda_6},$$

where the hazard ratios are proportional, and when $k = 1$ are equal.



Explanatory variables:

- Age groups: 35-39, 40-44, 45-49, 50-55
- Indicator for females
- Grade levels: Administrative (1), Professional/Executive (2), Clerical/Support (3)

Note: Small number of observations for transitions to F state from NF or LTF states. Therefore, restrict effects of explanatory variables for all transitions to the F state to be the same.

	Hazard Ratio (95% CI)		
	Risk of fatal event	Risk of non-fatal event	Risk of lost to follow up
	$(\lambda_1, \lambda_3(=\lambda_7), \lambda_5)$	(λ_2)	(λ_4)
Age [35-39]	1	1	1
Age [40-44]	2.38 (0.59-9.64)	1.00 (0.64-1.56)	0.94 (0.84-1.06)
Age [45-49]	10.20 (2.98-34.86)	2.48 (1.67-3.66)	0.98 (0.87-1.11)
Age [50-55]	13.57 (4.09-45.08)	3.25 (2.26-4.68)	0.97 (0.87-1.09)
Administrative	1	1	1
Prof/Exec	1.19 (0.64-2.24)	1.37 (1.02-1.83)	1.41 (1.25-1.58)
Cler/Supp	4.27 (2.21-8.25)	1.68 (1.13-2.50)	2.77 (2.43-3.16)
Gender (Female)	0.11 (0.05-0.23)	0.42 (0.30-0.60)	1.08 (0.98-1.19)

Table 2: Maximum likelihood estimates based on the multi–state model.

Results show:

- Higher risk of moving out of healthy state and or progression to death with older age.
- Increased risk for males.
- Increased risk in lower grade categories.
- Likelihood ratio test for grade effect (χ^2 test on 6 df): 142.68; $p < 0.0001$

	Hazard Ratio (95% CI)		
	(a) Time to F Event	(b) Time to NF Event	(c) Time to First Event
Age [35-39]	1	1	1
Age [40-44]	2.29 (0.57-9.17)	0.99 (0.64-1.55)	1.03 (0.67-1.57)
Age [45-49]	10.40 (3.09-34.97)	2.45 (1.66-3.63)	2.73 (1.88-3.96)
Age [50-55]	13.98 (4.28-45.60)	3.26 (2.27-4.68)	3.69 (2.61-5.20)
Administrative	1	1	1
Prof/Exec	1.27 (0.68-2.39)	1.36 (1.02-1.82)	1.37 (1.04-1.79)
Cler/Supp	5.23 (2.75-9.96)	1.65 (1.11-2.45)	1.97 (1.38-2.81)
Gender (Female)	0.10 (0.05-0.22)	0.43 (0.30-0.60)	0.36 (0.26-0.50)

Table 3: Independent analyses.

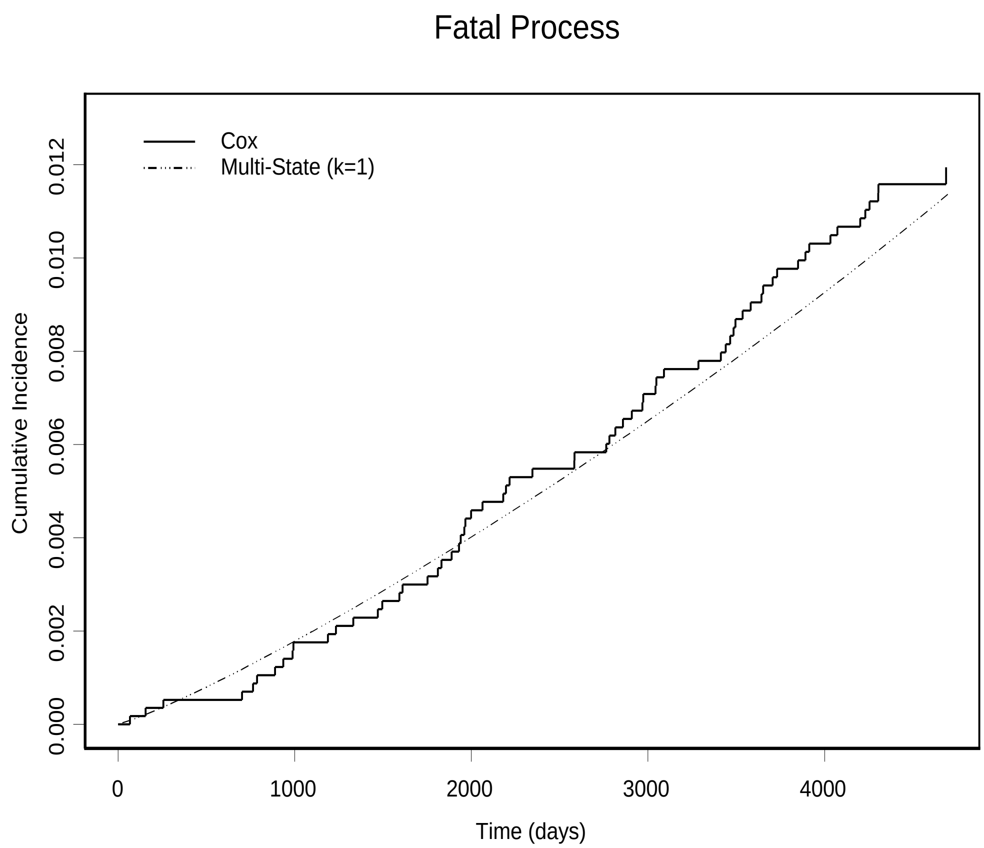


Figure 3: Comparison of cumulative incidence curves for fatal events derived from the relative risk regression analysis model with those derived from the multi-state model (age=40-45, grade=2, sex=male).

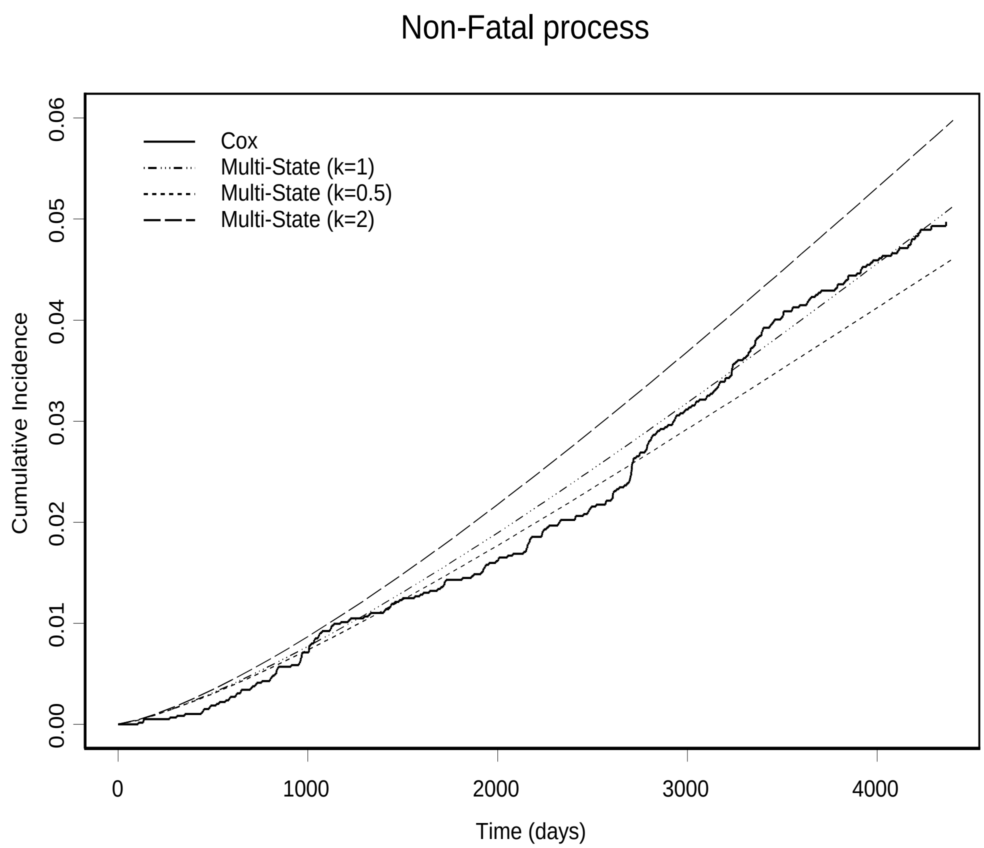


Figure 4: Comparison of the cumulative incidence curves for non–fatal events from the standard competing risks analysis with those from the analysis using the multi-state model (age=40-45, grade=2, sex=male).

Hazard Ratio (95% CI)				
(a)			(b)	
NF-Indic	3.31 (1.31-8.36)		LTF-Indic	2.53 (1.40-4.57)
Age [35-39]	1		Age [35-39]	1
Age [40-44]	2.26 (0.57-9.06)		Age [40-44]	2.30 (0.57-9.20)
Age [45-49]	10.02 (2.98-33.73)		Age [44-49]	10.39 (3.09-34.95)
Age [50-55]	13.26 (4.06-43.32)		Age [50-55]	14.05 (4.31-45.85)
Administrative	1		Administrative	1
Prof/Exec	1.25 (0.67-2.34)		Prof/Exec	1.22 (0.65-2.29)
Cler/Supp	5.10 (2.68-9.71)		Cler/Supp	4.38 (2.27-8.47)
Gender (Female)	0.11 (0.05-0.23)		Gender (Female)	0.10 (0.05-0.22)

Table 4: Time to F event analysis with (a) NF and (b) LTF event as time dependent covariate.

Test for independence based on multi-state model

- Compare fitted model to sub-model with restriction $\lambda_5 = \lambda_1$ or $\lambda_6 = \lambda_2$.
- Likelihood ratio test gives test statistic of 9.9 on 2 df: $p = 0.007$.

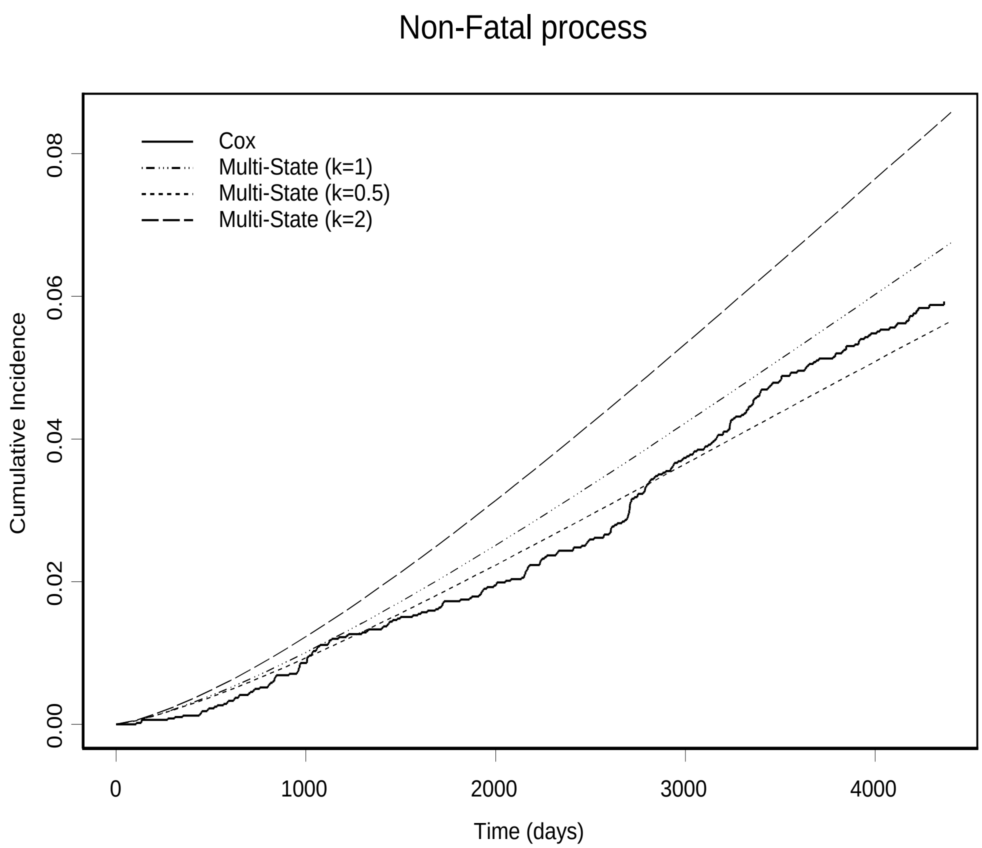


Figure 5: Comparison of the cumulative incidence curves for non–fatal events from the standard competing risks analysis with those from the analysis using the multi-state model (age=40-45, grade=3, sex=male).

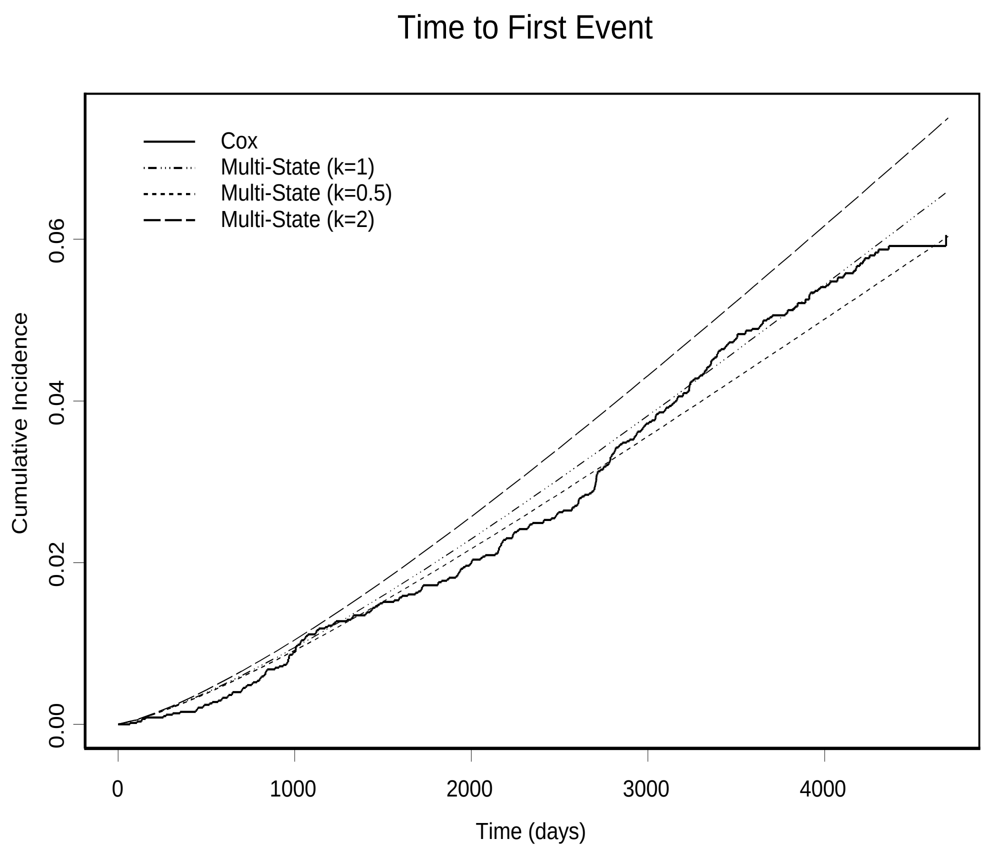


Figure 6: Comparison of cumulative incidence curves derived from the relative risk regression analysis model with those derived from the multi-state model (age=40-45, grade=2, sex=male).

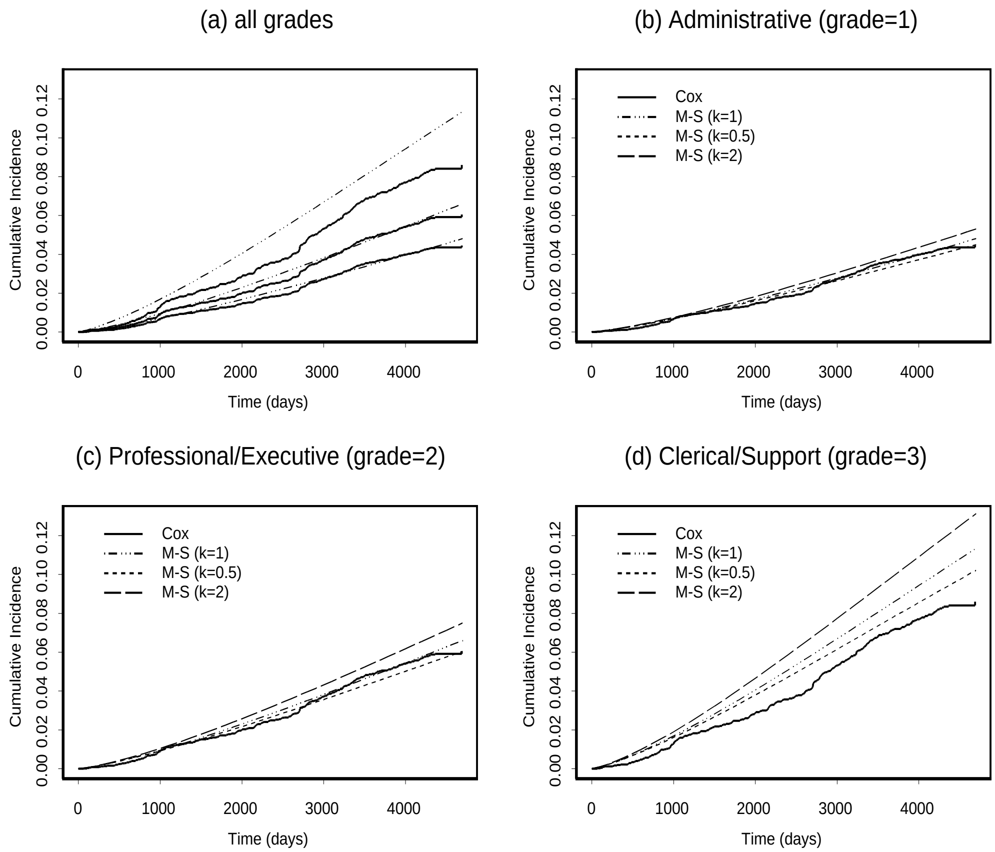


Figure 7: Comparison of time to first event cumulative incidence curves for different grade levels (age=45-49, sex=male).

REMARKS

- Standard methods do provide some information for the data discussed but various assumptions are required about censoring
- Analysis of time to first event is particularly problematic using statndard methods
- Multi-state model appears to provide a useful structure in which to think about semi-competing risk data
- In this study, there is evidence of informative censoring *however* the impact, as measured by comparison with independence based analyses, is not dramatic.
- The assumption that covariate effects were the same in all transitions to death is a strong one but limited data makes it necessary in this case.
- Note that k does have value for sensitivity analyses related to the model based assumptions required for identifiability. However, it is perhaps unusual in that there is no value of k that corresponds to uninformative censoring.