Estimating Crude and Net Mortality in the Framework of Relative Survival

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Methods and Applications for Population-Based Survival

Net Survival

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Key Assumption

Independence between mortality due to cancer and mortality due to other causes.

- Same interpretation/assumption for cause-specific survival.

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- But. How useful is it for patients?
- Patients do not live in this hypothetical world.
- Treatment decisions are made in the real world, which includes risk of dying of other causes.
- To calculate "real world" probabilities we need to borrow ideas from competing risks theory.

Crude and Net Probabilities

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Crude Probability of Death Due to Cancer	=	Probability of death due to cancer in the real world, where you may die of other causes before the cancer kills you

- Some people refer to the crude probability as cumulative incidence.

Life table calculation of crude mortality

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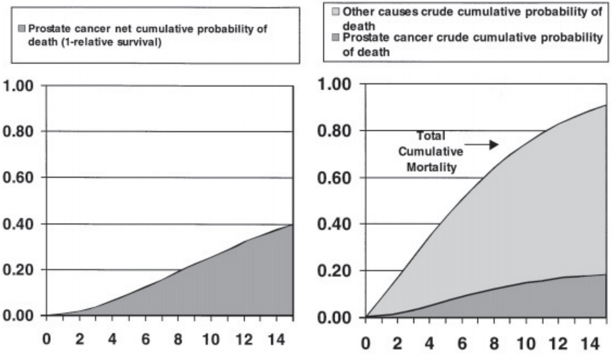
- No individual level prediction using continuous covariate.
- Can be estimated in Stata using `strs`.

Example from Cronin and Feuer [2].



Net and Crude probability of death in men with localized prostate cancer over the age of 70.

A model based approach

- Use flexible parametric survival model [4].
- Uses individual level data.
- No need to split the time scale.
- Use restricted cubic splines for baseline hazard.
- Simple to extend to non-proportional excess hazards (using splines).
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- More on these models later.

Data

- Data from England and Norway, but not Sweden.
- The data consists of
  - 303,657 women from England.
  - 24,919 women from Norway.
  - Year of Diagnosis was between 1996 and 2004.
- Extension of

Møller, H., Sandin, F., Bray, F., Klint, A., Linklater, K. M., Purushotham, A., Robinson, D. & Holmberg, L. Breast cancer survival in England, Norway and Sweden: a population-based comparison *International Journal of Cancer* 2010 (published online).

Flexible Parametric Models

$$H(t) = H^*(t) + \Lambda(t)$$

- Model $\ln[\Lambda(t)]$ scale which includes terms for

Baseline hazard (time)	-	Splines (6 parameters)
Country	-	1 dummy covariate
Age	-	Splines (4 parameters)
Age×Country	-	(4 parameters)
Country×Time	-	Splines (3 parameters)
Age×Time	-	$4\times3 = 12$ parameters

- Results extremely robust to number and locations of the knots.

Model Summary

- Relative survival model in continuous time.
- Continuous age
- Non-proportional excess hazards
- Interactions
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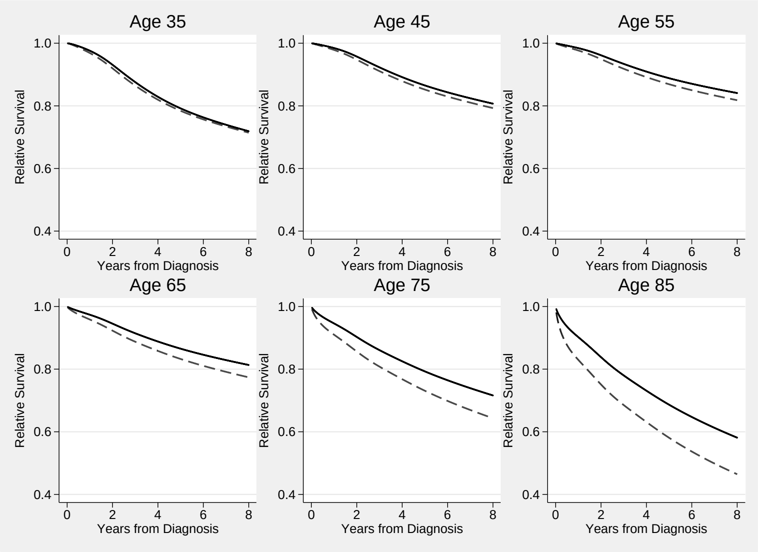
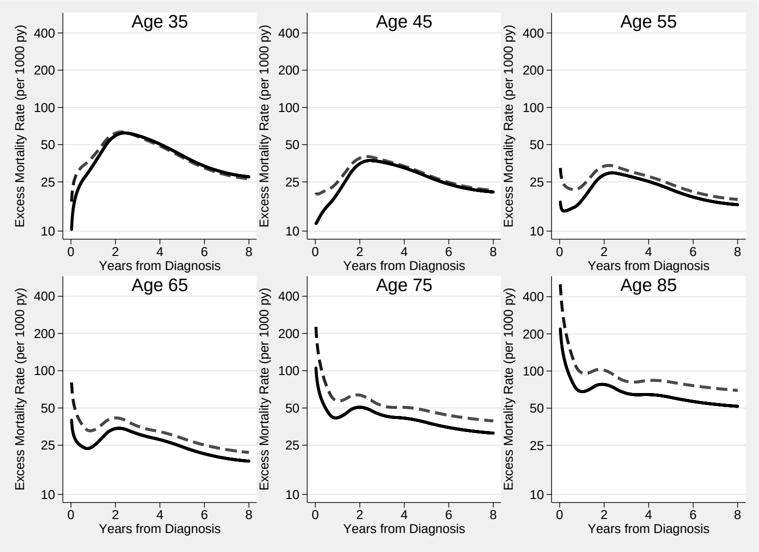
stpm2 code

```
. stpm2 england agercs* eng_agercs*,          ///
        scale(hazard) df(6) bhazard(rate) ///
        tvc(agercs* england) dftvc(3)
```

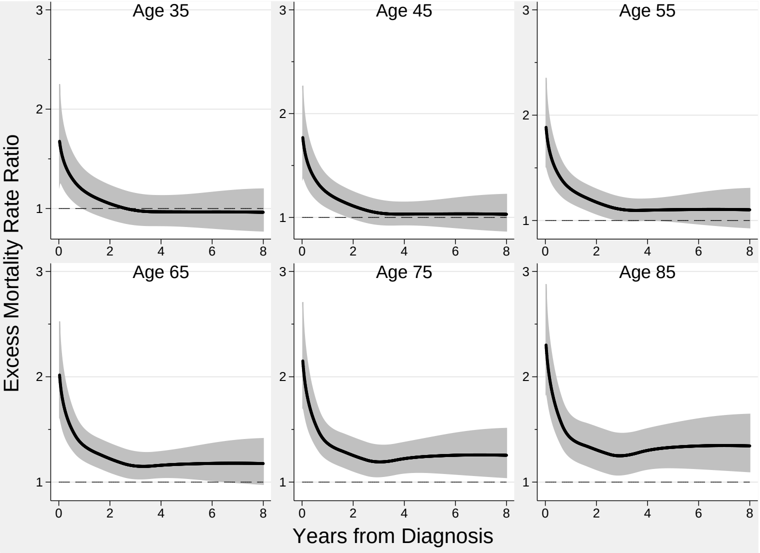
Relative Survival



Excess Mortality Rates



Excess Mortality Rate Ratios



Brief Mathematical Details[3]

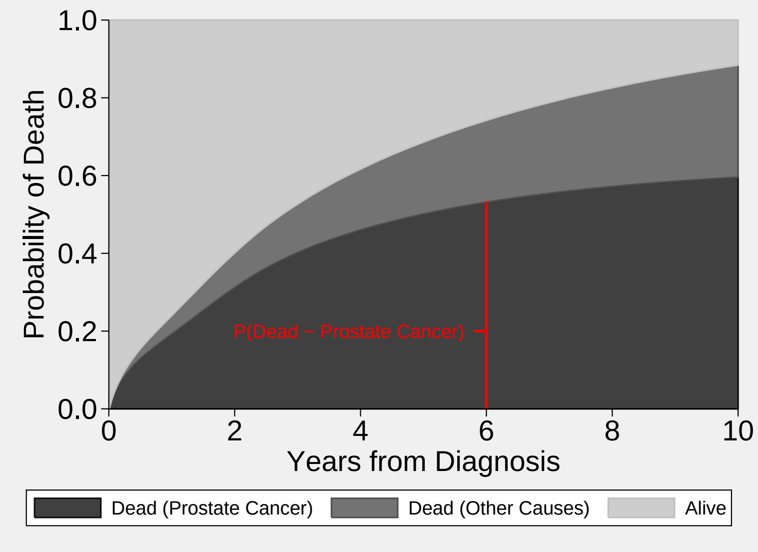
$h(t)$	-	all-cause mortality rate
$h^*(t)$	-	expected mortality rate
$\lambda(t)$	-	excess mortality rate
$S^*(t)$	-	Expected Survival
$R(t)$	-	Relative Survival

$$\text{Net Prob of Death} = 1 - R(t) = 1 - \exp\left(-\int_0^t \lambda(t)\right)$$

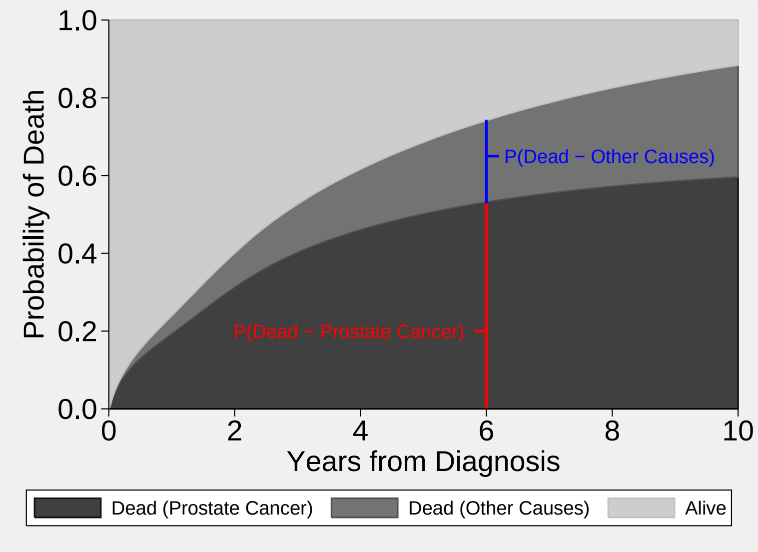
$$\text{Crude Prob of Death (cancer)} = \int_0^t S^*(t)R(t)\lambda(t)$$

$$\text{Crude Prob of Death (other causes)} = \int_0^t S^*(t)R(t)h^*(t)$$

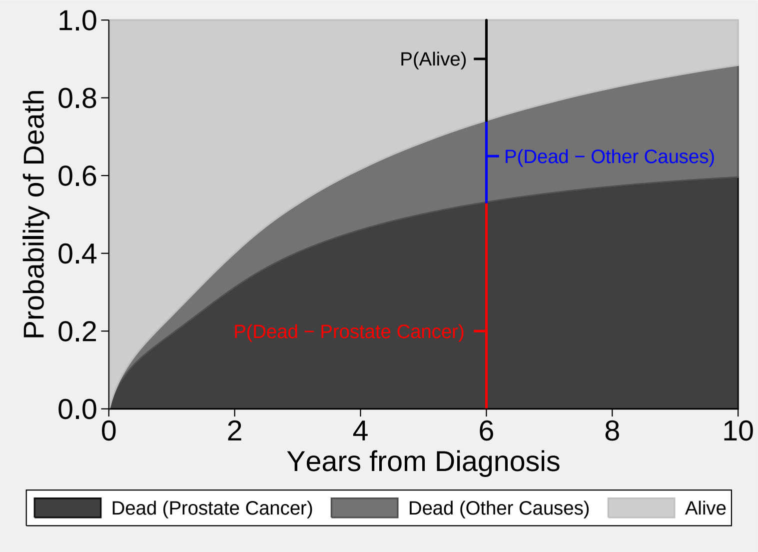
Crude Mortality



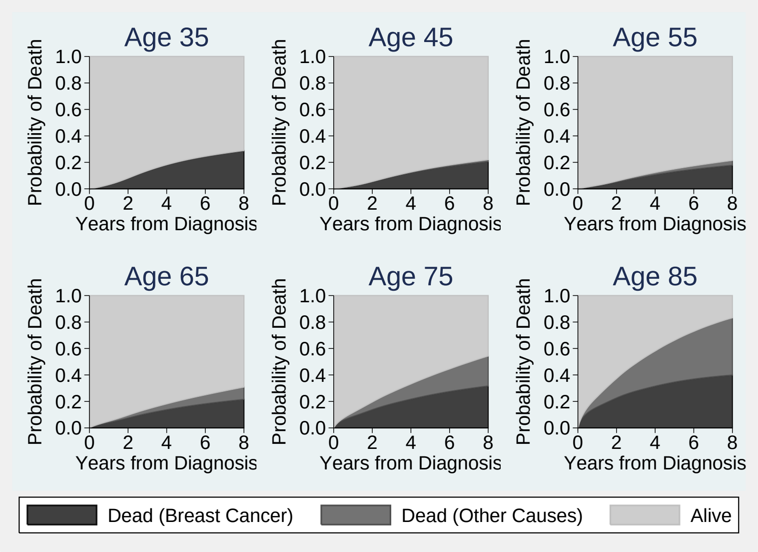
Crude Mortality



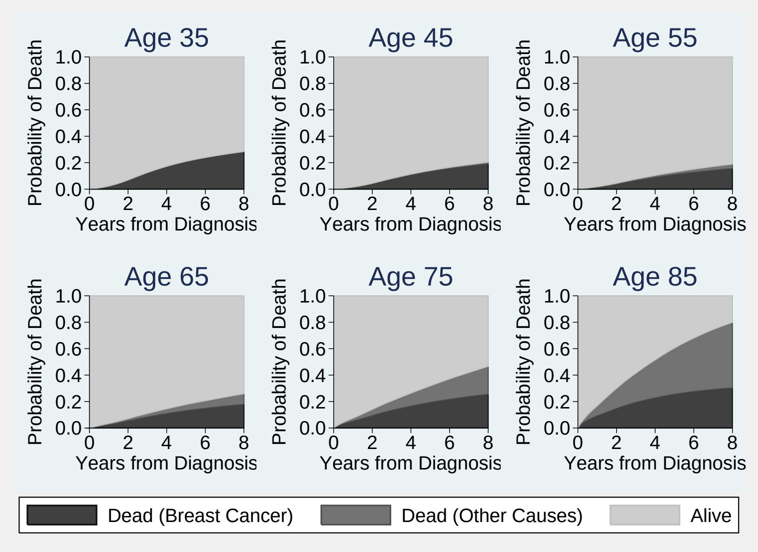
Crude Mortality



Breast Cancer England



Breast Cancer Norway



Probabilities at 5 Years

	Crude Probabilities			Net Probabilities	
Age	Cancer	Other	Alive	Dead	Alive
England					
45	0.15	0.01	0.84	0.15	0.85
55	0.13	0.02	0.85	0.13	0.87
65	0.16	0.06	0.78	0.17	0.83
75	0.25	0.14	0.61	0.27	0.73
85	0.35	0.32	0.33	0.42	0.58
Norway					
45	0.13	0.01	0.86	0.13	0.87
55	0.11	0.02	0.87	0.11	0.89
65	0.13	0.05	0.82	0.13	0.87
75	0.19	0.12	0.68	0.21	0.79
85	0.26	0.35	0.39	0.31	0.69

'Avoidable' Deaths

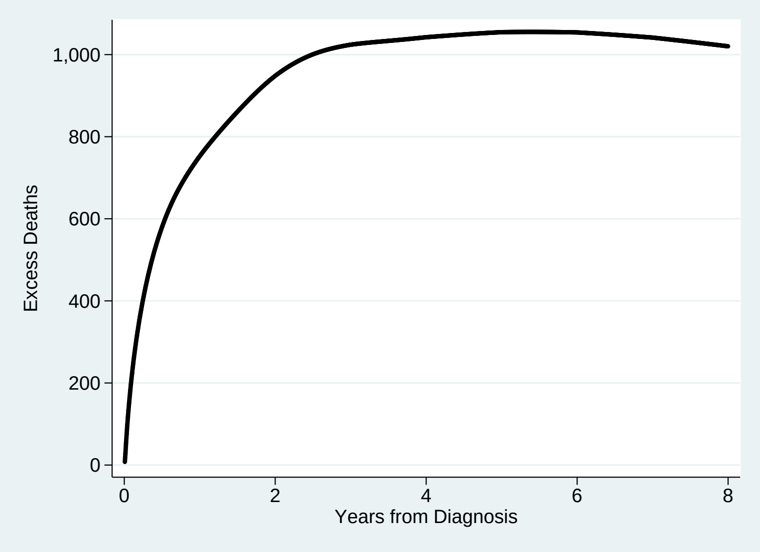
- Increased interest in use of avoidable deaths.

Question of Interest

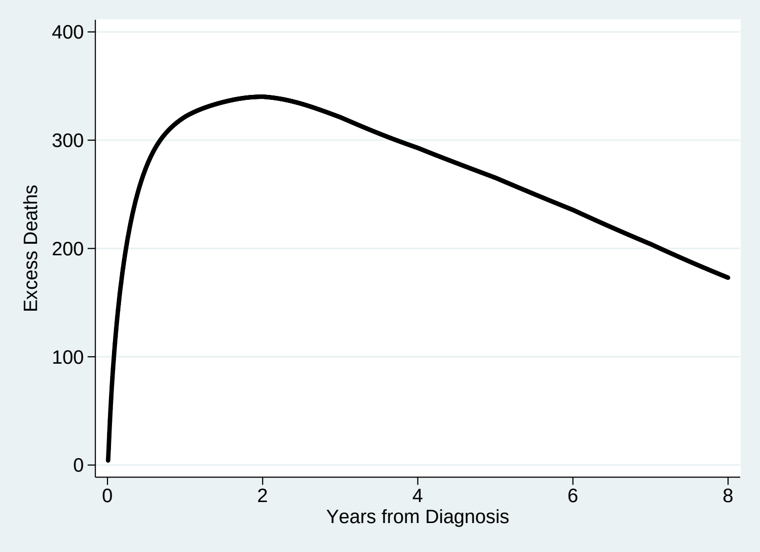
How many fewer deaths per year would there be in England if it were to have Norway's excess mortality rate.

- Usually presented at 5 years post diagnosis.
- Everyone will eventually die and so avoidable deaths will eventually be zero.
- Perhaps 'Postponable Deaths' is better [5].
- Using crude probabilities allows breakdown into reduction/increase in deaths due to cancer and deaths due to other causes.

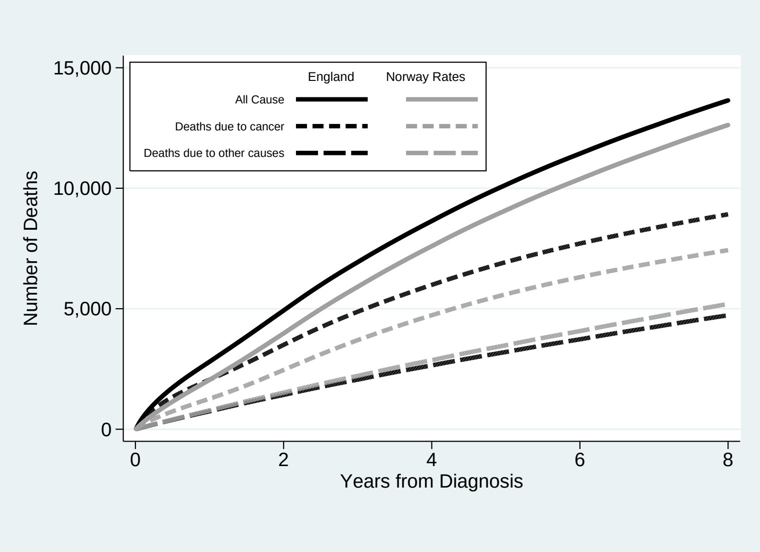
'Avoidable' Deaths



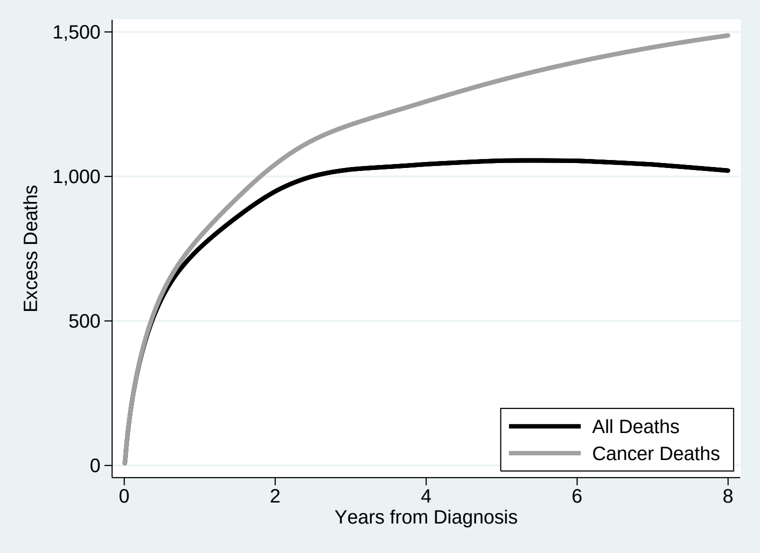
'Avoidable' Deaths 80+



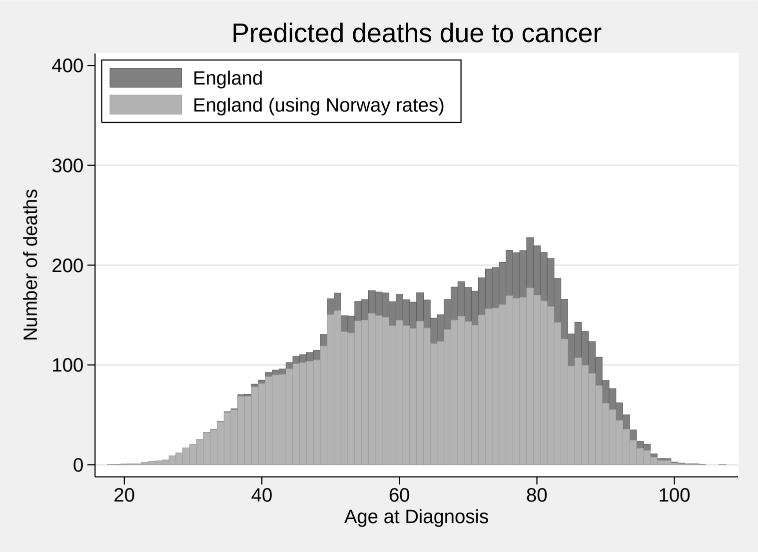
Breakdown of Deaths



Breakdown of Avoidable Deaths



Cancer Deaths by Age



Conclusions

- Modelling allows us to understand differences more.
- Crude probabilities more useful to patients.
- Relative survival or cause-specific survival?
- Avoidable deaths useful to understand impact.
    - Must understand time-dependence of estimates.

References I

[1] H. Brenner and O. Gefeller. Deriving more up-to-date estimates of long-term patient survival. *Journal of Clinical Epidemiology*, 50(2):211–216, 1997.

[2] K. A. Cronin and E. J. Feuer. Cumulative cause-specific mortality for cancer patients in the presence of other causes: a crude analogue of relative survival. *Statistics in Medicine*, 19(13):1729–1740, 2000.

[3] P. C. Lambert, P. W. Dickman, C. P. Nelson, and P. Royston. Estimating the crude probability of death due to cancer and other causes using relative survival models. *Statistics in Medicine*, 29:885 – 895, 2010.

[4] P. C. Lambert and P. Royston. Further development of flexible parametric models for survival analysis. *The Stata Journal*, 9:265–290, 2009.

[5] A. Pokhrel, P. Martikainen, E. Pukkala, M. Rautalahti, K. Sepp, and T. Hakulinen. Education, survival and avoidable deaths in cancer patients in finland. *British Journal of Cancer*, (in press), 2010.

Sensitivity to the number of knots

- A potential criticism of these models is the subjectivity in the number and the location of the knots.
- A small sensitivity analysis was carried out where the following models were fitted.

Model	Baseline df_b	Time-dependent df_t	age df_a	No. of Parameters	AIC	BIC
Model (a)	5	3	3	18	97250.11	97399.02
Model (b)	8	5	5	39	97059.30	97381.95
Model (c)	5	5	3	24	97235.68	97434.23
Model (d)	3	3	3	16	97447.35	97579.72
Model (e)	8	8	8	81	97105.8	97775.92

Knot sensitivity analysis