Modelling non-proportional hazards: time-dependent coefficients, parametric “double Cox” regression and Landmark analysis

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Disclaimer

What if the proportional hazards assumption is not met?

- For a Cox model $\mu(t|\beta, Z) = \mu_0(t)\exp(Z^{\mathrm{T}}\beta)$ we discussed two ways to cope with non-proportionality:
- Stratify the analysis on violating variable: $\mu_s(t|\beta, Z) = \mu_{0s}(t)e^{Z^{\mathrm{T}}\beta}$

  - baseline hazards vary by strata s;

  - Here we add an option of modelling shape of baseline hazards
- Include time-varying effects: $\mu(t, |\beta, Z) = \mu_0(t)e^{Z^{\mathrm{T}}\beta(t)}$

  - Coefficients $\beta(t)$ are continuous functions of time

  - Use landmark analysis

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Parametric "Double-Cox" regression

Components:

- A baseline hazard function (which changes over time).
- The risk factors Z have a log-linear contribution to the force of mortality which does not depend on time t.

The Cox parametric regression model

$$\mu(t|Z) = \mu_0(t|Z)\ \exp(Z^{\mathrm{T}}\beta)$$

Baseline hazard function

β is a vector of unknown parameters for scale and Z is a vector of covariates

Weibull or Gompertz baseline hazard function with scale λ and shape k. Shape k is modelled as k=k(Z).

$$\mu_0(t|Z) = \frac{k(Z)}{\lambda}\left(\frac{t}{\lambda}\right)^{k(Z)-1}$$

$$\mu_0(t|Z) = \lambda \exp(k(Z)t)$$

$$\mathrm{k(Z)} = k_0 e^{Z^{\mathrm{T}}\beta_k}$$

Additional regression model to allow varying shape depending on covariates

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Cox model with shared frailty

Proportional hazards model with frailty:

$$\boldsymbol{\mu}(t|U,Z) = \boldsymbol{\mu}_0(t)Ue^{Z^{\mathrm{T}}\beta},$$

For mathematical convenience, it is frequently assumed that frailty U is gamma-distributed with mean 1 and unknown variance σ^2:

$$U \sim Gamma(\sigma^{-2}, \sigma^{-2}).$$

The frailty variance σ^2 characterizes heterogeneity in the population.

Shared frailty assumption:

All patients from the same **unit** /clients from the same company are in the same cluster j, j=1,…,J and share the same frailty U_j.

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“Double-Cox” model with shared frailty

- Standard shared frailty Cox model : $\boldsymbol{\mu}(t|U,Z) = \boldsymbol{\mu}_0(t)Ue^{Z^{\mathrm{T}}\beta}$;
- Baseline hazard $\boldsymbol{\mu}_0(t)$=$\boldsymbol{\mu}_0(t;\lambda, k)$;
- Cox-like parameterization for the shape of the baseline hazard function: k(Z)=$k_0 e^{Z^{\mathrm{T}}\beta_k}$;
- Frailty U ~ Gamma with mean 1 and variance σ^2.
- If needed, competing risks can be introduced through correlated shared frailty components.

Find MLE of the vector of unknown parameters θ=(λ, k_0, σ^2, β, β_k).

This model was introduced in [1] for analysis of time to revision/

time to death after hip replacement.

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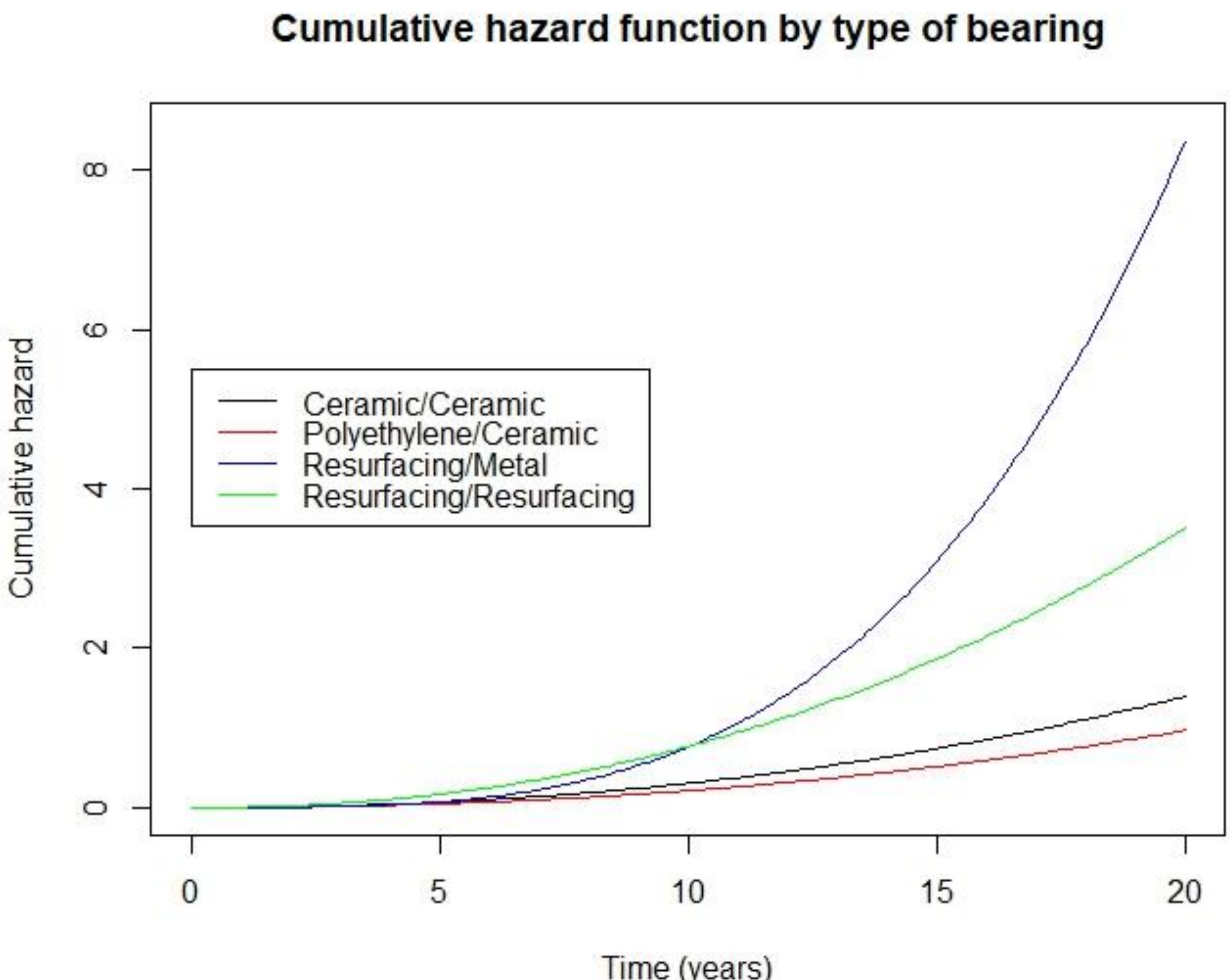
Different shapes of cumulative hazards for revision surgery after hip replacement



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Extended Cox regression with time-varying covariates and regression effects

A model may include both constant and time-varying effects:

$$\mu(t, |\beta, Z) = \mu_0(t) e^{Z(t)^{\mathrm{T}}\beta(t) + X(t)^{\mathrm{T}}\gamma}$$

- Here Z(t) and X(t) are time-varying covariates (updated over time).
- Z(t) are covariates with time-varying hazards β(t), and X(t) covariates have constant hazards γ.
- See Ch. 6 in the book by Martinussen&Scheike [2] and their R package *timereg* for analysis of extended multiplicative hazards models.
- Their program *timecox* can test for and fit models with both constant and time-varying effects.

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Inference in extended Cox model

- It is easier to estimate cumulative regression coefficients $B(t)=\int_0^t \beta(s)ds$, their estimates are $n^{1/2}$-consistent and asymptotically Normal.
- This allows to draw confidence bands for B(t) and to test hypotheses about them.
- A simple test of $\beta_p(t)=\beta_p$ is based on maximum deviation of the cumulative coefficient $B_p(t)$ from a straight line over an interval [0,T].
- Similarly, cumulative residuals are used for various diagnostic purposes.

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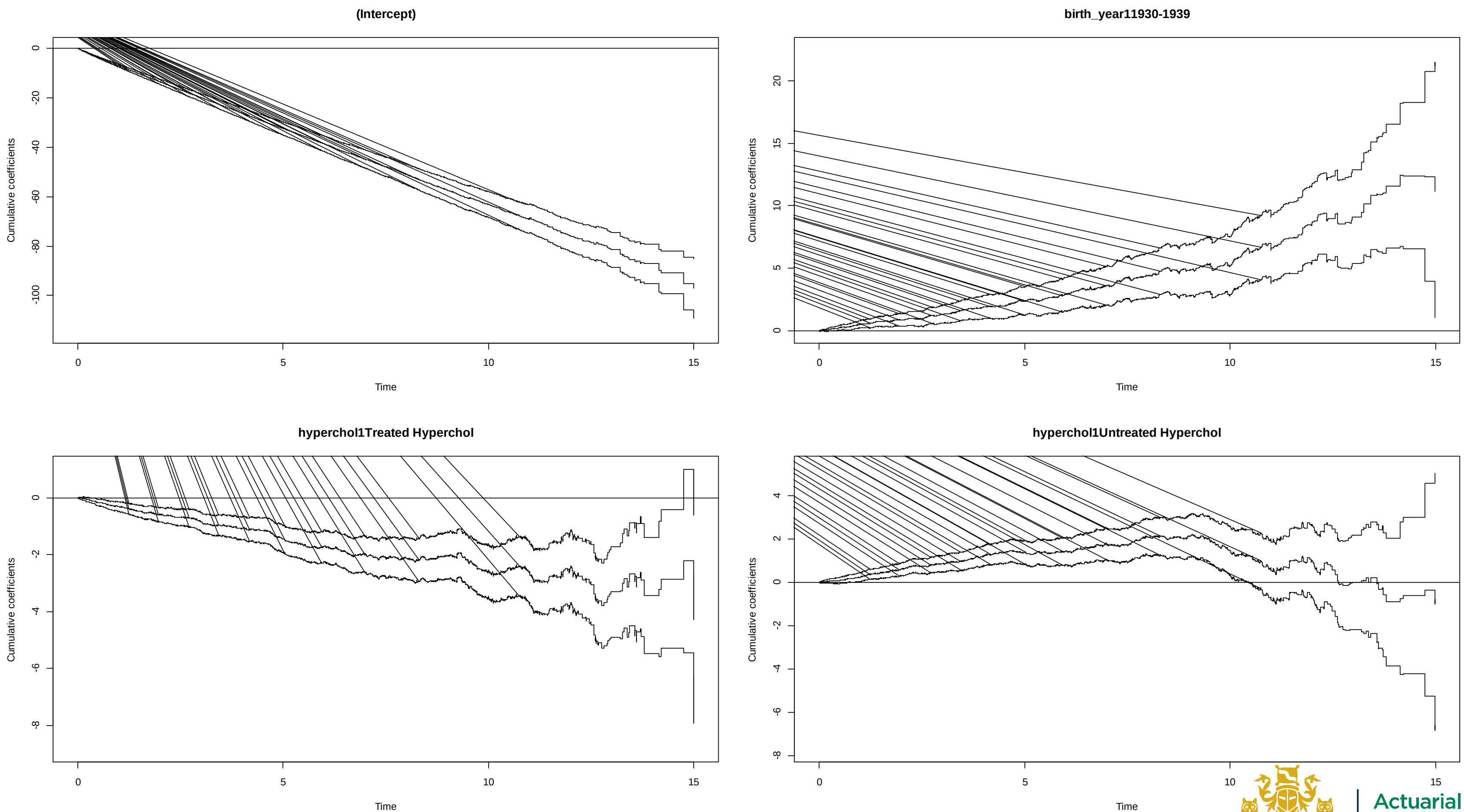
Plots of cumulative coefficients for DM2 study



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Robustness of the Cox model

Consider once more the extended Cox model

$$\mu(t|\beta, Z) = \mu_0(t)e^{Z^{\mathrm{T}}\beta(t)}.$$

The cumulative hazard *M(t|Z)=-ln(S(t|Z)*. The ratio

$$\frac{M(t|Z)}{M_0(t)} = \frac{\int \mu_0(s)\exp(\mathrm{Z}^{\mathrm{T}}\beta(s))\mathrm{ds}}{\int \mu_0(s)\mathrm{ds}} \approx \frac{\exp\int \mu_0(s)\,(\mathrm{Z}^{\mathrm{T}}\beta(s))\mathrm{ds}}{\int \mu_0(s)\mathrm{ds}} = \exp(\mathrm{Z}^{\mathrm{T}}\bar{\beta}(\mathrm{t})),$$

where $\bar{\beta}(\mathrm{t}) = \frac{\int \mu_0(s)\beta(s)\mathrm{ds}}{\int \mu_0(s)\mathrm{ds}}$, if the variance $\frac{\int \mu_0(s)\,(\mathrm{Z}^{\mathrm{T}}\,(\beta(s) - \bar{\beta}(\mathrm{t})))2\mathrm{ds}}{\int \mu_0(s)\mathrm{ds}}$ is small. This means that the Cox model gives approximately correct predictions of surviving up to time t.

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What is landmark analysis

In the landmarking approach, dynamic predictions for the conditional survival after t=t_{LM} is used on current information for all patients still alive just prior to t_{LM}. [Van Houwelingen, H. and Putter, H., 2011]

The sliding landmark model is the simple Cox model

$$h(t|x, t_{LM}, w) = h_0(t|t_{LM}, w)\exp(x^T \beta_{LM}), \qquad s \le t \le s + w$$

for the data set obtained by truncation at $s = t_{LM}$ and administrative censoring at t_{LM}+w.

$h_0(t|t_{LM}, w)$ is the baseline hazard or force of mortality.

This is a convenient way to obtain a dynamic prediction without fitting a complicated model with time-varying effects.

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Super-prediction data set

- Fix the prediction window w; [say, w=5 years]
- Select a set of prediction time points $\{s_1, \ldots, s_L\}$, 20 ≤ L ≤ 100; [say, every 6 months.]
- Create a prediction data set for each $t_{LM}=s_l$ by truncation and administrative censoring;
- Stack all these data into a single "Super-prediction data set". The subsets corresponding to a given prediction time $t_{LM}=s_l$ are "strata".
- The risk set R(t_i) for an event time t_i is present in all strata with $s \leq t_i \leq s + w$. Passing from stratum s to s+1 corresponds to sliding the window over the time range.
- Individual life *j* contributes up to w/$|s_{l+1} - s_l|$ times in each prediction window. [10 times when w=5 and the time shift $s_{l+1} - s_l$ is 6 months.]

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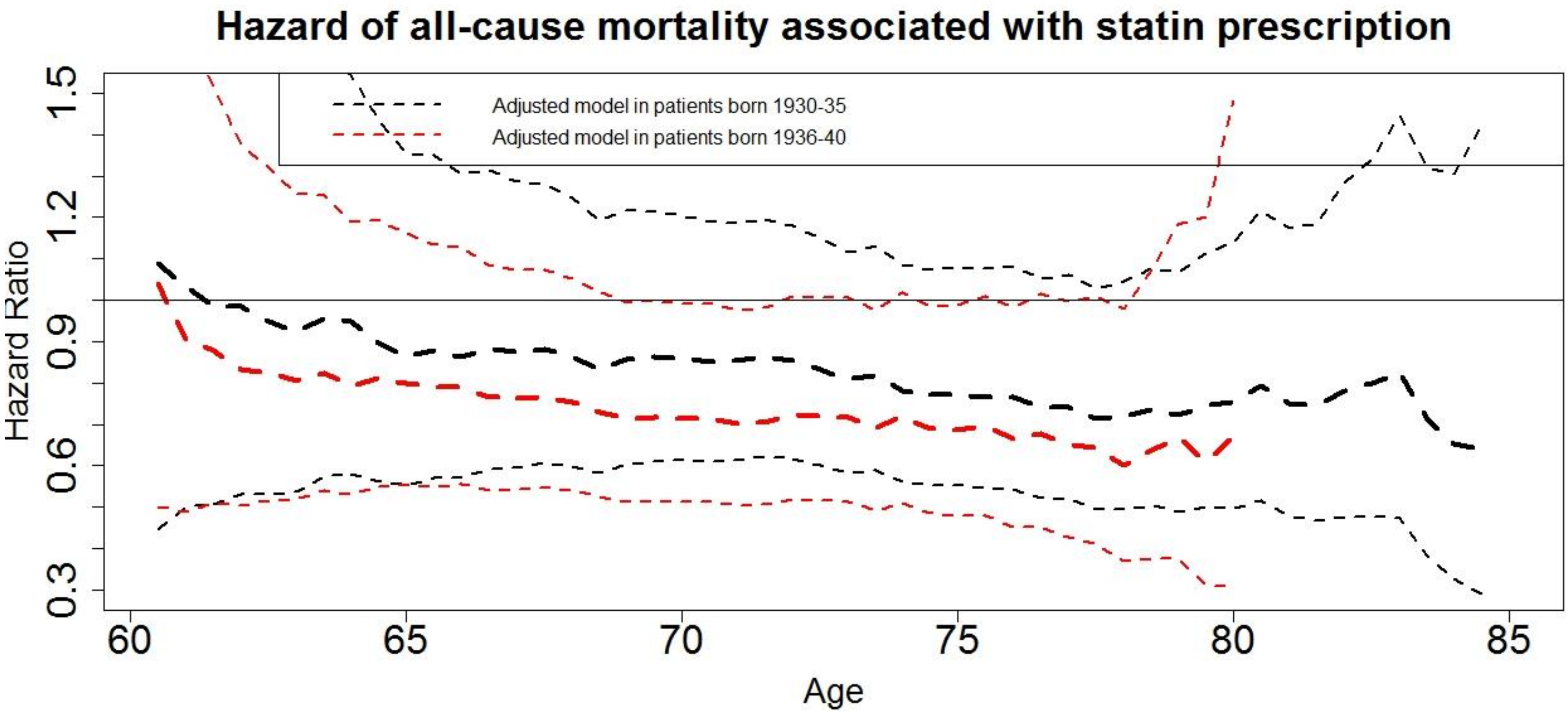
Sliding Cox model results (crude model)



Integrated partial log-likehood landmark model - ipl

The landmark super prediction model with window *w* and letting the regression coefficients β_{LM} depend on time t_{LM} is given by

$$h(t|x, t_{LM} = s, w) = h_0(t|s, w) \exp\left(x^T \beta_{LM}(s)\right), \qquad s \leq t \leq s + w$$

where $$\beta_{LM}(s) = \sum_{j=1}^{m} \gamma_j \; f_j(s).$$

- $f_j(s)$ are the basis functions, $f_1(s)$=1, $f_j(0)$=0 for j>1, and γ_j are the parameters, with $\beta_{LM}(0) = \gamma_1$.
- The parameters of this model are estimated by maximizing the integrated (over s) partial log-likelihood introduced by van Houwelingen (2007).
- This approach is based on a stratified (on s) analysis with smooth landmark dependent effect $\beta_{LM}(s)$ and separate estimated baseline hazards for each stratum.

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Pseudo-partial log-likelihood landmark model - ipl^*

In the $\boldsymbol{ipl^*}$ model, the baseline hazard is modelled directly as

$$h_0(t|s,w) = h_0(t)\exp\big(\theta(s)\big),$$

where $\theta(s)=\sum_{j=1}^{m} \eta_j \; g_j(s)$

for proper basis functions $g_j(s)$ with $g_j(s_1)=0$, resulting in

$$h(t|x,t_{LM}=s,w) = h_0(t)\exp\big(x^T\beta_{LM}(s)+\theta(s)\big), \qquad s \le t \le s+w,$$

where $\beta_{LM}(s)$ and $\theta(s)$ are the mth degree polynomials in s.

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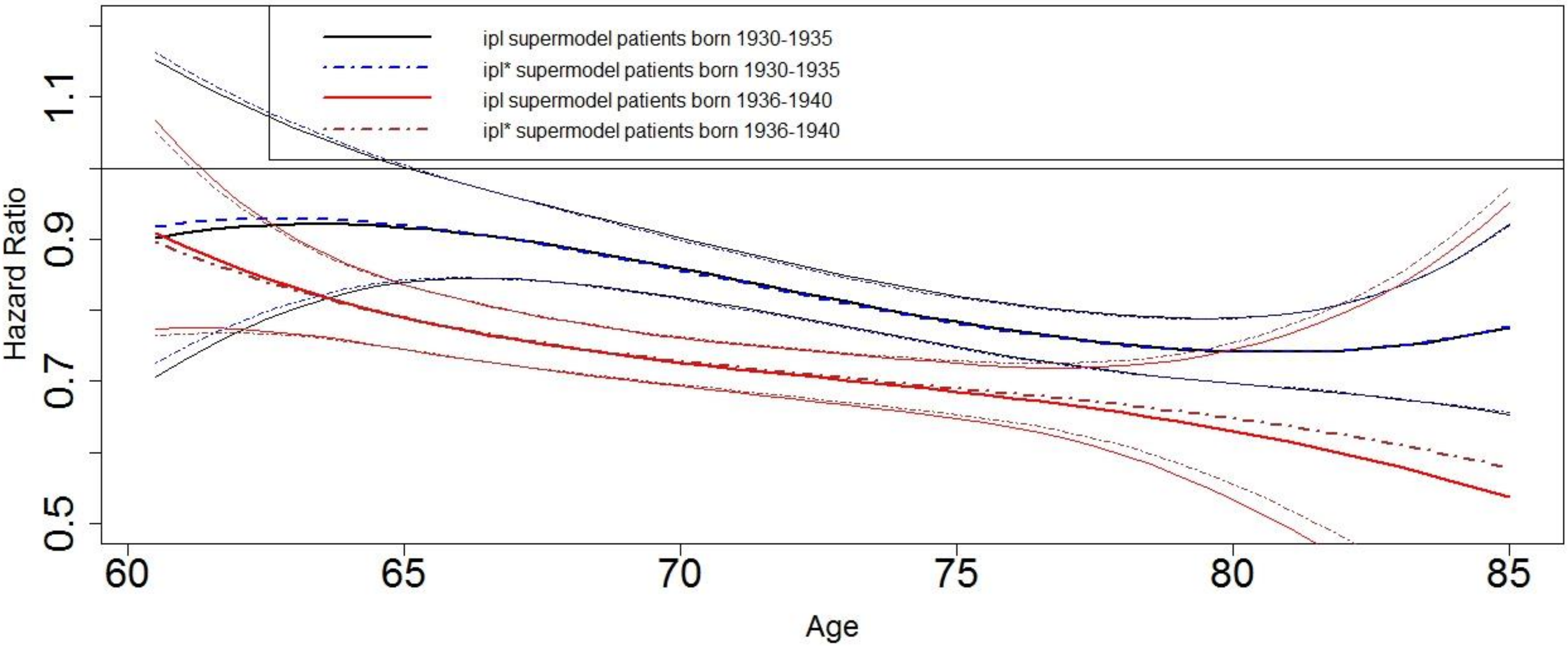
Adjusted hazard of all-cause mortality associated with current statin prescription



Predicted probabilities of survival in a window

Predictions for all s ϵ $[s_1, s_L]$ in the $\boldsymbol{ipl}^*$ model are obtained from estimated cumulative hazards

$$H(s+w|x, t_{LM}=s) = \exp(x^T \beta_{LM}(s) + \theta(s))\ (H_0^*(s+w) - H_0^*(s-))$$

This is because in the $\boldsymbol{ipl}^*$ model

$$h(t|x, t_{LM}=s, w) = h_0(t) \exp\left(x^T \beta_{LM}(s) + \theta(s)\right), \qquad s \leq t \leq s+w,$$

only the baseline hazard $h_0(t)$ depends on t.

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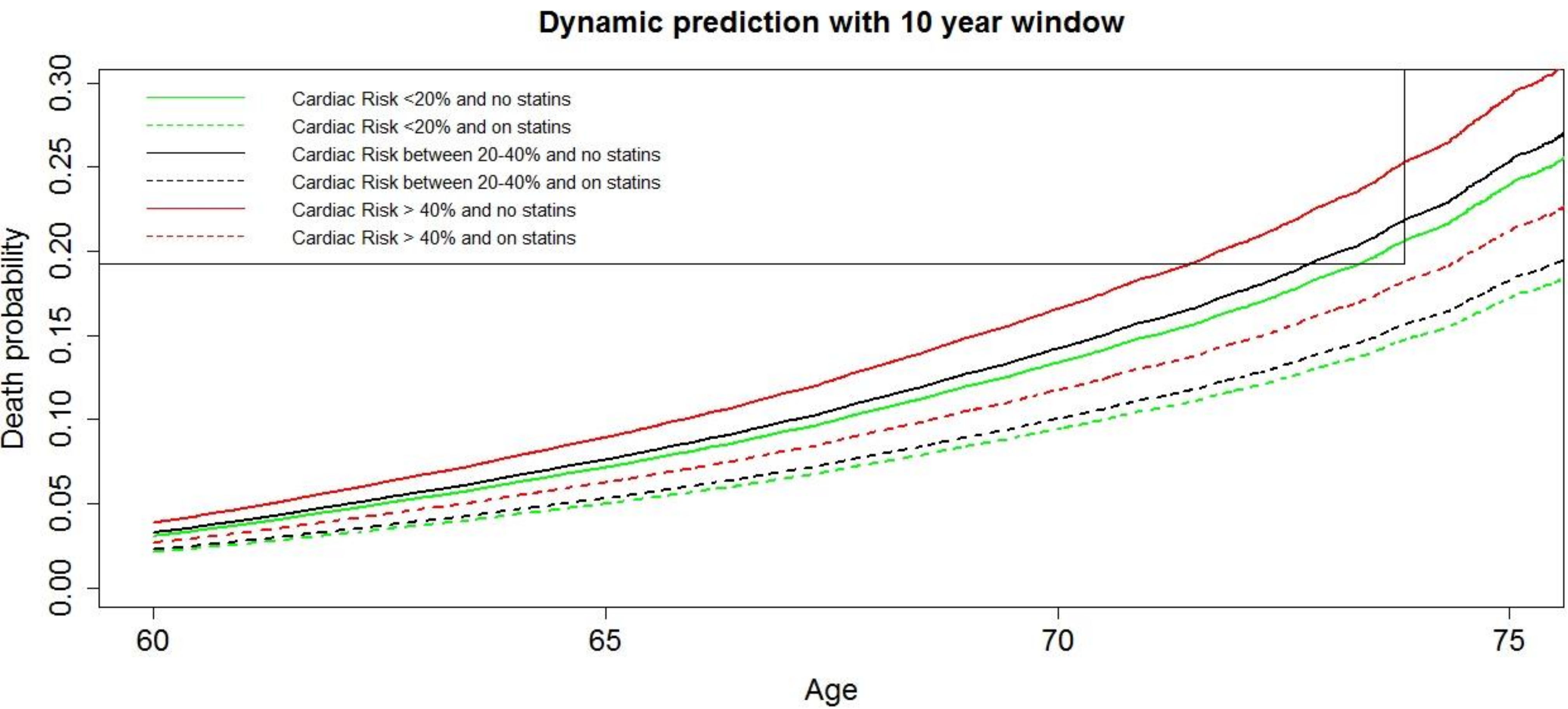
Probabilities of death for 1936-1940 cohort



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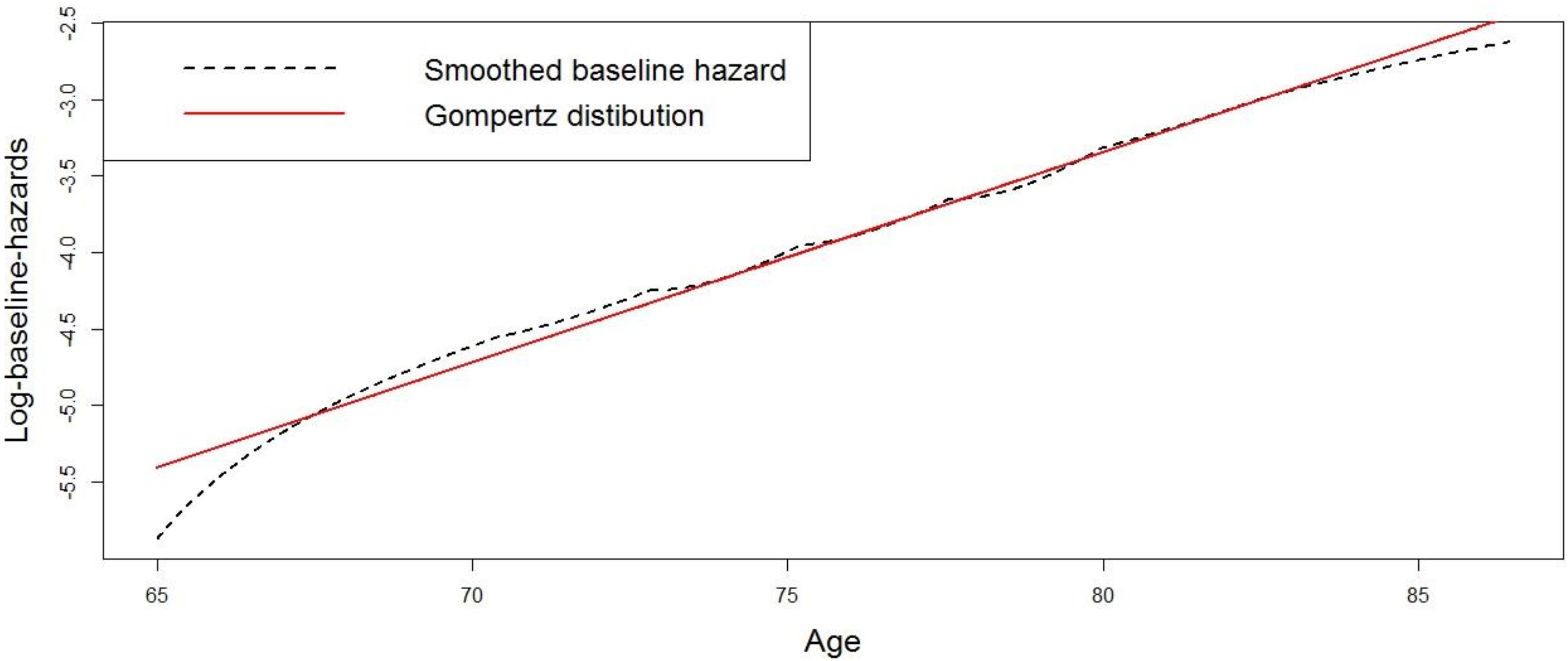
Baseline hazard in the statins landmark model



The baseline hazard is well approximated by the Gompertz hazard

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The $\boldsymbol{ipl^*}$ landmark model in actuarial research

In the $\boldsymbol{ipl^*}$ model, the hazards are modelled as

$$h(t|x, t_{LM} = s, w) = h_0(t)\exp\left(x^T(s)\beta_{LM}(s) + \theta(s)\right), \qquad s \le t \le s + w,$$

where $\beta_{LM}(s)$ and $\theta(s)$ are the *k*th and the (*k-1*)th degree polynomials of $s = t - t_0$.

The log-hazards are $\lambda(t|x, t_0)$= λ_0(t)+$x^T(s)\beta_{LM}(s)$ +$\theta(s)$.

For Gompertz baseline hazard, λ_0(t)=*a*+*bt*.

Values of *a* and *b* can be estimated from the estimated baseline hazard or substituted for a particular population. Next, we can obtain cumulative hazards, survival and period life expectancy for various scenarios of changing risks x(s).

Discussion and conclusions

- The most general form of extended Cox regression with time-dependent effects is difficult to use. To make it relevant to actuarial research we also need to consider the shape of the baseline hazards.
- Parametric "double-Cox" model is a useful replacement for the stratified Cox model which also models shape of baseline hazards and can be easily used for actuarial purposes.
- Landmark analysis is a convenient way to model dynamically changing survival data. The ipl* model conveniently lends itself to actuarial modelling.
- Extra development is required to use the results for population LE projections using methodology similar to that in Kulinskaya et al. (2019) .

References:

1. Begun A., Kulinskaya E. and MacGregor A. , 2019. Risk-adjusted CUSUM control charts for shared frailty survival models with application to hip replacement outcomes: a study using the NJR dataset. *BMC Medical Research Methodology, in print.*
2. Martinussen T, Scheike TH. *Dynamic Regression Models for Survival Data*. Springer: New York, 2006.
3. Van Houwelingen, H.C., 2007. Dynamic prediction by landmarking in event history analysis. *Scandinavian Journal of Statistics*, *34*(1), pp.70-85.
4. Van Houwelingen, H. and Putter, H., 2011. *Dynamic prediction in clinical survival analysis*. CRC Press.
5. Gitsels, L.A., Bakbergenuly, I., Steel, N. and Kulinskaya, E., 2019. Dynamic prediction of long-term survival effects of statin therapy: a landmarking analysis in the general population. *British Medical Journal* (under review)
6. Kulinskaya E., Gitsels, LA. and Bakbergenuly, I., 2019. Calculation of changes in individual and period life expectancy based on proportional hazards model of an intervention. *Insurance Mathematics and Economics,* under review.

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Questions

Comments

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