Methodological developments to describe the association between socioeconomic inequalities and cancer survival with an illustration using French population-based data

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LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Outline

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- Objectives

Mixed-effect hazard-based regression models
- Excess hazard regression model
- Shared frailty model
- Mixed-effect excess hazard regression model
- Likelihood function and estimation procedure
- Simulation study

R Package mexhaz

Illustration

Context 1/2

Describe the association between the socio-economic status and the cancer-specific hazard using population-based cancer registry data

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  - Level 1: individual's time-to-event
  - Level 2: cluster (area of residence, hospital, ...)

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⇒ Assumption of independence between individual's survival times is violated for individuals living in the same area (same level of deprivation, but also local medical practice, environmental factors...)

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  - Level 1: individual's time-to-event
  - Level 2: cluster (area of residence, hospital, ...)

⇒ Assumption of independence between individual's survival times is violated for individuals living in the same area (same level of deprivation, but also local medical practice, environmental factors...)

⇒ Correct statistical inference requires that the hierarchical structure of the data be taken into account.

Context 2/2

- Cancer-specific hazard without the cause of death?
  ⇒ excess hazard regression models
- Correlated data / hierarchical structure?
  ⇒ mixed effect models (multilevel models) provide a satisfying and convenient theoretical framework by introducing a random effect at the cluster level.

Mixed effect models have been developed in the context of overall survival
But lack of tools/development in the context of net survival/excess hazard regression models

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Epidemiological

- To describe the association between socioeconomic context and cancer survival using French population-based cancer registry data
- To provide some methodological guidelines

Excess hazard regression model 1/2

Classical method used to analyse population-based cancer registry data

The overall mortality hazard λ is split into an excess mortality hazard (due to cancer) λ_E and an expected (or population) mortality hazard λ_P [Estève 1990]:

$$\boxed{\lambda(t, \mathbf{x}, \mathbf{z}) = \lambda_E(t, \mathbf{x}) + \lambda_P(a + t, y + t, \mathbf{z})}$$

Where

- Covariates $\mathbf{x}$: age at diagnosis a, deprivation, stage at diagnosis, sex, year of diagnosis y, ...
- Variables defining the population mortality hazard in the life-table: age $a + t$, year $y + t$ and $\mathbf{z}$ (sex, region, deprivation, ...)

Excess hazard regression model 2/2

$$\boxed{\lambda(t,\mathbf{x},\mathbf{z}) = \lambda_E(t,\mathbf{x}) + \lambda_P(a+t, y+t, \mathbf{z})}$$

- The quantity λ_P is considered known
- The quantity to estimate is λ_E

Many different models have been proposed: more flexible and allowing time-dependent effects using splines [Bolard 2002, Giorgi 2003, Lambert 2005, Nelson 2007, Remontet 2007, Pohar-Perme 2009, ...]

But nothing has been done to fit an for excess hazard model on correlated data, without losing flexibility (parametric hazard, or piecewise step function [Dupont 2013])

The classical shared frailty hazard-based regression model

In survival analysis, random effect is usually called "frailty"

The frailty, u, can be viewed as a random variable that acts multiplicatively on the baseline hazard [Duchateau 2008, Wienke 2011].

$$\lambda(t; \mathbf{x}_{ij}, u_i) = \lambda_0(t) u_i \exp({}^t\mathbf{x}_{ij}\beta)$$

Each geographical unit i has a frailty value u_i $[= exp(w_i)]$ which is shared by all individuals j observed in unit i

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Usual assumptions:

- Parametric distribution for T (Weibull, piecewise constant,...)
- Gamma distribution for the frailty u

Mainly due to practical reasons (analytical expression of the marginal likelihood)

$\Rightarrow$ No tool for flexible (excess) hazard

Mixed-effect Excess hazard regression model

The flexible model proposed

$$\boxed{\lambda_E(t, \mathbf{x}_{ij}) = \lambda_0(t; \boldsymbol{\xi}) \cdot \exp(\beta_1 x_1 + f(x_2; \boldsymbol{\beta}_2) + g(t; \boldsymbol{\beta}_3) x_3 + w_i)}$$

Where

- λ_0 is the baseline hazard modelled with (exp of) B-splines (or piecewise step function or Weibull),
- β_1 the linear and proportional (fixed) effect of x_1,
- f and g are flexible functions (B-splines) allowing for non-linear and non-proportional effects for x_2 and x_3 (defined with $\boldsymbol{\beta}_2$ and $\boldsymbol{\beta}_3$), respectively,
- w_i is the random effect of cluster i, assumed to follow a normal distribution with mean 0 and standard deviation σ

Likelihood function: overview

1. Likelihood of one observation j in cluster i
2. Conditional Likelihood for cluster i
3. Marginal Log-Likelihood for cluster
4. Total Log-likelihood

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Conditional Likelihood for cluster *i*

For one observation *j* in cluster *i*: $\{t_{ij}, \delta_{ij}, \mathbf{x}_{ij}\}$

$$\mathrm{L}_{ij}^{C}(\boldsymbol{\beta}|w_i) =$$
$$\exp\left\{-\Lambda_E(t_{ij}, \mathbf{x}_{ij}, w_i) - \Lambda_P(a_{ij} + t_{ij}, \mathbf{z}_{ij})\right\}\left\{\lambda_E(t_{ij}, \mathbf{x}_{ij}, w_i) + \lambda_P(t_{ij}, \mathbf{z}_{ij})\right\}^{\delta_{ij}}$$

- Gauss-Legendre quadrature to approximate the cumulative excess hazard $\Lambda_E(t_{ij}, \mathbf{x}_{ij}, w_i) = \int_0^t \lambda(u, \mathbf{x}_{ij}, w_i)\, \mathrm{d}u$
- Last term of the exponential can be omitted (does not depend on the $\boldsymbol{\beta}$s)

For cluster *i*:

$$\mathrm{L}_{i}^{C}(\boldsymbol{\beta}|w_i) = \prod_{j=1}^{n_i}\left\{\mathrm{L}_{ij}^{C}(\boldsymbol{\beta}|w_i)\right\}$$

Likelihood function: overview

1. Likelihood of one observation *j* in cluster *i*
2. Conditional Likelihood for cluster *i*
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Marginal Likelihood for cluster i

We assume a normal distribution for the random effect, with mean=0 and variance=σ^2, $\phi(w,0,\sigma) = \frac{1}{\sigma\sqrt{2\pi}} \exp\left\{-\frac{w^2}{2\sigma^2}\right\}$

For cluster i

$$\mathrm{L}_i^M(\boldsymbol{\beta},\sigma) = \frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{+\infty} \mathrm{L}_i^C(\boldsymbol{\beta}|w) \exp\left\{-\frac{w^2}{2\sigma^2}\right\} \mathrm{d}w$$

- Problem : How to evaluate this likelihood ?
- A solution is to use the Gauss-Hermite Quadrature (GHQ)

Definition

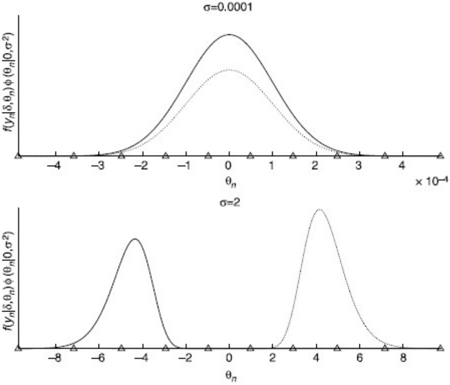
Gauss-Hermite Quadrature

$$\int_{-\infty}^{\infty} f(v)\exp\{-v^2\}\,\mathrm{d}v \approx \sum_{k=1}^{Q} \rho_k^H \cdot f(x_k^H)$$

- Nodes $= x_k^H$
- Weights $= \rho_k^H$

The nodes and weights depend only on Q (not on the integrand f...)

Illustration of the GHQ



Tuerlinckx F et al., British Journal of Mathematical and Statistical Psychology, 2006

A refinement of the GHQ : the **adaptive** GHQ

Basic idea:

- The quadrature locations are rescaled and translated so that they cover the region where the integrand varies most, i.e. around its mode
- To transform the integrand to obtain a new quadrature formula in which the new nodes and the corresponding weights depend on the integrand (and so on the cluster i)

The **adaptive** GHQ 1/2

Apply the LAPLACE approximation to :

$$g_i(w,\boldsymbol{\beta},\sigma) = \mathrm{L}_i^C(\boldsymbol{\beta}|w)\phi(w,0,\sigma) \quad \Rightarrow \quad \left\{ \begin{array}{l} \mu_i \\ \sigma_i \end{array} \right.$$

We have :

$$\mathrm{L}_i^M(\boldsymbol{\xi},\boldsymbol{\beta},\sigma) = \int_{-\infty}^{\infty} \underbrace{\frac{g_i(w,\boldsymbol{\beta},\sigma)}{\phi(w,\mu_i,\sigma_i)}}_{f_i^{\mathrm{A}}(w,\boldsymbol{\beta},\sigma)} \phi(w,\mu_i,\sigma_i)\,\mathrm{d}w$$

Using the GHQ, we approximate :

$$\mathrm{L}_i^M(\boldsymbol{\xi},\boldsymbol{\beta},\sigma) \approx \sum_{k=1}^{Q} \rho_k^N(\mu_i,\sigma_i) \cdot f_i^{\mathrm{A}}\left(x_k^N(\mu_i,\sigma_i),\boldsymbol{\beta},\sigma\right)$$

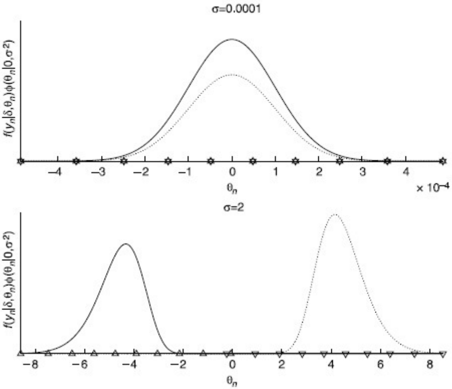
The **adaptive** GHQ 2/2

The modified nodes and weights are given (as functions of the original ones) by:

$$\begin{cases} x_k^N(\mu_i, \sigma_i) = \mu_i + \sigma_i\sqrt{2} \cdot x_k^H \\ \rho_k^N(\mu_i, \sigma_i) = \rho_k^H \cdot \sigma_i\sqrt{2\pi}\exp\{(x_k^H)^2\} \end{cases}$$

More details in Liu & Pierce [14] and Pinheiro & Bates [15]

Illustration of the Adaptive GHQ



More accurate approximation than GHQ and it needs less quadrature points

Tuerlinckx F et al., British Journal of Mathematical and Statistical Psychology, 2006

Likelihood function: overview

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Finally

Log-likelihood for cluster *i*

$$\ell_i^M(\boldsymbol{\beta},\sigma) \approx \log\left\{\sum_{k=1}^{Q} \rho_k^N(\mu_i,\sigma_i) \cdot f_i^{\mathrm{A}}\left(x_k^N(\mu_i,\sigma_i),\boldsymbol{\beta}\right)\right\}$$

Total Log-likelihood

$$\ell(\boldsymbol{\beta},\sigma) \approx \sum_{i=1}^{D} \ell_i^M(\boldsymbol{\beta},\sigma)$$

To estimate the parameters $(\widehat{\boldsymbol{\beta}},\widehat{\sigma})$, use a standard optimisation routine (such as the Newton-Raphson algorithm) on the quantity $\ell(\boldsymbol{\beta},\sigma)$
More details in Charvat *et al.*, StatMed 2016 [1]

Overview of the different simulated scenarios 1/2

Aim: to evaluate the performances of the proposed approach in different scenarios, in terms of its ability to estimate

- the baseline excess hazard
- the fixed effects of covariates defined **both** at the individual level and at the cluster level (including time-dependent effect)
- the variance of the random effect

Overview of the different simulated scenarios 2/2

In scenarios A and B, the **impact of the design** (number of clusters and number of patients by cluster) and the **level of the variance** of the random effect were studied

- scenario A: Balance-Design: N patients by cluster is fixed
- scenario B: UnBalance-Design: N patients by cluster is variable

In scenario C, we studied the ability of our approach to model **non proportional effect** ((NPH)) of covariates (with unbalanced design)

In scenario D, we checked the robustness of our approach in case of **miss-specified distribution of the random effect** (with unbalanced design)

Simulation study (I)

Design of the 1000 simulated dataset, with 1000 patients in each

- Age (25% [30, 65], 35% [65, 75], 40% [75, 85], with an uniform law in each age-class)
- Sex (Binomial distribution with P(sex=man)=0.5
- Cluster (the cluster ID (D = 10, 20, 50, 100))
- Deprivation Index (DI) defined at the cluster level (Normal(0,sd=1.5))

In scenarios A, Balance-Design: the number of patients by cluster is **exactly** equal to 10, 20, 50 or 100

In scenarios B, UnBalance-Design: the number of patients by cluster is **variable and equal, on average**, to 10, 20, 50 or 100 (one additional simulated condition with 800 clusters and 10 patients on average).

Simulation study (II)

- To simulate the time to death due to cancer T_1
  $\lambda_E(t, \mathrm{Age}_{ij}, \mathrm{Sex}_{ij}, \mathrm{DI}_i) =$
  $\lambda_0(t) \exp\{\beta_{\mathrm{Age}} \mathrm{Age}_{ij} + \beta_{\mathrm{Sex}} \mathrm{Sex}_{ij} + \beta_{\mathrm{DI}} \mathrm{DI}_i + w_i\}$
  - Weibull baseline hazard $\lambda_0(t) = \lambda \rho t^{\rho-1}$ ($\lambda = 0.25$; $\rho = 0.7$)
  - Age effect ($\beta_{\mathrm{Age}} = 0.05$ for 1 year increase)
  - Sex effect ($\beta_{\mathrm{Sex}} = 1$, Men vs. women)
  - DI effect ($\beta_{\mathrm{DI}} = 0.02$ for 1 unit increase)
  - Random effect w_i: Normal distribution with mean 0 and standard deviation $\sigma = 0.25$ or 0.5 or 1

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  - Sex effect ($\beta_{\mathrm{Sex}} = 1$, Men vs. women)
  - DI effect ($\beta_{\mathrm{DI}} = 0.02$ for 1 unit increase)
  - Random effect w_i: Normal distribution with mean 0 and standard deviation $\sigma = 0.25$ or 0.5 or 1
- To simulate the time to death due to other causes T_2 : yearly piecewise exponential law using mortality rates from the population lifetable
- $\Rightarrow$ Final time $T = \min(T_1, T_2)$, with the corresponding vital status δ

Simulation study (III)

For the scenario **NPH**, two different Weibull baseline hazards for men and women:

- Times to cancer-death in men = Weibull (shape=0.7, scale=0.25)
- Times to cancer-death in women = Weibull (shape=0.8, scale=0.18).

$\Rightarrow$ the Hazard Ratio between Men vs. Women is time-dependent

For the scenario **Robustness** The random effect was drawn from a normal distribution with $\sigma = 0.5$ **but**

- with mean=-1 for the first half of the clusters, and
- with mean=1 for the other half

$\Rightarrow$ standard deviation of the resulting distribution is $\sqrt{(}1.25) \approx 1.12$.

Simulation study (IV)

The model used to analyse the data

- in scenarios balance- and unbalance- Design and Robustness

$$\lambda_E(t, \mathrm{Age}_{ij}, \mathrm{Sex}_{ij}, \mathrm{DI}_i) =$$
$$\lambda_0(t)\exp\{\beta_{\mathrm{Age}}\mathrm{Age}_{ij} + \beta_{\mathrm{Sex}}\mathrm{Sex}_{ij} + \beta_{\mathrm{DI}}\mathrm{DI}_i + w_i\}$$

With $\lambda_0(t)$ modelled either as a Weibull or using a cubic B-spline (1 knot at 1 year)

- in scenarios NPH

$$\lambda_E(t, \mathrm{Age}_{ij}, \mathrm{Sex}_{ij}, \mathrm{DI}_i) =$$
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With $\lambda_0(t)$ and $\beta_{\mathrm{Sex}}(t)$ modelled using a cubic B-spline (1 knot at 1 year)

Overview of simulation results

Scenarios balance-Design, unbalance-Design and NPH

- Fixed-effect estimates of individual-level covariates unbiased and CP $\approx$ 95% whatever number and size of clusters, the level of heterogeneity simulated and the level of unbalance
- Same performances with B-spline instead of Weibull for the baseline hazard
- With small number of clusters (10 or 20), bias and CP less than 95% for cluster-level covariate (β_{DI}) and std.dev (σ) of the random effect
- RMSEs for β_{DI} and σ $\searrow$ when the number of clusters $\nearrow$
- Time-dependent effects correctly estimated

Scenario Robustness

- Fixed effect estimates of individual-level covariates unbiased and CP $\approx$ 95%
- Bias and bad CP for cluster-level covariate
- Bad CP for σ

R-package mexhaz

A R-package was developed: mexhaz, Mixed-effect EXcess HAZard model (available on the CRAN website https://cran.r-project.org/)
The mexhaz package allows

- to fit flexible hazard regression model
  - with/without introducing λ_P (i.e. to estimate overall or excess hazard)
  - with different baseline hazards: piecewise step function, Weibull or B-splines
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  - at several time points for one vector of covariates
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  - at several time points for one vector of covariates
  - for several vectors of covariates at one time point
- to plot the hazard and the corresponding survival

R-package mexhaz - Example of code

- **Estimation**

```
Mod1 <- mexhaz(formula=Surv(time=timesurv, event=vstat)~
agecr+depindex+IsexH+nph(agecr), data=simdatn1,
base="exp.bs", degree=3, knots=c(1,5), expected="popmrate",
random="clust")
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- **Prediction** at several time points for one vector of covariates

```
Pred_Mod1 <- predict(Mod1, time.pts=seq(0.1,10,by=0.1),
data.val=data.frame(agecr=0,depindex=0.5,IsexH=1),
conf.int="delta")
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- **Plot**

```
plot(Pred_Mod1, which="hazard")
```

Conclusions

We proposed an approach to fit a flexible excess hazard model, allowing for a random effect defined at the cluster level and time-dependent and/or non-linear effects of covariates [Charvat *StatMed* 2016]

- Numerical integration techniques:
  - Adaptive Gauss-Hermite Quadrature to calculate the cluster-specific marginal likelihood
  - Gauss-Legendre quadrature for the cumulative hazard
- Flexible functions (B-splines) used for the baseline and the time-dependent effects
- Good performances shown by simulation
- R-package available on the CRAN website

Illustration: Assessing the relationship between socio-economic environment and cancer survival in a French region

- Measure the socio-economic environment using a relevant and reproducible index on the whole population

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- Enable possibly complex association (non-linear and/or time-dependent)

Illustration: Assessing the relationship between socio-economic environment and cancer survival in a French region

- Measure the socio-economic environment using a relevant and reproducible index on the whole population
- Isolate cancer-specific mortality hazard
- Enable possibly complex association (non-linear and/or time-dependent)
- Deal with hierarchical structure of the data (socio-economic environment is an ecological variable) for correct inference

Our choices

- Measure of the socioeconomic environment?
  ⇒ the European Deprivation Index (EDI), built to be reproducible [16]

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- Cancer-specific mortality hazard without cause of death, and with possible complex effects?
  ⇒ Flexible Parametric Excess-hazard Model [4], with time-dependent and/or non-linear effects [8] combined with a model-building strategy [17]

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- Correlated data / hierarchical structure?
  ⇒ Mixed-effect/multilevel models with a random effect defined at the cluster level (from which the socioeconomic environment was assessed) [1]

Material 1/2

- Data from Calvados and Manche population-based cancer registries
- Patients over 15 years, diagnosed between 1997 and 2010 and followed up to 30/06/2013
- 17 cancer sites analysed, separately in men and women
- R software and the package `mexhaz` we developped (Mixed-effect EXcess HAZard model)

Material 2/2

Indicators produced for each cancer-site combination

- Age-Standardised Net Survival (ASNS) predicted at 1, 5 and 10 years after diagnosis, by deprivation quintiles of the French population (ICSS weights)
- Variation with time since diagnosis of the Excess Mortality Hazard for 3 values of age and EDI (10^{th}, 50^{th} and 90^{th} percentiles)
- Excess Hazard Ratio for 1-unit increase of the EDI (may be non-linear and time-dependent)

Summary of the results

Age-Standardised Net Survival at 5 years

- In men, absolute difference (Dep 1 vs. Dep 5) $>$ 10% in Lip-Oral Cavity-Pharynx and melanoma. Around 5% in colon-rectum, bladder, kidney and prostate
- In women, absolute difference $>$ 10% in Lip-Oral Cavity-Pharynx. Around 5% in bladder, breast and melanoma

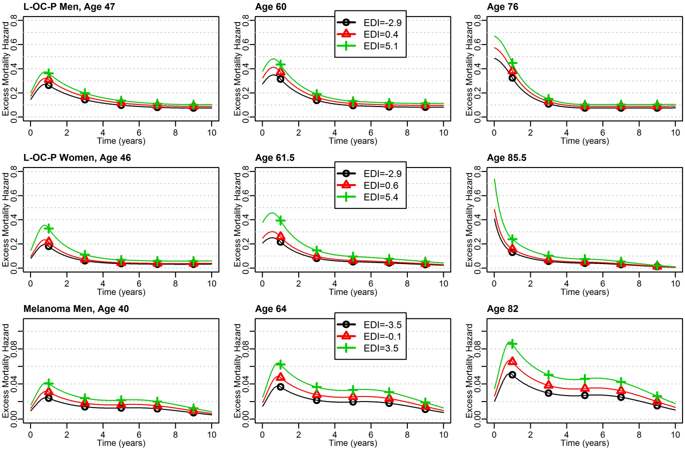
A linear and constant-in-time EDI's effect retained in most cases, except for

- Lip-Oral Cavity-Pharynx (NL effect in both sexes)
- Stomach (TD) and Pancreas (NL and TD) in men,
- Cervix uteri (NL and TD)

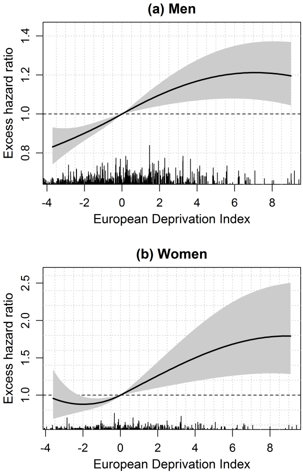
Paper available soon (hopefully) Belot *et al.* (*under review*) [2]

Variation with time since diagnosis of the excess mortality hazard according to EDI and age

For the 10^{th}, 50^{th} and 90^{th} percentiles of age and EDI distributions

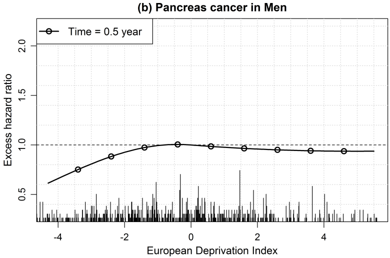


Non-linear effect of the EDI: Lip-Oral Cavity-Pharynx



Time-dependent and non-linear effect of the EDI
Example for pancreas cancer in men

Excess Hazard Ratio for EDI (Ref: EDI=0) at 6 months:

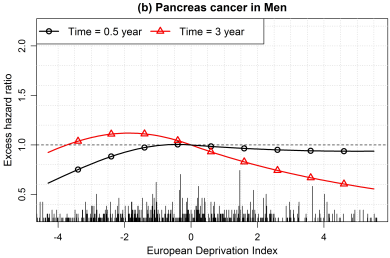


1-year ASNS by deprivation quintiles of the EDI (Q1-Q5):

Q1	Q2	Q3	Q4	Q5
36 [33;40]	26 [24;28]	23 [21;25]	24 [22;26]	25 [22;28]

Time-dependent and non-linear effect of the EDI Example for pancreas cancer in men

Excess Hazard Ratio for EDI (Ref: EDI=0) at 3 years:

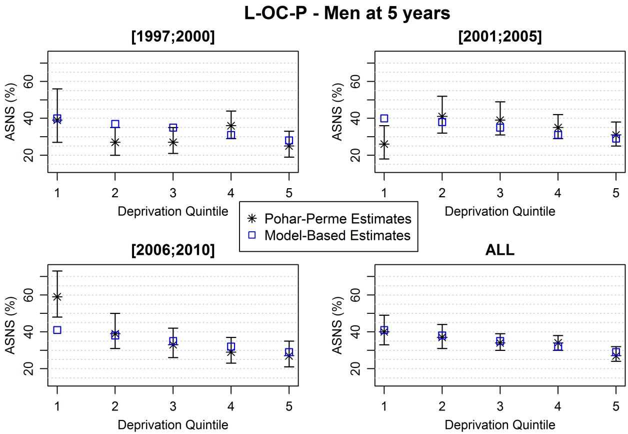


5-year ASNS by deprivation quintiles of the EDI (Q1-Q5):

Q1	Q2	Q3	Q4	Q5
8 [6;11]	4 [3;5]	4 [3;5]	5 [4;6]	7 [5;9]

Goodness of fit
Example for Lip-Oral Cavity-Pharynx

Predicted vs Non-Parametric ASNS (Pohar-Perme estimator [10])



Summary of our guidelines 1/3

Data

- Use data from a source that provides an unbiased picture of the whole population, such as population-based registries data
- Use an appropriate ecological deprivation measure, which can be (i) replicated in other countries (for comparison purposes); and, (ii) based on as small geographical unit as possible

Summary of our guidelines 2/3

Method

- Define the excess mortality hazard as your main quantity of interest
- Use flexible parametric multivariable regression models, which enable modelling non-linear as well as time-dependent effects of prognostic factors (such as the deprivation index)
- Take account of the multilevel/hierarchical structure of the data to derive correct statistical inference
- Use a model-building strategy or an information criterion to eliminate spurious non-linear and time-dependent effects

Summary of our guidelines 3/3

Results

- Provide model-based predictions of the ASNSs by deprivation quintile and compare them to the non-parametric estimates (to check the goodness-of-fit of the model)
- Give additional and clinically relevant information from the modelling approach:
    - the change with time since diagnosis of the excess mortality hazard for different values of the deprivation index
    - the Excess Hazard Ratios for the effect of the EDI (eventually non-linear and/or time-dependent)
- Quantify the impact of clustering on the excess mortality hazard using the General Contextual Effect and (whenever possible) an intra-class correlation coefficient

Conclusions/Discussion

- Those guidelines provide an efficient way to assess the association between socioeconomic inequalities and cancer survival
- Using flexible parametric models allow producing additional and relevant clinical information: variation with time of the excess-mortality hazard (instantaneous picture), non-linear and time-dependent effects
- Feasible with the R-package `mexhaz` we developped for this purpose

Conclusions/Discussion

- Those guidelines provide an efficient way to assess the association between socioeconomic inequalities and cancer survival
- Using flexible parametric models allow producing additional and relevant clinical information: variation with time of the excess-mortality hazard (instantaneous picture), non-linear and time-dependent effects
- Feasible with the R-package `mexhaz` we developped for this purpose

- No deprivation-specific life-table available in France, so probably slight over-estimation of the EDI's effect
- Studying the interactions between covariables (e.g. EDI and age) remains a challenge

Ongoing Work and Perspectives

- Extension of the R-package for allowing different shapes for the TD effects (degree/knots) than the ones used for the baseline hazard
- Extension to more than one random effect
- Use of this methodology to disentangle individual socioeconomic position from contextual deprivation

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APPENDIX

LAPLACE approximation

Let g be a strictly positive, unimodal function with mode μ_g and let us define l such that $l(x) = \log\{g(x)\}$.

In a neighbourhood of μ_g:

$$l(x) \approx l(\mu_g) + (x - \mu_g) l'(\mu_g) + \frac{(x-\mu_g)^2}{2} l''(\mu_g)$$

- μ_g extremum $\Rightarrow l'(\mu_g) = 0$
- μ_g maximum $\Rightarrow l''(\mu_g) < 0$

$$g(x) \approx g(\mu_g) \underbrace{\exp\left\{\frac{(x-\mu_g)^2}{2} l''(\mu_g)\right\}}_{\propto\, \phi(x,\mu_g,\sigma_g)} \quad \text{with} \quad \sigma_g = \frac{1}{\sqrt{-l''(\mu_g)}}$$

Median Excess Hazard Ratio

Indicators produced for each cancer-site combination:
General Contextual Effect, Median Excess Hazard Ratio with and without adjusting on the EDI (median of HRs comparing 2 patients randomly selected from 2 clusters with higher vs. lower excess mortality)

Results
Important General Contextual effect in Lip-Oral Cavity-Pharynx in both sexes, and in men for prostate, melanoma and pancreas (for those sex-cancer, EDI explains an important part of the variability between clusters)

Strategy of analysis

Model-building strategy [Wynant 2014]

Separately for each gender,

- Start from the most complex multilevel excess hazard model
  - Non-linear and time-dependent effects for the continuous covariables age, year of diagnosis and EDI (quadratic B-splines, with knots located at 1 and 5 years for baseline and TD effects, and at 70-years, in 2000 and at 0 for NLIN effect of age, year and EDI, resp.)
  - a random effect defined at the cluster level (normal distribution with mean 0 and standard deviation σ)

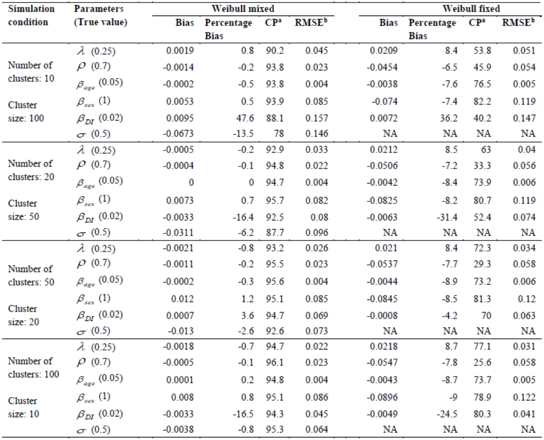
$$\boxed{\lambda_E(t,a,y,i \mid w) = \lambda_0(t) \cdot \exp(g(a) + h(t)a + j(y) + k(t)y + m(i) + n(t)i + w)}$$

- Backward Elimination procedure to successively eliminate spurious non-linear and time-dependent effects

Note: Compared to Wynant's proposal, we kept all the main effects

Simulation results

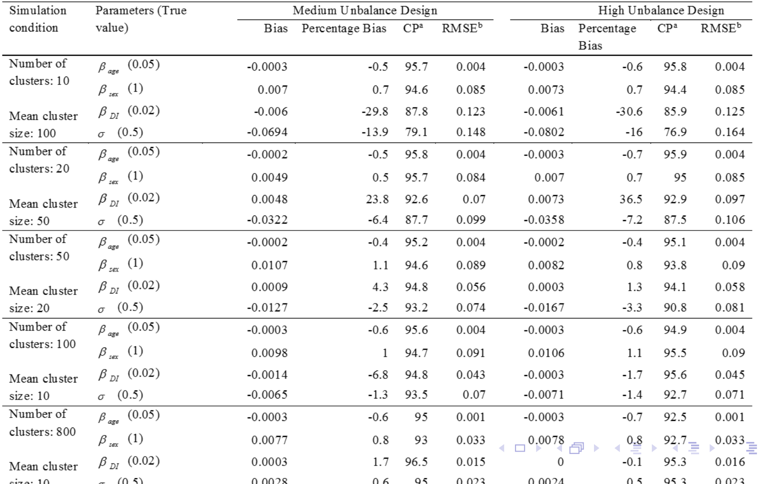
What about neglecting the hierarchical structure of the data ?



Simulation condition	Parameters (True value)	Weibull mixed				Weibull fixed			
		Bias	Percentage Bias	CP^{a}	RMSE^{b}	Bias	Percentage Bias	CP^{a}	RMSE^{b}
Number of clusters: 10 Cluster size: 100	λ (0.25)	0.0019	0.8	90.2	0.045	0.0209	8.4	53.8	0.051
	ρ (0.7)	-0.0014	-0.2	93.8	0.023	-0.0454	-6.5	45.9	0.054
	β_{age} (0.05)	-0.0002	-0.5	93.8	0.004	-0.0038	-7.6	76.5	0.005
	β_{sex} (1)	0.0053	0.5	93.9	0.085	-0.074	-7.4	82.2	0.119
	β_{DI} (0.02)	0.0095	47.6	88.1	0.157	0.0072	36.2	40.2	0.147
	σ (0.5)	-0.0673	-13.5	78	0.146	NA	NA	NA	NA
Number of clusters: 20 Cluster size: 50	λ (0.25)	-0.0005	-0.2	92.9	0.033	0.0212	8.5	63	0.04
	ρ (0.7)	-0.0004	-0.1	94.8	0.022	-0.0506	-7.2	33.3	0.056
	β_{age} (0.05)	0	0	94.7	0.004	-0.0042	-8.4	73.9	0.006
	β_{sex} (1)	0.0073	0.7	95.7	0.082	-0.0825	-8.2	80.7	0.119
	β_{DI} (0.02)	-0.0033	-16.4	92.5	0.08	-0.0063	-31.4	52.4	0.074
	σ (0.5)	-0.0311	-6.2	87.7	0.096	NA	NA	NA	NA
Number of clusters: 50 Cluster size: 20	λ (0.25)	-0.0021	-0.8	93.2	0.026	0.021	8.4	72.3	0.034
	ρ (0.7)	-0.0011	-0.2	95.5	0.023	-0.0537	-7.7	29.3	0.058
	β_{age} (0.05)	-0.0002	-0.3	95.6	0.004	-0.0044	-8.9	73.2	0.006
	β_{sex} (1)	0.012	1.2	95.1	0.085	-0.0845	-8.5	81.3	0.12
	β_{DI} (0.02)	0.0007	3.6	94.7	0.069	-0.0008	-4.2	70	0.063
	σ (0.5)	-0.013	-2.6	92.6	0.073	NA	NA	NA	NA
Number of clusters: 100 Cluster size: 10	λ (0.25)	-0.0018	-0.7	94.7	0.022	0.0218	8.7	77.1	0.031
	ρ (0.7)	-0.0005	-0.1	96.1	0.023	-0.0547	-7.8	25.6	0.058
	β_{age} (0.05)	0.0001	0.2	94.8	0.004	-0.0043	-8.7	73.7	0.005
	β_{sex} (1)	0.008	0.8	95.1	0.086	-0.0896	-9	78.9	0.122
	β_{DI} (0.02)	-0.0033	-16.5	94.3	0.045	-0.0049	-24.5	80.3	0.041
	σ (0.5)	-0.0038	-0.8	95.3	0.064	NA	NA	NA	NA

Simulation results

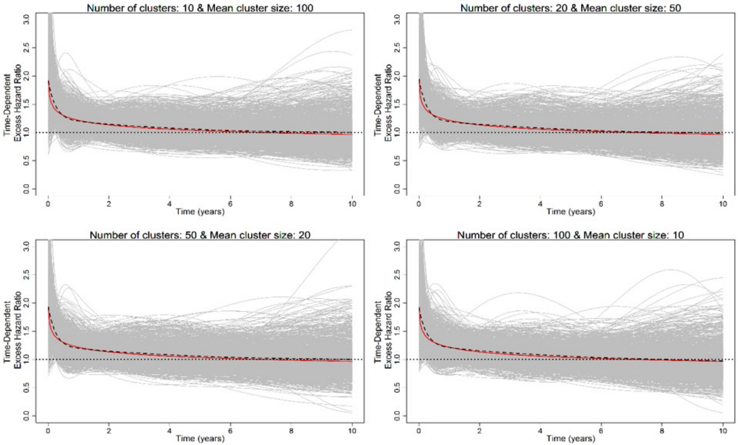
Scenario unbalance-Design



Simulation condition	Parameters (True value)	Medium Unbalance Design				High Unbalance Design			
		Bias	Percentage Bias	CP[a]	RMSE[b]	Bias	Percentage Bias	CP[a]	RMSE[b]
Number of clusters: 10	β_{age} (0.05)	-0.0003	-0.5	95.7	0.004	-0.0003	-0.6	95.8	0.004
	β_{sex} (1)	0.007	0.7	94.6	0.085	0.0073	0.7	94.4	0.085
Mean cluster size: 100	β_{DI} (0.02)	-0.006	-29.8	87.8	0.123	-0.0061	-30.6	85.9	0.125
	σ (0.5)	-0.0694	-13.9	79.1	0.148	-0.0802	-16	76.9	0.164
Number of clusters: 20	β_{age} (0.05)	-0.0002	-0.5	95.8	0.004	-0.0003	-0.7	95.9	0.004
	β_{sex} (1)	0.0049	0.5	95.7	0.084	0.007	0.7	95	0.085
Mean cluster size: 50	β_{DI} (0.02)	0.0048	23.8	92.6	0.07	0.0073	36.5	92.9	0.097
	σ (0.5)	-0.0322	-6.4	87.7	0.099	-0.0358	-7.2	87.5	0.106
Number of clusters: 50	β_{age} (0.05)	-0.0002	-0.4	95.2	0.004	-0.0002	-0.4	95.1	0.004
	β_{sex} (1)	0.0107	1.1	94.6	0.089	0.0082	0.8	93.8	0.09
Mean cluster size: 20	β_{DI} (0.02)	0.0009	4.3	94.8	0.056	0.0003	1.3	94.1	0.058
	σ (0.5)	-0.0127	-2.5	93.2	0.074	-0.0167	-3.3	90.8	0.081
Number of clusters: 100	β_{age} (0.05)	-0.0003	-0.6	95.6	0.004	-0.0003	-0.6	94.9	0.004
	β_{sex} (1)	0.0098	1	94.7	0.091	0.0106	1.1	95.5	0.09
Mean cluster size: 10	β_{DI} (0.02)	-0.0014	-6.8	94.8	0.043	-0.0003	-1.7	95.6	0.045
	σ (0.5)	-0.0065	-1.3	93.5	0.07	-0.0071	-1.4	92.7	0.071
Number of clusters: 800	β_{age} (0.05)	-0.0003	-0.6	95	0.001	-0.0003	-0.7	92.5	0.001
	β_{sex} (1)	0.0077	0.8	93	0.033	0.0078	0.8	92.7	0.033
Mean cluster size: 10	β_{DI} (0.02)	0.0003	1.7	96.5	0.015	0	-0.1	95.3	0.016
	σ (0.5)	0.0028	0.6	95	0.023	0.0024	0.5	95.3	0.023

Simulation results

Scenario NPH



Quick reminder on survival quantities 1/2

Survival at time t : $S(t) = P(T \geq t)$

Instantaneous mortality hazard :

$$\lambda(t) = \lim_{\delta t \to 0} \left\{ \frac{P(t \leq T < t + \delta t \,|\, T \geq t)}{\delta t} \right\}$$

Cumulative Mortality hazard : $\Lambda(t) = \displaystyle\int_0^t \lambda(u)\, \mathrm{d}u$

The following relationship holds :

$$S(t) = \exp\{-\Lambda(t)\} \qquad\qquad S(t) = 1 - \int_0^t \lambda(u) \cdot S(u)\, \mathrm{d}u$$

Quick reminder on survival quantities 2/2

For each patient j, we observe:

- the time to death (or of last known vital status) t_j
- the failure indicator δ_j
- possibly some covariates $\mathbf{x}_j$

The Log-Likelihood (assuming non informative censoring)

$$loglik = \prod_{j=1}^{N} S(t_j, \mathbf{x}_j)\lambda(t_j, \mathbf{x}_j)^{\delta_j}$$