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Mortality by education level at late-adult ages in Turin: a survival analysis using frailty models with period and cohort approaches.

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Abstract

Background. Unobserved heterogeneity of frailty can lead to biased estimates of coefficients in survival analysis models. This study investigated the role of unobserved frailty on the estimation of mortality differentials from age 50 on by education level.

Methods. We used data of a 36 years follow up from the Turin Longitudinal Study containing 391 170 men and 456 216 women. As Turin underwent strong immigration flows during the post war industrialization, also the macro-region of birth was controlled for. We fitted survival analysis models with and without the unobserved heterogeneity component, controlling for mortality improvement from both cohort and period perspectives.

Results. We found that in the majority of the cases, the models without frailty estimated a smaller educational gradient then the models with frailty.

Conclusions. The results draw the attention on the potential underestimation of the mortality inequalities by socioeconomic levels in survival models when not controlling for frailty.

Introduction

An extensive literature shows significant differential mortality by socioeconomic condition (1-3). Elderly show decreasing relative social inequalities in general mortality with increasing age (4-8). The age-as-leveler hypothesis attributes this to factors that contribute to the leveling-off of differences at old ages: governmental support to the elderly (9-11), disengagement from systems of social stratification (12) and general vulnerability (13, 14). However, this phenomenon could also be an artifact of selection due to unobserved characteristics of the individuals: selective effects of earlier higher mortality, experienced by the disadvantaged group, would leave more robust individuals at old ages, causing the convergence with the risk of the lower mortality group, that is subject to weaker selection (15-18). Neglecting these hidden differences in survival chances (called unobserved frailty), has been shown to lead to biased estimates of the mortality hazard and of the effect of the covariates on the survival probability (19-25).

In differential mortality analysis it is important to control for hidden frailty. First, because not controlling for it, in survival models, could lead to biased estimates of the effect of the social position on the mortality risk: the statistical literature shows that the bias is towards zero (24-26). This would lead to underestimation of the relative differences in the mortality risks by socioeconomic group. Second, because selection due to unobserved frailty could provide an explanation for the phenomenon of decreasing relative differences in death rates by socioeconomic group at old ages. To control for unobserved frailty and to evaluate the impact on the observed mortality dynamics, frailty models have been developed (27) .

This study investigated the presence of selection processes in the mortality patterns of the Turin population (North-West Italy) from age 50 on. Adopting a longitudinal perspective, this study aimed 1) to investigate whether the theoretical framework of the frailty models can explain the observed pattern of convergence of mortality differentials by social position 2) to investigate if the estimates of the mortality differentials are affected by the introduction of the unobserved heterogeneity component into the models: this would strengthen the validity of the selection hypothesis as an alternative explanation for the reduction of the differences in socioeconomic mortality at old ages.

Data and Methods

We used high quality census linked data from the Turin Longitudinal Study (TLS), which includes 1971, 1981, 1991 and 2001 census data for the Turin population. TLS records the individual census socio-demographic information and, through record linkage with the local population registry and other local health information systems, collects information on vital status, cause of death and other health indicators (28, 29).

For this study, the individuals registered in Turin during at least one of the four censuses were selected. Their migration and vital status was followed up until the end of July 2007. The result is an observation window of 36 years (from October 24th 1971, official date of the census, to the end of July 2007, end of the linkage) during which the individuals were followed up until death, emigration from the city or end of observation period. The follow up started at age 50. The study population contains 391 170 men and 456 216 women.

Study information includes individual's date of birth, date of exit from the study, cause of exit (death or emigration), sex, macro-region of birth and education level.

Consistent with the literature (30-33) education level was used as an indicator of social position.

The study also controlled for the individual macro region of birth, as Turin is characterized by a history of immigration from other regions of the country (34).

To facilitate the comparison over a long follow up and different cohorts, we created three broad educational groups: high (high school diploma or higher), medium (junior high school) and low (primary school or lower).

We estimated parametric survival models stratified by gender and as a function of macro-region of birth and education level, with and without a parameter for the unobserved heterogeneity component. The parametric choice is justified by the wide demographic literature showing that human adult mortality can be accurately described by a Gompertz function (35) or by some Gompertz-like variants, like Makeham. To identify the best functional form for the baseline we compared the models with the AIC (36).

The data are both right censored (due to emigration or end of follow up) and left truncated (due to the different age at entry in the study of the individuals).

The study includes many cohorts, each passing through the 36 years of observation at different ages. However, from 1971 to 2007 a significant mortality improvement occurred and younger cohorts experience lower age specific mortality than older cohorts. To take into account this factor we used two strategies.

First, we regarded the improvement as a cohort phenomenon, including a covariate for the cohort to which the individuals belong. In this setting, controlling for unobserved heterogeneity was implemented with univariate frailty models, which estimate the baseline parameters, the coefficients of the covariates and the variance of frailty (assumed to follow a gamma distribution with mean 1 and variance σ^2 to be estimated).

We then considered the improvement as a period phenomenon and split the time into several calendar period covariates, as well as the survival spell of the individuals, according to which period they were passing through. This implied organizing the data into clusters, where each cluster represents one individual's survival spells. In this setting, to control for unobserved heterogeneity shared frailty models are needed, where the spells in each cluster pertain to the same individual and share the same hidden frailty. For computational reasons, the estimation of these highly complex models required the use of random subsampling (37-39). We repeated the estimation 250 times on a 1% sample of the dataset, randomly drawn without replacement and stratified by the major variables in analysis. The aim is to approximate the parameters estimates based on the empirical distribution of the repeated estimates.

In the model without frailty it was possible to include a finer calendar period division, 12 period variables of 3 years each (1971-1973, 1974-1976…), while in the model with frailty, for computational reasons, the number of variables was reduced to 2 broader periods: 1971-1990 and 1991-2007.

Computations were realized with the software R (40). Formal details are in appendix A.

Results

Figure 1 shows that the log-death rates by education level and gender, for the cohort aged 50-59 in 1971, converge at old ages. Other cohorts showed very similar patterns.

A preliminary analysis found that the reduction of the gradient over age is statistically significant and slightly more pronounced among women (results are reported in appendix B table B1).

Figure 1 here

Frailty modeling

Table 1 shows the AIC of the survival models, fitted to the all population mortality, with Gompertz and Makeham baselines. It also shows the results of the fit when unobserved frailty was controlled for. The comparison reveals that Gompertz baseline was a better fit for the male data, while Makeham was better for the female. In both cases, the models controlling for unobserved heterogeneity performed a better fit (table 1).

Table 1. Model selection of 4 different hazard models based on the AIC.

	Gompertz	Makeham	Gam-Gompertz	Gam-Makeham
	ae^{bx}	$ae^{bx}+c$	$\frac{ae^{bx}}{1+\sigma^2\frac{a}{b}\left(e^{bx}-1\right)}$	$\frac{ae^{bx}+c}{1+\sigma^2\frac{a}{b}\left(e^{bx}-1\right)+cx}$
AIC women	1 327 474	1 326 878	1 327 476	1 326 695
AIC men	1 303 693	1 303 695	1 303 655	1 303 693

We then estimated the mortality differentials, using a cohort and a period approach to control for mortality improvement over time. We included in the analysis the variables for education level (high, medium and low) and region of birth (North-West, North-East, Center, South and Abroad).

Tables A2 and A3 in the appendix report the results. Figure 2 compares the results for the educational gradient obtained by the models with and without frailty.

Educational gradient

In the model with the cohort improvement approach, the introduction of the frailty term made the male differences widen significantly, consistent with the statistical literature. The rate ratios with respect to high education changed from 1.16 (95% CI 1.15-1.19) to 1.22 (1.20-1.24) for medium education and from 1.24 (1.22-1.26) to 1.30 (1.28-1.32) low education (figure 2 panel a). Among women there was a slight but not significant reduction: for medium education the rate ratio went from 1.14 (1.12-1.17) to 1.11 (1.08-1.14) and for low education from 1.25 (1.22-1.27) to 1.22 (1.19-1.24) (figure 2 panel b). The AIC indicates that the models with frailty fit the data significantly better than the model without.

Figure 2 here

In the model adopting the period improvement approach, the AIC comparison of the models with and without frailty was not possible, because the utilization of random subsampling for the estimation of the frailty model (37-39) did not allow obtaining a likelihood value comparable with the values of the models without frailty. Moreover, it is necessary to consider that we are comparing conventional point estimates and confidence intervals with values obtained via bootstrapping methods, whose confidence regions are usually wider than conventional confidence intervals. Nevertheless, a comparison is still possible.

The introduction of frailty affected the mortality gradient by education. Although the uncertainty around the estimates does not allow assessing a precise effect, the rate ratios of medium and low education in respect to high education in the models with frailty lie in a higher confidence region than in the models without: among women with a medium education level, it lies between 1.05 and 1.34 compared to 1.08 and 1.13 of the model without frailty and for the low education group, between 1.1 and 1.6, compared to 1.18 and 1.23. The same pattern can be observed among men.

The male difference between medium and low education group, on the contrary, was not as clear as that among women.

Other results and the impact of the macro-region of birth on mortality

As expected, the variance of frailty in the cohort models was smaller than in the period models, since periods are more heterogeneous than cohorts.

Women were more heterogeneous than men: 0.09 (0.08-0.11) versus 0.04 (0.03-0.05) in the cohort models and 0.29 (0.17-0.37) versus 0.27 (0.-0.36) in the period models.

In the cohort models the introduction of unobserved frailty affected the coefficient for the macro-region of birth significantly. Among men, holding education equal, those born in the South show a significant survival advantage over the natives of the North-West, while in the model without frailty there was no such advantage. Among women, the model without frailty showed a significant survival advantage for those born in the South but when frailty was controlled for, this became not significant.

The pattern also resembles the regional mortality macro-dynamics that have characterized Italy for most of the 20th century (although the two patterns refer to different phenomena, the first one referring to mortality by region of birth), when male mortality in the South was lower than in the North (41-44). Cohort based analyses have highlighted that in more recent cohorts (those born after WWII) there is a reversing trend (44, 45).

The models with period perspective did not identify any significant geographical differences. This could be due to the utilization of random subsampling of a 1% sample. Although 250 repetitions is considered by the literature a sufficient number for very complex models (46-48), it is possible that it was inadequate to identify a clear pattern from the small sample.

For more detailed results see tables C1 and C2 in appendix C.

Discussion

The interest in the role of unobserved heterogeneity in a life course approach to socioeconomic mortality differences has recently increased. Most of the studies focus on health outcomes (49-54) while fewer studies also analyze mortality (55-57). Their findings are not consistent and fuel a still controversial debate.

In this study we investigated the role of unobserved individual heterogeneity on the estimation of mortality differentials at adult-old ages by education level in a longitudinal perspective. This study investigated 1) whether the framework of the frailty models can explain the observed pattern of convergence of the mortality risk by social position at old ages 2) if the estimates of the mortality differentials are affected by the introduction of the unobserved heterogeneity component into the models.

We fitted survival analysis models with and without controlling for the unobserved heterogeneity and we found that, when this component was included, the models gave a significantly better fit.

We also found that in the majority of the cases, the educational gradient estimated by the models with frailty was higher than the one estimated by the models without frailty. When big uncertainty around the estimates did not allow assessing a precise value, the confidence regions in the models with frailty spanned over higher values than those in the models without frailty. This is consistent with the statistical literature about unobserved heterogeneity, which shows that neglecting its selective action, in duration dependence models, leads to underestimation of the covariates effect (19-26).

Among men such a pattern was found in both the cohort and period approaches. Among women, on the contrary, this pattern was less clear: in the cohort model, controlling for hidden frailty resulted in a slight reduction of the mortality gradient. Social determinants act on mortality also through risk factors that are known to affect more men than women. Moreover, because of a lag in the smoking and fertility transitions, highly educated women in Turin are more exposed to risk factors like cigarette smoking and smaller number of children. Therefore, controlling for hidden frailty in the case of women might reduce the educational gradient.

In the models with cohort perspective controlling for the hidden frailty affected also the estimates of the differentials by macro-region of birth, showing a survival advantage of the men born in the South, but not of the women, for whom an advantage was instead detected by the model that did not control for frailty.

The healthy migrant effect (58-63) could cause this pattern. Among the cohorts involved in the migration women were likely to be more passive actors than men in the migratory decision (64-66) and this might have selected them more than men. Frailty is a general concept embedding all the hidden factors that affect the individual survival chances:

innate and acquired frailty, exposure to risk factors, life style factors and so on. Therefore, controlling for frailty reduced the survival advantage of the women, who might have been less health selected than men by the migration, while uncovered the advantage of the men. However, another recent study on the impact of migration on all-cause mortality in Turin did not find particularly strong gender differences in the so called healthy migrant effect (62) and this point deserves future further investigation.

The study spanned over a long observation window of 36 years. Therefore it was important to control for the general mortality improvement that took place during this time. We did so by adopting both a period and a cohort approach.

The period models, as expected, estimated higher heterogeneity than the cohort models. Periods aggregate different generations and are expected to be more heterogeneous than the cohorts themselves. In both period and cohort models the female variance of frailty was higher than for the males, indicating that men are more homogeneous than women. This could be attributed to a stronger selection process due to mortality that is usually observed to be higher among men than among women.

On the other hand, it is also possible that the industrialization process and the internal migration experienced by Italy after WWII (34) played a role. The vast majority of less educated individuals in Turin came from the South, seeking a job in the car factories of the city. As less educated men were mainly employed in heavier and riskier jobs and were exposed to higher mortality, it is possible that during their life they were selected at a faster pace than other educational groups and women. This might have reduced the differences in susceptibility to death among men, contributing to determining a lower level of heterogeneity than among women.

Conclusion

This study found that neglecting selection effects due to unobserved heterogeneity in longitudinal analyses, could lead to underestimation of mortality differentials by social class. In the majority of the cases, the models that controlled for unobserved heterogeneity, estimated higher educational differences in mortality than the models that did not control for it.

Moreover, the models that controlled for unobserved heterogeneity gave a statistically significant better fit than the models that did not control for it. This strengthens the validity of the selection hypothesis as explanation for the reduction of the gradient in socioeconomic mortality.

This analysis also has important policies facets. Specifically, when studying differential survival chances in socioeconomic groups, the tendency to dismiss the importance of such differences in old ages, because they are observed to diminish, should be avoided. Individuals might experience a disadvantaged position throughout their life which does not fade away when they age. The lessening of differences at old ages could be the result of a stronger selection due to early higher mortality that disadvantaged groups are still subject to.

Summary

<ins>Article Focus</ins>

- Neglecting the presence of unobserved heterogeneity in survival analysis models has been showed to potentially lead to underestimating the effect of the covariates included in the analysis.
- Although frailty models have been widely developed to account for unobserved heterogeneity, in differential mortality analyses this source of variation is seldom controlled for. This study has applied these models to a longitudinal mortality analysis by education level.

<ins>Key messages</ins>

- Mortality differentials by education (or by any other variable used as proxy of socioeconomic status) could be larger than those estimated with standard survival analysis approaches that do not control for unobserved heterogeneity.
- Relative mortality differences at old ages between socioeconomic groups are often observed to decline. However, this pattern could be the result of a stronger selection due to early higher mortality that disadvantaged groups are still subject to.

Strengths and limitations

The strength of this study lies in the population based longitudinal data. The long observational time (36 years) for more than 847 000 individuals gives a solid base for statistical power and detection of trends.

The limitation consists in the lack of individual information on life style factors and health events, which could certainly help to better model the concept of unobserved individual frailty by uncovering part of it.

Competing Interest. None to declare.

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Contributorship. Virginia Zarulli: conception and design of the study, analysis and interpretation of data and results, drafting the article and revising it; Graziella Caselli: interpretation of the results, drafting the article and revising it critically; Chiara Marinacci and Giuseppe Costa: revising the article for important intellectual content.

Data sharing. There is no additional data available.

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Appendix

A. Frailty models and Survival Analysis

According to the literature on frailty models every individual has a specific level of unobserved frailty, *z*, that defines the individual hazard in a context of proportional hazard models.

Assuming that unobserved frailty follows a Gamma distribution, the population hazard $\overline{\mu}(x)$ at any age *x* is expressed as a mixture of individual hazards $\mu(x)$, by the following relationship:

$$\overline{\mu}(x) = \frac{\mu(x)}{1+\sigma^2 \int_0^x \mu(t)dt} \tag{1}$$

where σ^2 is the variance of the frailty distribution with mean 1 at the initial age and $\mu(x)$ is the hazard experienced by the standard individual with frailty 1. The optimization problem estimates the baseline hazard parameters and the variance of the frailty in the population.

Survival analysis without unobserved heterogeneity

The only variability controlled for is the one explained by the observed covariates, *u*, included in the model. Their effect on the baseline hazard $\mu_0(x)$ is estimated as follows:

$$\mu_i(x \mid u_i) = \mu_0(x)e^{\beta u_i} \tag{2}$$

The likelihood function in case of right censored and left truncated survival data is:

$$L(\beta,\theta) = \prod_{i=1}^{n} \frac{\left(\mu(x_i,\theta)e^{u_i\beta}\right)^{\delta_i} S(x_i,\theta)^{e^{u_i\beta}}}{S(y_i,\theta)^{e^{u_i\beta}}} \tag{3}$$

Where for each individual *i*, y_i is the entry time, x_i in the exit time, δ_i is the status (1=dead, 0=right censored), u_i is the covariate profile with effect β and $\mu(.)$ denotes the hazard, $S(.)$ the survival function and θ is the vector of parameters of the baseline hazard.

Univariate frailty models

An individual random effect for the frailty is introduced in the model as a multiplicative term on the baseline hazard:

$$\mu_i(x \mid u_i, z_i) = z_i \mu_0(x) e^{\beta u_i} \qquad (4)$$

The likelihood function in case of right censored and left truncated survival data is:

$$L(\beta,\theta,\sigma^2) = \prod_{i=1}^{n} \frac{\left(\frac{\mu(x_i,\theta)e^{u_i\beta}}{1+\sigma^2 M(x_i,\theta)e^{u_i\beta}}\right)^{\delta_i} \left(1+\sigma^2 M(x_i,\theta)e^{u_i\beta}\right)^{-\frac{1}{\sigma^2}}}{\left(1+\sigma^2 M(y_i,\theta)e^{u_i\beta}\right)^{-\frac{1}{\sigma^2}}} \qquad (5)$$

Where for each individual i, y_i is the entry time, x_i in the exit time, δ_i is the status (1=dead, 0=right censored), u_i is the covariate profile with effect β and $\mu(.)$ denotes the hazard, $M(.)$ the cumulative hazard, θ is the vector of parameters of the baseline hazard and σ^2 is the variance of frailty.

Shared frailty models

In the case of repeated survival spells for the same individual i, the shared frailty models assume that those spells share the same hidden frailty, as showed by equation (6):

$$\mu_i(x \mid u_{i,j}, z_i) = z_i \mu_0(x) e^{\beta u_{i,j}} \qquad (6)$$

Where the indexes j and i represent the survival spell j of the individual (cluster) i.

The cluster (individual) likelihood function in case of right censored and left truncated survival data is (1):

$$L_i = \left(\prod_{j=1}^{n_i} \left(\mu(x_{ij},\theta) e^{u_{ij}\beta} \right)^{\delta_{ij}} \right) \frac{\Gamma\left(\frac{1}{\sigma^2} + D_i \right)}{\Gamma\left(\frac{1}{\sigma^2} \right)} \left(\sigma^2 \right)^{D_i} \left(1 - \sigma^2 \sum_{j=1}^{n_i} \ln\left(S_{ij}\left(y_{ij},\theta \right)^{e^{u_{ij}\beta}} \right) \right)^{\frac{1}{\sigma^2}} \tag{7}$$

$$\left(1 - \sigma^2 \sum_{j=1}^{n_i} \ln\left(S_{ij}\left(x_{ij},\theta \right)^{e^{u_{ij}\beta}} \right) \right)^{-\frac{1}{\sigma^2} - D_i}$$

Where for each j-th individual in the i-th cluster, y_{ij} is the entry time, x_{ij} in the exit time, δ_{ij} is the status (1=dead, 0=right censored), u_{ij} is the covariate profile with effect β and $\mu(.)$ denotes the hazard, $S(.)$ the survival function, θ is the vector of parameters of the baseline hazard, σ^2 is the variance of frailty and $D_i = \sum \delta_{ij}$.

The overall likelihood function is simply:

$$L(\beta,\theta,\sigma^2) = \prod_{i=1}^{n} L_i \tag{8}$$

B. Exponential model

Table B1 reports the results of the exponential model with age as covariate. The exponential baseline hazard, $\mu(x)=\lambda$, is constant and does not change with age. This allows us to include the age as a covariate and to have it interact with the covariate for education level. The aim is to investigate whether there is convergence of hazards at old ages by education group by testing whether the interaction term is significant.

The single parameter baseline hazard was modulated by the covariate for the age groups. The identity between an exponential hazard modulated by an age covariate and the Gompertz model makes such exponential models appropriate for human adult mortality data.

Table B1. Mortality rate ratios between education groups and age groups estimated from an exponential survival hazard model with covariates education, age and their interaction. The table also reports the likelihood ratio test between this model and a model without an age-education interaction term.

	Men				Women			
	50-80 years		80+ years		50-80 years		80+ years	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
High	1	-	1	-	1	-	1	-
Medium	1.234	1.209-1.259	1.082	1.048-1.116	1.250	1.213-1.289	1.040	1.008-1.073
Low	1.571	1.544-1.598	1.172	1.143-1.202	1.594	1.552-1.637	1.170	1.136-1.202
Likelihood ratio test with reduced model (without age-education interaction)								
	D statistics: 395.193		Df: 2	p-value:0.000	D statistics:319.833		Df: 2	p-value:0.000

C. Survival Models with and without unobserved heterogeneity

Tables C1 and C2 report the results of the models estimated with and without the unobserved heterogeneity component: the parameters of the baseline hazard (a and b of the Gompertz function for men and a, b and c of the Makeham function for women), the variance of frailty in the population and the rate ratios of the mortality differentials by education level and region of birth.

Models with cohort covariate

Table C1. Results of the regression models with cohort covariates. Baseline parameters (Gompertz for men and Makeham for women) and rate ratios of the differentials by education and region of birth.

	Men				Women			
	Model without frailty		Model with frailty		Model without frailty		Model with frailty	
	Estimate	95% CI	Estimate	95% CI	0.000	0.000-0.000	0.000	0.000-0.000
A	0.000	0.000-0.000	0.000	0.000-0.000	0.106	0.105-0.107	0.117	0.115-0.119
B	0.083	0.080-0.082	0.083	0.082-0.084	0.001	0.001-0.001	0.001	0.001-0.001
C	-	-	-	-	-	-	0.096	0.082-0.111
$Sigma^2$	-	-	0.035	0.027-0.045	0.016	0.015-0.016	0.017	0.016-0.017
cohort	0.016	0.015-0.016	*cohort*	0.016	0.000	0.000-0.000	0.000	0.000-0.000
Education level								
High	1	-	1	-	1	-	1	-
Medium	1.166	1.147-1.186	1.221	1.200-1.243	1.141	1.116-1.166	1.111	1.086-1.137
Low	1.239	1.221-1.257	1.302	1.283-1.322	1.246	1.222-1.270	1.213	1.188-1.238
Region of birth								
North-West	1	-	1	-	1	-	1	-
North-East	1.053	1.036-1.070	1.060	1.042-1.077)	0.989	0.973-1.004	0.974	0.958-0.991
Center	1.011	0.984-1.038	0.996	0.969-1.024	0.939	0.913-0.966	0.968	0.939-0.998
South	1.000	0.988-1.012	0.950	0.938-0.962	0.932	0.919-0.945	0.987	0.973-1.002
Abroad	1.031	1.006-1.057	0.998	0.974-1.024	1.071	1.047-1.096	0.993	0.968-1.018
logLk	-651 219		-651 082		-663 238		-663 098	
AIC	1 302 456		1 302 184		1 326 496		1 326 218	

Models with period covariates

Table C2. Results of the regression models with period covariates. Baseline parameters (Gompertz for men and Makeham for women) and rate ratios of the differentials by education and region of birth.

*The model with frailty does not report conventional point estimates and confidence intervals, but the mean value and the 0.025-0.975 quantiles of the empirical distribution of the parameters obtained from the repeated estimates via random subsampling.

	Men				Women			
	Model without frailty		Model with frailty*		Model without frailty		Model with frailty*	
	Estimate	95% CI	Mean	0.025-0.0975	Estimate	95% CI	Mean	0.025-0.0975
A	0.000	(0.000-0.000)	0.004	(0.000-0.010)	0.000	(0.000-0.000)	0.008	(0.000-0.016)
B	0.096	(0.095-0.096)	0.069	(0.061-0.163)	0.121	(0.120-0.122)	0.084	(0.073-0.106)
C	-	-	-	-	0.001	(0.001-0.002)	0.000	(0.000-0.000)
$Sigma^2$	-	-	0.269	(0.026-0.367)	-	-	0.292	(0.174-0.367)
Calendar period								
1971-1973	1	-			1	-		
1974-1976	0.999	0.972-1.027			0.978	0.950-1.007		
1977-1979	0.947	0.921-0.973			0.919	0.893-0.946		
1980-1982	0.928	0.903-0.953			0.896	0.871-0.922		
1983-1985	0.943	0.918-0.969			0.967	0.941-0.994		
1986-1988	0.870	0.847-0.894	1	-	0.848	0.824-0.872	1	-
1989-1991	0.820	0.798-0.843	0.728	0.613-0.985	0.796	0.774-0.818	0.888	0.671-1.035
1992-1994	0.796	0.774-0.817			0.757	0.736-0.778		
1995-1997	0.741	0.721-0.762			0.704	0.684-0.724		
1998-2000	0.701	0.682-0.721			0.682	0.663-0.701		
2001-2003	0.670	0.652-0.689			0.657	0.639-0.676		
2004-2007	0.631	0.615-0.648			0.625	0.608-0.642		
High	1	-	1	-	1	-	1	-
Medium	1.204	(1.184-1.225)	1.277	(1.054-1.349)	1.107	(1.083-1.131)	1.256	(1.053-1.347)
Low	1.301	(1.282-1.320)	1.268	(1.074-1.591)	1.209	(1.186-1.232)	1.475	(1.103-1.641)
North-West	1	-	1	-	1	-	1	-
North-East	1.040	(1.024-1.057)	1.075	(0.855-1.220)	0.963	(0.948-0.978)	1.122	(0.888-1.217)
Center	0.943	(0.917-0.969)	1.081	(0.854-1.212)	0.964	(0.938-0.992)	1.102	(0.864-1.218)
South	0.900	(0.889-0.911)	1.037	(0.854-1.216)	0.962	(0.949-0.975)	1.130	(0.904-1.220)
Abroad	0.965	(0.941-0.989)	1.082	(0.864-1.218)	0.985	(0.962-1.009)	1.082	(0.847-1.215)
logLk	-650 997		Na		-663 081		Na	
AIC	1 302 034		Na		1 326 204		Na	

1. Van den Berg GJ, Drepper B. Inference for Shared-Frailty Survival Models with Left-Truncated Data. IZA Discussion Paper No 6031. 2011.

Figures

Figure 1. Death rates, on logarithmic scale, for the birth cohort aged 50-59 at the beginning of the follow-up (1971) by three education levels: high, medium and low.

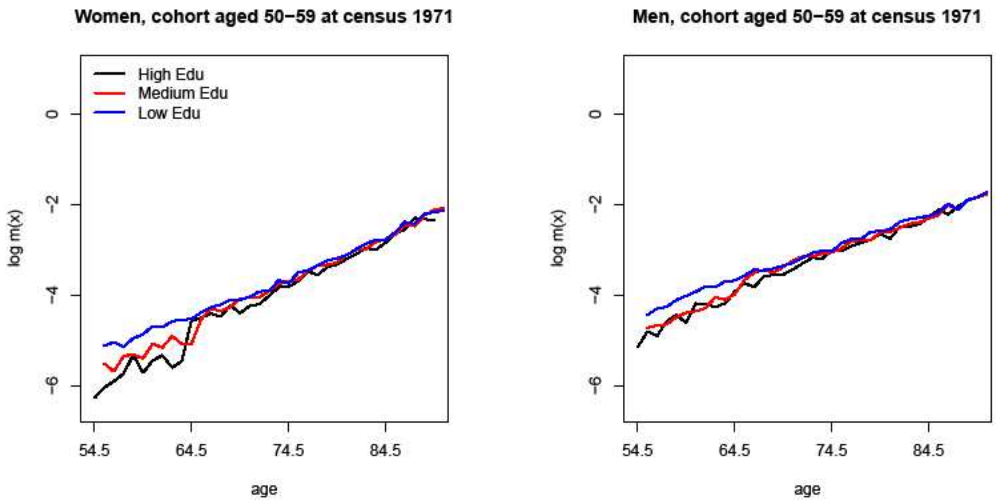
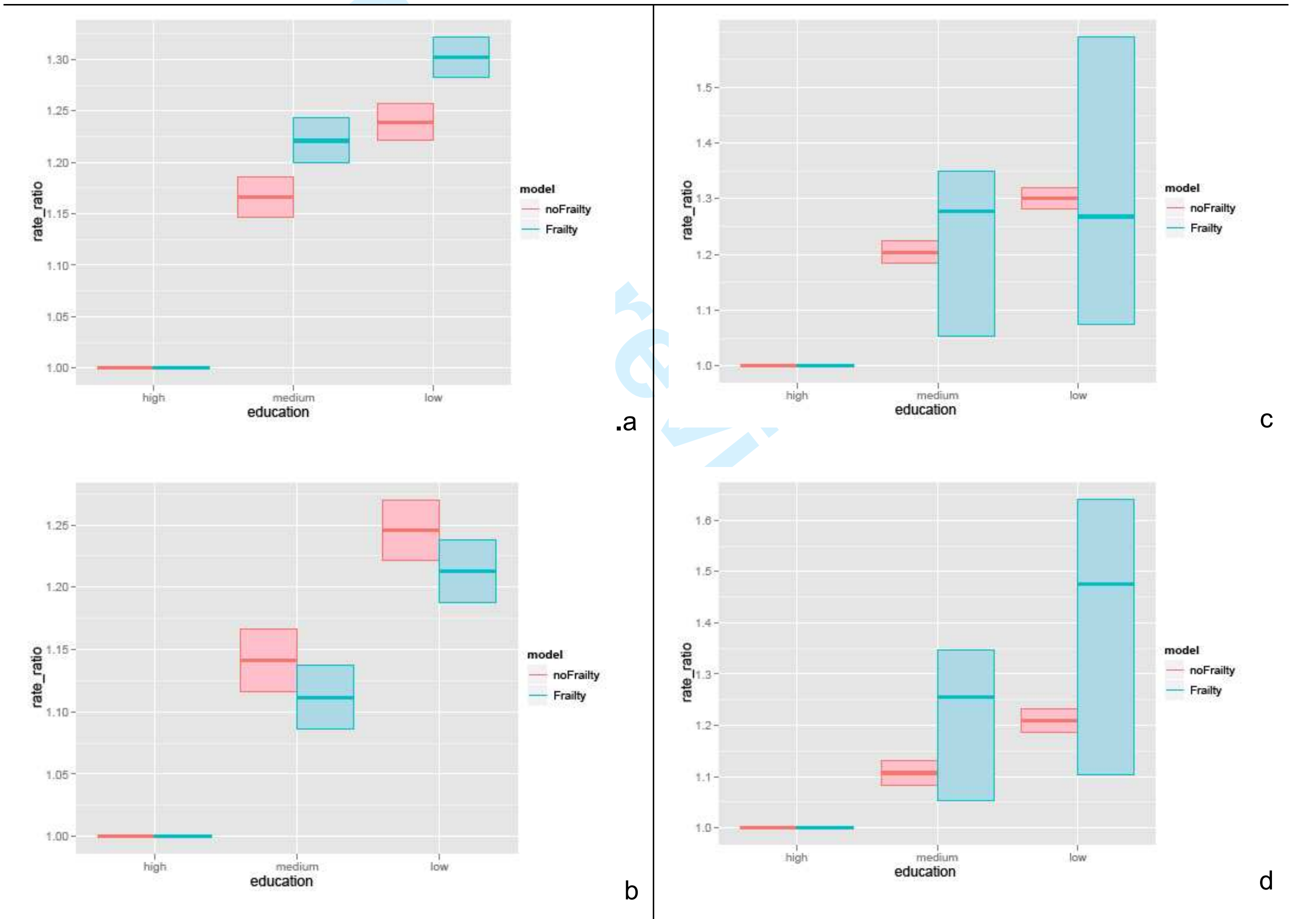


Figure 2. Mortality rate ratios by education level in the models with cohort and period improvements, without and with frailty. a) Men, cohort model; b) Women, cohort model; c) Men, period model; d) Women, period model.

Model with cohort improvement | Model with period improvement



	Men (a)		Women (b)	
	No frailty	Frailty	No frailty	Frailty
LogLik	-651 219	-651 082	-663 238	-663 098
AIC	1302456	1302184	1326496	1326218

	Men (c)		Women (d)	
	No frailty	Frailty	No frailty	Frailty
LogLik	-663 081	Na	-650 997	Na
AIC	1326204	Na	1302034	Na

Mortality by education level at late-adult ages in Turin: a survival analysis using frailty models with period and cohort approaches.

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Mortality by education level at late-adult ages in Turin: a survival analysis using frailty models with period and cohort approaches.

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Abstract

Background. Unobserved heterogeneity of frailty can lead to biased estimates of coefficients in survival analysis models. This study investigated the role of unobserved frailty on the estimation of mortality differentials from age 50 on by education level.

Methods. We used data of a 36 years follow up from the Turin Longitudinal Study containing 391 170 men and 456 216 women. As Turin underwent strong immigration flows during the post war industrialization, also the macro-region of birth was controlled for. We fitted survival analysis models with and without the unobserved heterogeneity component, controlling for mortality improvement from both cohort and period perspectives.

Results. We found that in the majority of the cases, the models without frailty estimated a smaller educational gradient then the models with frailty.

Conclusions. The results draw the attention on the potential underestimation of the mortality inequalities by socioeconomic levels in survival models when not controlling for frailty.

Introduction

An extensive literature shows significant differential mortality by socioeconomic condition (1-3). Elderly show decreasing relative social inequalities in general mortality with increasing age (4-8). The age-as-leveler hypothesis attributes this to factors that contribute to the leveling-off of differences at old ages: governmental support to the elderly (9-11), disengagement from systems of social stratification (12) and general vulnerability (13, 14). However, this phenomenon could also be an artifact of selection due to unobserved characteristics of the individuals: selective effects of earlier higher mortality, experienced by the disadvantaged group, would leave more robust individuals at old ages, causing the convergence with the risk of the lower mortality group, that is subject to weaker selection (15-18). Neglecting these hidden differences in survival chances (called unobserved frailty), has been shown to lead to biased estimates of the mortality hazard and of the effect of the covariates on the survival probability (19-25).

In longitudinal analyses on differential mortality it is important to control for hidden frailty. First, because not controlling for it, in survival models, could lead to biased estimates of the effect of the social position on the mortality risk: the statistical literature shows that the bias is towards zero (24-26). This would lead to underestimation of the relative differences in the mortality risks by socioeconomic group. Second, because selection due to unobserved frailty could provide an explanation for the phenomenon of decreasing relative differences in death rates by socioeconomic group at old ages. To control for unobserved frailty and to evaluate the impact on the observed mortality dynamics, frailty models have been developed (27) . For more detailed explanations of the frailty models and how they relate to differential mortality analyses, please, see appendix A.

This study investigated the presence of selection processes in the mortality patterns of the Turin population (North-West Italy) from age 50 on. Adopting a longitudinal perspective, this study aimed 1) to investigate whether the theoretical framework of the frailty models can explain the observed pattern of convergence of mortality differentials by social position 2) to investigate if the estimates of the mortality differentials are affected by the introduction of the unobserved heterogeneity component into the models.

Data and Methods

We used high quality census linked data from the Turin Longitudinal Study (TLS), which includes 1971, 1981, 1991 and 2001 census data for the Turin population. TLS records the individual census socio-demographic information and, through record linkage with the local population registry and other local health information systems, collects information on vital status, cause of death and other health indicators (28, 29).

For this study, the individuals registered in Turin during at least one of the four censuses were selected. Their migration and vital status was followed up until the end of July 2007. The result is an observation window of 36 years (from October 24th 1971, official date of the census, to the end of July 2007, end of the linkage) during which the individuals were followed up until death, emigration from the city or end of observation period. The follow up started at age 50. The study population contains 391 170 men and 456 216 women.

Study information includes individual's date of birth, date of exit from the study, cause of exit (death or emigration), sex, macro-region of birth and education level.

Consistent with the literature (30-33) education level was used as an indicator of social position.

The study also controlled for the individual macro region of birth, as Turin is characterized by a history of immigration from other regions of the country (34).

To facilitate the comparison over a long follow up and different cohorts, we created three broad educational groups: high (high school diploma or higher), medium (junior high school) and low (primary school or lower).

We estimated parametric survival models stratified by gender and as a function of macro-region of birth and education level, with and without a parameter for the unobserved heterogeneity component. The parametric choice is justified by the wide demographic literature showing that human adult mortality can be accurately described by a Gompertz function (35) or by some Gompertz-like variants, like Makeham. To identify the best functional form for the baseline we compared the models with the AIC (36).

The data are both right censored (due to emigration or end of follow up) and left truncated (due to the different age at entry in the study of the individuals).

The study includes many cohorts, each passing through the 36 years of observation at different ages. However, from 1971 to 2007 a significant mortality improvement occurred and younger cohorts experience lower age specific mortality than older cohorts.

Time is a complex variable including three dimensions: age, period and cohort. Controlling adequately for the effect of time would require to asses simultaneously the three components but such models have been proved to be not identifiable because of linear dependence between the three dimensions (37-39).

Therefore, we decided to adopt two approaches for the control of time, corresponding to an age-cohort approach and an age-period approach, being aware that they represent two different dimensions of time.

First, we regarded the improvement as a cohort phenomenon, including a covariate for the cohort to which the individuals belong. In this setting, controlling for unobserved heterogeneity was implemented with univariate frailty models, which estimate the baseline parameters, the coefficients of the covariates and the variance of frailty (assumed to follow a gamma distribution with mean 1 and variance σ^2 to be estimated).

We then considered the improvement as a period phenomenon and split the time into several calendar period covariates, as well as the survival spell of the individuals, according to which period they were passing through. This implied organizing the data into clusters, where each cluster represents one individual's survival spells. In this setting, to control for unobserved heterogeneity shared frailty models are needed, where the spells in each cluster pertain to the same individual and share the same hidden frailty. For computational reasons, the estimation of these highly complex models required the use of random subsampling (40-42). We repeated the estimation 250 times on a 1% sample of the dataset, randomly drawn without replacement and stratified by the major variables in analysis. The aim is to approximate the parameters estimates based on the empirical distribution of the repeated estimates.

In the model without frailty it was possible to include a finer calendar period division, 12 period variables of 3 years each (1971-1973, 1974-1976…), while in the model with frailty, for computational reasons, the number of variables was reduced to 2 broader periods: 1971-1990 and 1991-2007.

Computations were realized with the software R (43). Formal details are in appendix A.

Results

Figure 1 shows that the log-death rates by education level and gender, for the cohort aged 50-59 in 1971, converge at old ages. Other cohorts showed very similar patterns.

A preliminary analysis found that the reduction of the gradient over age is statistically significant and more pronounced among women (results are reported in appendix B table B1).

Figure 1 here

Frailty modeling

Table 1 shows the AIC of the survival models, fitted to the all population mortality, with Gompertz and Makeham baselines. It also shows the results of the fit when unobserved frailty was controlled for. The comparison reveals that Gompertz baseline was a better fit for the male data, while Makeham was better for the female. In both cases, the models controlling for unobserved heterogeneity performed a better fit (table 1).

Table 1. Model selection of 4 different hazard models based on the AIC.

	Gompertz	Makeham	Gam-Gompertz	Gam-Makeham
	ae^{bx}	$ae^{bx}+c$	$\frac{ae^{bx}}{1+\sigma^2\frac{a}{b}\left(e^{bx}-1\right)}$	$\frac{ae^{bx}+c}{1+\sigma^2\frac{a}{b}\left(e^{bx}-1\right)+cx}$
AIC women	1 327 474	1 326 878	1 327 476	1 326 695
AIC men	1 303 693	1 303 695	1 303 655	1 303 693

We then estimated the mortality differentials, using a cohort and a period approach to control for mortality improvement over time. We included in the analysis the variables for education level (high, medium and low) and region of birth (North-West, North-East, Center, South and Abroad).

Tables 2 and 3 report the results of the models estimated with and without the unobserved heterogeneity component: the parameters of the baseline hazard (a and b of the Gompertz function for men and a, b and c of the Makeham function for women), the variance of frailty in the population and the rate ratios of the mortality differentials by education level and region of birth. Figure 2 compares the results for the educational gradient obtained by the models with and without frailty.

Table 2. Results of the regression models with cohort covariates. Baseline parameters (Gompertz for men and Makeham for women) and rate ratios of the differentials by education and region of birth.

	Men		Women	
	Model without frailty	Model with frailty	Model without frailty	Model with frailty

	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
a	5.241×10^{-5}	5.237×10^{-5}-5.245×10^{-5}	4.495×10^{-5}	4.488×10^{-5}-4.501×10^{-5}	3.767×10^{-6}	3.755×10^{-6}-3.779×10^{-6}	1.605×10^{-6}	1.588×10^{-6}-1.623×10^{-6}
b	0.081	0.080-0.082	0.083	0.082-0.084	0.106	0.105-0.107	0.117	0.115-0.119
c	-	-	-	-	0.001	0.001-0.001	0.001	0.001-0.001
Sigma^2	-	-	0.035	0.027-0.045	-	-	0.096	0.082-0.111
cohort	0.016	0.015-0.016	0.016	0.015-0.016	0.016	0.015-0.016	0.017	0.016-0.017
Education level								
High	1	-	1	-	1	-	1	-
Medium	1.166	1.147-1.186	1.221	1.200-1.243	1.141	1.116-1.166	1.111	1.086-1.137
Low	1.239	1.221-1.257	1.302	1.283-1.322	1.246	1.222-1.270	1.213	1.188-1.238
Region of birth								
North-West	1	-	1	-	1	-	1	-
North-East	1.053	1.036-1.070	1.060	1.042-1.077)	0.989	0.973-1.004	0.974	0.958-0.991
Center	1.011	0.984-1.038	0.996	0.969-1.024	0.939	0.913-0.966	0.968	0.939-0.998
South	1.000	0.988-1.012	0.950	0.938-0.962	0.932	0.919-0.945	0.987	0.973-1.002
Abroad	1.031	1.006-1.057	0.998	0.974-1.024	1.071	1.047-1.096	0.993	0.968-1.018
logLk	-651 219		-651 082		-663 238		-663 098	
AIC	1 302 456		1 302 184		1 326 496		1 326 218	

Table 3. Results of the regression models with period covariates. Baseline parameters (Gompertz for men and Makeham for women) and rate ratios of the differentials by education and region of birth.
*The model with frailty does not report conventional point estimates and confidence intervals, but the mean value and the 0.025-0.975 quantiles of the empirical distribution of the parameters obtained from the repeated estimates via random subsampling.

	Men				Women			
	Model without frailty		Model with frailty*		Model without frailty		Model with frailty*	
	Estimate	95% CI	Mean	0.025-0.0975	Estimate	95% CI	Mean	0.025-0.0975
a	4.159×10^{-5}	3.196×10^{-5}-5.410×10^{-5}	0.004	(0.000-0.010)	8.031×10^{-6}	6.028×10^{-6}-1.070×10^{-5}	0.008	(0.000-0.016)
b	0.096	(0.095-0.096)	0.069	(0.061-0.163)	0.121	(0.120-0.122)	0.084	(0.073-0.106)
c	-	-	-	-	0.001	(0.001-0.002)	2.852×10^{-6}	8.610×10^{-7}-2.997×10^{-5}
Sigma^2	-	-	0.269	(0.026-0.367)	-	-	0.292	(0.174-0.367)
Calendar period								
1971-1973	1	-			1	-		
1974-1976	0.999	0.972-1.027			0.978	0.950-1.007		
1977-1979	0.947	0.921-0.973			0.919	0.893-0.946		
1980-1982	0.928	0.903-0.953	1	-	0.896	0.871-0.922	1	-

1983-1985	0.943	0.918-0.969			0.967	0.941-0.994		
1986-1988	0.870	0.847-0.894			0.848	0.824-0.872		
1989-1991	0.820	0.798-0.843	0.728	0.613-0.985	0.796	0.774-0.818	0.888	0.671-1.035
1992-1994	0.796	0.774-0.817			0.757	0.736-0.778		
1995-1997	0.741	0.721-0.762			0.704	0.684-0.724		
1998-2000	0.701	0.682-0.721			0.682	0.663-0.701		
2001-2003	0.670	0.652-0.689			0.657	0.639-0.676		
2004-2007	0.631	0.615-0.648			0.625	0.608-0.642		
High	1	-	1	-	1	-	1	-
Medium	1.204	(1.184-1.225)	1.277	(1.054-1.349)	1.107	(1.083-1.131)	1.256	(1.053-1.347)
Low	1.301	(1.282-1.320)	1.268	(1.074-1.591)	1.209	(1.186-1.232)	1.475	(1.103-1.641)
North-West	1	-	1	-	1	-	1	-
North-East	1.040	(1.024-1.057)	1.075	(0.855-1.220)	0.963	(0.948-0.978)	1.122	(0.888-1.217)
Center	0.943	(0.917-0.969)	1.081	(0.854-1.212)	0.964	(0.938-0.992)	1.102	(0.864-1.218)
South	0.900	(0.889-0.911)	1.037	(0.854-1.216)	0.962	(0.949-0.975)	1.130	(0.904-1.220)
Abroad	0.965	(0.941-0.989)	1.082	(0.864-1.218)	0.985	(0.962-1.009)	1.082	(0.847-1.215)
logLk	-650 997		Na		-663 081		Na	
AIC	1 302 034		Na		1 326 204		Na	

Educational gradient

In the model with the age-cohort improvement approach, the introduction of the frailty term made the male differences widen significantly, consistent with the statistical literature. The rate ratios with respect to high education changed from 1.16 (95% CI 1.15-1.19) to 1.22 (1.20-1.24) for medium education and from 1.24 (1.22-1.26) to 1.30 (1.28-1.32) low education (figure 2 panel a). Among women, on the contrary, there was a slight reduction but the confidence regions of the estimates in the two cases overlap: for medium education the rate ratio went from 1.14 (1.12-1.17) to 1.11 (1.08-1.14) and for low education from 1.25 (1.22-1.27) to 1.22 (1.19-1.24) (figure 2 panel b). The AIC indicates that the models with frailty fit the data significantly better than the model without.

Figure 2 here

In the model adopting the age-period improvement approach, the AIC comparison of the models with and without frailty was not possible, because the utilization of random subsampling for the estimation of the frailty model (40-42) did not allow obtaining a likelihood value comparable with the values of the models without frailty. Moreover, it is necessary to consider that we are comparing conventional point estimates and confidence intervals with values obtained via bootstrapping methods, whose confidence regions are usually wider than conventional confidence intervals. Nevertheless, a comparison is still possible.

The introduction of frailty affected the mortality gradient by education. Although the uncertainty around the estimates does not allow assessing a precise effect, the rate ratios of medium and low education in respect to high education in the models with frailty lie in a higher confidence region than in the models without: among women with a medium education level, it lies between 1.05 and 1.34 compared to 1.08 and 1.13 of the model without frailty and for the low education group, between 1.1 and 1.6, compared to 1.18 and 1.23. The same pattern can be observed among men.

The male difference between medium and low education group, on the contrary, was not as clear as that among women.

Other results and the impact of the macro-region of birth on mortality

As expected, the variance of frailty in the cohort models was smaller than in the period models, since periods are more heterogeneous than cohorts.

Women were more heterogeneous than men: 0.09 (0.08-0.11) versus 0.04 (0.03-0.05) in the age-cohort models and 0.29 (0.17-0.37) versus 0.27 (0.-0.36) in the age-period models.

This is consistent with the more pronounced convergence of the hazards by education at old age found among women compared to the men. According to the framework of the frailty models, converging hazards are the result of the effect of selection on the population hazards, due to how much variance of unobserved frailty is present in the population at the initial age of observation. The bigger the variance the stronger the convergence is. For more information about frailty models, the process of selection and how they relate to narrowing mortality differentials at old ages, please see appendix A.

In the age-cohort models the introduction of unobserved frailty affected the coefficient for the macro-region of birth significantly. Among men, holding education equal, those born in the South show a significant survival advantage over the natives of the North-West, while in the model without frailty there was no such advantage. Among women, the model without frailty showed a significant survival advantage for those born in the South but when frailty was controlled for, this became not significant.

The pattern also resembles the regional mortality macro-dynamics that have characterized Italy for most of the 20th century (although the two patterns refer to different phenomena, the first one referring to mortality by region of birth), when male mortality in the South was lower than in the North (44-47). Cohort based analyses have highlighted that in more recent cohorts (those born after WWII) there is a reversing trend (47, 48).

The models with age-period perspective did not identify any significant geographical differences. This could be due to the utilization of random subsampling of a 1% sample. Although 250 repetitions is considered by the literature a sufficient number for very complex models (49-51), it is possible that it was inadequate to identify a clear pattern from the small sample. For more detailed results see tables 1 and 2.

Discussion

The interest in the role of unobserved heterogeneity in a life course approach to socioeconomic mortality differences has recently increased. Most of the studies focus on health outcomes (52-57) while fewer studies also analyze mortality (58-60). Their findings are not consistent and fuel a still controversial debate.

In this study we investigated the role of unobserved individual heterogeneity on the estimation of mortality differentials at adult-old ages by education level in a longitudinal perspective. This study investigated 1) whether the framework of the frailty models can explain the observed pattern of convergence of the mortality risk by social position at old ages 2) if the estimates of the mortality differentials are affected by the introduction of the unobserved heterogeneity component into the models.

We fitted survival analysis models with and without controlling for the unobserved heterogeneity and we found that, when this component was included, the models gave a significantly better fit.

We also found that in the majority of the cases, the educational gradient estimated by the models with frailty was higher than the one estimated by the models without frailty. When big uncertainty around the estimates did not allow assessing a precise value, the confidence regions in the models with frailty spanned over higher values than those in the models without frailty. It must be pointed out that, in the age-period approach, to the peculiar statistical procedure used to estimate the frailty models did not allow obtaining a likelihood value comparable with the one of the model without frailty. Thus, the statistical comparison of the models via the AIC was not possible, making this evidence somehow weaker. Nevertheless, the results point to a direction that is consistent with the statistical literature about unobserved heterogeneity and show that neglecting its selective action, in duration dependence models, might lead to underestimate the effect of the covariates (19-26).

Among men such a pattern was found in both the age-cohort and age-period approaches. Among women, on the contrary, this pattern was less clear: in the age-cohort model, controlling for hidden frailty resulted in a slight reduction of the mortality gradient. Social determinants act on mortality also through risk factors that are known to affect more men than women. Moreover, because of a lag in the smoking and fertility transitions, highly educated women in Turin are more exposed to risk factors like cigarette smoking and smaller number of children. Therefore, controlling for hidden frailty in the case of women might reduce the educational gradient.

In the models with age-cohort perspective controlling for the hidden frailty affected also the estimates of the differentials by macro-region of birth, showing a survival advantage of the men born in the South, but not of the women, for whom an advantage was instead detected by the model that did not control for frailty.

The healthy migrant effect (61-66) could cause this pattern. Among the cohorts involved in the migration women were likely to be more passive actors than men in the migratory decision (67-69) and this might have selected them more than men. Frailty is a general concept embedding all the hidden factors that affect the individual survival chances: innate and acquired frailty, exposure to risk factors, life style factors and so on. Therefore, controlling for frailty reduced the survival advantage of the women, who might have been less health selected than men by the migration, while uncovered the advantage of the men. However, another recent study on the impact of migration on all-cause mortality in Turin did not find particularly strong gender differences in the so called healthy migrant effect (65) and this point deserves future further investigation.

The study spanned over a long observation window of 36 years. Therefore it was important to control for the general mortality improvement that took place during this time. We did so by adopting both an age-period and an age-cohort approach.

The age-period models, as expected, estimated higher heterogeneity than the age-cohort models. Periods aggregate different generations and are expected to be more heterogeneous than the cohorts themselves. In both period and cohort models the female variance of frailty was higher than for the males, indicating that men are more homogeneous than women. This could be attributed to a stronger selection process due to mortality that is usually observed to be higher among men than among women.

On the other hand, it is also possible that the industrialization process and the internal migration experienced by Italy after WWII (34) played a role. The vast majority of less educated individuals in Turin came from the South, seeking a job in the car factories of the city. As less educated men were mainly employed in heavier and riskier jobs and were exposed to higher mortality, it is possible that during their life they were selected at a faster pace than other educational groups and women. This might have reduced the differences in susceptibility to death among men, contributing to determining a lower level of heterogeneity than among women.

Conclusion

This study found that neglecting selection effects due to unobserved heterogeneity in longitudinal analyses, could lead to underestimation of mortality differentials by social class. In the majority of the cases, the models that controlled for unobserved heterogeneity, estimated higher educational differences in mortality than the models that did not control for it.

Moreover, when compared with via the AIC, the models that controlled for unobserved heterogeneity gave a statistically significant better fit than the models that did not control for it. Although the best AIC shows just that the more complex model approximates better the data and this does not represent an unequivocal proof of the selection hypothesis, the results point to the possibility that the data could be better described by this hypothesis. This strengthens its validity as possible explanatory mechanism for the reduction of the gradient in socioeconomic mortality.

This analysis also has important policies facets. Specifically, when studying differential survival chances in socioeconomic groups and observing decreasing relative differences at old ages, it is important to be aware that individuals might experience a disadvantaged position throughout their life which does not fade away when they age. The lessening of differences at old ages could be the result of a stronger selection due to early higher mortality that disadvantaged groups are still subject to.

Summary

Article Focus

- Neglecting the presence of unobserved heterogeneity in survival analysis models has been showed to potentially lead to underestimating the effect of the covariates included in the analysis.
- Although frailty models have been widely developed to account for unobserved heterogeneity, in differential mortality analyses this source of variation is seldom controlled for. This study has applied these models to a longitudinal mortality analysis by education level.

Key messages

- Mortality differentials by education (or by any other variable used as proxy of socioeconomic status) could be larger than those estimated with standard survival analysis approaches that do not control for unobserved heterogeneity.
- Relative mortality differences at old ages between socioeconomic groups are often observed to decline. However, this pattern could be the result of a stronger selection due to early higher mortality that disadvantaged groups are still subject to.

Strengths and limitations

The strength of this study lies in the population based longitudinal data. The long observational time (36 years) for more than 847 000 individuals gives a solid base for statistical power and detection of trends.

The limitation consists in the lack of individual information on life style factors and health events, which could certainly help to better model the concept of unobserved individual frailty by uncovering part of it.

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Contributorship. Virginia Zarulli: conception and design of the study, analysis and interpretation of data and results, drafting the article and revising it; Graziella Caselli: interpretation of the results, drafting the article and revising it critically; Chiara Marinacci and Giuseppe Costa: revising the article for important intellectual content.

Data sharing. There is no additional data available.

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Mortality by education level at late-adult ages in Turin: a survival analysis using frailty models with period and cohort approaches.

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Abstract

Background. Unobserved heterogeneity of frailty can lead to biased estimates of coefficients in survival analysis models. This study investigated the role of unobserved frailty on the estimation of mortality differentials from age 50 on by education level.

Methods. We used data of a 36 years follow up from the Turin Longitudinal Study containing 391 170 men and 456 216 women. As Turin underwent strong immigration flows during the post war industrialization, also the macro-region of birth was controlled for. We fitted survival analysis models with and without the unobserved heterogeneity component, controlling for mortality improvement from both cohort and period perspectives.

Results. We found that in the majority of the cases, the models without frailty estimated a smaller educational gradient then the models with frailty.

Conclusions. The results draw the attention on the potential underestimation of the mortality inequalities by socioeconomic levels in survival models when not controlling for frailty.

Introduction

An extensive literature shows significant differential mortality by socioeconomic condition (1-3). Elderly show decreasing relative social inequalities in general mortality with increasing age (4-8). The age-as-leveler hypothesis attributes this to factors that contribute to the leveling-off of differences at old ages: governmental support to the elderly (9-11), disengagement from systems of social stratification (12) and general vulnerability (13, 14). However, this phenomenon could also be an artifact of selection due to unobserved characteristics of the individuals: selective effects of earlier higher mortality, experienced by the disadvantaged group, would leave more robust individuals at old ages, causing the convergence with the risk of the lower mortality group, that is subject to weaker selection (15-18). Neglecting these hidden differences in survival chances (called unobserved frailty), has been shown to lead to biased estimates of the mortality hazard and of the effect of the covariates on the survival probability (19-25).

In longitudinal analyses on differential mortality it is important to control for hidden frailty. First, because not controlling for it, in survival models, could lead to biased estimates of the effect of the social position on the mortality risk: the statistical literature shows that the bias is towards zero (24-26). This would lead to underestimation of the relative differences in the mortality risks by socioeconomic group. Second, because selection due to unobserved frailty could provide an explanation for the phenomenon of decreasing relative differences in death rates by socioeconomic group at old ages. To control for unobserved frailty and to evaluate the impact on the observed mortality dynamics, frailty models have been developed (27) . For more detailed explanations of the frailty models and how they relate to differential mortality analyses, please, see appendix A.

This study investigated the presence of selection processes in the mortality patterns of the Turin population (North-West Italy) from age 50 on. Adopting a longitudinal perspective, this study aimed 1) to investigate whether the theoretical framework of the frailty models can explain the observed pattern of convergence of mortality differentials by social position 2) to investigate if the estimates of the mortality differentials are affected by the introduction of the unobserved heterogeneity component into the models.

Data and Methods

We used high quality census linked data from the Turin Longitudinal Study (TLS), which includes 1971, 1981, 1991 and 2001 census data for the Turin population. TLS records the individual census socio-demographic information and, through record linkage with the local population registry and other local health information systems, collects information on vital status, cause of death and other health indicators (28, 29).

For this study, the individuals registered in Turin during at least one of the four censuses were selected. Their migration and vital status was followed up until the end of July 2007. The result is an observation window of 36 years (from October 24th 1971, official date of the census, to the end of July 2007, end of the linkage) during which the individuals were followed up until death, emigration from the city or end of observation period. The follow up started at age 50. The study population contains 391 170 men and 456 216 women.

Study information includes individual's date of birth, date of exit from the study, cause of exit (death or emigration), sex, macro-region of birth and education level.

Consistent with the literature (30-33) education level was used as an indicator of social position.

The study also controlled for the individual macro region of birth, as Turin is characterized by a history of immigration from other regions of the country (34).

To facilitate the comparison over a long follow up and different cohorts, we created three broad educational groups: high (high school diploma or higher), medium (junior high school) and low (primary school or lower).

We estimated parametric survival models stratified by gender and as a function of macro-region of birth and education level, with and without a parameter for the unobserved heterogeneity component. The parametric choice is justified by the wide demographic literature showing that human adult mortality can be accurately described by a Gompertz function (35) or by some Gompertz-like variants, like Makeham. To identify the best functional form for the baseline we compared the models with the AIC (36).

The data are both right censored (due to emigration or end of follow up) and left truncated (due to the different age at entry in the study of the individuals).

The study includes many cohorts, each passing through the 36 years of observation at different ages. However, from 1971 to 2007 a significant mortality improvement occurred and younger cohorts experience lower age specific mortality than older cohorts.

Time is a complex variable including three dimensions: age, period and cohort. Controlling adequately for the effect of time would require to asses simultaneously the three components but such models have been proved to be not identifiable because of linear dependence between the three dimensions (37-39).

Therefore, we decided to adopt two approaches for the control of time, corresponding to an age-cohort approach and an age-period approach, being aware that they represent two different dimensions of time.

First, we regarded the improvement as a cohort phenomenon, including a covariate for the cohort to which the individuals belong. In this setting, controlling for unobserved heterogeneity was implemented with univariate frailty models, which estimate the baseline parameters, the coefficients of the covariates and the variance of frailty (assumed to follow a gamma distribution with mean 1 and variance σ^2 to be estimated).

We then considered the improvement as a period phenomenon and split the time into several calendar period covariates, as well as the survival spell of the individuals, according to which period they were passing through. This implied organizing the data into clusters, where each cluster represents one individual's survival spells. In this setting, to control for unobserved heterogeneity shared frailty models are needed, where the spells in each cluster pertain to the same individual and share the same hidden frailty. For computational reasons, the estimation of these highly complex models required the use of random subsampling (40-42). We repeated the estimation 250 times on a 1% sample of the dataset, randomly drawn without replacement and stratified by the major variables in analysis. The aim is to approximate the parameters estimates based on the empirical distribution of the repeated estimates.

In the model without frailty it was possible to include a finer calendar period division, 12 period variables of 3 years each (1971-1973, 1974-1976…), while in the model with frailty, for computational reasons, the number of variables was reduced to 2 broader periods: 1971-1990 and 1991-2007.

Computations were realized with the software R (43). Formal details are in appendix A.

Results

Figure 1 shows that the log-death rates by education level and gender, for the cohort aged 50-59 in 1971, converge at old ages. Other cohorts showed very similar patterns.

A preliminary analysis found that the reduction of the gradient over age is statistically significant and more pronounced among women (results are reported in appendix B table B1).

Figure 1 here

Frailty modeling

Table 1 shows the AIC of the survival models, fitted to the all population mortality, with Gompertz and Makeham baselines. It also shows the results of the fit when unobserved frailty was controlled for. The comparison reveals that Gompertz baseline was a better fit for the male data, while Makeham was better for the female. In both cases, the models controlling for unobserved heterogeneity performed a better fit (table 1).

Table 1. Model selection of 4 different hazard models based on the AIC.

	Gompertz	Makeham	Gam-Gompertz	Gam-Makeham
	ae^{bx}	$ae^{bx}+c$	$\frac{ae^{bx}}{1+\sigma^2\frac{a}{b}\left(e^{bx}-1\right)}$	$\frac{ae^{bx}+c}{1+\sigma^2\frac{a}{b}\left(e^{bx}-1\right)+cx}$
AIC women	1 327 474	1 326 878	1 327 476	1 326 695
AIC men	1 303 693	1 303 695	1 303 655	1 303 693

We then estimated the mortality differentials, using a cohort and a period approach to control for mortality improvement over time. We included in the analysis the variables for education level (high, medium and low) and region of birth (North-West, North-East, Center, South and Abroad).

Tables 2 and 3 report the results of the models estimated with and without the unobserved heterogeneity component: the parameters of the baseline hazard (a and b of the Gompertz function for men and a, b and c of the Makeham function for women), the variance of frailty in the population and the rate ratios of the mortality differentials by education level and region of birth. Figure 2 compares the results for the educational gradient obtained by the models with and without frailty.

Table 2. Results of the regression models with cohort covariates. Baseline parameters (Gompertz for men and Makeham for women) and rate ratios of the differentials by education and region of birth.

	Men		Women	
	Model without frailty	Model with frailty	Model without frailty	Model with frailty

	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
a	5.241×10^{-5}	5.237×10^{-5}-5.245×10^{-5}	4.495×10^{-5}	4.488×10^{-5}-4.501×10^{-5}	3.767×10^{-6}	3.755×10^{-6}-3.779×10^{-6}	1.605×10^{-6}	1.588×10^{-6}-1.623×10^{-6}
b	0.081	0.080-0.082	0.083	0.082-0.084	0.106	0.105-0.107	0.117	0.115-0.119
c	-	-	-	-	0.001	0.001-0.001	0.001	0.001-0.001
$Sigma^2$	-	-	0.035	0.027-0.045	-	-	0.096	0.082-0.111
cohort	0.016	0.015-0.016	0.016	0.015-0.016	0.016	0.015-0.016	0.017	0.016-0.017
Education level								
High	1	-	1	-	1	-	1	-
Medium	1.166	1.147-1.186	1.221	1.200-1.243	1.141	1.116-1.166	1.111	1.086-1.137
Low	1.239	1.221-1.257	1.302	1.283-1.322	1.246	1.222-1.270	1.213	1.188-1.238
Region of birth								
North-West	1	-	1	-	1	-	1	-
North-East	1.053	1.036-1.070	1.060	1.042-1.077)	0.989	0.973-1.004	0.974	0.958-0.991
Center	1.011	0.984-1.038	0.996	0.969-1.024	0.939	0.913-0.966	0.968	0.939-0.998
South	1.000	0.988-1.012	0.950	0.938-0.962	0.932	0.919-0.945	0.987	0.973-1.002
Abroad	1.031	1.006-1.057	0.998	0.974-1.024	1.071	1.047-1.096	0.993	0.968-1.018
logLk	-651 219		-651 082		-663 238		-663 098	
AIC	1 302 456		1 302 184		1 326 496		1 326 218	

Table 3. Results of the regression models with period covariates. Baseline parameters (Gompertz for men and Makeham for women) and rate ratios of the differentials by education and region of birth.

*The model with frailty does not report conventional point estimates and confidence intervals, but the mean value and the 0.025-0.975 quantiles of the empirical distribution of the parameters obtained from the repeated estimates via random subsampling.

	Men				Women			
	Model without frailty		Model with frailty*		Model without frailty		Model with frailty*	
	Estimate	95% CI	Mean	0.025-0.0975	Estimate	95% CI	Mean	0.025-0.0975
a	4.159×10^{-5}	3.196×10^{-5}-5.410×10^{-5}	0.004	(0.000-0.010)	8.031×10^{-6}	6.028×10^{-6}-1.070×10^{-5}	0.008	(0.000-0.016)
b	0.096	(0.095-0.096)	0.069	(0.061-0.163)	0.121	(0.120-0.122)	0.084	(0.073-0.106)
c	-	-	-	-	0.001	(0.001-0.002)	2.852×10^{-6}	8.610×10^{-7}-2.997×10^{-5}
$Sigma^2$	-	-	0.269	(0.026-0.367)	-	-	0.292	(0.174-0.367)
Calendar period								
1971-1973	1	-			1	-		
1974-1976	0.999	0.972-1.027			0.978	0.950-1.007		
1977-1979	0.947	0.921-0.973			0.919	0.893-0.946		
1980-1982	0.928	0.903-0.953	1	-	0.896	0.871-0.922	1	-

1983-1985	0.943	0.918-0.969			0.967	0.941-0.994		
1986-1988	0.870	0.847-0.894			0.848	0.824-0.872		
1989-1991	0.820	0.798-0.843	0.728	0.613-0.985	0.796	0.774-0.818	0.888	0.671-1.035
1992-1994	0.796	0.774-0.817			0.757	0.736-0.778		
1995-1997	0.741	0.721-0.762			0.704	0.684-0.724		
1998-2000	0.701	0.682-0.721			0.682	0.663-0.701		
2001-2003	0.670	0.652-0.689			0.657	0.639-0.676		
2004-2007	0.631	0.615-0.648			0.625	0.608-0.642		

High	1	-	1	-	1	-	1	-
Medium	1.204	(1.184-1.225)	1.277	(1.054-1.349)	1.107	(1.083-1.131)	1.256	(1.053-1.347)
Low	1.301	(1.282-1.320)	1.268	(1.074-1.591)	1.209	(1.186-1.232)	1.475	(1.103-1.641)

North-West	1	-	1	-	1	-	1	-
North-East	1.040	(1.024-1.057)	1.075	(0.855-1.220)	0.963	(0.948-0.978)	1.122	(0.888-1.217)
Center	0.943	(0.917-0.969)	1.081	(0.854-1.212)	0.964	(0.938-0.992)	1.102	(0.864-1.218)
South	0.900	(0.889-0.911)	1.037	(0.854-1.216)	0.962	(0.949-0.975)	1.130	(0.904-1.220)
Abroad	0.965	(0.941-0.989)	1.082	(0.864-1.218)	0.985	(0.962-1.009)	1.082	(0.847-1.215)
logLk	-650 997		Na		-663 081		Na	
AIC	1 302 034		Na		1 326 204		Na	

Educational gradient

In the model with the age-cohort improvement approach, the introduction of the frailty term made the male differences widen significantly, consistent with the statistical literature. The rate ratios with respect to high education changed from 1.16 (95% CI 1.15-1.19) to 1.22 (1.20-1.24) for medium education and from 1.24 (1.22-1.26) to 1.30 (1.28-1.32) low education (figure 2 panel a). Among women, on the contrary, there was a slight reduction but the confidence regions of the estimates in the two cases overlap: for medium education the rate ratio went from 1.14 (1.12-1.17) to 1.11 (1.08-1.14) and for low education from 1.25 (1.22-1.27) to 1.22 (1.19-1.24) (figure 2 panel b). The AIC indicates that the models with frailty fit the data significantly better than the model without.

Figure 2 here

In the model adopting the age-period improvement approach, the AIC comparison of the models with and without frailty was not possible, because the utilization of random subsampling for the estimation of the frailty model (40-42) did not allow obtaining a likelihood value comparable with the values of the models without frailty. Moreover, it is necessary to consider that we are comparing conventional point estimates and confidence intervals with values obtained via bootstrapping methods, whose confidence regions are usually wider than conventional confidence intervals. Nevertheless, a comparison is still possible.

The introduction of frailty affected the mortality gradient by education. Although the uncertainty around the estimates does not allow assessing a precise effect, the rate ratios of medium and low education in respect to high education in the models with frailty lie in a higher confidence region than in the models without: among women with a medium education level, it lies between 1.05 and 1.34 compared to 1.08 and 1.13 of the model without frailty and for the low education group, between 1.1 and 1.6, compared to 1.18 and 1.23. The same pattern can be observed among men.

The male difference between medium and low education group, on the contrary, was not as clear as that among women.

Other results and the impact of the macro-region of birth on mortality

As expected, the variance of frailty in the cohort models was smaller than in the period models, since periods are more heterogeneous than cohorts.

Women were more heterogeneous than men: 0.09 (0.08-0.11) versus 0.04 (0.03-0.05) in the age-cohort models and 0.29 (0.17-0.37) versus 0.27 (0.-0.36) in the age-period models.

This is consistent with the more pronounced convergence of the hazards by education at old age found among women compared to the men. According to the framework of the frailty models, converging hazards are the result of the effect of selection on the population hazards, due to how much variance of unobserved frailty is present in the population at the initial age of observation. The bigger the variance the stronger the convergence is. For more information about frailty models, the process of selection and how they relate to narrowing mortality differentials at old ages, please see appendix A.

In the age-cohort models the introduction of unobserved frailty affected the coefficient for the macro-region of birth significantly. Among men, holding education equal, those born in the South show a significant survival advantage over the natives of the North-West, while in the model without frailty there was no such advantage. Among women, the model without frailty showed a significant survival advantage for those born in the South but when frailty was controlled for, this became not significant.

The pattern also resembles the regional mortality macro-dynamics that have characterized Italy for most of the 20th century (although the two patterns refer to different phenomena, the first one referring to mortality by region of birth), when male mortality in the South was lower than in the North (44-47). Cohort based analyses have highlighted that in more recent cohorts (those born after WWII) there is a reversing trend (47, 48).

The models with age-period perspective did not identify any significant geographical differences. This could be due to the utilization of random subsampling of a 1% sample. Although 250 repetitions is considered by the literature a sufficient number for very complex models (49-51), it is possible that it was inadequate to identify a clear pattern from the small sample. For more detailed results see tables 1 and 2.

Discussion

The interest in the role of unobserved heterogeneity in a life course approach to socioeconomic mortality differences has recently increased. Most of the studies focus on health outcomes (52-57) while fewer studies also analyze mortality (58-60). Their findings are not consistent and fuel a still controversial debate.

In this study we investigated the role of unobserved individual heterogeneity on the estimation of mortality differentials at adult-old ages by education level in a longitudinal perspective. This study investigated 1) whether the framework of the frailty models can explain the observed pattern of convergence of the mortality risk by social position at old ages 2) if the estimates of the mortality differentials are affected by the introduction of the unobserved heterogeneity component into the models.

We fitted survival analysis models with and without controlling for the unobserved heterogeneity and we found that, when this component was included, the models gave a significantly better fit.

We also found that in the majority of the cases, the educational gradient estimated by the models with frailty was higher than the one estimated by the models without frailty. When big uncertainty around the estimates did not allow assessing a precise value, the confidence regions in the models with frailty spanned over higher values than those in the models without frailty. It must be pointed out that, in the age-period approach, to the peculiar statistical procedure used to estimate the frailty models did not allow obtaining a likelihood value comparable with the one of the model without frailty. Thus, the statistical comparison of the models via the AIC was not possible, making this evidence somehow weaker. Nevertheless, the results point to a direction that is consistent with the statistical literature about unobserved heterogeneity and show that neglecting its selective action, in duration dependence models, might lead to underestimate the effect of the covariates (19-26).

Among men such a pattern was found in both the age-cohort and age-period approaches. Among women, on the contrary, this pattern was less clear: in the age-cohort model, controlling for hidden frailty resulted in a slight reduction of the mortality gradient. Social determinants act on mortality also through risk factors that are known to affect more men than women. Moreover, because of a lag in the smoking and fertility transitions, highly educated women in Turin are more exposed to risk factors like cigarette smoking and smaller number of children. Therefore, controlling for hidden frailty in the case of women might reduce the educational gradient.

In the models with age-cohort perspective controlling for the hidden frailty affected also the estimates of the differentials by macro-region of birth, showing a survival advantage of the men born in the South, but not of the women, for whom an advantage was instead detected by the model that did not control for frailty.

The healthy migrant effect (61-66) could cause this pattern. Among the cohorts involved in the migration women were likely to be more passive actors than men in the migratory decision (67-69) and this might have selected them more than men. Frailty is a general concept embedding all the hidden factors that affect the individual survival chances: innate and acquired frailty, exposure to risk factors, life style factors and so on. Therefore, controlling for frailty reduced the survival advantage of the women, who might have been less health selected than men by the migration, while uncovered the advantage of the men. However, another recent study on the impact of migration on all-cause mortality in Turin did not find particularly strong gender differences in the so called healthy migrant effect (65) and this point deserves future further investigation.

The study spanned over a long observation window of 36 years. Therefore it was important to control for the general mortality improvement that took place during this time. We did so by adopting both an age-period and an age-cohort approach.

The age-period models, as expected, estimated higher heterogeneity than the age-cohort models. Periods aggregate different generations and are expected to be more heterogeneous than the cohorts themselves. In both period and cohort models the female variance of frailty was higher than for the males, indicating that men are more homogeneous than women. This could be attributed to a stronger selection process due to mortality that is usually observed to be higher among men than among women.

On the other hand, it is also possible that the industrialization process and the internal migration experienced by Italy after WWII (34) played a role. The vast majority of less educated individuals in Turin came from the South, seeking a job in the car factories of the city. As less educated men were mainly employed in heavier and riskier jobs and were exposed to higher mortality, it is possible that during their life they were selected at a faster pace than other educational groups and women. This might have reduced the differences in susceptibility to death among men, contributing to determining a lower level of heterogeneity than among women.

Conclusion

This study found that neglecting selection effects due to unobserved heterogeneity in longitudinal analyses, could lead to underestimation of mortality differentials by social class. In the majority of the cases, the models that controlled for unobserved heterogeneity, estimated higher educational differences in mortality than the models that did not control for it.

Moreover, when compared with via the AIC, the models that controlled for unobserved heterogeneity gave a statistically significant better fit than the models that did not control for it. Although the best AIC shows just that the more complex model approximates better the data and this does not represent an unequivocal proof of the selection hypothesis, the results point to the possibility that the data could be better described by this hypothesis. This strengthens its validity as possible explanatory mechanism for the reduction of the gradient in socioeconomic mortality.

This analysis also has important policies facets. Specifically, when studying differential survival chances in socioeconomic groups and observing decreasing relative differences at old ages, it is important to be aware that individuals might experience a disadvantaged position throughout their life which does not fade away when they age. The lessening of differences at old ages could be the result of a stronger selection due to early higher mortality that disadvantaged groups are still subject to.

Summary

Article Focus

- Neglecting the presence of unobserved heterogeneity in survival analysis models has been showed to potentially lead to underestimating the effect of the covariates included in the analysis.
- Although frailty models have been widely developed to account for unobserved heterogeneity, in differential mortality analyses this source of variation is seldom controlled for. This study has applied these models to a longitudinal mortality analysis by education level.

Key messages

- Mortality differentials by education (or by any other variable used as proxy of socioeconomic status) could be larger than those estimated with standard survival analysis approaches that do not control for unobserved heterogeneity.
- Relative mortality differences at old ages between socioeconomic groups are often observed to decline. However, this pattern could be the result of a stronger selection due to early higher mortality that disadvantaged groups are still subject to.

Strengths and limitations

The strength of this study lies in the population based longitudinal data. The long observational time (36 years) for more than 847 000 individuals gives a solid base for statistical power and detection of trends.

The limitation consists in the lack of individual information on life style factors and health events, which could certainly help to better model the concept of unobserved individual frailty by uncovering part of it.

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Data sharing. There is no additional data available.

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Appendix

A. Frailty models and Survival Analysis

Frailty models

Hidden differences in survival chances make individuals differ in their susceptibility to death. This complex set of characteristics, called unobserved frailty, does not distinguish between acquired weakness, life style factors, environmental risks and innate biological frailty, but it indicates a general susceptibility to death (1).

In cohort analyses, as the population ages, frailer individuals die faster and gradually select the survivors in terms of robustness, because the population undergoes a compositional change. This causes the population hazard to decelerate at very old ages because, at every age, the death rate is computed based on a population at risk whose composition is gradually converging towards the low frailty individuals, who have also lower mortality. The greater the variance of unobserved heterogeneity of frailty at the initial age of observation, the stronger the selection process and, therefore, the faster the deceleration of the hazard observed at the population level as age goes by.

Neglecting the presence of unobserved frailty and its selection processes can lead in survival analysis models to possible biases in the estimates of the regression coefficients. In the case of mortality by socioeconomic position, education level or income groups, higher mortality groups are selected at a faster rate than lower mortality groups (because the higher the mortality the stronger the force of selection). Therefore, the frailest individuals in these groups are selected out at a faster pace. Consequently, at the same age, what is left in the high mortality group is a more selected population in terms of robustness, compared to the low mortality group, which undergoes a slower pace of selection. The difference between the rates of selection causes the mortality curves to converge and gives the impression that the effect of the covariate that defines the two groups (for example education level) declines with age. Also in this case, the greater the variance of unobserved heterogeneity in the population at the initial age of observation, the stronger the selection process and, therefore, the stronger the convergence between subgroups at old ages.

Main equations of the framework of the frailty models.

Frailty models assume that every individual has a specific level of unobserved frailty, z, that defines its hazard in a context of proportional hazard models. There is a standard individual, whose frailty z, is standardized to 1, and all the others have a frailty that is proportional to the frailty of the standard individual. If $\mu(x)$ is the hazard of the standard individual (or baseline hazard), defined as a function of age and frailty:

$$\mu(x,z) = z\mu(x)$$

at any age, what is observed at the population level is the mean mortality rate at that age, $\bar{\mu}(x)$, for the survivors of each frailty. That is, the standard individual hazard multiplied by the mean frailty among survivors at that age, which is a decreasing quantity:

$\bar{\mu}(x) = \mu(x)\bar{z}(x)$ Assuming that unobserved frailty follows a Gamma distribution, the population hazard $\bar{\mu}(x)$ at any age x is expressed as a mixture of individual hazards $\mu(x)$, by the following relationship:

$$\bar{\mu}(x) = \frac{\mu(x)}{1+\sigma^2 \int_0^x \mu(t)dt} \qquad (1)$$

where σ^2 is the variance of the frailty distribution with mean 1 at the initial age and $\mu(x)$ is the hazard experienced by the standard individual with frailty 1. The optimization problem estimates the baseline hazard parameters and the variance of the frailty in the population.

Survival analysis without unobserved heterogeneity

The only variability controlled for is the one explained by the observed covariates, u, included in the model. Their effect on the baseline hazard $\mu_0(x)$ is estimated as follows:

$$\mu_i(x \mid u_i) = \mu_0(x) e^{\beta u_i} \tag{2}$$

The likelihood function in case of right censored and left truncated survival data is:

$$L(\beta,\theta) = \prod_{i=1}^{n} \frac{\left(\mu(x_i,\theta) e^{u_i\beta}\right)^{\delta_i} S(x_i,\theta)^{e^{u_i\beta}}}{S(y_i,\theta)^{e^{u_i\beta}}} \tag{3}$$

Where for each individual i, y_i is the entry time, x_i in the exit time, δ_i is the status (1=dead, 0=right censored), u_i is the covariate profile with effect β and $\mu(.)$ denotes the hazard, $S(.)$ the survival function and θ is the vector of parameters of the baseline hazard.

Univariate frailty models

An individual random effect for the frailty is introduced in the model as a multiplicative term on the baseline hazard:

$$\mu_i(x \mid u_i, z_i) = z_i \mu_0(x) e^{\beta u_i} \tag{4}$$

The likelihood function in case of right censored and left truncated survival data is:

$$L(\beta,\theta,\sigma^2) = \prod_{i=1}^{n} \frac{\left(\frac{\mu(x_i,\theta) e^{u_i\beta}}{1+\sigma^2 M(x_i,\theta) e^{u_i\beta}}\right)^{\delta_i} \left(1+\sigma^2 M(x_i,\theta) e^{u_i\beta}\right)^{-\frac{1}{\sigma^2}}}{\left(1+\sigma^2 M(y_i,\theta) e^{u_i\beta}\right)^{-\frac{1}{\sigma^2}}} \tag{5}$$

Where for each individual *i*, y_i is the entry time, x_i in the exit time, δ_i is the status (1=dead, 0=right censored), u_i is the covariate profile with effect β and $\mu(.)$ denotes the hazard, $M(.)$ the cumulative hazard, θ is the vector of parameters of the baseline hazard and σ^2 is the variance of frailty.

Shared frailty models

In the case of repeated survival spells for the same individual i, the shared frailty models assume that those spells share the same hidden frailty, as showed by equation (6):

$$\mu_i(x \mid u_{i,j}, z_i) = z_i \mu_0(x) e^{\beta u_{i,j}} \qquad (6)$$

Where the indexes *j* and *i* represent the survival spell *j* of the individual (cluster) *i*.

The cluster (individual) likelihood function in case of right censored and left truncated survival data is (2):

$$L_i = \left(\prod_{j=1}^{n_i} \left(\mu(x_{ij}, \theta) e^{u_{ij}\beta} \right)^{\delta_{ij}} \right) \frac{\Gamma\left(\frac{1}{\sigma^2} + D_i \right)}{\Gamma\left(\frac{1}{\sigma^2} \right)} \left(\sigma^2 \right)^{D_i} \left(1 - \sigma^2 \sum_{j=1}^{n_i} \ln \left(S_{ij} \left(y_{ij}, \theta \right)^{e^{u_{ij}\beta}} \right) \right)^{\frac{1}{\sigma^2}} \left(1 - \sigma^2 \sum_{j=1}^{n_i} \ln \left(S_{ij} \left(x_{ij}, \theta \right)^{e^{u_{ij}\beta}} \right) \right)^{-\frac{1}{\sigma^2} - D_i} \qquad (7)$$

Where for each j-th individual in the i-th cluster, y_{ij} is the entry time, x_{ij} in the exit time, δ_{ij} is the status (1=dead, 0=right censored), u_{ij} is the covariate profile with effect β and $\mu(.)$ denotes the hazard, $S(.)$ the survival function, θ is the vector of parameters of the baseline hazard, σ^2 is the variance of frailty and $D_i = \sum \delta_{ij}$.

The overall likelihood function is simply:

$$L(\beta,\theta,\sigma^2)=\prod_{i=1}^{n}L_i \tag{8}$$

B. Exponential model

Table B1 reports the results of the exponential model with age as covariate. The exponential baseline hazard, $\mu(x)=\lambda$, is constant and does not change with age. This allows us to include the age as a covariate and to have it interacted with the covariate for education level. The aim is to investigate whether there is a statistically detectable convergence of hazards at old ages by education group, by testing whether there is a significant interaction between the variables education and age.

The single parameter baseline hazard was modulated by the covariate for the age groups. Equations 9 and 10 describe the hazard and the survival functions of the exponential model with covariates.

$$\mu(x) = \lambda e^{\beta\ cov} \tag{9}$$

$$S(x) = (e^{-\lambda x})^{e^{\beta\ cov}} \tag{10}$$

The identity between an exponential hazard modulated by an age covariate and the Gompertz model makes such exponential models appropriate for human adult mortality data. The age was divided into two groups: 50-80 and 80+. Education was divided into three groups: low, medium and high. In addition to age and education, the model controlled also for period effects by introducing a variable for the calendar years.

For the sake of simplicity table B1 does not report the coefficients for the period variable and for the λ parameter of the exponential hazard. The results show that the risk of death is inversely proportional to the educational level. However, the relative difference between low education and high education narrows at older ages and the reduction is more pronounced among women than among men.

A likelihood ratio test between the simple model without age-education interaction and the model which includes such interaction was performed. The test showed that the interaction term significantly improved the fit of the model.

Table B1. Mortality rate ratios between education groups and age groups estimated from an exponential survival hazard model with covariates education, age and their interaction. The table also reports the likelihood ratio test between this model and a model without an age-education interaction term.

	Men				Women			
	50-80 years		80+ years		50-80 years		80+ years	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
High	1	-	1	-	1	-	1	-
Medium	1.234	1.209-1.259	1.082	1.048-1.116	1.250	1.213-1.289	1.040	1.008-1.073
Low	1.571	1.544-1.598	1.172	1.143-1.202	1.594	1.552-1.637	1.170	1.136-1.202
Likelihood ratio test with reduced model (without age-education interaction)								
	D statistics: 395.193		Df: 2	p-value:0.000	D statistics:319.833		Df: 2	p-value:0.000

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Figures

Figure 1. Death rates, on logarithmic scale, for the birth cohort aged 50-59 at the beginning of the follow-up (1971) by three education levels: high, medium and low.

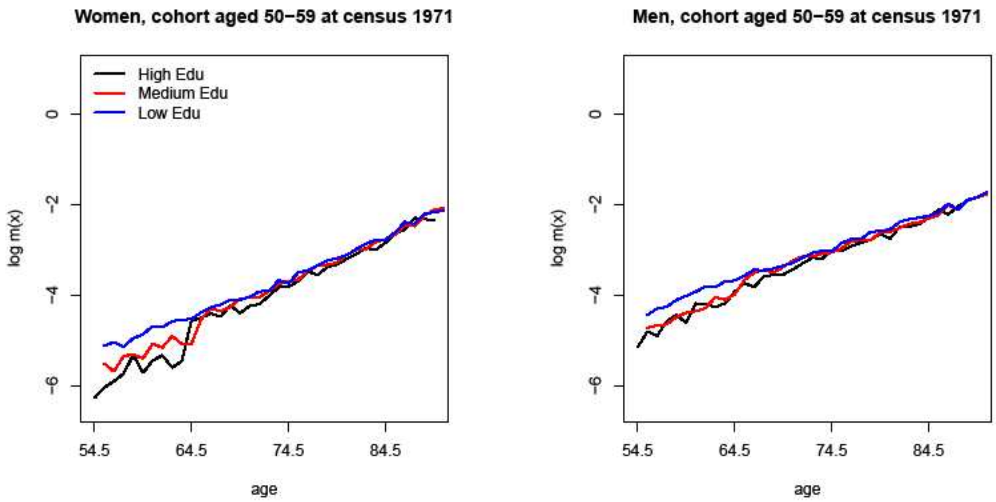
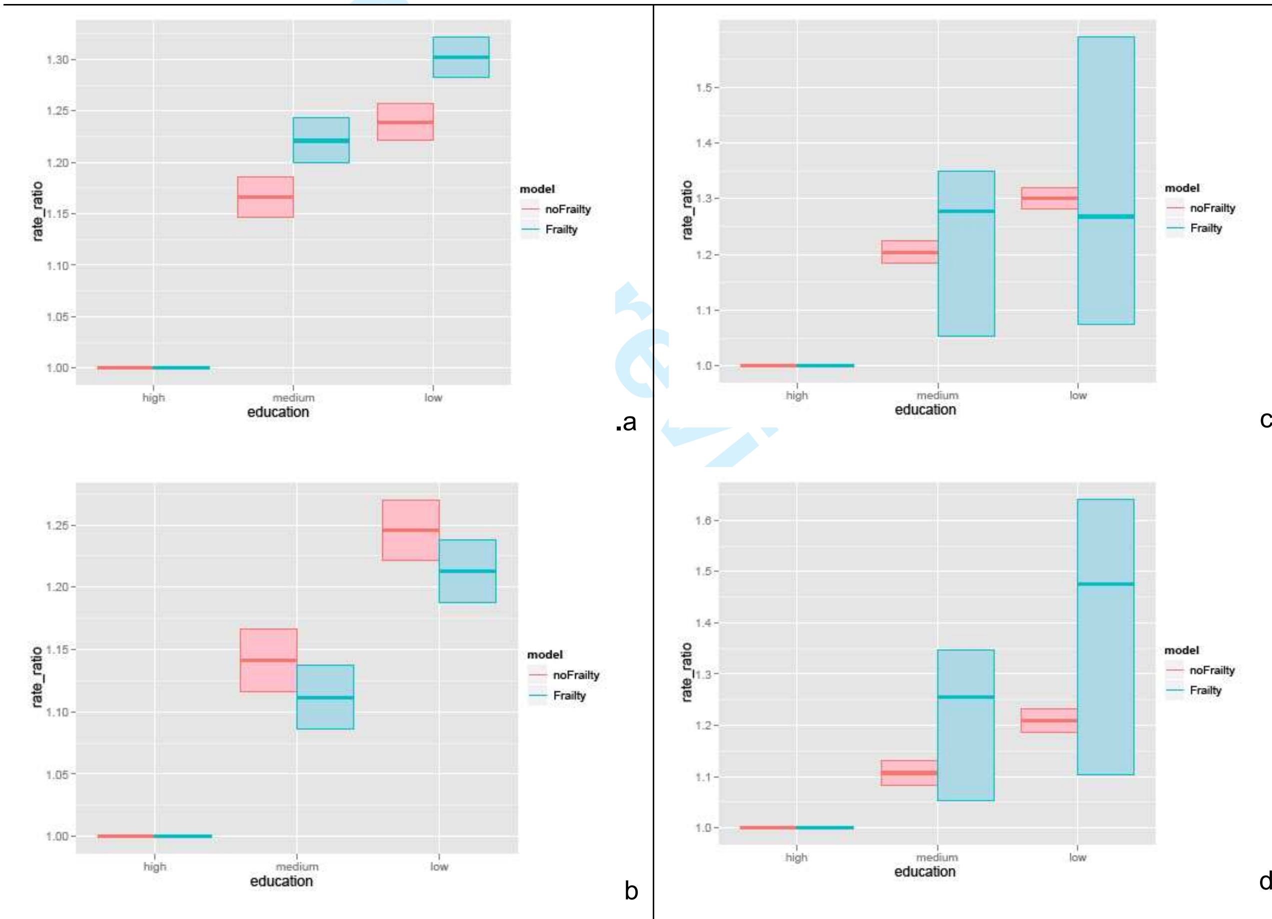


Figure 2. Mortality rate ratios by education level in the models with cohort and period improvements, without and with frailty. a) Men, cohort model; b) Women, cohort model; c) Men, period model; d) Women, period model.

Model with cohort improvement

Model with period improvement



	Men (a)		Women (b)	
	No frailty	Frailty	No frailty	Frailty
LogLik	-651 219	-651 082	-663 238	-663 098
AIC	1302456	1302184	1326496	1326218

	Men (c)		Women (d)	
	No frailty	Frailty	No frailty	Frailty
LogLik	-663 081	Na	-650 997	Na
AIC	1326204	Na	1302034	Na

Mortality by education level at late-adult ages in Turin: a survival analysis using frailty models with period and cohort approaches.

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Mortality by education level at late-adult ages in Turin: a survival analysis using frailty models with period and cohort approaches.

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Summary

Article Focus

- Neglecting the presence of unobserved heterogeneity in survival analysis models has been showed to potentially lead to underestimating the effect of the covariates included in the analysis.
- Although frailty models have been widely developed to account for unobserved heterogeneity, in differential mortality analyses this source of variation is seldom controlled for. This study has applied these models to a longitudinal mortality analysis by education level.

Key messages

- Mortality differentials by education (or by any other variable used as proxy of socioeconomic status) could be larger than those estimated with standard survival analysis approaches that do not control for unobserved heterogeneity.

Strengths and limitations

The strength of this study lies in the population based longitudinal data. The long observational time (36 years) for more than 847 000 individuals gives a solid base for statistical power and detection of trends.

The limitation consists in the lack of individual information on life style factors and health events, which could certainly help to better model the concept of unobserved individual frailty by uncovering part of it.

Abstract

Background. Unobserved heterogeneity of frailty can lead to biased estimates of coefficients in survival analysis models. This study investigated the role of unobserved frailty on the estimation of mortality differentials from age 50 on by education level.

Methods. We used data of a 36 years follow up from the Turin Longitudinal Study containing 391 170 men and 456 216 women. As Turin underwent strong immigration flows during the post war industrialization, also the macro-region of birth was controlled for. We fitted survival analysis models with and without the unobserved heterogeneity component, controlling for mortality improvement from both cohort and period perspectives.

Results. We found that in the majority of the cases, the models without frailty estimated a smaller educational gradient then the models with frailty.

Conclusions. The results draw the attention on the potential underestimation of the mortality inequalities by socioeconomic levels in survival models when not controlling for frailty.

Introduction

An extensive literature shows significant differential mortality by socioeconomic condition (1-3). Elderly show decreasing relative social inequalities in general mortality with increasing age (4-8). The age-as-leveler hypothesis attributes this to factors that contribute to the leveling-off of differences at old ages: governmental support to the elderly (9-11), disengagement from systems of social stratification (12) and general vulnerability (13, 14). However, this phenomenon could also be an artifact of selection due to unobserved characteristics of the individuals: selective effects of earlier higher mortality, experienced by the disadvantaged group, would leave more robust individuals at old ages, causing the convergence with the risk of the lower mortality group, that is subject to weaker selection (15-18). Neglecting these hidden differences in survival chances (called unobserved frailty), has been shown to lead to biased estimates of the mortality hazard and of the effect of the covariates on the survival probability (19-25).

In longitudinal analyses on differential mortality it is important to control for hidden frailty because, not controlling for it, in models of survival analysis, could lead to biased estimates of the effect of the social position on the mortality risk. The statistical literature shows that the bias is towards zero (24-26). This would lead to underestimation of the relative differences in the mortality risks by socioeconomic group. To control for unobserved frailty and to evaluate the impact on the observed mortality dynamics, frailty models have been developed (27) . For more detailed explanations of the frailty models and how they relate to differential mortality analyses, please, see appendix A.

This study investigated the presence of selection processes in the mortality patterns of the Turin population (North-West Italy) from age 50 on. Adopting a longitudinal perspective, this study aimed to investigate if the estimates of the mortality differentials are affected by the introduction of the unobserved heterogeneity component into the models.

Data and Methods

We used high quality census linked data from the Turin Longitudinal Study (TLS), which includes 1971, 1981, 1991 and 2001 census data for the Turin population. TLS records the individual census socio-demographic information and, through record linkage with the local population registry and other local health information systems, collects information on vital status, cause of death and other health indicators (28, 29).

For this study, the individuals registered in Turin during at least one of the four censuses were selected. Their migration and vital status was followed up until the end of July 2007. The result is an observation window of 36 years (from October 24th 1971, official date of the census, to the end of July 2007, end of the linkage) during which the individuals were followed up until death, emigration from the city or end of observation period. The follow up started at age 50. The study population contains 391 170 men and 456 216 women.

Study information includes individual's date of birth, date of exit from the study, cause of exit (death or emigration), sex, macro-region of birth and education level.

Consistent with the literature (30-33) education level was used as an indicator of social position.

The study also controlled for the individual macro region of birth, as Turin is characterized by a history of immigration from other regions of the country (34).

To facilitate the comparison over a long follow up and different cohorts, we created three broad educational groups: high (high school diploma or higher), medium (junior high school) and low (primary school or lower).

We estimated parametric survival models stratified by gender and as a function of macro-region of birth and education level, with and without a parameter for the unobserved heterogeneity component. The parametric choice is justified by the wide demographic literature showing that human adult mortality can be accurately described by a Gompertz function (35) or by some Gompertz-like variants, like Makeham. To identify the best functional form for the baseline we compared the models with the AIC (36).

The data are both right censored (due to emigration or end of follow up) and left truncated (due to the different age at entry in the study of the individuals).

The study includes many cohorts, each passing through the 36 years of observation at different ages. However, from 1971 to 2007 a significant mortality improvement occurred and younger cohorts experience lower age specific mortality than older cohorts.

Time is a complex variable including three dimensions: age, period and cohort. Controlling adequately for the effect of time would require to asses simultaneously the three components but such models have been not identifiable for a long time because of linear dependence between the three dimensions (37-39). Recently it has been showed that through the introduction of the GLMM (generalized linear mixed models) framework, new estimation methods and model specifications can be used to tackle the identification problem (40). However, this goes beyond the scope of our study.

We adopted two approaches for the control of time, corresponding to an age-cohort approach and an age-period approach, being aware that they represent two different dimensions of time.

First, we regarded the improvement as a cohort phenomenon, including a covariate for the cohort to which the individuals belong. In this setting, controlling for unobserved heterogeneity was implemented with univariate frailty models, which estimate the baseline parameters, the coefficients of the covariates and the variance of frailty (assumed to follow a gamma distribution with mean 1 and variance σ^2 to be estimated).

We then considered the improvement as a period phenomenon and split the time into several calendar period covariates, as well as the survival spell of the individuals, according to which period they were passing through. This implied organizing the data into clusters, where each cluster represents one individual's survival spells. In this setting, to control for unobserved heterogeneity shared frailty models are needed, where the spells in each cluster pertain to the same individual and share the same hidden frailty. For computational reasons, the estimation of these highly complex models required the use of random subsampling (41-43). We repeated the estimation 250 times on a 1% sample of the dataset, randomly drawn without replacement and stratified by the major variables in analysis. The aim is to approximate the parameters estimates based on the empirical distribution of the repeated estimates.

In the model without frailty it was possible to include a finer calendar period division, 12 period variables of 3 years each (1971-1973, 1974-1976…), while in the model with frailty, for computational reasons, the number of variables was reduced to 2 broader periods: 1971-1990 and 1991-2007.

Computations were realized with the software R (44). Formal details are in appendix A.

Results

Figure 1 shows that the log-death rates by education level and gender, for the cohort aged 50-59 in 1971, converge at old ages. Other cohorts showed very similar patterns.

A preliminary analysis found that the reduction of the gradient over age is statistically significant and more pronounced among women (results are reported in appendix B table B1).

Figure 1 here

Frailty modeling

Table 1 shows the AIC of the survival models, fitted to the all population mortality, with Gompertz and Makeham baselines. It also shows the results of the fit when unobserved frailty was controlled for. The comparison reveals that Gompertz baseline was a better fit for the male data, while Makeham was better for the female. In both cases, the models controlling for unobserved heterogeneity performed a better fit (table 1).

Table 1. Model selection for the baseline hazard and comparison of the model with best baseline hazard and unobserved heterogeneity of frailty component. Comparison is based on the AIC.

	Model with different baseline hazards		Model with best baseline hazard and frailty	
	Gompertz ae^{bx}	Makeham $ae^{bx}+c$	Gamma-Gompertz $\frac{ae^{bx}}{1+\sigma^2\frac{a}{b}\left(e^{bx}-1\right)}$	Gamma-Makeham $\frac{ae^{bx}+c}{1+\sigma^2\frac{a}{b}\left(e^{bx}-1\right)+cx}$
AIC women	1 327 474	1 326 878	-	1 326 695
AIC men	1 303 693	1 303 695	1 303 655	-

We then estimated the mortality differentials, using a cohort and a period approach to control for mortality improvement over time. We included in the analysis the variables for education level (high, medium and low) and region of birth (North-West, North-East, Center, South and Abroad).

Tables 2 and 3 report the results of the models estimated with and without the unobserved heterogeneity component: the parameters of the baseline hazard (a and b of the Gompertz function for men and a, b and c of the Makeham function for women), the variance of frailty in the population and the rate ratios of the mortality differentials by education level and region of birth. Figure 2 compares the results for the educational gradient obtained by the models with and without frailty.

Table 2. Results of the regression models with cohort covariates. Baseline parameters (Gompertz for men and Makeham for women) and rate ratios of the differentials by education and region of birth.

	Men				Women			
	Model without frailty		Model with frailty		Model without frailty		Model with frailty	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
a	5.241×10^{-5}	5.237×10^{-5}-5.245×10^{-5}	4.495×10^{-5}	4.488×10^{-5}-4.501×10^{-5}	3.767×10^{-6}	3.755×10^{-6}-3.779×10^{-6}	1.605×10^{-6}	1.588×10^{-6}-1.623×10^{-6}
b	0.081	0.080-0.082	0.083	0.082-0.084	0.106	0.105-0.107	0.117	0.115-0.119
c	-	-	-	-	0.001	0.001-0.001	0.001	0.001-0.001
Sigma^2	-	-	0.035	0.027-0.045	-	-	0.096	0.082-0.111
cohort	0.016	0.015-0.016	0.016	0.015-0.016	0.016	0.015-0.016	0.017	0.016-0.017
Education level								
High	1	-	1	-	1	-	1	-
Medium	1.166	1.147-1.186	1.221	1.200-1.243	1.141	1.116-1.166	1.111	1.086-1.137
Low	1.239	1.221-1.257	1.302	1.283-1.322	1.246	1.222-1.270	1.213	1.188-1.238
Region of birth								
North-West	1	-	1	-	1	-	1	-
North-East	1.053	1.036-1.070	1.060	1.042-1.077)	0.989	0.973-1.004	0.974	0.958-0.991
Center	1.011	0.984-1.038	0.996	0.969-1.024	0.939	0.913-0.966	0.968	0.939-0.998
South	1.000	0.988-1.012	0.950	0.938-0.962	0.932	0.919-0.945	0.987	0.973-1.002
Abroad	1.031	1.006-1.057	0.998	0.974-1.024	1.071	1.047-1.096	0.993	0.968-1.018
logLk	-651 219		-651 082		-663 238		-663 098	
AIC	1 302 456		1 302 184		1 326 496		1 326 218	

Table 3. Results of the regression models with period covariates. Baseline parameters (Gompertz for men and Makeham for women) and rate ratios of the differentials by education and region of birth.
*The model with frailty does not report conventional point estimates and confidence intervals, but the mean value and the 0.025-0.975 quantiles of the empirical distribution of the parameters obtained from the repeated estimates via random subsampling.

	Men				Women			
	Model without frailty		Model with frailty*		Model without frailty		Model with frailty*	
	Estimate	95% CI	Mean	0.025-0.0975	Estimate	95% CI	Mean	0.025-0.0975
a	4.159×10^{-5}	3.196×10^{-5}-5.410×10^{-5}	0.004	(0.000-0.010)	8.031×10^{-6}	6.028×10^{-6}-1.070×10^{-5}	0.008	(0.000-0.016)
b	0.096	(0.095-0.096)	0.069	(0.061-0.163)	0.121	(0.120-0.122)	0.084	(0.073-0.106)
c	-	-	-	-	0.001	(0.001-0.002)	2.852×10^{-6}	8.610×10^{-7}-2.997×10^{-5}
$Sigma^2$	-	-	0.269	(0.026-0.367)	-	-	0.292	(0.174-0.367)
Calendar period								
1971-1973	1	-			1	-		
1974-1976	0.999	0.972-1.027			0.978	0.950-1.007		
1977-1979	0.947	0.921-0.973			0.919	0.893-0.946		
1980-1982	0.928	0.903-0.953			0.896	0.871-0.922		
1983-1985	0.943	0.918-0.969			0.967	0.941-0.994		
1986-1988	0.870	0.847-0.894	1	-	0.848	0.824-0.872	1	-
1989-1991	0.820	0.798-0.843	0.728	0.613-0.985	0.796	0.774-0.818	0.888	0.671-1.035
1992-1994	0.796	0.774-0.817			0.757	0.736-0.778		
1995-1997	0.741	0.721-0.762			0.704	0.684-0.724		
1998-2000	0.701	0.682-0.721			0.682	0.663-0.701		
2001-2003	0.670	0.652-0.689			0.657	0.639-0.676		
2004-2007	0.631	0.615-0.648			0.625	0.608-0.642		
High	1	-	1	-	1	-	1	-
Medium	1.204	(1.184-1.225)	1.277	(1.054-1.349)	1.107	(1.083-1.131)	1.256	(1.053-1.347)
Low	1.301	(1.282-1.320)	1.268	(1.074-1.591)	1.209	(1.186-1.232)	1.475	(1.103-1.641)
North-West	1	-	1	-	1	-	1	-
North-East	1.040	(1.024-1.057)	1.075	(0.855-1.220)	0.963	(0.948-0.978)	1.122	(0.888-1.217)
Center	0.943	(0.917-0.969)	1.081	(0.854-1.212)	0.964	(0.938-0.992)	1.102	(0.864-1.218)
South	0.900	(0.889-0.911)	1.037	(0.854-1.216)	0.962	(0.949-0.975)	1.130	(0.904-1.220)
Abroad	0.965	(0.941-0.989)	1.082	(0.864-1.218)	0.985	(0.962-1.009)	1.082	(0.847-1.215)
logLk	-650 997		Na		-663 081		Na	
AIC	1 302 034		Na		1 326 204		Na	

Educational gradient

In the model with the age-cohort improvement approach, the introduction of the frailty term made the male differences widen significantly, consistent with the statistical literature. The rate ratios with respect to high education changed from 1.16 (95% CI 1.15-1.19) to 1.22 (1.20-1.24) for medium education and from 1.24 (1.22-1.26) to 1.30 (1.28-1.32) low education (figure 2 panel a). Among women, on the contrary, there was a slight reduction but the confidence regions of the estimates in the two cases overlap: for medium education the rate ratio went from 1.14 (1.12-1.17) to 1.11 (1.08-1.14) and for low education from 1.25 (1.22-1.27) to 1.22 (1.19-1.24) (figure 2 panel b). The AIC indicates that the models with frailty fit the data significantly better than the model without.

Figure 2 here

In the model adopting the age-period improvement approach, the AIC comparison of the models with and without frailty was not possible, because the utilization of random subsampling for the estimation of the frailty model (41-43) did not allow obtaining a likelihood value comparable with the values of the models without frailty. Moreover, it is necessary to consider that we are comparing conventional point estimates and confidence intervals with values obtained via bootstrapping methods, whose confidence regions are usually wider than conventional confidence intervals. Nevertheless, a comparison is still possible.

The introduction of frailty affected the mortality gradient by education. Although the uncertainty around the estimates does not allow assessing a precise effect, the rate ratios of medium and low education in respect to high education in the models with frailty lie in a higher confidence region than in the models without: among women with a medium education level, it lies between 1.05 and 1.34 compared to 1.08 and 1.13 of the model without frailty and for the low education group, between 1.1 and 1.6, compared to 1.18 and 1.23. The same pattern can be observed among men.

The male difference between medium and low education group, on the contrary, was not as clear as that among women.

Other results and the impact of the macro-region of birth on mortality

As expected, the variance of frailty in the cohort models was smaller than in the period models, since periods are more heterogeneous than cohorts.

Women were more heterogeneous than men: 0.09 (0.08-0.11) versus 0.04 (0.03-0.05) in the age-cohort models and 0.29 (0.17-0.37) versus 0.27 (0.-0.36) in the age-period models.

This is consistent with the more pronounced convergence of the hazards by education at old age found among women compared to the men. According to the framework of the frailty models, converging hazards are the result of the effect of selection on the population hazards, due to how much variance of unobserved frailty is present in the population at the initial age of observation. The bigger the variance the stronger the convergence is. For more information about frailty models, the process of selection and how they relate to narrowing mortality differentials at old ages, please see appendix A.

In the age-cohort models the introduction of unobserved frailty affected the coefficient for the macro-region of birth significantly. Among men, holding education equal, those born in the South show a significant survival advantage over the natives of the North-West, while in the model without frailty there was no such advantage. Among women, the model without frailty showed a significant survival advantage for those born in the South but when frailty was controlled for, this became not significant.

The pattern also resembles the regional mortality macro-dynamics that have characterized Italy for most of the 20th century (although the two patterns refer to different phenomena, the first one referring to mortality by region of birth), when male mortality in the

South was lower than in the North (45-48). Cohort based analyses have highlighted that in more recent cohorts (those born after WWII) there is a reversing trend (48, 49).

The models with age-period perspective did not identify any significant geographical differences. This could be due to the utilization of random subsampling of a 1% sample. Although 250 repetitions is considered by the literature a sufficient number for very complex models (50-52), it is possible that it was inadequate to identify a clear pattern from the small sample. For more detailed results see tables 1 and 2.

Discussion

The interest in the role of unobserved heterogeneity in a life course approach to socioeconomic mortality differences has recently increased. Most of the studies focus on health outcomes (53-58) while fewer studies also analyze mortality (59-61). Their findings are not consistent and fuel a still controversial debate.

In this study we investigated the role of unobserved individual heterogeneity on the estimation of mortality differentials at adult-old ages by education level in a longitudinal perspective. This study investigated if the estimates of the mortality differentials are affected by the introduction of the unobserved heterogeneity component into the models.

We fitted survival analysis models with and without controlling for the unobserved heterogeneity and we found that, when this component was included, the models gave a significantly better fit.

We also found that in the majority of the cases, the educational gradient estimated by the models with frailty was higher than the one estimated by the models without frailty. When big uncertainty around the estimates did not allow assessing a precise value, the confidence regions in the models with frailty spanned over higher values than those in the models without frailty. It must be pointed out that, in the age-period approach, to the peculiar statistical procedure used to estimate the frailty models did not allow obtaining a likelihood value comparable with the one of the model without frailty. Thus, the statistical comparison of the models via the AIC was not possible, making this evidence weaker. Nevertheless, the results seem to point to a direction that is consistent with the statistical literature about unobserved heterogeneity (19-26).

Among men such a pattern was found in both the age-cohort and age-period approaches. Among women, on the contrary, this pattern was less clear: in the age-cohort model, controlling for hidden frailty resulted in a slight reduction of the mortality gradient. Social determinants act on mortality also through risk factors that are known to affect more men than women. Moreover, because of a lag in the smoking and fertility transitions, highly educated women in Turin are more exposed to risk factors like cigarette smoking and smaller number of children. Therefore, controlling for hidden frailty in the case of women might reduce the educational gradient.

In the models with age-cohort perspective controlling for the hidden frailty affected also the estimates of the differentials by macro-region of birth, showing a survival advantage of the men born in the South, but not of the women, for whom an advantage was instead detected by the model that did not control for frailty.

The healthy migrant effect (62-67) could cause this pattern. Among the cohorts involved in the migration women were likely to be more passive actors than men in the migratory decision (68-70) and this might have selected them more than men. Frailty is a general concept embedding all the hidden factors that affect the individual survival chances: innate and acquired frailty, exposure to risk factors, life style factors and so on. Therefore, controlling for frailty reduced the survival advantage of the women, who might have been less health selected than men by the migration, while uncovered the advantage of the men. However, another recent study on the impact of migration on all-cause mortality in Turin did not find particularly strong gender differences in the so called healthy migrant effect (66) and this point deserves future further investigation.

The study spanned over a long observation window of 36 years. Therefore it was important to control for the general mortality improvement that took place during this time. We did so by adopting both an age-period and an age-cohort approach.

The age-period models, as expected, estimated higher heterogeneity than the age-cohort models. Periods aggregate different generations and are expected to be more heterogeneous than the cohorts themselves. In both period and cohort models the female variance of frailty was higher than for the males, indicating that men are more homogeneous than women. This could be attributed to a stronger selection process due to mortality that is usually observed to be higher among men than among women.

On the other hand, it is also possible that the industrialization process and the internal migration experienced by Italy after WWII (34) played a role. The vast majority of less educated individuals in Turin came from the South, seeking a job in the car factories of the city. As less educated men were mainly employed in heavier and riskier jobs and were exposed to higher mortality, it is possible that during their life they were selected at a faster pace than other educational groups and women. This might have reduced the differences in susceptibility to death among men, contributing to determining a lower level of heterogeneity than among women.

Conclusion

This study found that neglecting selection effects due to unobserved heterogeneity in longitudinal analyses, could lead to underestimation of mortality differentials by social class. In the majority of the cases, the models that controlled for unobserved heterogeneity, estimated higher educational differences in mortality than the models that did not control for it.

Moreover, when compared with via the AIC, the models that controlled for unobserved heterogeneity gave a statistically significant better fit than the models that did not control for it. Although the best AIC shows just that the more complex model approximates better the data and this does not represent an unequivocal proof of the selection hypothesis, the results point to the possibility that the data could be better described by this hypothesis.

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Contributorship. Virginia Zarulli: conception and design of the study, analysis and interpretation of data and results, drafting the article and revising it; Graziella Caselli: interpretation of the results, drafting the article and revising it critically; Chiara Marinacci and Giuseppe Costa: revising the article for important intellectual content.

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Mortality by education level at late-adult ages in Turin: a survival analysis using frailty models with period and cohort approaches.

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Abstract

Background. Unobserved heterogeneity of frailty can lead to biased estimates of coefficients in survival analysis models. This study investigated the role of unobserved frailty on the estimation of mortality differentials from age 50 on by education level.

Methods. We used data of a 36 years follow up from the Turin Longitudinal Study containing 391 170 men and 456 216 women. As Turin underwent strong immigration flows during the post war industrialization, also the macro-region of birth was controlled for. We fitted survival analysis models with and without the unobserved heterogeneity component, controlling for mortality improvement from both cohort and period perspectives.

Results. We found that in the majority of the cases, the models without frailty estimated a smaller educational gradient then the models with frailty.

Conclusions. The results draw the attention on the potential underestimation of the mortality inequalities by socioeconomic levels in survival models when not controlling for frailty.

Introduction

An extensive literature shows significant differential mortality by socioeconomic condition (1-3). Elderly show decreasing relative social inequalities in general mortality with increasing age (4-8). The age-as-leveler hypothesis attributes this to factors that contribute to the leveling-off of differences at old ages: governmental support to the elderly (9-11), disengagement from systems of social stratification (12) and general vulnerability (13, 14). However, this phenomenon could also be an artifact of selection due to unobserved characteristics of the individuals: selective effects of earlier higher mortality, experienced by the disadvantaged group, would leave more robust individuals at old ages, causing the convergence with the risk of the lower mortality group, that is subject to weaker selection (15-18). Neglecting these hidden differences in survival chances (called unobserved frailty), has been shown to lead to biased estimates of the mortality hazard and of the effect of the covariates on the survival probability (19-25).

In longitudinal analyses on differential mortality it is important to control for hidden frailty because, not controlling for it, in models of survival analysis, could lead to biased estimates of the effect of the social position on the mortality risk. The statistical literature shows that the bias is towards zero (24-26). This would lead to underestimation of the relative differences in the mortality risks by socioeconomic group. To control for unobserved frailty and to evaluate the impact on the observed mortality dynamics, frailty models have been developed (27) . For more detailed explanations of the frailty models and how they relate to differential mortality analyses, please, see appendix A.

This study investigated the presence of selection processes in the mortality patterns of the Turin population (North-West Italy) from age 50 on. Adopting a longitudinal perspective, this study aimed to investigate if the estimates of the mortality differentials are affected by the introduction of the unobserved heterogeneity component into the models.

Data and Methods

We used high quality census linked data from the Turin Longitudinal Study (TLS), which includes 1971, 1981, 1991 and 2001 census data for the Turin population. TLS records the individual census socio-demographic information and, through record linkage with the local population registry and other local health information systems, collects information on vital status, cause of death and other health indicators (28, 29).

For this study, the individuals registered in Turin during at least one of the four censuses were selected. Their migration and vital status was followed up until the end of July 2007. The result is an observation window of 36 years (from October 24th 1971, official date of the census, to the end of July 2007, end of the linkage) during which the individuals were followed up until death, emigration from the city or end of observation period. The follow up started at age 50. The study population contains 391 170 men and 456 216 women.

Study information includes individual's date of birth, date of exit from the study, cause of exit (death or emigration), sex, macro-region of birth and education level.

Consistent with the literature (30-33) education level was used as an indicator of social position.

The study also controlled for the individual macro region of birth, as Turin is characterized by a history of immigration from other regions of the country (34).

To facilitate the comparison over a long follow up and different cohorts, we created three broad educational groups: high (high school diploma or higher), medium (junior high school) and low (primary school or lower).

We estimated parametric survival models stratified by gender and as a function of macro-region of birth and education level, with and without a parameter for the unobserved heterogeneity component. The parametric choice is justified by the wide demographic literature showing that human adult mortality can be accurately described by a Gompertz function (35) or by some Gompertz-like variants, like Makeham. To identify the best functional form for the baseline we compared the models with the AIC (36).

The data are both right censored (due to emigration or end of follow up) and left truncated (due to the different age at entry in the study of the individuals).

The study includes many cohorts, each passing through the 36 years of observation at different ages. However, from 1971 to 2007 a significant mortality improvement occurred and younger cohorts experience lower age specific mortality than older cohorts.

Time is a complex variable including three dimensions: age, period and cohort. Controlling adequately for the effect of time would require to asses simultaneously the three components but such models have been not identifiable for a long time because of linear dependence between the three dimensions (37-39). Recently it has been showed that through the introduction of the GLMM (generalized linear mixed models) framework, new estimation methods and model specifications can be used to tackle the identification problem (40). However, this goes beyond the scope of our study.

We adopted two approaches for the control of time, corresponding to an age-cohort approach and an age-period approach, being aware that they represent two different dimensions of time.

First, we regarded the improvement as a cohort phenomenon, including a covariate for the cohort to which the individuals belong. In this setting, controlling for unobserved heterogeneity was implemented with univariate frailty models, which estimate the baseline parameters, the coefficients of the covariates and the variance of frailty (assumed to follow a gamma distribution with mean 1 and variance σ^2 to be estimated).

We then considered the improvement as a period phenomenon and split the time into several calendar period covariates, as well as the survival spell of the individuals, according to which period they were passing through. This implied organizing the data into clusters, where each cluster represents one individual's survival spells. In this setting, to control for unobserved heterogeneity shared frailty models are needed, where the spells in each cluster pertain to the same individual and share the same hidden frailty. For computational reasons, the estimation of these highly complex models required the use of random subsampling (41-43). We repeated the estimation 250 times on a 1% sample of the dataset, randomly drawn without replacement and stratified by the major variables in analysis. The aim is to approximate the parameters estimates based on the empirical distribution of the repeated estimates.

In the model without frailty it was possible to include a finer calendar period division, 12 period variables of 3 years each (1971-1973, 1974-1976…), while in the model with frailty, for computational reasons, the number of variables was reduced to 2 broader periods: 1971-1990 and 1991-2007.

Computations were realized with the software R (44). Formal details are in appendix A.

Results

Figure 1 shows that the log-death rates by education level and gender, for the cohort aged 50-59 in 1971, converge at old ages. Other cohorts showed very similar patterns.

A preliminary analysis found that the reduction of the gradient over age is statistically significant and more pronounced among women (results are reported in appendix B table B1).

Figure 1 here

Frailty modeling

Table 1 shows the AIC of the survival models, fitted to the all population mortality, with Gompertz and Makeham baselines. It also shows the results of the fit when unobserved frailty was controlled for. The comparison reveals that Gompertz baseline was a better fit for the male data, while Makeham was better for the female. In both cases, the models controlling for unobserved heterogeneity performed a better fit (table 1).

Table 1. Model selection for the baseline hazard and comparison of the model with best baseline hazard and unobserved heterogeneity of frailty component. Comparison is based on the AIC.

	Model with different baseline hazards		Model with best baseline hazard and frailty	
	Gompertz	Makeham	Gamma-Gompertz	Gamma-Makeham
	ae^{bx}	$ae^{bx}+c$	$\frac{ae^{bx}}{1+\sigma^2\frac{a}{b}\left(e^{bx}-1\right)}$	$\frac{ae^{bx}+c}{1+\sigma^2\frac{a}{b}\left(e^{bx}-1\right)+cx}$
AIC women	1 327 474	1 326 878	-	1 326 695
AIC men	1 303 693	1 303 695	1 303 655	-

We then estimated the mortality differentials, using a cohort and a period approach to control for mortality improvement over time. We included in the analysis the variables for education level (high, medium and low) and region of birth (North-West, North-East, Center, South and Abroad).

Tables 2 and 3 report the results of the models estimated with and without the unobserved heterogeneity component: the parameters of the baseline hazard (a and b of the Gompertz function for men and a, b and c of the Makeham function for women), the variance of frailty in the population and the rate ratios of the mortality differentials by education level and region of birth. Figure 2 compares the results for the educational gradient obtained by the models with and without frailty.

Table 2. Results of the regression models with cohort covariates. Baseline parameters (Gompertz for men and Makeham for women) and rate ratios of the differentials by education and region of birth.

	Men				Women			
	Model without frailty		Model with frailty		Model without frailty		Model with frailty	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI

a	5.241×10^{-5}	5.237×10^{-5}-5.245×10^{-5}	4.495×10^{-5}	4.488×10^{-5}-4.501×10^{-5}	3.767×10^{-6}	3.755×10^{-6}-3.779×10^{-6}	1.605×10^{-6}	1.588×10^{-6}-1.623×10^{-6}
b	0.081	0.080-0.082	0.083	0.082-0.084	0.106	0.105-0.107	0.117	0.115-0.119
c	-	-	-	-	0.001	0.001-0.001	0.001	0.001-0.001
Sigma^2	-	-	0.035	0.027-0.045	-	-	0.096	0.082-0.111
cohort	0.016	0.015-0.016	0.016	0.015-0.016	0.016	0.015-0.016	0.017	0.016-0.017
Education level								
High	1	-	1	-	1	-	1	-
Medium	1.166	1.147-1.186	1.221	1.200-1.243	1.141	1.116-1.166	1.111	1.086-1.137
Low	1.239	1.221-1.257	1.302	1.283-1.322	1.246	1.222-1.270	1.213	1.188-1.238
Region of birth								
North-West	1	-	1	-	1	-	1	-
North-East	1.053	1.036-1.070	1.060	1.042-1.077)	0.989	0.973-1.004	0.974	0.958-0.991
Center	1.011	0.984-1.038	0.996	0.969-1.024	0.939	0.913-0.966	0.968	0.939-0.998
South	1.000	0.988-1.012	0.950	0.938-0.962	0.932	0.919-0.945	0.987	0.973-1.002
Abroad	1.031	1.006-1.057	0.998	0.974-1.024	1.071	1.047-1.096	0.993	0.968-1.018
logLk	-651 219		-651 082		-663 238		-663 098	
AIC	1 302 456		1 302 184		1 326 496		1 326 218	

Table 3. Results of the regression models with period covariates. Baseline parameters (Gompertz for men and Makeham for women) and rate ratios of the differentials by education and region of birth.
*The model with frailty does not report conventional point estimates and confidence intervals, but the mean value and the 0.025-0.975 quantiles of the empirical distribution of the parameters obtained from the repeated estimates via random subsampling.

	Men				Women			
	Model without frailty		Model with frailty*		Model without frailty		Model with frailty*	
	Estimate	95% CI	Mean	0.025-0.0975	Estimate	95% CI	Mean	0.025-0.0975
a	4.159×10^{-5}	3.196×10^{-5}-5.410×10^{-5}	0.004	(0.000-0.010)	8.031×10^{-6}	6.028×10^{-6}-1.070×10^{-5}	0.008	(0.000-0.016)
b	0.096	(0.095-0.096)	0.069	(0.061-0.163)	0.121	(0.120-0.122)	0.084	(0.073-0.106)
c	-	-	-	-	0.001	(0.001-0.002)	2.852×10^{-6}	8.610×10^{-7}-2.997×10^{-5}
Sigma^2	-	-	0.269	(0.026-0.367)	-	-	0.292	(0.174-0.367)
Calendar period								
1971-1973	1	-			1	-		
1974-1976	0.999	0.972-1.027			0.978	0.950-1.007		
1977-1979	0.947	0.921-0.973			0.919	0.893-0.946		
1980-1982	0.928	0.903-0.953			0.896	0.871-0.922		
1983-1985	0.943	0.918-0.969	1	-	0.967	0.941-0.994	1	-

1986-1988	0.870	0.847-0.894			0.848	0.824-0.872		
1989-1991	0.820	0.798-0.843	0.728	0.613-0.985	0.796	0.774-0.818	0.888	0.671-1.035
1992-1994	0.796	0.774-0.817			0.757	0.736-0.778		
1995-1997	0.741	0.721-0.762			0.704	0.684-0.724		
1998-2000	0.701	0.682-0.721			0.682	0.663-0.701		
2001-2003	0.670	0.652-0.689			0.657	0.639-0.676		
2004-2007	0.631	0.615-0.648			0.625	0.608-0.642		
High	1	-	1	-	1	-	1	-
Medium	1.204	(1.184-1.225)	1.277	(1.054-1.349)	1.107	(1.083-1.131)	1.256	(1.053-1.347)
Low	1.301	(1.282-1.320)	1.268	(1.074-1.591)	1.209	(1.186-1.232)	1.475	(1.103-1.641)
North-West	1	-	1	-	1	-	1	-
North-East	1.040	(1.024-1.057)	1.075	(0.855-1.220)	0.963	(0.948-0.978)	1.122	(0.888-1.217)
Center	0.943	(0.917-0.969)	1.081	(0.854-1.212)	0.964	(0.938-0.992)	1.102	(0.864-1.218)
South	0.900	(0.889-0.911)	1.037	(0.854-1.216)	0.962	(0.949-0.975)	1.130	(0.904-1.220)
Abroad	0.965	(0.941-0.989)	1.082	(0.864-1.218)	0.985	(0.962-1.009)	1.082	(0.847-1.215)
logLk	-650 997		Na		-663 081		Na	
AIC	1 302 034		Na		1 326 204		Na	

Educational gradient

In the model with the age-cohort improvement approach, the introduction of the frailty term made the male differences widen significantly, consistent with the statistical literature. The rate ratios with respect to high education changed from 1.16 (95% CI 1.15-1.19) to 1.22 (1.20-1.24) for medium education and from 1.24 (1.22-1.26) to 1.30 (1.28-1.32) low education (figure 2 panel a). Among women, on the contrary, there was a slight reduction but the confidence regions of the estimates in the two cases overlap: for medium education the rate ratio went from 1.14 (1.12-1.17) to 1.11 (1.08-1.14) and for low education from 1.25 (1.22-1.27) to 1.22 (1.19-1.24) (figure 2 panel b). The AIC indicates that the models with frailty fit the data significantly better than the model without.

Figure 2 here

In the model adopting the age-period improvement approach, the AIC comparison of the models with and without frailty was not possible, because the utilization of random subsampling for the estimation of the frailty model (41-43) did not allow obtaining a likelihood value comparable with the values of the models without frailty. Moreover, it is necessary to consider that we are comparing conventional point estimates and confidence intervals with values obtained via bootstrapping methods, whose confidence regions are usually wider than conventional confidence intervals. Nevertheless, a comparison is still possible.

The introduction of frailty affected the mortality gradient by education. Although the uncertainty around the estimates does not allow assessing a precise effect, the rate ratios of medium and low education in respect to high education in the models with frailty lie in a higher confidence region than in the models without: among women with a medium education level, it lies between 1.05 and 1.34 compared to 1.08 and 1.13 of the model without frailty and for the low education group, between 1.1 and 1.6, compared to 1.18 and 1.23. The same pattern can be observed among men.

The male difference between medium and low education group, on the contrary, was not as clear as that among women.

Other results and the impact of the macro-region of birth on mortality

As expected, the variance of frailty in the cohort models was smaller than in the period models, since periods are more heterogeneous than cohorts.

Women were more heterogeneous than men: 0.09 (0.08-0.11) versus 0.04 (0.03-0.05) in the age-cohort models and 0.29 (0.17-0.37) versus 0.27 (0.-0.36) in the age-period models.

This is consistent with the more pronounced convergence of the hazards by education at old age found among women compared to the men. According to the framework of the frailty models, converging hazards are the result of the effect of selection on the population hazards, due to how much variance of unobserved frailty is present in the population at the initial age of observation. The bigger the variance the stronger the convergence is. For more information about frailty models, the process of selection and how they relate to narrowing mortality differentials at old ages, please see appendix A.

In the age-cohort models the introduction of unobserved frailty affected the coefficient for the macro-region of birth significantly. Among men, holding education equal, those born in the South show a significant survival advantage over the natives of the North-West, while in the model without frailty there was no such advantage. Among women, the model without frailty showed a significant survival advantage for those born in the South but when frailty was controlled for, this became not significant.

The pattern also resembles the regional mortality macro-dynamics that have characterized Italy for most of the 20th century (although the two patterns refer to different phenomena, the first one referring to mortality by region of birth), when male mortality in the South was lower than in the North (45-48). Cohort based analyses have highlighted that in more recent cohorts (those born after WWII) there is a reversing trend (48, 49).

The models with age-period perspective did not identify any significant geographical differences. This could be due to the utilization of random subsampling of a 1% sample. Although 250 repetitions is considered by the literature a sufficient number for very complex models (50-52), it is possible that it was inadequate to identify a clear pattern from the small sample. For more detailed results see tables 1 and 2.

Discussion

The interest in the role of unobserved heterogeneity in a life course approach to socioeconomic mortality differences has recently increased. Most of the studies focus on health outcomes (53-58) while fewer studies also analyze mortality (59-61). Their findings are not consistent and fuel a still controversial debate.

In this study we investigated the role of unobserved individual heterogeneity on the estimation of mortality differentials at adult-old ages by education level in a longitudinal perspective. This study investigated if the estimates of the mortality differentials are affected by the introduction of the unobserved heterogeneity component into the models.

We fitted survival analysis models with and without controlling for the unobserved heterogeneity and we found that, when this component was included, the models gave a significantly better fit.

We also found that in the majority of the cases, the educational gradient estimated by the models with frailty was higher than the one estimated by the models without frailty. When big uncertainty around the estimates did not allow assessing a precise value, the confidence regions in the models with frailty spanned over higher values than those in the models without frailty. It must be pointed out that, in the age-period approach, to the peculiar statistical procedure used to estimate the frailty models did not allow obtaining a likelihood value comparable with the one of the model without frailty. Thus, the statistical comparison of the models via the AIC was not possible, making this evidence weaker. Nevertheless, the results seem to point to a direction that is consistent with the statistical literature about unobserved heterogeneity (19-26).

Among men such a pattern was found in both the age-cohort and age-period approaches. Among women, on the contrary, this pattern was less clear: in the age-cohort model, controlling for hidden frailty resulted in a slight reduction of the mortality gradient. Social determinants act on mortality also through risk factors that are known to affect more men than women. Moreover, because of a lag in the smoking and fertility transitions, highly educated women in Turin are more exposed to risk factors like cigarette smoking and smaller number of children. Therefore, controlling for hidden frailty in the case of women might reduce the educational gradient.

In the models with age-cohort perspective controlling for the hidden frailty affected also the estimates of the differentials by macro-region of birth, showing a survival advantage of the men born in the South, but not of the women, for whom an advantage was instead detected by the model that did not control for frailty.

The healthy migrant effect (62-67) could cause this pattern. Among the cohorts involved in the migration women were likely to be more passive actors than men in the migratory decision (68-70) and this might have selected them more than men. Frailty is a general concept embedding all the hidden factors that affect the individual survival chances: innate and acquired frailty, exposure to risk factors, life style factors and so on. Therefore, controlling for frailty reduced the survival advantage of the women, who might have been less health selected than men by the migration, while uncovered the advantage of the men. However, another recent study on the impact of migration on all-cause mortality in Turin did not find particularly strong gender differences in the so called healthy migrant effect (66) and this point deserves future further investigation.

The study spanned over a long observation window of 36 years. Therefore it was important to control for the general mortality improvement that took place during this time. We did so by adopting both an age-period and an age-cohort approach.

The age-period models, as expected, estimated higher heterogeneity than the age-cohort models. Periods aggregate different generations and are expected to be more heterogeneous than the cohorts themselves. In both period and cohort models the female variance of frailty was higher than for the males, indicating that men are more homogeneous than women. This could be attributed to a stronger selection process due to mortality that is usually observed to be higher among men than among women.

On the other hand, it is also possible that the industrialization process and the internal migration experienced by Italy after WWII (34) played a role. The vast majority of less educated individuals in Turin came from the South, seeking a job in the car factories of the city. As less educated men were mainly employed in heavier and riskier jobs and were exposed to higher mortality, it is possible that during their life they were selected at a faster pace than other educational groups and women. This might have reduced the differences in susceptibility to death among men, contributing to determining a lower level of heterogeneity than among women.

Conclusion

This study found that neglecting selection effects due to unobserved heterogeneity in longitudinal analyses, could lead to underestimation of mortality differentials by social class. In the majority of the cases, the models that controlled for unobserved heterogeneity, estimated higher educational differences in mortality than the models that did not control for it.

Moreover, when compared with via the AIC, the models that controlled for unobserved heterogeneity gave a statistically significant better fit than the models that did not control for it. Although the best AIC shows just that the more complex model approximates better the data and this does not represent an unequivocal proof of the selection hypothesis, the results point to the possibility that the data could be better described by this hypothesis.

Summary

Article Focus

- Neglecting the presence of unobserved heterogeneity in survival analysis models has been showed to potentially lead to underestimating the effect of the covariates included in the analysis.

- Although frailty models have been widely developed to account for unobserved heterogeneity, in differential mortality analyses this source of variation is seldom controlled for. This study has applied these models to a longitudinal mortality analysis by education level.

Key messages

- Mortality differentials by education (or by any other variable used as proxy of socioeconomic status) could be larger than those estimated with standard survival analysis approaches that do not control for unobserved heterogeneity.

Strengths and limitations

The strength of this study lies in the population based longitudinal data. The long observational time (36 years) for more than 847 000 individuals gives a solid base for statistical power and detection of trends.

The limitation consists in the lack of individual information on life style factors and health events, which could certainly help to better model the concept of unobserved individual frailty by uncovering part of it.

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Contributorship. Virginia Zarulli: conception and design of the study, analysis and interpretation of data and results, drafting the article and revising it; Graziella Caselli: interpretation of the results, drafting the article and revising it critically; Chiara Marinacci and Giuseppe Costa: revising the article for important intellectual content.

Data sharing. There is no additional data available.

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Appendix

A. Frailty models and Survival Analysis

Frailty models

Hidden differences in survival chances make individuals differ in their susceptibility to death. This complex set of characteristics, called unobserved frailty, does not distinguish between acquired weakness, life style factors, environmental risks and innate biological frailty, but it indicates a general susceptibility to death (1).

In cohort analyses, as the population ages, frailer individuals die faster and gradually select the survivors in terms of robustness, because the population undergoes a compositional change. This causes the population hazard to decelerate at very old ages because, at every age, the death rate is computed based on a population at risk whose composition is gradually converging towards the low frailty individuals, who have also lower mortality. The greater the variance of unobserved heterogeneity of frailty at the initial age of observation, the stronger the selection process and, therefore, the faster the deceleration of the hazard observed at the population level as age goes by.

Neglecting the presence of unobserved frailty and its selection processes can lead in survival analysis models to possible biases in the estimates of the regression coefficients. In the case of mortality by socioeconomic position, education level or income groups, higher mortality groups are selected at a faster rate than lower mortality groups (because the higher the mortality the stronger the force of selection). Therefore, the frailest individuals in these groups are selected out at a faster pace. Consequently, at the same age, what is left in the high mortality group is a more selected population in terms of robustness, compared to the low mortality group, which undergoes a slower pace of selection. The difference between the rates of selection causes the mortality curves to converge and gives the impression that the effect of the covariate that defines the two groups (for example education level) declines with age. Also in this case, the greater the variance of unobserved heterogeneity in the population at the initial age of observation, the stronger the selection process and, therefore, the stronger the convergence between subgroups at old ages.

Main equations of the framework of the frailty models.

Frailty models assume that every individual has a specific level of unobserved frailty, *z*, that defines its hazard in a context of proportional hazard models. There is a standard individual, whose frailty *z*, is standardized to 1, and all the others have a frailty that is proportional to the frailty of the standard individual. If $\mu(x)$ is the hazard of the standard individual (or baseline hazard), defined as a function of age and frailty:

$$\mu(x,z) = z\mu(x)$$

at any age, what is observed at the population level is the mean mortality rate at that age, $\bar{\mu}(x)$, for the survivors of each frailty. That is, the standard individual hazard multiplied by the mean frailty among survivors at that age, which is a decreasing quantity:

$\bar{\mu}(x) = \mu(x)\bar{z}(x)$ Assuming that unobserved frailty follows a Gamma distribution, the population hazard $\bar{\mu}(x)$ at any age *x* is expressed as a mixture of individual hazards $\mu(x)$, by the following relationship:

$$\bar{\mu}(x) = \frac{\mu(x)}{1 + \sigma^2 \int_0^x \mu(t)dt} \qquad (1)$$

where σ^2 is the variance of the frailty distribution with mean 1 at the initial age and $\mu(x)$ is the hazard experienced by the standard individual with frailty 1. The optimization problem estimates the baseline hazard parameters and the variance of the frailty in the population.

Survival analysis without unobserved heterogeneity

The only variability controlled for is the one explained by the observed covariates, u, included in the model. Their effect on the baseline hazard $\mu_0(x)$ is estimated as follows:

$$\mu_i(x \mid u_i) = \mu_0(x)e^{\beta u_i} \qquad (2)$$

The likelihood function in case of right censored and left truncated survival data is:

$$L(\beta,\theta) = \prod_{i=1}^{n} \frac{\left(\mu(x_i,\theta)e^{u_i\beta}\right)^{\delta_i} S(x_i,\theta)^{e^{u_i\beta}}}{S(y_i,\theta)^{e^{u_i\beta}}} \qquad (3)$$

Where for each individual i, y_i is the entry time, x_i in the exit time, δ_i is the status (1=dead, 0=right censored), u_i is the covariate profile with effect β and $\mu(.)$ denotes the hazard, $S(.)$ the survival function and θ is the vector of parameters of the baseline hazard.

Univariate frailty models

An individual random effect for the frailty is introduced in the model as a multiplicative term on the baseline hazard:

$$\mu_i(x \mid u_i, z_i) = z_i \mu_0(x)e^{\beta u_i} \qquad (4)$$

The likelihood function in case of right censored and left truncated survival data is:

$$L(\beta,\theta,\sigma^2) = \prod_{i=1}^{n} \frac{\left(\dfrac{\mu(x_i,\theta)e^{u_i\beta}}{1+\sigma^2 M(x_i,\theta)e^{u_i\beta}}\right)^{\delta_i} \left(1+\sigma^2 M(x_i,\theta)e^{u_i\beta}\right)^{-\frac{1}{\sigma^2}}}{\left(1+\sigma^2 M(y_i,\theta)e^{u_i\beta}\right)^{-\frac{1}{\sigma^2}}} \qquad (5)$$

Where for each individual i, y_i is the entry time, x_i in the exit time, δ_i is the status (1=dead, 0=right censored), u_i is the covariate profile with effect β and $\mu(.)$ denotes the hazard, $M(.)$ the cumulative hazard, θ is the vector of parameters of the baseline hazard and σ^2 is the variance of frailty.

Shared frailty models

In the case of repeated survival spells for the same individual i, the shared frailty models assume that those spells share the same hidden frailty, as showed by equation (6):

$$\mu_i(x \mid u_{i,j}, z_i) = z_i \mu_0(x) e^{\beta u_{i,j}} \qquad (6)$$

Where the indexes j and i represent the survival spell j of the individual (cluster) i.

The cluster (individual) likelihood function in case of right censored and left truncated survival data is (2):

$$L_i = \left(\prod_{j=1}^{n_i} \left(\mu(x_{ij}, \theta) e^{u_{ij}\beta} \right)^{\delta_{ij}} \right) \frac{\Gamma\left(\frac{1}{\sigma^2} + D_i\right)}{\Gamma\left(\frac{1}{\sigma^2}\right)} \left(\sigma^2\right)^{D_i} \left(1 - \sigma^2 \sum_{j=1}^{n_i} \ln\left(S_{ij}\left(y_{ij}, \theta\right)^{e^{u_{ij}\beta}} \right) \right)^{\frac{1}{\sigma^2}} \left(1 - \sigma^2 \sum_{j=1}^{n_i} \ln\left(S_{ij}\left(x_{ij}, \theta\right)^{e^{u_{ij}\beta}} \right) \right)^{-\frac{1}{\sigma^2} - D_i} \qquad (7)$$

Where for each j-th individual in the i-th cluster, y_{ij} is the entry time, x_{ij} in the exit time, δ_{ij} is the status (1=dead, 0=right censored), u_{ij} is the covariate profile with effect β and $\mu(.)$ denotes the hazard, $S(.)$ the survival function, θ is the vector of parameters of the baseline hazard, σ^2 is the variance of frailty and $D_i = \sum \delta_{ij}$.

The overall likelihood function is simply:

$$L(\beta,\theta,\sigma^2)=\prod_{i=1}^{n}L_i \qquad (8)$$

B. Exponential model

Table B1 reports the results of the exponential model with age as covariate. The exponential baseline hazard, $\mu(x)=\lambda$, is constant and does not change with age. This allows us to include the age as a covariate and to have it interacted with the covariate for education level. The aim is to investigate whether there is a statistically detectable convergence of hazards at old ages by education group, by testing whether there is a significant interaction between the variables education and age.

The single parameter baseline hazard was modulated by the covariate for the age groups. Equations 9 and 10 describe the hazard and the survival functions of the exponential model with covariates.

$$\mu(x) = \lambda e^{\beta\, cov} \qquad (9)$$

$$S(x) = (e^{-\lambda x})^{e^{\beta\, cov}} \qquad (10)$$

The identity between an exponential hazard modulated by an age covariate and the Gompertz model makes such exponential models appropriate for human adult mortality data. The age was divided into two groups: 50-80 and 80+. Education was divided into three groups: low, medium and high. In addition to age and education, the model controlled also for period effects by introducing a variable for the calendar years.

For the sake of simplicity table B1 does not report the coefficients for the period variable and for the λ parameter of the exponential hazard. The results show that the risk of death is inversely proportional to the educational level. However, the relative difference between low education and high education narrows at older ages and the reduction is more pronounced among women than among men.

A likelihood ratio test between the simple model without age-education interaction and the model which includes such interaction was performed. The test showed that the interaction term significantly improved the fit of the model.

Table B1. Mortality rate ratios between education groups and age groups estimated from an exponential survival hazard model with covariates education, age and their interaction. The table also reports the likelihood ratio test between this model and a model without an age-education interaction term.

	Men				Women			
	50-80 years		80+ years		50-80 years		80+ years	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
High	1	-	1	-	1	-	1	-
Medium	1.234	1.209-1.259	1.082	1.048-1.116	1.250	1.213-1.289	1.040	1.008-1.073
Low	1.571	1.544-1.598	1.172	1.143-1.202	1.594	1.552-1.637	1.170	1.136-1.202
Likelihood ratio test with reduced model (without age-education interaction)								
	D statistics: 395.193		Df: 2	p-value:0.000	D statistics:319.833		Df: 2	p-value:0.000

1. Manton KG, Stallard E, Vaupel JW. Methods for comparing the mortality experience of heterogeneous populations. Demography. 1981;18(3):389-410.
2. Van den Berg GJ, Drepper B. Inference for Shared-Frailty Survival Models with Left-Truncated Data. IZA Discussion Paper No 6031. 2011.

Figures

Figure 1. Death rates, on logarithmic scale, for the birth cohort aged 50-59 at the beginning of the follow-up (1971) by three education levels: high, medium and low.

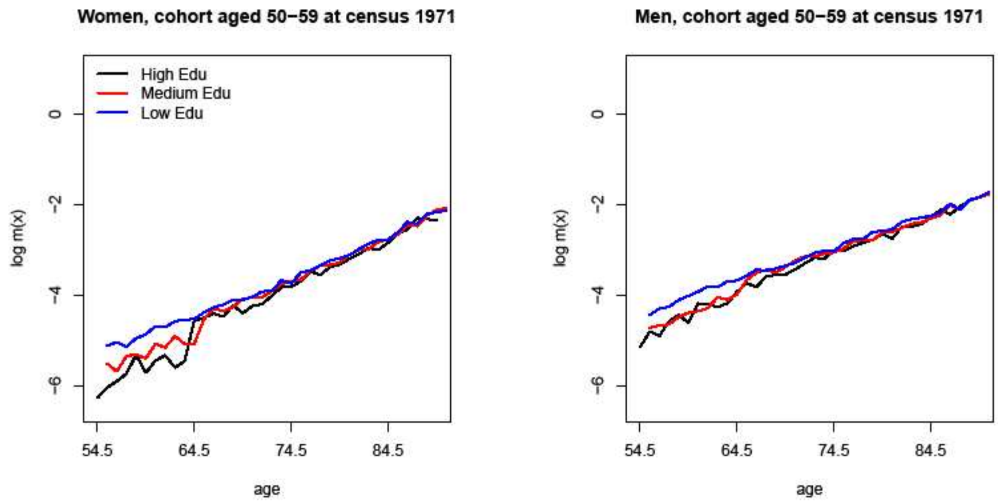
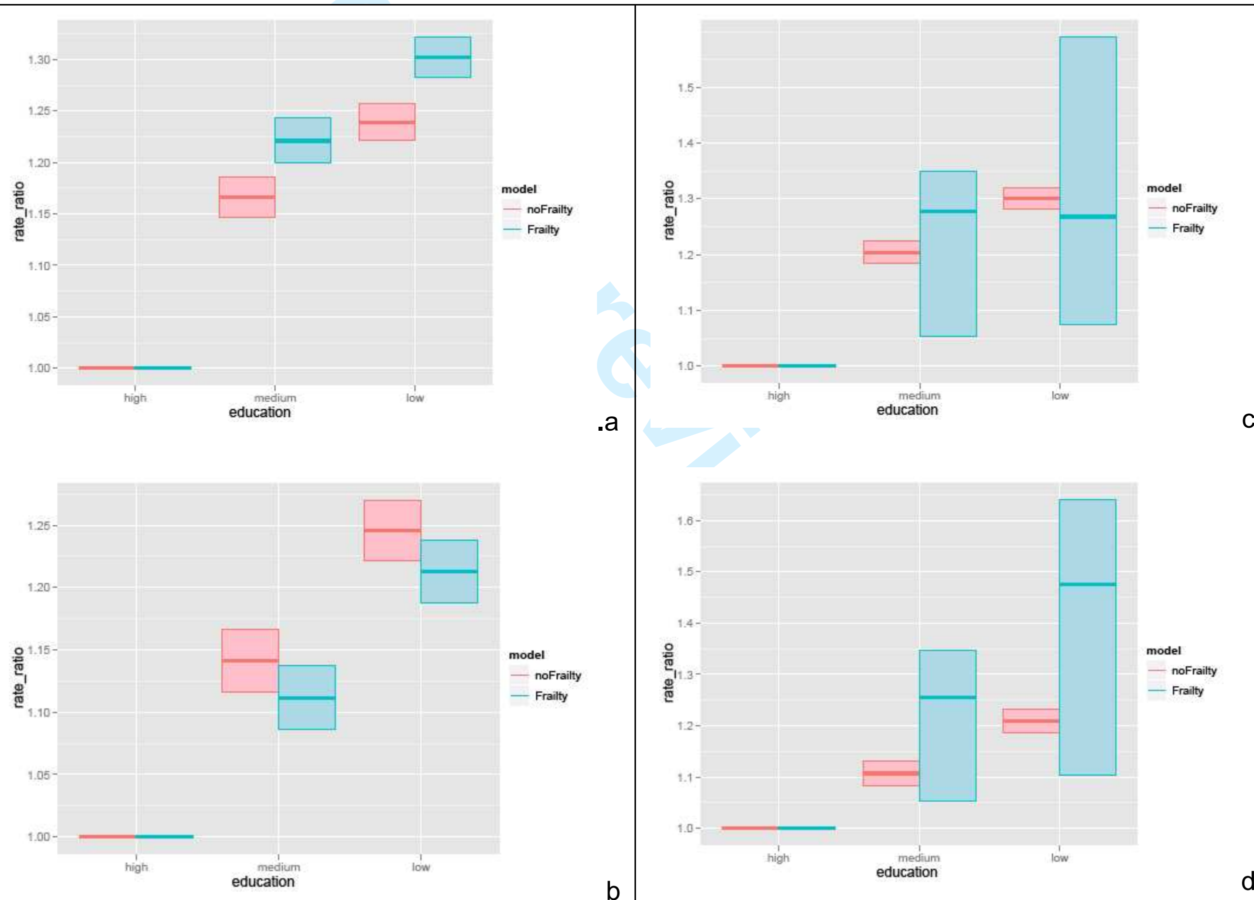


Figure 2. Mortality rate ratios by education level in the models with cohort and period improvements, without and with frailty. a) Men, cohort model; b) Women, cohort model; c) Men, period model; d) Women, period model.

Model with cohort improvement | Model with period improvement



	Men (a)		Women (b)	
	No frailty	Frailty	No frailty	Frailty
LogLik	-651 219	-651 082	-663 238	-663 098
AIC	1302456	1302184	1326496	1326218

	Men (c)		Women (d)	
	No frailty	Frailty	No frailty	Frailty
LogLik	-663 081	Na	-650 997	Na
AIC	1326204	Na	1302034	Na