



**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 than 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

1  
2 unobserved heterogeneity component into the models: this would strengthen the validity of  
3  
4 the selection hypothesis as an alternative explanation for the reduction of the differences in  
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6 socioeconomic mortality at old ages.  
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## 10 **Data and Methods**

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12 We used high quality census linked data from the Turin Longitudinal Study (TLS), which  
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14 includes 1971, 1981, 1991 and 2001 census data for the Turin population. TLS records the  
15  
16 individual census socio-demographic information and, through record linkage with the local  
17  
18 population registry and other local health information systems, collects information on vital  
19  
20 status, cause of death and other health indicators (28, 29).  
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24  
25 For this study, the individuals registered in Turin during at least one of the four  
26  
27 censuses were selected. Their migration and vital status was followed up until the end of July  
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29 2007. The result is an observation window of 36 years (from October 24<sup>th</sup> 1971, official date  
30  
31 of the census, to the end of July 2007, end of the linkage) during which the individuals were  
32  
33 followed up until death, emigration from the city or end of observation period. The follow up  
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35 started at age 50. The study population contains 391 170 men and 456 216 women.  
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38  
39 Study information includes individual's date of birth, date of exit from the study, cause  
40  
41 of exit (death or emigration), sex, macro-region of birth and education level.

42  
43 Consistent with the literature (30-33) education level was used as an indicator of  
44  
45 social position.

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47 The study also controlled for the individual macro region of birth, as Turin is  
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49 characterized by a history of immigration from other regions of the country (34).  
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51  
52 To facilitate the comparison over a long follow up and different cohorts, we created  
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54 three broad educational groups: high (high school diploma or higher), medium (junior high  
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56 school) and low (primary school or lower).  
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2 We estimated parametric survival models stratified by gender and as a function of  
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4 macro-region of birth and education level, with and without a parameter for the unobserved  
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6 heterogeneity component. The parametric choice is justified by the wide demographic  
7  
8 literature showing that human adult mortality can be accurately described by a Gompertz  
9  
10 function (35) or by some Gompertz-like variants, like Makeham. To identify the best  
11  
12 functional form for the baseline we compared the models with the AIC (36).  
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15  
16 The data are both right censored (due to emigration or end of follow up) and left  
17  
18 truncated (due to the different age at entry in the study of the individuals).  
19

20  
21 The study includes many cohorts, each passing through the 36 years of observation at  
22  
23 different ages. However, from 1971 to 2007 a significant mortality improvement occurred and  
24  
25 younger cohorts experience lower age specific mortality than older cohorts. To take into  
26  
27 account this factor we used two strategies.  
28

29  
30 First, we regarded the improvement as a cohort phenomenon, including a covariate for  
31  
32 the cohort to which the individuals belong. In this setting, controlling for unobserved  
33  
34 heterogeneity was implemented with univariate frailty models, which estimate the baseline  
35  
36 parameters, the coefficients of the covariates and the variance of frailty (assumed to follow a  
37  
38 gamma distribution with mean 1 and variance  $\sigma^2$  to be estimated).  
39

40  
41 We then considered the improvement as a period phenomenon and split the time into  
42  
43 several calendar period covariates, as well as the survival spell of the individuals, according to  
44  
45 which period they were passing through. This implied organizing the data into clusters, where  
46  
47 each cluster represents one individual's survival spells. In this setting, to control for  
48  
49 unobserved heterogeneity shared frailty models are needed, where the spells in each cluster  
50  
51 pertain to the same individual and share the same hidden frailty. For computational reasons,  
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53 the estimation of these highly complex models required the use of random subsampling (37-  
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55 39). We repeated the estimation 250 times on a 1% sample of the dataset, randomly drawn  
56  
57 without replacement and stratified by the major variables in analysis. The aim is to  
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1  
2 approximate the parameters estimates based on the empirical distribution of the repeated  
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4 estimates.  
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7 In the model without frailty it was possible to include a finer calendar period division,  
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9 12 period variables of 3 years each (1971-1973, 1974-1976...), while in the model with  
10  
11 frailty, for computational reasons, the number of variables was reduced to 2 broader periods:  
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13 1971-1990 and 1991-2007.  
14

15 Computations were realized with the software R (40). Formal details are in appendix  
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17 A.  
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## 20 21 22 **Results**

23  
24 Figure 1 shows that the log-death rates by education level and gender, for the cohort aged 50-  
25  
26 59 in 1971, converge at old ages. Other cohorts showed very similar patterns.  
27

28  
29 A preliminary analysis found that the reduction of the gradient over age is statistically  
30  
31 significant and slightly more pronounced among women (results are reported in appendix B  
32  
33 table B1).  
34

35  
36 Figure 1 here

### 37 38 *Frailty modeling*

39  
40 Table 1 shows the AIC of the survival models, fitted to the all population mortality, with  
41  
42 Gompertz and Makeham baselines. It also shows the results of the fit when unobserved frailty  
43  
44 was controlled for. The comparison reveals that Gompertz baseline was a better fit for the  
45  
46 male data, while Makeham was better for the female. In both cases, the models controlling for  
47  
48 unobserved heterogeneity performed a better fit (table 1).  
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**Table 1. Model selection of 4 different hazard models based on the AIC.**

|           | Gompertz  | Makeham       | Gam-Gompertz   | Gam-Makeham   |
|-----------|-----------|---------------|--|---|
|           | $ae^{bx}$ | $ae^{bx} + c$ | $\frac{ae^{bx}}{1 + \sigma^2 \frac{a}{b}(e^{bx} - 1)}$ | $\frac{ae^{bx} + c}{1 + \sigma^2 \frac{a}{b}(e^{bx} - 1) + cx}$ |
| 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

1  
2 subsampling for the estimation of the frailty model (37-39) did not allow obtaining a  
3  
4 likelihood value comparable with the values of the models without frailty. Moreover, it is  
5  
6 necessary to consider that we are comparing conventional point estimates and confidence  
7  
8 intervals with values obtained via bootstrapping methods, whose confidence regions are  
9  
10 usually wider than conventional confidence intervals. Nevertheless, a comparison is still  
11  
12 possible.  
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14  
15 The introduction of frailty affected the mortality gradient by education. Although the  
16  
17 uncertainty around the estimates does not allow assessing a precise effect, the rate ratios of  
18  
19 medium and low education in respect to high education in the models with frailty lie in a  
20  
21 higher confidence region than in the models without: among women with a medium education  
22  
23 level, it lies between 1.05 and 1.34 compared to 1.08 and 1.13 of the model without frailty  
24  
25 and for the low education group, between 1.1 and 1.6, compared to 1.18 and 1.23. The same  
26  
27 pattern can be observed among men.  
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30 The male difference between medium and low education group, on the contrary, was not as  
31  
32 clear as that among women.  
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### 35 36 37 *Other results and the impact of the macro-region of birth on mortality*

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39 As expected, the variance of frailty in the cohort models was smaller than in the period  
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41 models, since periods are more heterogeneous than cohorts.  
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45 Women were more heterogeneous than men: 0.09 (0.08-0.11) versus 0.04 (0.03-0.05)  
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47 in the cohort models and 0.29 (0.17-0.37) versus 0.27 (0.-0.36) in the period models.  
48

49  
50 In the cohort models the introduction of unobserved frailty affected the coefficient for  
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52 the macro-region of birth significantly. Among men, holding education equal, those born in  
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54 the South show a significant survival advantage over the natives of the North-West, while in  
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56 the model without frailty there was no such advantage. Among women, the model without  
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2 frailty showed a significant survival advantage for those born in the South but when frailty  
3 was controlled for, this became not significant.  
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7 The pattern also resembles the regional mortality macro-dynamics that have  
8 characterized Italy for most of the 20<sup>th</sup> century (although the two patterns refer to different  
9 phenomena, the first one referring to mortality by region of birth), when male mortality in the  
10 South was lower than in the North (41-44). Cohort based analyses have highlighted that in  
11 more recent cohorts (those born after WWII) there is a reversing trend (44, 45).  
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18 The models with period perspective did not identify any significant geographical  
19 differences. This could be due to the utilization of random subsampling of a 1% sample.  
20 Although 250 repetitions is considered by the literature a sufficient number for very complex  
21 models (46-48), it is possible that it was inadequate to identify a clear pattern from the small  
22 sample.  
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29 For more detailed results see tables C1 and C2 in appendix C.  
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## 32 33 **Discussion**

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35 The interest in the role of unobserved heterogeneity in a life course approach to  
36 socioeconomic mortality differences has recently increased. Most of the studies focus on  
37 health outcomes (49-54) while fewer studies also analyze mortality (55-57). Their findings are  
38 not consistent and fuel a still controversial debate.  
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45 In this study we investigated the role of unobserved individual heterogeneity on the  
46 estimation of mortality differentials at adult-old ages by education level in a longitudinal  
47 perspective. This study investigated 1) whether the framework of the frailty models can  
48 explain the observed pattern of convergence of the mortality risk by social position at old ages  
49 2) if the estimates of the mortality differentials are affected by the introduction of the  
50 unobserved heterogeneity component into the models.  
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2 We fitted survival analysis models with and without controlling for the unobserved  
3 heterogeneity and we found that, when this component was included, the models gave a  
4 significantly better fit.  
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9 We also found that in the majority of the cases, the educational gradient estimated by  
10 the models with frailty was higher than the one estimated by the models without frailty. When  
11 big uncertainty around the estimates did not allow assessing a precise value, the confidence  
12 regions in the models with frailty spanned over higher values than those in the models without  
13 frailty. This is consistent with the statistical literature about unobserved heterogeneity, which  
14 shows that neglecting its selective action, in duration dependence models, leads to  
15 underestimation of the covariates effect (19-26).  
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24 Among men such a pattern was found in both the cohort and period approaches.  
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26 Among women, on the contrary, this pattern was less clear: in the cohort model, controlling  
27 for hidden frailty resulted in a slight reduction of the mortality gradient. Social determinants  
28 act on mortality also through risk factors that are known to affect more men than women.  
29 Moreover, because of a lag in the smoking and fertility transitions, highly educated women in  
30 Turin are more exposed to risk factors like cigarette smoking and smaller number of children.  
31 Therefore, controlling for hidden frailty in the case of women might reduce the educational  
32 gradient.  
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42 In the models with cohort perspective controlling for the hidden frailty affected also  
43 the estimates of the differentials by macro-region of birth, showing a survival advantage of  
44 the men born in the South, but not of the women, for whom an advantage was instead  
45 detected by the model that did not control for frailty.  
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51 The healthy migrant effect (58-63) could cause this pattern. Among the cohorts  
52 involved in the migration women were likely to be more passive actors than men in the  
53 migratory decision (64-66) and this might have selected them more than men. Frailty is a  
54 general concept embedding all the hidden factors that affect the individual survival chances:  
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1  
2 innate and acquired frailty, exposure to risk factors, life style factors and so on. Therefore,  
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4 controlling for frailty reduced the survival advantage of the women, who might have been less  
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6 health selected than men by the migration, while uncovered the advantage of the men.  
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8 However, another recent study on the impact of migration on all-cause mortality in Turin did  
9  
10 not find particularly strong gender differences in the so called healthy migrant effect (62) and  
11  
12 this point deserves future further investigation.  
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15  
16 The study spanned over a long observation window of 36 years. Therefore it was  
17  
18 important to control for the general mortality improvement that took place during this time.  
19  
20 We did so by adopting both a period and a cohort approach.  
21

22  
23 The period models, as expected, estimated higher heterogeneity than the cohort  
24  
25 models. Periods aggregate different generations and are expected to be more heterogeneous  
26  
27 than the cohorts themselves. In both period and cohort models the female variance of frailty  
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29 was higher than for the males, indicating that men are more homogeneous than women. This  
30  
31 could be attributed to a stronger selection process due to mortality that is usually observed to  
32  
33 be higher among men than among women.  
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35  
36 On the other hand, it is also possible that the industrialization process and the internal  
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38 migration experienced by Italy after WWII (34) played a role. The vast majority of less  
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40 educated individuals in Turin came from the South, seeking a job in the car factories of the  
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42 city. As less educated men were mainly employed in heavier and riskier jobs and were  
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44 exposed to higher mortality, it is possible that during their life they were selected at a faster  
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46 pace than other educational groups and women. This might have reduced the differences in  
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48 susceptibility to death among men, contributing to determining a lower level of heterogeneity  
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50 than among women.  
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## 52 53 54 55 56 **Conclusion** 57 58 59 60

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2 This study found that neglecting selection effects due to unobserved heterogeneity in  
3 longitudinal analyses, could lead to underestimation of mortality differentials by social class.  
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6 In the majority of the cases, the models that controlled for unobserved heterogeneity,  
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8 estimated higher educational differences in mortality than the models that did not control for  
9  
10 it.  
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12  
13 Moreover, the models that controlled for unobserved heterogeneity gave a statistically  
14 significant better fit than the models that did not control for it. This strengthens the validity of  
15 the selection hypothesis as explanation for the reduction of the gradient in socioeconomic  
16 mortality.  
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22 This analysis also has important policies facets. Specifically, when studying  
23 differential survival chances in socioeconomic groups, the tendency to dismiss the importance  
24 of such differences in old ages, because they are observed to diminish, should be avoided.  
25  
26 Individuals might experience a disadvantaged position throughout their life which does not  
27 fade away when they age. The lessening of differences at old ages could be the result of a  
28 stronger selection due to early higher mortality that disadvantaged groups are still subject to.  
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## 37 **Summary**

### 38 Article Focus

- 39 • Neglecting the presence of unobserved heterogeneity in survival analysis models has  
40 been showed to potentially lead to underestimating the effect of the covariates  
41 included in the analysis.  
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- 43 • Although frailty models have been widely developed to account for unobserved  
44 heterogeneity, in differential mortality analyses this source of variation is seldom  
45 controlled for. This study has applied these models to a longitudinal mortality analysis  
46 by education level.  
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### 57 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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1  
2 *Contributorship.* Virginia Zarulli: conception and design of the study, analysis and  
3 interpretation of data and results, drafting the article and revising it; Graziella Caselli:  
4 interpretation of the results, drafting the article and revising it critically; Chiara Marinacci and  
5 Giuseppe Costa: revising the article for important intellectual content.  
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13 *Data sharing.* There is no additional data available.  
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### 19 References

- 20  
21 1. Mackenbach JP, Kunst AE, Cavelaars AEJM, Groenhouf F, Geurts JJM, others.  
22 Socioeconomic inequalities in morbidity and mortality in western Europe. *The Lancet*.  
23 1997;349(9066):1655-9.
- 24 2. Mackenbach JP, Kunst AE, Groenhouf F, Borgan JK, Costa G, Faggiano F, et al.  
25 Socioeconomic inequalities in mortality among women and among men: an international  
26 study. *American Journal of Public Health*. 1999;89(12):1800-6.
- 27 3. Mackenbach JP, Stirbu I, Roskam AJR, Schaap MM, Menvielle G, Leinsalu M, et al.  
28 Socioeconomic inequalities in health in 22 European countries. *New England Journal of*  
29 *Medicine*. 2008;358(23):2468-81.
- 30 4. Antonovsky A. Social class, life expectancy and overall mortality. *The Milbank*  
31 *Memorial Fund Quarterly*. 1967;45(2):31-73.
- 32 5. Huisman M, Kunst AE, Mackenbach JP. Socioeconomic inequalities in morbidity  
33 among the elderly; a European overview. *Social Science & Medicine*. 2003;57(5):861-73.
- 34 6. Dalstra J, Kunst A, Mackenbach J, others. A comparative appraisal of the relationship  
35 of education, income and housing tenure with less than good health among the elderly in  
36 Europe. *Social Science & Medicine*. 2006;62(8):2046-60.
- 37 7. Martelin T. Mortality by indicators of socioeconomic status among the Finnish  
38 elderly. *Social Science & Medicine*. 1994;38(9):1257-78.
- 39 8. Huisman M, Kunst AE, Andersen O, Bopp M, Borgan JK, Borrell C, et al.  
40 Socioeconomic inequalities in mortality among elderly people in 11 European populations.  
41 *Journal of Epidemiology and Community Health*. 2004;58(6):468-75.
- 42 9. House JS, Lepkowski JM, Kinney AM, Mero RP, Kessler RC, Herzog AR. The social  
43 stratification of aging and health. *Journal of Health and Social Behavior*. 1994:213-34.
- 44 10. Decker S, Rapaport C. Medicare and disparities in women's health. *National Bureau of*  
45 *Economic Research*, 2002.
- 46 11. Dor A, Sudano J, Baker DW. The effect of private insurance on the health of older,  
47 working age adults: evidence from the Health and Retirement Study. *Health services research*.  
48 2006;41(3p1):759-87.
- 49 12. Marmot MG, Shipley MJ. Do socioeconomic differences in mortality persist after  
50 retirement? 25 year follow up of civil servants from the first Whitehall study. *Bmj*.  
51 1996;313(7066):1177-80.
- 52 13. Elo IT, Preston SH. Educational differentials in mortality: United States, 1979-1985.  
53 *Social Science & Medicine*. 1996;42(1):47-57.  
54  
55  
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14. Liang J, Bennett J, Krause N, Kobayashi E, Kim H, Brown JW, et al. Old age mortality in Japan. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. 2002;57(5):S294.
15. Caselli G, Vaupel JW, Yashin AI. Explanation of the decline in mortality among the oldest-old: A demographic point of view. *Human Longevity, Individual Life Duration, and the Growth of the Oldest-Old Population*. 2006:395-413.
16. Manton KG, Stallard E, others. Methods for evaluating the heterogeneity of aging processes in human populations using vital statistics data: explaining the black/white mortality crossover by a model of mortality selection. *Human biology; an international record of research*. 1981;53(1):47.
17. Vaupel JW, Manton KG, Stallard E. The impact of heterogeneity in individual frailty on the dynamics of mortality. *Demography*. 1979;16(3):439-54.
18. Vaupel JW, Yashin AI. Heterogeneity's ruses: some surprising effects of selection on population dynamics. *American statistician*. 1985:176-85.
19. Aalen OO. Effects of frailty in survival analysis. *Statistical Methods in Medical Research*. 1994;3(3):227.
20. Aalen OO. Heterogeneity in survival analysis. *Statistics in medicine*. 1988;7(11):1121-37.
21. Gail MH, Wieand S, Piantadosi S. Biased estimates of treatment effect in randomized experiments with nonlinear regressions and omitted covariates. *Biometrika*. 1984;71(3):431.
22. Trussell J, Rodriguez G. Heterogeneity in demographic research. *Convergent issues in genetics and demography*. 1990.
23. Chamberlain G. Heterogeneity, omitted variable bias, and duration dependence. *Longitudinal Analysis of Labor Market Data*, ed JJ Heckman, B Singer. 1985:3-38.
24. Schumacher M, Olschewski M, Schmoor C. The impact of heterogeneity on the comparison of survival times. *Statistics in medicine*. 1987;6(7):773-84.
25. Schmoor C, Schumacher M. Effects of covariate omission and categorization when analysing randomized trials with the Cox model. *Statistics in medicine*. 1997;16(3):225-37.
26. Bretagnolle J, Huber-Carol C. Effects of omitting covariates in Cox's model for survival data. *Scandinavian Journal of Statistics*. 1988:125-38.
27. Wienke A. *Frailty models in survival analysis*: Chapman & Hall/CRC; 2010.
28. Marinacci C, Spadea T, Biggeri A, Demaria M, Caiazzo A, Costa G. The role of individual and contextual socioeconomic circumstances on mortality: analysis of time variations in a city of north west Italy. *Journal of epidemiology and community health*. 2004;58(3):199-207.
29. Costa G, Cardano M, Demaria M. Torino. *Storie di salute in una grande città*. Città di Torino, Ufficio di statistica, Osservatorio socioeconomico torinese. 1998.
30. Doblhammer G, Hoffmann R, Muth E, Westphal C, Kruse A. A systematic literature review of studies analyzing the effect of sex, age, education, marital status, obesity, and smoking on health transitions. *Demographic Research*. 2009;20(5):37-64.
31. Krieger N, Williams DR, Moss NE. Measuring social class in US public health research: concepts, methodologies, and guidelines. *Annual Review of Public Health*. 1997;18(1):341-78.
32. Mirowsky J, Ross CE. *Education, social status, and health*: Aldine de Gruyter; 2003.
33. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Smith GD. Indicators of socioeconomic position (part 1). *Journal of Epidemiology and Community Health*. 2006;60(1):7-12.
34. Bonifazi C, Heins F. Long-term trends of internal migration in Italy. *International Journal of Population Geography*. 2000;6(2):111-31.



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35. Gompertz B. On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. *Philosophical transactions of the Royal Society of London*. 1825;115:513-83.
36. Akaike H. A new look at the statistical model identification. *Automatic Control, IEEE Transactions on*. 1974;19(6):716-23.
37. Hartigan JA. Using subsample values as typical values. *Journal of the American Statistical Association*. 1969:1303-17.
38. Politis DN, Romano JP. Large sample confidence regions based on subsamples under minimal assumptions. *The Annals of Statistics*. 1994;22(4):2031-50.
39. Efron B. Bootstrap methods: another look at the jackknife. *The annals of Statistics*. 1979;7(1):1-26.
40. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria 2011.
41. Barbi E, Caselli G. Selection effects on regional differences in survivorship in Italy. *Genus*. 2003:37-61.
42. Caselli G, Egidi V. Le differenze territoriali di mortalità in Italia. *Tavole di mortalità provinciali (1971-72)*. 1980.
43. Caselli G, Egidi V. L'analyse des données multidimensionnelles dan l'étude des relations entre mortalité et variable socio-économiques d' environment et de comportement individuel [Multivariate methods in the analysis of the relations between mortality and socio-economic, environmental and behavioural variables]. *Genus*. 1981;37(3/4):57-91.
44. Caselli G, Reale A. Does cohort analysis contribute to the study of the geography of mortality? *Genus*. 1999:27-59.
45. Biggeri A, Accetta G, Egidi V. Evoluzione del profilo di mortalità 30-74 anni per le coorti di nascita dal 1889 al 1968 nelle regioni italiane [Mortality Time Trends 30-74 years by Birth Cohorts 1889-1968 in the Italian Regions]. *Epidemiologia & Prevenzione*. 2011;35(5-6):50-67.
46. Efron B, Tibshirani R. *An introduction to the bootstrap*: Chapman & Hall/CRC; 1993.
47. Manly BFJ. *Randomization, bootstrap and Monte Carlo methods in biology*: Chapman & Hall/CRC; 1997.
48. Pattengale ND, Alipour M, Bininda-Emonds ORP, Moret BME, Stamatakis A. How many bootstrap replicates are necessary? *Journal of Computational Biology*. 2010;17(3):337-54.
49. Beckett M. Converging health inequalities in later life-an artifact of mortality selection? *Journal of Health and Social Behavior*. 2000:106-19.
50. Ferraro KF, Farmer MM. Double jeopardy, aging as leveler, or persistent health inequality? A longitudinal analysis of white and black Americans. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. 1996;51(6):S319.
51. Herd P. Do functional health inequalities decrease in old age? *Research on Aging*. 2006;28(3):375-92.
52. Kim J, Durden E. Socioeconomic status and age trajectories of health. *Social science & medicine*. 2007;65(12):2489-502.
53. Lynch SM. Cohort and life-course patterns in the relationship between education and health: A hierarchical approach. *Demography*. 2003;40(2):309-31.
54. McMunn A, Nazroo J, Breeze E. Inequalities in health at older ages: a longitudinal investigation of the onset of illness and survival effects in England. *Age and ageing*. 2009;38(2):181.
55. Dupre ME. Educational differences in age-related patterns of disease: Reconsidering the cumulative disadvantage and age-as-leveler hypotheses. *Journal of Health and Social Behavior*. 2007;48(1):1-15.



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56. Hoffmann R. Do socioeconomic mortality differences decrease with rising age? *Demographic Research*. 2005;13(2):35-62.
57. Hoffmann R. Socioeconomic inequalities in old-age mortality: A comparison of Denmark and the USA. *Social Science & Medicine*. 2011;72(12):1986 - 92.
58. Anson J. The migrant mortality advantage: a 70 month follow-up of the Brussels population. *European Journal of Population/Revue Européenne de Démographie*. 2004;20(3):191-218.
59. Feinleib M, Lambert PM, Zeiner-Henriksen T, Rogot E, Hunt BM, Ingster-Moore L. The British-Norwegian migrant study--analysis of parameters of mortality differentials associated with angina. *Biometrics*. 1982:55-71.
60. Kington R, Carlisle D, McCaffrey D, Myers H, Allen W. Racial differences in functional status among elderly US migrants from the south. *Social Science & Medicine*. 1998;47(6):831-40.
61. Norman P, Boyle P, Rees P. Selective migration, health and deprivation: a longitudinal analysis. *Social science & medicine*. 2005;60(12):2755-71.
62. Rasulo D, Spadea T, Onorati R, Costa G. The impact of migration in all-cause mortality: The Turin Longitudinal Study, 1971–2005. *Social Science & Medicine*. 2012.
63. Singh GK, Siahpush M. All-cause and cause-specific mortality of immigrants and native born in the United States. *American Journal of Public Health*. 2001;91(3):392.
64. Bielby WT, Bielby DD. I will follow him: Family ties, gender-role beliefs, and reluctance to relocate for a better job. *American Journal of Sociology*. 1992:1241-67.
65. Cooke TJ. Gender role beliefs and family migration. *Population, Space and Place*. 2008;14(3):163-75.
66. Mincer J. Family Migration Decisions. *Journal of Political Economy*. 1978;86:749-75.

## 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  $\bar{\mu}(x)$  at any age  $x$  is expressed as a mixture of individual hazards  $\mu(x)$ , by the following relationship:

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

where  $\sigma^2$  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:

$$\mu_i(x | u_i) = \mu_0(x) e^{\beta u_i} \quad (2)$$

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

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

Where for each individual  $i$ ,  $y_i$  is the entry time,  $x_i$  in the exit time,  $\delta_i$  is the status (1=dead, 0=right censored),  $u_i$  is the covariate profile with effect  $\beta$  and  $\mu(\cdot)$  denotes the hazard,  $S(\cdot)$  the survival function and  $\theta$  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:

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

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

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

Where for each individual  $i$ ,  $y_i$  is the entry time,  $x_i$  in the exit time,  $\delta_i$  is the status (1=dead, 0=right censored),  $u_i$  is the covariate profile with effect  $\beta$  and  $\mu(\cdot)$  denotes the hazard,  $M(\cdot)$  the cumulative hazard,  $\theta$  is the vector of parameters of the baseline hazard and  $\sigma^2$  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):

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

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):

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

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

The overall likelihood function is simply:

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

## 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      | Estimate              | 95% CI      | Estimate           | 95% CI      |
|                    | 0.000                 | 0.000-0.000 | 0.000              | 0.000-0.000 | 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 <sup>2</sup> | -                     | -           | 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 | <i>cohort</i>      | 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 <sup>2</sup> | -                     | -             | 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.

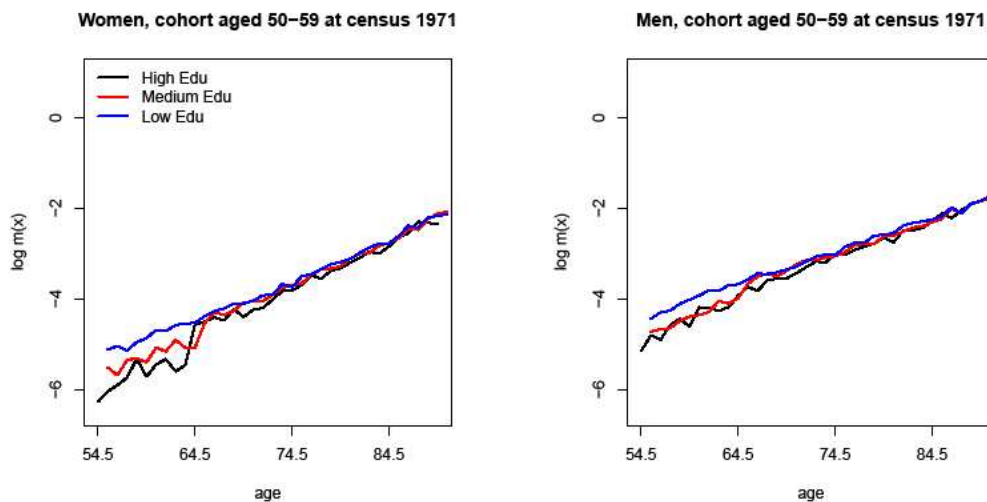
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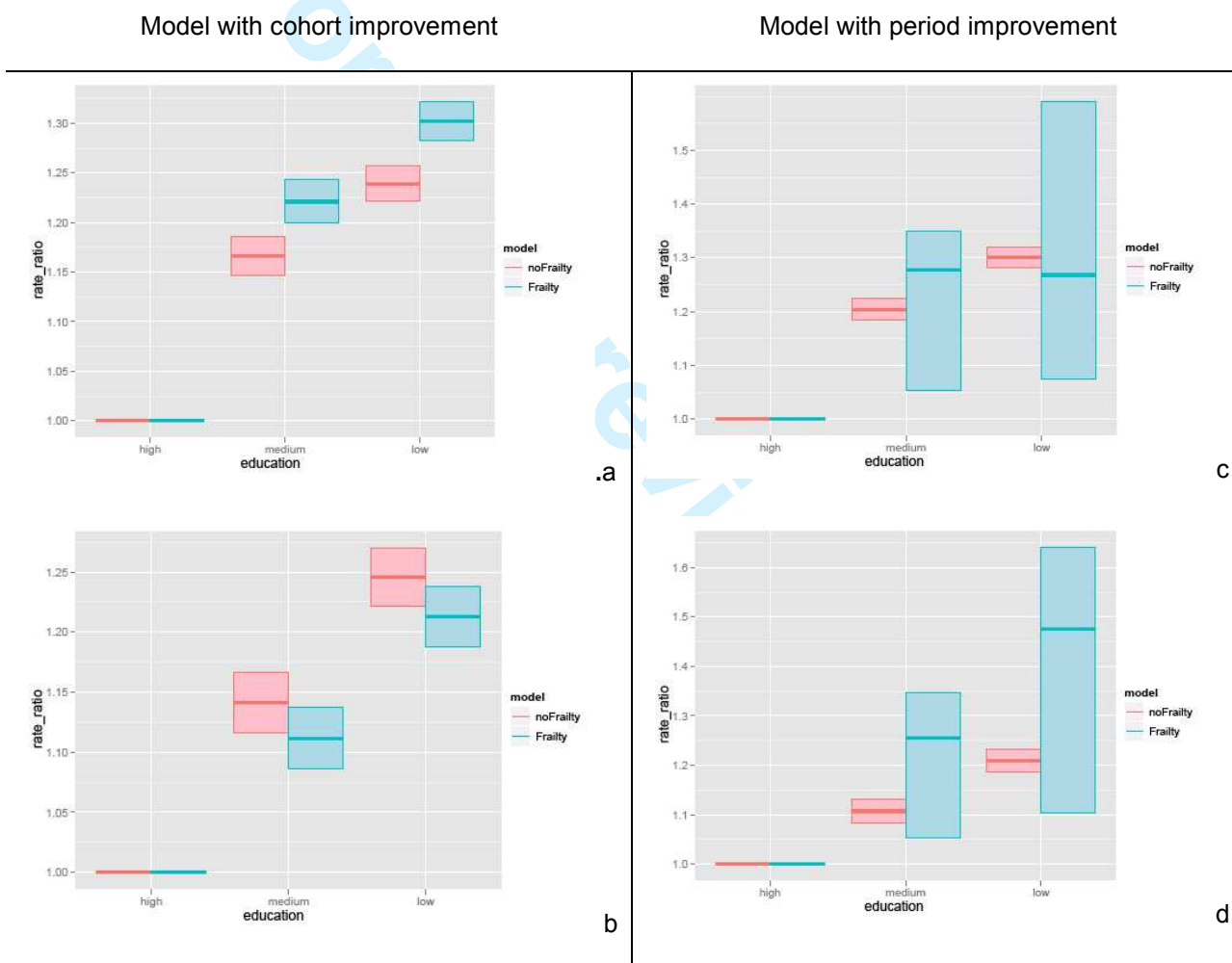
Figures

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.



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**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.**



|        | Men (a)    |          | Women (b)  |          | Men (c)    |         | Women (d)  |         |
|--------|------------|----------|------------|----------|------------|---------|------------|---------|
|        | No frailty | Frailty  | No frailty | Frailty  | No frailty | Frailty | No frailty | Frailty |
| LogLik | -651 219   | -651 082 | -663 238   | -663 098 | -663 081   | Na      | -650 997   | Na      |
| AIC    | 1302456    | 1302184  | 1326496    | 1326218  | 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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**Key words:** Mortality, inequality, education, frailty.

**Word count:** 2781

### **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 than the models with frailty.

1  
2 Conclusions. The results draw the attention on the potential underestimation of the mortality  
3  
4 inequalities by socioeconomic levels in survival models when not controlling for frailty.  
5  
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7

## 8 9 **Introduction**

10 An extensive literature shows significant differential mortality by socioeconomic condition  
11  
12 (1-3). Elderly show decreasing relative social inequalities in general mortality with increasing  
13  
14 age (4-8). The age-as-leveler hypothesis attributes this to factors that contribute to the  
15  
16 leveling-off of differences at old ages: governmental support to the elderly (9-11),  
17  
18 disengagement from systems of social stratification (12) and general vulnerability (13, 14).  
19  
20 However, this phenomenon could also be an artifact of selection due to unobserved  
21  
22 characteristics of the individuals: selective effects of earlier higher mortality, experienced by  
23  
24 the disadvantaged group, would leave more robust individuals at old ages, causing the  
25  
26 convergence with the risk of the lower mortality group, that is subject to weaker selection (15-  
27  
28 18). Neglecting these hidden differences in survival chances (called unobserved frailty), has  
29  
30 been shown to lead to biased estimates of the mortality hazard and of the effect of the  
31  
32 covariates on the survival probability (19-25).  
33  
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36  
37

38 In longitudinal analyses on differential mortality it is important to control for hidden  
39  
40 frailty. First, because not controlling for it, in survival models, could lead to biased estimates  
41  
42 of the effect of the social position on the mortality risk: the statistical literature shows that the  
43  
44 bias is towards zero (24-26). This would lead to underestimation of the relative differences in  
45  
46 the mortality risks by socioeconomic group. Second, because selection due to unobserved  
47  
48 frailty could provide an explanation for the phenomenon of decreasing relative differences in  
49  
50 death rates by socioeconomic group at old ages. To control for unobserved frailty and to  
51  
52 evaluate the impact on the observed mortality dynamics, frailty models have been developed  
53  
54 (27). For more detailed explanations of the frailty models and how they relate to differential  
55  
56 mortality analyses, please, see appendix A.  
57  
58  
59  
60

1  
2 This study investigated the presence of selection processes in the mortality patterns of  
3  
4 the Turin population (North-West Italy) from age 50 on. Adopting a longitudinal perspective,  
5  
6 this study aimed 1) to investigate whether the theoretical framework of the frailty models can  
7  
8 explain the observed pattern of convergence of mortality differentials by social position 2) to  
9  
10 investigate if the estimates of the mortality differentials are affected by the introduction of the  
11  
12 unobserved heterogeneity component into the models.  
13  
14

### 15 16 17 18 **Data and Methods**

19  
20 We used high quality census linked data from the Turin Longitudinal Study (TLS), which  
21  
22 includes 1971, 1981, 1991 and 2001 census data for the Turin population. TLS records the  
23  
24 individual census socio-demographic information and, through record linkage with the local  
25  
26 population registry and other local health information systems, collects information on vital  
27  
28 status, cause of death and other health indicators (28, 29).  
29  
30

31 For this study, the individuals registered in Turin during at least one of the four  
32  
33 censuses were selected. Their migration and vital status was followed up until the end of July  
34  
35 2007. The result is an observation window of 36 years (from October 24<sup>th</sup> 1971, official date  
36  
37 of the census, to the end of July 2007, end of the linkage) during which the individuals were  
38  
39 followed up until death, emigration from the city or end of observation period. The follow up  
40  
41 started at age 50. The study population contains 391 170 men and 456 216 women.  
42  
43

44 Study information includes individual's date of birth, date of exit from the study, cause  
45  
46 of exit (death or emigration), sex, macro-region of birth and education level.  
47  
48

49 Consistent with the literature (30-33) education level was used as an indicator of social  
50  
51 position.  
52

53 The study also controlled for the individual macro region of birth, as Turin is  
54  
55 characterized by a history of immigration from other regions of the country (34).  
56  
57  
58  
59  
60

1  
2 To facilitate the comparison over a long follow up and different cohorts, we created  
3  
4 three broad educational groups: high (high school diploma or higher), medium (junior high  
5  
6 school) and low (primary school or lower).  
7

8  
9 We estimated parametric survival models stratified by gender and as a function of  
10  
11 macro-region of birth and education level, with and without a parameter for the unobserved  
12  
13 heterogeneity component. The parametric choice is justified by the wide demographic  
14  
15 literature showing that human adult mortality can be accurately described by a Gompertz  
16  
17 function (35) or by some Gompertz-like variants, like Makeham. To identify the best  
18  
19 functional form for the baseline we compared the models with the AIC (36).  
20  
21

22 The data are both right censored (due to emigration or end of follow up) and left  
23  
24 truncated (due to the different age at entry in the study of the individuals).  
25  
26

27 The study includes many cohorts, each passing through the 36 years of observation at  
28  
29 different ages. However, from 1971 to 2007 a significant mortality improvement occurred and  
30  
31 younger cohorts experience lower age specific mortality than older cohorts.  
32

33 Time is a complex variable including three dimensions: age, period and cohort.  
34  
35 Controlling adequately for the effect of time would require to asses simultaneously the three  
36  
37 components but such models have been proved to be not identifiable because of linear  
38  
39 dependence between the three dimensions (37-39).  
40  
41

42 Therefore, we decided to adopt two approaches for the control of time, corresponding  
43  
44 to an age-cohort approach and an age-period approach, being aware that they represent two  
45  
46 different dimensions of time.  
47  
48

49 First, we regarded the improvement as a cohort phenomenon, including a covariate for  
50  
51 the cohort to which the individuals belong. In this setting, controlling for unobserved  
52  
53 heterogeneity was implemented with univariate frailty models, which estimate the baseline  
54  
55 parameters, the coefficients of the covariates and the variance of frailty (assumed to follow a  
56  
57 gamma distribution with mean 1 and variance  $\sigma^2$  to be estimated).  
58  
59  
60

1  
2 We then considered the improvement as a period phenomenon and split the time into  
3  
4 several calendar period covariates, as well as the survival spell of the individuals, according to  
5  
6 which period they were passing through. This implied organizing the data into clusters, where  
7  
8 each cluster represents one individual's survival spells. In this setting, to control for  
9  
10 unobserved heterogeneity shared frailty models are needed, where the spells in each cluster  
11  
12 pertain to the same individual and share the same hidden frailty. For computational reasons,  
13  
14 the estimation of these highly complex models required the use of random subsampling (40-  
15  
16 42). We repeated the estimation 250 times on a 1% sample of the dataset, randomly drawn  
17  
18 without replacement and stratified by the major variables in analysis. The aim is to  
19  
20 approximate the parameters estimates based on the empirical distribution of the repeated  
21  
22 estimates.  
23  
24  
25

26  
27 In the model without frailty it was possible to include a finer calendar period division,  
28  
29 12 period variables of 3 years each (1971-1973, 1974-1976...), while in the model with  
30  
31 frailty, for computational reasons, the number of variables was reduced to 2 broader periods:  
32  
33 1971-1990 and 1991-2007.  
34

35 Computations were realized with the software R (43). Formal details are in appendix  
36  
37 A.  
38

## 39 40 41 42 **Results**

43  
44 Figure 1 shows that the log-death rates by education level and gender, for the cohort aged 50-  
45  
46 59 in 1971, converge at old ages. Other cohorts showed very similar patterns.  
47  
48

49 A preliminary analysis found that the reduction of the gradient over age is statistically  
50  
51 significant and more pronounced among women (results are reported in appendix B table B1).  
52

53  
54 Figure 1 here

55  
56 *Frailty modeling*  
57  
58  
59  
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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   |
|-----------|-----------|---------------|--|---|
|           | $ae^{bx}$ | $ae^{bx} + c$ | $\frac{ae^{bx}}{1 + \sigma^2 \frac{a}{b}(e^{bx} - 1)}$ | $\frac{ae^{bx} + c}{1 + \sigma^2 \frac{a}{b}(e^{bx} - 1) + cx}$ |
| 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 $\times 10^5$ | 5.237 $\times 10^5$ - | 4.495 $\times 10^5$ | 4.488 $\times 10^5$ - | 3.767 $\times 10^5$ | 3.755 $\times 10^5$ - | 1.605 $\times 10^5$ | 1.588 $\times 10^5$ - |
|                    |                     | 5.245 $\times 10^5$   |                     | 4.501 $\times 10^5$   |                     | 3.779 $\times 10^5$   |                     | 1.623 $\times 10^5$   |
| 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 <sup>2</sup> | -                   | -                     | 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 $\times 10^5$   | 3.196 $\times 10^5$ - | 0.004               | (0.000-0.010) | 8.031 $\times 10^5$   | 6.028 $\times 10^5$ - | 0.008               | (0.000-0.016)         |
|                    |                       | 5.410 $\times 10^5$   |                     |               |                       | 1.070 $\times 10^5$   |                     |                       |
| 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 $\times 10^6$ | 8.610 $\times 10^7$ - |
|                    |                       |                       |                     |               |                       |                       | 2.997 $\times 10^5$ |                       |
| Sigma <sup>2</sup> | -                     | -                     | 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.

1  
2 This is consistent with the more pronounced convergence of the hazards by education  
3  
4 at old age found among women compared to the men. According to the framework of the  
5  
6 frailty models, converging hazards are the result of the effect of selection on the population  
7  
8 hazards, due to how much variance of unobserved frailty is present in the population at the  
9  
10 initial age of observation. The bigger the variance the stronger the convergence is. For more  
11  
12 information about frailty models, the process of selection and how they relate to narrowing  
13  
14 mortality differentials at old ages, please see appendix A.  
15  
16

17  
18 In the age-cohort models the introduction of unobserved frailty affected the coefficient  
19  
20 for the macro-region of birth significantly. Among men, holding education equal, those born  
21  
22 in the South show a significant survival advantage over the natives of the North-West, while  
23  
24 in the model without frailty there was no such advantage. Among women, the model without  
25  
26 frailty showed a significant survival advantage for those born in the South but when frailty  
27  
28 was controlled for, this became not significant.  
29  
30

31 The pattern also resembles the regional mortality macro-dynamics that have  
32  
33 characterized Italy for most of the 20<sup>th</sup> century (although the two patterns refer to different  
34  
35 phenomena, the first one referring to mortality by region of birth), when male mortality in the  
36  
37 South was lower than in the North (44-47). Cohort based analyses have highlighted that in  
38  
39 more recent cohorts (those born after WWII) there is a reversing trend (47, 48).  
40  
41

42 The models with age-period perspective did not identify any significant geographical  
43  
44 differences. This could be due to the utilization of random subsampling of a 1% sample.  
45  
46 Although 250 repetitions is considered by the literature a sufficient number for very complex  
47  
48 models (49-51), it is possible that it was inadequate to identify a clear pattern from the small  
49  
50 sample. For more detailed results see tables 1 and 2.  
51  
52

## 53 54 55 **Discussion** 56 57 58 59 60

1  
2 The interest in the role of unobserved heterogeneity in a life course approach to  
3 socioeconomic mortality differences has recently increased. Most of the studies focus on  
4 health outcomes (52-57) while fewer studies also analyze mortality (58-60). Their findings are  
5 not consistent and fuel a still controversial debate.  
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11 In this study we investigated the role of unobserved individual heterogeneity on the  
12 estimation of mortality differentials at adult-old ages by education level in a longitudinal  
13 perspective. This study investigated 1) whether the framework of the frailty models can  
14 explain the observed pattern of convergence of the mortality risk by social position at old ages  
15 2) if the estimates of the mortality differentials are affected by the introduction of the  
16 unobserved heterogeneity component into the models.  
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24 We fitted survival analysis models with and without controlling for the unobserved  
25 heterogeneity and we found that, when this component was included, the models gave a  
26 significantly better fit.  
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31 We also found that in the majority of the cases, the educational gradient estimated by  
32 the models with frailty was higher than the one estimated by the models without frailty. When  
33 big uncertainty around the estimates did not allow assessing a precise value, the confidence  
34 regions in the models with frailty spanned over higher values than those in the models without  
35 frailty. It must be pointed out that, in the age-period approach, to the peculiar statistical  
36 procedure used to estimate the frailty models did not allow obtaining a likelihood value  
37 comparable with the one of the model without frailty. Thus, the statistical comparison of the  
38 models via the AIC was not possible, making this evidence somehow weaker. Nevertheless,  
39 the results point to a direction that is consistent with the statistical literature about unobserved  
40 heterogeneity and show that neglecting its selective action, in duration dependence models,  
41 might lead to underestimate the effect of the covariates (19-26).  
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55 Among men such a pattern was found in both the age-cohort and age-period  
56 approaches. Among women, on the contrary, this pattern was less clear: in the age-cohort  
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1  
2 model, controlling for hidden frailty resulted in a slight reduction of the mortality gradient.  
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4 Social determinants act on mortality also through risk factors that are known to affect more  
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6 men than women. Moreover, because of a lag in the smoking and fertility transitions, highly  
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8 educated women in Turin are more exposed to risk factors like cigarette smoking and smaller  
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10 number of children. Therefore, controlling for hidden frailty in the case of women might  
11  
12 reduce the educational gradient.  
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15  
16 In the models with age-cohort perspective controlling for the hidden frailty affected  
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18 also the estimates of the differentials by macro-region of birth, showing a survival advantage  
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20 of the men born in the South, but not of the women, for whom an advantage was instead  
21  
22 detected by the model that did not control for frailty.  
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24  
25 The healthy migrant effect (61-66) could cause this pattern. Among the cohorts  
26  
27 involved in the migration women were likely to be more passive actors than men in the  
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29 migratory decision (67-69) and this might have selected them more than men. Frailty is a  
30  
31 general concept embedding all the hidden factors that affect the individual survival chances:  
32  
33 innate and acquired frailty, exposure to risk factors, life style factors and so on. Therefore,  
34  
35 controlling for frailty reduced the survival advantage of the women, who might have been less  
36  
37 health selected than men by the migration, while uncovered the advantage of the men.  
38  
39 However, another recent study on the impact of migration on all-cause mortality in Turin did  
40  
41 not find particularly strong gender differences in the so called healthy migrant effect (65) and  
42  
43 this point deserves future further investigation.  
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46  
47 The study spanned over a long observation window of 36 years. Therefore it was  
48  
49 important to control for the general mortality improvement that took place during this time.  
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51 We did so by adopting both an age-period and an age-cohort approach.  
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54 The age-period models, as expected, estimated higher heterogeneity than the age-  
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56 cohort models. Periods aggregate different generations and are expected to be more  
57  
58 heterogeneous than the cohorts themselves. In both period and cohort models the female  
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2 variance of frailty was higher than for the males, indicating that men are more homogeneous  
3  
4 than women. This could be attributed to a stronger selection process due to mortality that is  
5  
6 usually observed to be higher among men than among women.  
7

8  
9 On the other hand, it is also possible that the industrialization process and the internal  
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11 migration experienced by Italy after WWII (34) played a role. The vast majority of less  
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13 educated individuals in Turin came from the South, seeking a job in the car factories of the  
14  
15 city. As less educated men were mainly employed in heavier and riskier jobs and were  
16  
17 exposed to higher mortality, it is possible that during their life they were selected at a faster  
18  
19 pace than other educational groups and women. This might have reduced the differences in  
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21 susceptibility to death among men, contributing to determining a lower level of heterogeneity  
22  
23 than among women.  
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## 28 29 **Conclusion**

30  
31 This study found that neglecting selection effects due to unobserved heterogeneity in  
32  
33 longitudinal analyses, could lead to underestimation of mortality differentials by social class.  
34  
35 In the majority of the cases, the models that controlled for unobserved heterogeneity,  
36  
37 estimated higher educational differences in mortality than the models that did not control for  
38  
39 it.  
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43 Moreover, when compared with via the AIC, the models that controlled for  
44  
45 unobserved heterogeneity gave a statistically significant better fit than the models that did not  
46  
47 control for it. Although the best AIC shows just that the more complex model approximates  
48  
49 better the data and this does not represent an unequivocal proof of the selection hypothesis,  
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51 the results point to the possibility that the data could be better described by this hypothesis.  
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53 This strengthens its validity as possible explanatory mechanism for the reduction of the  
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55 gradient in socioeconomic mortality.  
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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.

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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.
- 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

1  
2 The strength of this study lies in the population based longitudinal data. The long  
3  
4 observational time (36 years) for more than 847 000 individuals gives a solid base for  
5  
6 statistical power and detection of trends.  
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8  
9 The limitation consists in the lack of individual information on life style factors and health  
10  
11 events, which could certainly help to better model the concept of unobserved individual frailty  
12  
13 by uncovering part of it.  
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43  
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45  
46 interpretation of data and results, drafting the article and revising it; Graziella Caselli:  
47  
48 interpretation of the results, drafting the article and revising it critically; Chiara Marinacci and  
49  
50 Giuseppe Costa: revising the article for important intellectual content.  
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55 *Data sharing.* There is no additional data available.  
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## References

1. Mackenbach JP, Kunst AE, Cavelaars AEJM, Groenhouf F, Geurts JJM, others. Socioeconomic inequalities in morbidity and mortality in western Europe. *The Lancet*. 1997;349(9066):1655-9.
2. Mackenbach JP, Kunst AE, Groenhouf F, Borgan JK, Costa G, Faggiano F, et al. Socioeconomic inequalities in mortality among women and among men: an international study. *American Journal of Public Health*. 1999;89(12):1800-6.
3. Mackenbach JP, Stirbu I, Roskam AJR, Schaap MM, Menvielle G, Leinsalu M, et al. Socioeconomic inequalities in health in 22 European countries. *New England Journal of Medicine*. 2008;358(23):2468-81.
4. Antonovsky A. Social class, life expectancy and overall mortality. *The Milbank Memorial Fund Quarterly*. 1967;45(2):31-73.
5. Huisman M, Kunst AE, Mackenbach JP. Socioeconomic inequalities in morbidity among the elderly; a European overview. *Social Science & Medicine*. 2003;57(5):861-73.
6. Dalstra J, Kunst A, Mackenbach J, others. A comparative appraisal of the relationship of education, income and housing tenure with less than good health among the elderly in Europe. *Social Science & Medicine*. 2006;62(8):2046-60.
7. Martelin T. Mortality by indicators of socioeconomic status among the Finnish elderly. *Social Science & Medicine*. 1994;38(9):1257-78.
8. Huisman M, Kunst AE, Andersen O, Bopp M, Borgan JK, Borrell C, et al. Socioeconomic inequalities in mortality among elderly people in 11 European populations. *Journal of Epidemiology and Community Health*. 2004;58(6):468-75.
9. House JS, Lepkowski JM, Kinney AM, Mero RP, Kessler RC, Herzog AR. The social stratification of aging and health. *Journal of Health and Social Behavior*. 1994:213-34.
10. Decker S, Rapaport C. Medicare and disparities in women's health. National Bureau of Economic Research, 2002.
11. Dor A, Sudano J, Baker DW. The effect of private insurance on the health of older, working age adults: evidence from the Health and Retirement Study. *Health Services Research*. 2006;41(3p1):759-87.
12. Marmot MG, Shipley MJ. Do socioeconomic differences in mortality persist after retirement? 25 year follow up of civil servants from the first Whitehall study. *BMJ*. 1996;313(7066):1177-80.
13. Elo IT, Preston SH. Educational differentials in mortality: United States, 1979-1985. *Social Science & Medicine*. 1996;42(1):47-57.
14. Liang J, Bennett J, Krause N, Kobayashi E, Kim H, Brown JW, et al. Old age mortality in Japan. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. 2002;57(5):S294.
15. Caselli G, Vaupel JW, Yashin AI. Explanation of the decline in mortality among the oldest-old: A demographic point of view. *Human Longevity, Individual Life Duration, and the Growth of the Oldest-Old Population*. 2006:395-413.
16. Manton KG, Stallard E, others. Methods for evaluating the heterogeneity of aging processes in human populations using vital statistics data: explaining the black/white mortality crossover by a model of mortality selection. *Human Biology*. 1981;53(1):47.
17. Vaupel JW, Manton KG, Stallard E. The impact of heterogeneity in individual frailty on the dynamics of mortality. *Demography*. 1979;16(3):439-54.
18. Vaupel JW, Yashin AI. Heterogeneity's ruses: some surprising effects of selection on population dynamics. *American Statistician*. 1985:176-85.

19. Aalen OO. Effects of frailty in survival analysis. *Statistical Methods in Medical Research*. 1994;3(3):227.
20. Aalen OO. Heterogeneity in survival analysis. *Statistics in Medicine*. 1988;7(11):1121-37.
21. Gail MH, Wieand S, Piantadosi S. Biased estimates of treatment effect in randomized experiments with nonlinear regressions and omitted covariates. *Biometrika*. 1984;71(3):431.
22. Trussell J, Rodriguez G. Heterogeneity in demographic research. *Convergent issues in genetics and demography*: Oxford University Press, USA; 1990. p. 111-32.
23. Chamberlain G. Heterogeneity, omitted variable bias, and duration dependence. *Longitudinal Analysis of Labor Market Data*, ed JJ Heckman, B Singer. 1985:3-38.
24. Schumacher M, Olschewski M, Schmoor C. The impact of heterogeneity on the comparison of survival times. *Statistics in Medicine*. 1987;6(7):773-84.
25. Schmoor C, Schumacher M. Effects of covariate omission and categorization when analysing randomized trials with the Cox model. *Statistics in Medicine*. 1997;16(3):225-37.
26. Bretagnolle J, Huber-Carol C. Effects of omitting covariates in Cox's model for survival data. *Scandinavian Journal of Statistics*. 1988:125-38.
27. Wienke A. *Frailty models in survival analysis*: Chapman & Hall/CRC; 2010.
28. Marinacci C, Spadea T, Biggeri A, Demaria M, Caiazzo A, Costa G. The role of individual and contextual socioeconomic circumstances on mortality: analysis of time variations in a city of north west Italy. *Journal of Epidemiology and Community Health*. 2004;58(3):199-207.
29. Costa G, Cardano M, Demaria M. Torino. *Storie di salute in una grande città*. Città di Torino, Ufficio di statistica, Osservatorio socioeconomico torinese. 1998.
30. Doblhammer G, Hoffmann R, Muth E, Westphal C, Kruse A. A systematic literature review of studies analyzing the effect of sex, age, education, marital status, obesity, and smoking on health transitions. *Demographic Research*. 2009;20(5):37-64.
31. Krieger N, Williams DR, Moss NE. Measuring social class in US public health research: concepts, methodologies, and guidelines. *Annual Review of Public Health*. 1997;18(1):341-78.
32. Mirowsky J, Ross CE. *Education, social status, and health*: Aldine de Gruyter; 2003.
33. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Smith GD. Indicators of socioeconomic position (part 1). *Journal of Epidemiology and Community Health*. 2006;60(1):7-12.
34. Bonifazi C, Heins F. Long-term trends of internal migration in Italy. *International Journal of Population Geography*. 2000;6(2):111-31.
35. Gompertz B. On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. *Philosophical Transactions of the Royal Society of London*. 1825;115:513-83.
36. Akaike H. A new look at the statistical model identification. *Automatic Control, IEEE Transactions on*. 1974;19(6):716-23.
37. Holford TR. Analysing the temporal effects of age, period and cohort. *Statistical Methods in Medical Research*. 1992;1(3):317-37.
38. Osmond C, Gardner M. Age, period, and cohort models. Non-overlapping cohorts don't resolve the identification problem. *American Journal of Epidemiology*. 1989;129(1):31.
39. Glenn ND. Cohort analysts' futile quest: Statistical attempts to separate age, period and cohort effects. *American Sociological Review*. 1976;41(5):900-4.
40. Hartigan JA. Using subsample values as typical values. *Journal of the American Statistical Association*. 1969:1303-17.
41. Politis DN, Romano JP. Large sample confidence regions based on subsamples under minimal assumptions. *The Annals of Statistics*. 1994;22(4):2031-50.

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42. Efron B. Bootstrap methods: another look at the jackknife. *The Annals of Statistics*. 1979;7(1):1-26.
  43. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria 2011.
  44. Barbi E, Caselli G. Selection effects on regional differences in survivorship in Italy. *Genus*. 2003;37-61.
  45. Caselli G, Egidi V. Le differenze territoriali di mortalità in Italia. *Tavole di mortalità provinciali (1971-72)*. 1980.
  46. Caselli G, Egidi V. L'analyse des données multidimensionnelles dans l'étude des relations entre mortalité et variable socio-économiques d'environnement et de comportement individuel [Multivariate methods in the analysis of the relations between mortality and socio-economic, environmental and behavioural variables]. *Genus*. 1981;37(3/4):57-91.
  47. Caselli G, Reale A. Does cohort analysis contribute to the study of the geography of mortality? *Genus*. 1999:27-59.
  48. Biggeri A, Accetta G, Egidi V. Evoluzione del profilo di mortalità 30-74 anni per le coorti di nascita dal 1889 al 1968 nelle regioni italiane [Mortality Time Trends 30-74 years by Birth Cohorts 1889-1968 in the Italian Regions]. *Epidemiologia & Prevenzione*. 2011;35(5-6):50-67.
  49. Efron B, Tibshirani R. *An introduction to the bootstrap*: Chapman & Hall/CRC; 1993.
  50. Manly BFJ. *Randomization, bootstrap and Monte Carlo methods in biology*: Chapman & Hall/CRC; 1997.
  51. Pattengale ND, Alipour M, Bininda-Emonds ORP, Moret BME, Stamatakis A. How many bootstrap replicates are necessary? *Journal of Computational Biology*. 2010;17(3):337-54.
  52. Beckett M. Converging health inequalities in later life—an artifact of mortality selection? *Journal of Health and Social Behavior*. 2000:106-19.
  53. Ferraro KF, Farmer MM. Double jeopardy, aging as leveler, or persistent health inequality? A longitudinal analysis of white and black Americans. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. 1996;51(6):S319.
  54. Herd P. Do functional health inequalities decrease in old age? *Research on Aging*. 2006;28(3):375-92.
  55. Kim J, Durden E. Socioeconomic status and age trajectories of health. *Social Science & Medicine*. 2007;65(12):2489-502.
  56. Lynch SM. Cohort and life-course patterns in the relationship between education and health: A hierarchical approach. *Demography*. 2003;40(2):309-31.
  57. McMunn A, Nazroo J, Breeze E. Inequalities in health at older ages: a longitudinal investigation of the onset of illness and survival effects in England. *Age and Ageing*. 2009;38(2):181.
  58. Dupre ME. Educational differences in age-related patterns of disease: Reconsidering the cumulative disadvantage and age-as-leveler hypotheses. *Journal of Health and Social Behavior*. 2007;48(1):1-15.
  59. Hoffmann R. Do socioeconomic mortality differences decrease with rising age? *Demographic Research*. 2005;13(2):35-62.
  60. Hoffmann R. Socioeconomic inequalities in old-age mortality: A comparison of Denmark and the USA. *Social Science & Medicine*. 2011;72(12):1986 - 92.
  61. Anson J. The migrant mortality advantage: a 70 month follow-up of the Brussels population. *European Journal of Population/Revue Européenne de Démographie*. 2004;20(3):191-218.
  62. Feinleib M, Lambert PM, Zeiner-Henriksen T, Rogot E, Hunt BM, Ingster-Moore L. The British-Norwegian migrant study--analysis of parameters of mortality differentials associated with angina. *Biometrics*. 1982:55-71.

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63. Kington R, Carlisle D, McCaffrey D, Myers H, Allen W. Racial differences in functional status among elderly US migrants from the south. *Social Science & Medicine*. 1998;47(6):831-40.
64. Norman P, Boyle P, Rees P. Selective migration, health and deprivation: a longitudinal analysis. *Social Science & Medicine*. 2005;60(12):2755-71.
65. Rasulo D, Spadea T, Onorati R, Costa G. The impact of migration in all-cause mortality: The Turin Longitudinal Study, 1971–2005. *Social Science & Medicine*. 2012.
66. Singh GK, Siahpush M. All-cause and cause-specific mortality of immigrants and native born in the United States. *American Journal of Public Health*. 2001;91(3):392.
67. Bielby WT, Bielby DD. I will follow him: Family ties, gender-role beliefs, and reluctance to relocate for a better job. *American Journal of Sociology*. 1992:1241-67.
68. Cooke TJ. Gender role beliefs and family migration. *Population, Space and Place*. 2008;14(3):163-75.
69. Mincer J. Family Migration Decisions. *Journal of Political Economy*. 1978;86:749-75.



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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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**Key words:** Mortality, inequality, education, frailty.

**Word count:** 2781

### 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 than the models with frailty.

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2 Conclusions. The results draw the attention on the potential underestimation of the mortality  
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4 inequalities by socioeconomic levels in survival models when not controlling for frailty.  
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## 8 9 **Introduction**

10 An extensive literature shows significant differential mortality by socioeconomic condition  
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12 (1-3). Elderly show decreasing relative social inequalities in general mortality with increasing  
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14 age (4-8). The age-as-leveler hypothesis attributes this to factors that contribute to the  
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16 leveling-off of differences at old ages: governmental support to the elderly (9-11),  
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18 disengagement from systems of social stratification (12) and general vulnerability (13, 14).  
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20 However, this phenomenon could also be an artifact of selection due to unobserved  
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22 characteristics of the individuals: selective effects of earlier higher mortality, experienced by  
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24 the disadvantaged group, would leave more robust individuals at old ages, causing the  
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26 convergence with the risk of the lower mortality group, that is subject to weaker selection (15-  
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28 18). Neglecting these hidden differences in survival chances (called unobserved frailty), has  
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30 been shown to lead to biased estimates of the mortality hazard and of the effect of the  
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32 covariates on the survival probability (19-25).  
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37 In longitudinal analyses on differential mortality it is important to control for hidden  
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39 frailty. First, because not controlling for it, in survival models, could lead to biased estimates  
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41 of the effect of the social position on the mortality risk: the statistical literature shows that the  
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43 bias is towards zero (24-26). This would lead to underestimation of the relative differences in  
44  
45 the mortality risks by socioeconomic group. Second, because selection due to unobserved  
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47 frailty could provide an explanation for the phenomenon of decreasing relative differences in  
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49 death rates by socioeconomic group at old ages. To control for unobserved frailty and to  
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51 evaluate the impact on the observed mortality dynamics, frailty models have been developed  
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53 (27). For more detailed explanations of the frailty models and how they relate to differential  
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55 mortality analyses, please, see appendix A.  
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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 24<sup>th</sup> 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).

1  
2 To facilitate the comparison over a long follow up and different cohorts, we created  
3  
4 three broad educational groups: high (high school diploma or higher), medium (junior high  
5  
6 school) and low (primary school or lower).  
7

8  
9 We estimated parametric survival models stratified by gender and as a function of  
10  
11 macro-region of birth and education level, with and without a parameter for the unobserved  
12  
13 heterogeneity component. The parametric choice is justified by the wide demographic  
14  
15 literature showing that human adult mortality can be accurately described by a Gompertz  
16  
17 function (35) or by some Gompertz-like variants, like Makeham. To identify the best  
18  
19 functional form for the baseline we compared the models with the AIC (36).  
20  
21

22 The data are both right censored (due to emigration or end of follow up) and left  
23  
24 truncated (due to the different age at entry in the study of the individuals).  
25  
26

27 The study includes many cohorts, each passing through the 36 years of observation at  
28  
29 different ages. However, from 1971 to 2007 a significant mortality improvement occurred and  
30  
31 younger cohorts experience lower age specific mortality than older cohorts.  
32

33 Time is a complex variable including three dimensions: age, period and cohort.  
34  
35 Controlling adequately for the effect of time would require to assess simultaneously the three  
36  
37 components but such models have been proved to be not identifiable because of linear  
38  
39 dependence between the three dimensions (37-39).  
40  
41

42 Therefore, we decided to adopt two approaches for the control of time, corresponding  
43  
44 to an age-cohort approach and an age-period approach, being aware that they represent two  
45  
46 different dimensions of time.  
47  
48

49 First, we regarded the improvement as a cohort phenomenon, including a covariate for  
50  
51 the cohort to which the individuals belong. In this setting, controlling for unobserved  
52  
53 heterogeneity was implemented with univariate frailty models, which estimate the baseline  
54  
55 parameters, the coefficients of the covariates and the variance of frailty (assumed to follow a  
56  
57 gamma distribution with mean 1 and variance  $\sigma^2$  to be estimated).  
58  
59  
60

1  
2 We then considered the improvement as a period phenomenon and split the time into  
3  
4 several calendar period covariates, as well as the survival spell of the individuals, according to  
5  
6 which period they were passing through. This implied organizing the data into clusters, where  
7  
8 each cluster represents one individual's survival spells. In this setting, to control for  
9  
10 unobserved heterogeneity shared frailty models are needed, where the spells in each cluster  
11  
12 pertain to the same individual and share the same hidden frailty. For computational reasons,  
13  
14 the estimation of these highly complex models required the use of random subsampling (40-  
15  
16 42). We repeated the estimation 250 times on a 1% sample of the dataset, randomly drawn  
17  
18 without replacement and stratified by the major variables in analysis. The aim is to  
19  
20 approximate the parameters estimates based on the empirical distribution of the repeated  
21  
22 estimates.  
23  
24  
25

26  
27 In the model without frailty it was possible to include a finer calendar period division,  
28  
29 12 period variables of 3 years each (1971-1973, 1974-1976...), while in the model with  
30  
31 frailty, for computational reasons, the number of variables was reduced to 2 broader periods:  
32  
33 1971-1990 and 1991-2007.  
34

35 Computations were realized with the software R (43). Formal details are in appendix  
36  
37 A.  
38

## 39 40 41 42 **Results**

43  
44 Figure 1 shows that the log-death rates by education level and gender, for the cohort aged 50-  
45  
46 59 in 1971, converge at old ages. Other cohorts showed very similar patterns.  
47  
48

49 A preliminary analysis found that the reduction of the gradient over age is statistically  
50  
51 significant and more pronounced among women (results are reported in appendix B table B1).  
52

53  
54 Figure 1 here

55  
56 *Frailty modeling*  
57  
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59  
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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   |
|-----------|-----------|---------------|--|---|
|           | $ae^{bx}$ | $ae^{bx} + c$ | $\frac{ae^{bx}}{1 + \sigma^2 \frac{a}{b}(e^{bx} - 1)}$ | $\frac{ae^{bx} + c}{1 + \sigma^2 \frac{a}{b}(e^{bx} - 1) + cx}$ |
| 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                             |
|--------------------------|----------------------------------|------------------------------------|----------------------------------|------------------------------------|----------------------------------|------------------------------------|----------------------------------|------------------------------------|
| <b>a</b>                 | 5.241 <sub>x10<sup>4</sup></sub> | 5.237 <sub>x10<sup>4</sup></sub> - | 4.495 <sub>x10<sup>4</sup></sub> | 4.488 <sub>x10<sup>4</sup></sub> - | 3.767 <sub>x10<sup>4</sup></sub> | 3.755 <sub>x10<sup>4</sup></sub> - | 1.605 <sub>x10<sup>4</sup></sub> | 1.588 <sub>x10<sup>4</sup></sub> - |
|                          |                                  | 5.245 <sub>x10<sup>4</sup></sub>   |                                  | 4.501 <sub>x10<sup>4</sup></sub>   |                                  | 3.779 <sub>x10<sup>4</sup></sub>   |                                  | 1.623 <sub>x10<sup>4</sup></sub>   |
| <b>b</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                        |
| <b>c</b>                 | ‡                                | ‡                                  | ‡                                | ‡                                  | 0.001                            | 0.001-0.001                        | 0.001                            | 0.001-0.001                        |
| <b>Sigma<sup>2</sup></b> | ‡                                | ‡                                  | 0.035                            | 0.027-0.045                        | ‡                                | ‡                                  | 0.096                            | 0.082-0.111                        |
| <b>cohort</b>            | 0.016                            | 0.015-0.016                        | 0.016                            | 0.015-0.016                        | 0.016                            | 0.015-0.016                        | 0.017                            | 0.016-0.017                        |
| <b>Education level</b>   |                                  |                                    |                                  |                                    |                                  |                                    |                                  |                                    |
| <b>High</b>              | ‡                                | ‡                                  | ‡                                | ‡                                  | ‡                                | ‡                                  | ‡                                | ‡                                  |
| <b>Medium</b>            | 1.166                            | 1.147-1.186                        | 1.221                            | 1.200-1.243                        | 1.141                            | 1.116-1.166                        | 1.111                            | 1.086-1.137                        |
| <b>Low</b>               | 1.239                            | 1.221-1.257                        | 1.302                            | 1.283-1.322                        | 1.246                            | 1.222-1.270                        | 1.213                            | 1.188-1.238                        |
| <b>Region of birth</b>   |                                  |                                    |                                  |                                    |                                  |                                    |                                  |                                    |
| <b>North-West</b>        | ‡                                | ‡                                  | ‡                                | ‡                                  | ‡                                | ‡                                  | ‡                                | ‡                                  |
| <b>North-East</b>        | 1.053                            | 1.036-1.070                        | 1.060                            | 1.042-1.077                        | 0.989                            | 0.973-1.004                        | 0.974                            | 0.958-0.991                        |
| <b>Center</b>            | 1.011                            | 0.984-1.038                        | 0.996                            | 0.969-1.024                        | 0.939                            | 0.913-0.966                        | 0.968                            | 0.939-0.998                        |
| <b>South</b>             | 1.000                            | 0.988-1.012                        | 0.950                            | 0.938-0.962                        | 0.932                            | 0.919-0.945                        | 0.987                            | 0.973-1.002                        |
| <b>Abroad</b>            | 1.031                            | 1.006-1.057                        | 0.998                            | 0.974-1.024                        | 1.071                            | 1.047-1.096                        | 0.993                            | 0.968-1.018                        |
| <b>logLk</b>             |                                  | -651 219                           |                                  | -651 082                           |                                  | -663 238                           |                                  | -663 098                           |
| <b>AIC</b>               |                                  | 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                       |
| <b>a</b>                 | 4.159 <sub>x10<sup>4</sup></sub> | 3.196 <sub>x10<sup>4</sup></sub> - | 0.004               | (0.000-0.010) | 8.031 <sub>x10<sup>4</sup></sub> | 6.028 <sub>x10<sup>4</sup></sub> - | 0.008                            | (0.000-0.016)                      |
|                          |                                  | 5.410 <sub>x10<sup>4</sup></sub>   |                     |               |                                  | 1.070 <sub>x10<sup>4</sup></sub>   |                                  |                                    |
| <b>b</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)                      |
| <b>c</b>                 | ‡                                | ‡                                  | ‡                   | ‡             | 0.001                            | (0.001-0.002)                      | 2.852 <sub>x10<sup>4</sup></sub> | 8.610 <sub>x10<sup>4</sup></sub> - |
|                          |                                  |                                    |                     |               |                                  |                                    |                                  | 2.997 <sub>x10<sup>4</sup></sub>   |
| <b>Sigma<sup>2</sup></b> | ‡                                | ‡                                  | 0.269               | (0.026-0.367) | ‡                                | ‡                                  | 0.292                            | (0.174-0.367)                      |
| <b>Calendar period</b>   |                                  |                                    |                     |               |                                  |                                    |                                  |                                    |
| <b>1971-1973</b>         | ‡                                | ‡                                  |                     |               | ‡                                | ‡                                  |                                  |                                    |
| <b>1974-1976</b>         | 0.999                            | 0.972-1.027                        |                     |               | 0.978                            | 0.950-1.007                        |                                  |                                    |
| <b>1977-1979</b>         | 0.947                            | 0.921-0.973                        |                     |               | 0.919                            | 0.893-0.946                        |                                  |                                    |
| <b>1980-1982</b>         | 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 |       | 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.

1  
2 This is consistent with the more pronounced convergence of the hazards by education  
3  
4 at old age found among women compared to the men. According to the framework of the  
5  
6 frailty models, converging hazards are the result of the effect of selection on the population  
7  
8 hazards, due to how much variance of unobserved frailty is present in the population at the  
9  
10 initial age of observation. The bigger the variance the stronger the convergence is. For more  
11  
12 information about frailty models, the process of selection and how they relate to narrowing  
13  
14 mortality differentials at old ages, please see appendix A.  
15  
16

17  
18 In the age-cohort models the introduction of unobserved frailty affected the coefficient  
19  
20 for the macro-region of birth significantly. Among men, holding education equal, those born  
21  
22 in the South show a significant survival advantage over the natives of the North-West, while  
23  
24 in the model without frailty there was no such advantage. Among women, the model without  
25  
26 frailty showed a significant survival advantage for those born in the South but when frailty  
27  
28 was controlled for, this became not significant.  
29  
30

31 The pattern also resembles the regional mortality macro-dynamics that have  
32  
33 characterized Italy for most of the 20<sup>th</sup> century (although the two patterns refer to different  
34  
35 phenomena, the first one referring to mortality by region of birth), when male mortality in the  
36  
37 South was lower than in the North (44-47). Cohort based analyses have highlighted that in  
38  
39 more recent cohorts (those born after WWII) there is a reversing trend (47, 48).  
40  
41

42 The models with age-period perspective did not identify any significant geographical  
43  
44 differences. This could be due to the utilization of random subsampling of a 1% sample.  
45  
46 Although 250 repetitions is considered by the literature a sufficient number for very complex  
47  
48 models (49-51), it is possible that it was inadequate to identify a clear pattern from the small  
49  
50 sample. For more detailed results see tables 1 and 2.  
51  
52

## 53 54 55 Discussion



1  
2 The interest in the role of unobserved heterogeneity in a life course approach to  
3 socioeconomic mortality differences has recently increased. Most of the studies focus on  
4 health outcomes (52-57) while fewer studies also analyze mortality (58-60). Their findings are  
5 not consistent and fuel a still controversial debate.  
6  
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10  
11 In this study we investigated the role of unobserved individual heterogeneity on the  
12 estimation of mortality differentials at adult-old ages by education level in a longitudinal  
13 perspective. This study investigated 1) whether the framework of the frailty models can  
14 explain the observed pattern of convergence of the mortality risk by social position at old ages  
15 2) if the estimates of the mortality differentials are affected by the introduction of the  
16 unobserved heterogeneity component into the models.  
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24 We fitted survival analysis models with and without controlling for the unobserved  
25 heterogeneity and we found that, when this component was included, the models gave a  
26 significantly better fit.  
27  
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31 We also found that in the majority of the cases, the educational gradient estimated by  
32 the models with frailty was higher than the one estimated by the models without frailty. When  
33 big uncertainty around the estimates did not allow assessing a precise value, the confidence  
34 regions in the models with frailty spanned over higher values than those in the models without  
35 frailty. It must be pointed out that, in the age-period approach, to the peculiar statistical  
36 procedure used to estimate the frailty models did not allow obtaining a likelihood value  
37 comparable with the one of the model without frailty. Thus, the statistical comparison of the  
38 models via the AIC was not possible, making this evidence somehow weaker. Nevertheless,  
39 the results point to a direction that is consistent with the statistical literature about unobserved  
40 heterogeneity and show that neglecting its selective action, in duration dependence models,  
41 might lead to underestimate the effect of the covariates (19-26).  
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55 Among men such a pattern was found in both the age-cohort and age-period  
56 approaches. Among women, on the contrary, this pattern was less clear: in the age-cohort  
57  
58  
59  
60

1  
2 model, controlling for hidden frailty resulted in a slight reduction of the mortality gradient.  
3  
4 Social determinants act on mortality also through risk factors that are known to affect more  
5  
6 men than women. Moreover, because of a lag in the smoking and fertility transitions, highly  
7  
8 educated women in Turin are more exposed to risk factors like cigarette smoking and smaller  
9  
10 number of children. Therefore, controlling for hidden frailty in the case of women might  
11  
12 reduce the educational gradient.  
13  
14

15  
16 In the models with age-cohort perspective controlling for the hidden frailty affected  
17  
18 also the estimates of the differentials by macro-region of birth, showing a survival advantage  
19  
20 of the men born in the South, but not of the women, for whom an advantage was instead  
21  
22 detected by the model that did not control for frailty.  
23

24  
25 The healthy migrant effect (61-66) could cause this pattern. Among the cohorts  
26  
27 involved in the migration women were likely to be more passive actors than men in the  
28  
29 migratory decision (67-69) and this might have selected them more than men. Frailty is a  
30  
31 general concept embedding all the hidden factors that affect the individual survival chances:  
32  
33 innate and acquired frailty, exposure to risk factors, life style factors and so on. Therefore,  
34  
35 controlling for frailty reduced the survival advantage of the women, who might have been less  
36  
37 health selected than men by the migration, while uncovered the advantage of the men.  
38  
39 However, another recent study on the impact of migration on all-cause mortality in Turin did  
40  
41 not find particularly strong gender differences in the so called healthy migrant effect (65) and  
42  
43 this point deserves future further investigation.  
44  
45

46  
47 The study spanned over a long observation window of 36 years. Therefore it was  
48  
49 important to control for the general mortality improvement that took place during this time.  
50  
51 We did so by adopting both an age-period and an age-cohort approach.  
52

53  
54 The age-period models, as expected, estimated higher heterogeneity than the age-  
55  
56 cohort models. Periods aggregate different generations and are expected to be more  
57  
58 heterogeneous than the cohorts themselves. In both period and cohort models the female  
59  
60

1  
2 variance of frailty was higher than for the males, indicating that men are more homogeneous  
3  
4 than women. This could be attributed to a stronger selection process due to mortality that is  
5  
6 usually observed to be higher among men than among women.  
7

8  
9 On the other hand, it is also possible that the industrialization process and the internal  
10  
11 migration experienced by Italy after WWII (34) played a role. The vast majority of less  
12  
13 educated individuals in Turin came from the South, seeking a job in the car factories of the  
14  
15 city. As less educated men were mainly employed in heavier and riskier jobs and were  
16  
17 exposed to higher mortality, it is possible that during their life they were selected at a faster  
18  
19 pace than other educational groups and women. This might have reduced the differences in  
20  
21 susceptibility to death among men, contributing to determining a lower level of heterogeneity  
22  
23 than among women.  
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## 28 29 **Conclusion**

30  
31 This study found that neglecting selection effects due to unobserved heterogeneity in  
32  
33 longitudinal analyses, could lead to underestimation of mortality differentials by social class.  
34  
35 In the majority of the cases, the models that controlled for unobserved heterogeneity,  
36  
37 estimated higher educational differences in mortality than the models that did not control for  
38  
39 it.  
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42 Moreover, when compared with via the AIC, the models that controlled for  
43  
44 unobserved heterogeneity gave a statistically significant better fit than the models that did not  
45  
46 control for it. Although the best AIC shows just that the more complex model approximates  
47  
48 better the data and this does not represent an unequivocal proof of the selection hypothesis,  
49  
50 the results point to the possibility that the data could be better described by this hypothesis.  
51  
52 This strengthens its validity as possible explanatory mechanism for the reduction of the  
53  
54 gradient in socioeconomic mortality.  
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1  
2 This analysis also has important policies facets. Specifically, when studying  
3 differential survival chances in socioeconomic groups and observing decreasing relative  
4 differences at old ages, it is important to be aware that individuals might experience a  
5 disadvantaged position throughout their life which does not fade away when they age. The  
6 lessening of differences at old ages could be the result of a stronger selection due to early  
7 higher mortality that disadvantaged groups are still subject to.  
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## 17 18 **Summary**

### 19 20 Article Focus

- 21  
22 • Neglecting the presence of unobserved heterogeneity in survival analysis models has  
23 been showed to potentially lead to underestimating the effect of the covariates  
24 included in the analysis.
- 25  
26 • Although frailty models have been widely developed to account for unobserved  
27 heterogeneity, in differential mortality analyses this source of variation is seldom  
28 controlled for. This study has applied these models to a longitudinal mortality analysis  
29 by education level.

### 30 31 32 33 34 35 36 37 38 Key messages

- 39  
40 • Mortality differentials by education (or by any other variable used as proxy of  
41 socioeconomic status) could be larger than those estimated with standard survival  
42 analysis approaches that do not control for unobserved heterogeneity.
- 43  
44 • Relative mortality differences at old ages between socioeconomic groups are often  
45 observed to decline. However, this pattern could be the result of a stronger selection  
46 due to early higher mortality that disadvantaged groups are still subject to.

### 47 48 49 50 51 52 53 54 Strengths and limitations

1  
2 The strength of this study lies in the population based longitudinal data. The long  
3  
4 observational time (36 years) for more than 847 000 individuals gives a solid base for  
5  
6 statistical power and detection of trends.  
7

8  
9 The limitation consists in the lack of individual information on life style factors and health  
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11 events, which could certainly help to better model the concept of unobserved individual frailty  
12  
13 by uncovering part of it.  
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43  
44 *Contributorship.* Virginia Zarulli: conception and design of the study, analysis and  
45  
46 interpretation of data and results, drafting the article and revising it; Graziella Caselli:  
47  
48 interpretation of the results, drafting the article and revising it critically; Chiara Marinacci and  
49  
50 Giuseppe Costa: revising the article for important intellectual content.  
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55 *Data sharing.* There is no additional data available.  
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## References

1. Mackenbach JP, Kunst AE, Cavelaars AEJM, Groenhouf F, Geurts JJM, others. Socioeconomic inequalities in morbidity and mortality in western Europe. *The Lancet*. 1997;349(9066):1655-9.
2. Mackenbach JP, Kunst AE, Groenhouf F, Borgan JK, Costa G, Faggiano F, et al. Socioeconomic inequalities in mortality among women and among men: an international study. *American Journal of Public Health*. 1999;89(12):1800-6.
3. Mackenbach JP, Stirbu I, Roskam AJR, Schaap MM, Menvielle G, Leinsalu M, et al. Socioeconomic inequalities in health in 22 European countries. *New England Journal of Medicine*. 2008;358(23):2468-81.
4. Antonovsky A. Social class, life expectancy and overall mortality. *The Milbank Memorial Fund Quarterly*. 1967;45(2):31-73.
5. Huisman M, Kunst AE, Mackenbach JP. Socioeconomic inequalities in morbidity among the elderly; a European overview. *Social Science & Medicine*. 2003;57(5):861-73.
6. Dalstra J, Kunst A, Mackenbach J, others. A comparative appraisal of the relationship of education, income and housing tenure with less than good health among the elderly in Europe. *Social Science & Medicine*. 2006;62(8):2046-60.
7. Martelin T. Mortality by indicators of socioeconomic status among the Finnish elderly. *Social Science & Medicine*. 1994;38(9):1257-78.
8. Huisman M, Kunst AE, Andersen O, Bopp M, Borgan JK, Borrell C, et al. Socioeconomic inequalities in mortality among elderly people in 11 European populations. *Journal of Epidemiology and Community Health*. 2004;58(6):468-75.
9. House JS, Lepkowski JM, Kinney AM, Mero RP, Kessler RC, Herzog AR. The social stratification of aging and health. *Journal of Health and Social Behavior*. 1994:213-34.
10. Decker S, Rapaport C. Medicare and disparities in women's health. *National Bureau of Economic Research*, 2002.
11. Dor A, Sudano J, Baker DW. The effect of private insurance on the health of older, working age adults: evidence from the Health and Retirement Study. *Health Services Research*. 2006;41(3p1):759-87.
12. Marmot MG, Shipley MJ. Do socioeconomic differences in mortality persist after retirement? 25 year follow up of civil servants from the first Whitehall study. *BMJ*. 1996;313(7066):1177-80.
13. Elo IT, Preston SH. Educational differentials in mortality: United States, 1979-1985. *Social Science & Medicine*. 1996;42(1):47-57.
14. Liang J, Bennett J, Krause N, Kobayashi E, Kim H, Brown JW, et al. Old age mortality in Japan. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. 2002;57(5):S294.
15. Caselli G, Vaupel JW, Yashin AI. Explanation of the decline in mortality among the oldest-old: A demographic point of view. *Human Longevity, Individual Life Duration, and the Growth of the Oldest-Old Population*. 2006:395-413.
16. Manton KG, Stallard E, others. Methods for evaluating the heterogeneity of aging processes in human populations using vital statistics data: explaining the black/white mortality crossover by a model of mortality selection. *Human Biology*. 1981;53(1):47.
17. Vaupel JW, Manton KG, Stallard E. The impact of heterogeneity in individual frailty on the dynamics of mortality. *Demography*. 1979;16(3):439-54.
18. Vaupel JW, Yashin AI. Heterogeneity's ruses: some surprising effects of selection on population dynamics. *American Statistician*. 1985:176-85.

19. Aalen OO. Effects of frailty in survival analysis. *Statistical Methods in Medical Research*. 1994;3(3):227.
20. Aalen OO. Heterogeneity in survival analysis. *Statistics in Medicine*. 1988;7(11):1121-37.
21. Gail MH, Wieand S, Piantadosi S. Biased estimates of treatment effect in randomized experiments with nonlinear regressions and omitted covariates. *Biometrika*. 1984;71(3):431.
22. Trussell J, Rodriguez G. Heterogeneity in demographic research. Convergent issues in genetics and demography: *Oxford University Press, USA; 1990. p. 111-32.*
23. Chamberlain G. Heterogeneity, omitted variable bias, and duration dependence. *Longitudinal Analysis of Labor Market Data*, ed JJ Heckman, B Singer. 1985:3-38.
24. Schumacher M, Olschewski M, Schmoor C. The impact of heterogeneity on the comparison of survival times. *Statistics in Medicine*. 1987;6(7):773-84.
25. Schmoor C, Schumacher M. Effects of covariate omission and categorization when analysing randomized trials with the Cox model. *Statistics in Medicine*. 1997;16(3):225-37.
26. Bretagnolle J, Huber-Carol C. Effects of omitting covariates in Cox's model for survival data. *Scandinavian Journal of Statistics*. 1988:125-38.
27. Wienke A. *Frailty models in survival analysis: Chapman & Hall/CRC; 2010.*
28. Marinacci C, Spadea T, Biggeri A, Demaria M, Caiazzo A, Costa G. The role of individual and contextual socioeconomic circumstances on mortality: analysis of time variations in a city of north west Italy. *Journal of Epidemiology and Community Health*. 2004;58(3):199-207.
29. Costa G, Cardano M, Demaria M. Torino. *Storie di salute in una grande città. Città di Torino, Ufficio di statistica, Osservatorio socioeconomico torinese. 1998.*
30. Doblhammer G, Hoffmann R, Muth E, Westphal C, Kruse A. A systematic literature review of studies analyzing the effect of sex, age, education, marital status, obesity, and smoking on health transitions. *Demographic Research*. 2009;20(5):37-64.
31. Krieger N, Williams DR, Moss NE. Measuring social class in US public health research: concepts, methodologies, and guidelines. *Annual Review of Public Health*. 1997;18(1):341-78.
32. Mirowsky J, Ross CE. *Education, social status, and health: Aldine de Gruyter; 2003.*
33. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Smith GD. Indicators of socioeconomic position (part 1). *Journal of Epidemiology and Community Health*. 2006;60(1):7-12.
34. Bonifazi C, Heins F. Long-term trends of internal migration in Italy. *International Journal of Population Geography*. 2000;6(2):111-31.
35. Gompertz B. On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. *Philosophical Transactions of the Royal Society of London*. 1825;115:513-83.
36. Akaike H. A new look at the statistical model identification. *Automatic Control, IEEE Transactions on*. 1974;19(6):716-23.
37. Holford TR. Analysing the temporal effects of age, period and cohort. *Statistical Methods in Medical Research*. 1992;1(3):317-37.
38. Osmond C, Gardner M. Age, period, and cohort models. Non-overlapping cohorts don't resolve the identification problem. *American Journal of Epidemiology*. 1989;129(1):31.
39. Glenn ND. Cohort analysts' futile quest: Statistical attempts to separate age, period and cohort effects. *American Sociological Review*. 1976;41(5):900-4.
40. Hartigan JA. Using subsample values as typical values. *Journal of the American Statistical Association*. 1969:1303-17.
41. Politis DN, Romano JP. Large sample confidence regions based on subsamples under minimal assumptions. *The Annals of Statistics*. 1994;22(4):2031-50.



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42. Efron B. Bootstrap methods: another look at the jackknife. *The Annals of Statistics*. 1979;7(1):1-26.
43. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria 2011.
44. Barbi E, Caselli G. Selection effects on regional differences in survivorship in Italy. *Genus*. 2003;37-61.
45. Caselli G, Egidi V. Le differenze territoriali di mortalità in Italia. *Tavole di mortalità provinciali (1971-72)*. 1980.
46. Caselli G, Egidi V. L'analyse des données multidimensionnelles dans l'étude des relations entre mortalité et variables socio-économiques d'environnement et de comportement individuel [Multivariate methods in the analysis of the relations between mortality and socio-economic, environmental and behavioural variables]. *Genus*. 1981;37(3/4):57-91.
47. Caselli G, Reale A. Does cohort analysis contribute to the study of the geography of mortality? *Genus*. 1999:27-59.
48. Biggeri A, Accetta G, Egidi V. Evoluzione del profilo di mortalità 30-74 anni per le coorti di nascita dal 1889 al 1968 nelle regioni italiane [Mortality Time Trends 30-74 years by Birth Cohorts 1889-1968 in the Italian Regions]. *Epidemiologia & Prevenzione*. 2011;35(5-6):50-67.
49. Efron B, Tibshirani R. *An introduction to the bootstrap*: Chapman & Hall/CRC; 1993.
50. Manly BFJ. *Randomization, bootstrap and Monte Carlo methods in biology*: Chapman & Hall/CRC; 1997.
51. Pattengale ND, Alipour M, Bininda-Emonds ORP, Moret BME, Stamatakis A. How many bootstrap replicates are necessary? *Journal of Computational Biology*. 2010;17(3):337-54.
52. Beckett M. Converging health inequalities in later life-an artifact of mortality selection? *Journal of Health and Social Behavior*. 2000:106-19.
53. Ferraro KF, Farmer MM. Double jeopardy, aging as leveler, or persistent health inequality? A longitudinal analysis of white and black Americans. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. 1996;51(6):S319.
54. Herd P. Do functional health inequalities decrease in old age? *Research on Aging*. 2006;28(3):375-92.
55. Kim J, Durden E. Socioeconomic status and age trajectories of health. *Social Science & Medicine*. 2007;65(12):2489-502.
56. Lynch SM. Cohort and life-course patterns in the relationship between education and health: A hierarchical approach. *Demography*. 2003;40(2):309-31.
57. McMunn A, Nazroo J, Breeze E. Inequalities in health at older ages: a longitudinal investigation of the onset of illness and survival effects in England. *Age and Ageing*. 2009;38(2):181.
58. Dupre ME. Educational differences in age-related patterns of disease: Reconsidering the cumulative disadvantage and age-as-leveler hypotheses. *Journal of Health and Social Behavior*. 2007;48(1):1-15.
59. Hoffmann R. Do socioeconomic mortality differences decrease with rising age? *Demographic Research*. 2005;13(2):35-62.
60. Hoffmann R. Socioeconomic inequalities in old-age mortality: A comparison of Denmark and the USA. *Social Science & Medicine*. 2011;72(12):1986 - 92.
61. Anson J. The migrant mortality advantage: a 70 month follow-up of the Brussels population. *European Journal of Population/Revue Européenne de Démographie*. 2004;20(3):191-218.
62. Feinleib M, Lambert PM, Zeiner-Henriksen T, Rogot E, Hunt BM, Ingster-Moore L. The British-Norwegian migrant study--analysis of parameters of mortality differentials associated with angina. *Biometrics*. 1982:55-71.



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63. Kington R, Carlisle D, McCaffrey D, Myers H, Allen W. Racial differences in functional status among elderly US migrants from the south. *Social Science & Medicine*. 1998;47(6):831-40.
64. Norman P, Boyle P, Rees P. Selective migration, health and deprivation: a longitudinal analysis. *Social Science & Medicine*. 2005;60(12):2755-71.
65. Rasulo D, Spadea T, Onorati R, Costa G. The impact of migration in all-cause mortality: The Turin Longitudinal Study, 1971–2005. *Social Science & Medicine*. 2012.
66. Singh GK, Siahpush M. All-cause and cause-specific mortality of immigrants and native born in the United States. *American Journal of Public Health*. 2001;91(3):392.
67. Bielby WT, Bielby DD. I will follow him: Family ties, gender-role beliefs, and reluctance to relocate for a better job. *American Journal of Sociology*. 1992:1241-67.
68. Cooke TJ. Gender role beliefs and family migration. *Population, Space and Place*. 2008;14(3):163-75.
69. Mincer J. Family Migration Decisions. *Journal of Political Economy*. 1978;86:749-75.

## 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:

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

where  $\sigma^2$  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:

$$\mu_i(x | u_i) = \mu_0(x) e^{\beta u_i} \quad (2)$$

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

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

Where for each individual  $i$ ,  $y_i$  is the entry time,  $x_i$  in the exit time,  $\delta_i$  is the status (1=dead, 0=right censored),  $u_i$  is the covariate profile with effect  $\beta$  and  $\mu(\cdot)$  denotes the hazard,  $S(\cdot)$  the survival function and  $\theta$  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:

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

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

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

Where for each individual  $i$ ,  $y_i$  is the entry time,  $x_i$  in the exit time,  $\delta_i$  is the status (1=dead, 0=right censored),  $u_i$  is the covariate profile with effect  $\beta$  and  $\mu(\cdot)$  denotes the hazard,  $M(\cdot)$  the cumulative hazard,  $\theta$  is the vector of parameters of the baseline hazard and  $\sigma^2$  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):

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

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):

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

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

The overall likelihood function is simply:

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

## 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.

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

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

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  $\lambda$  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.

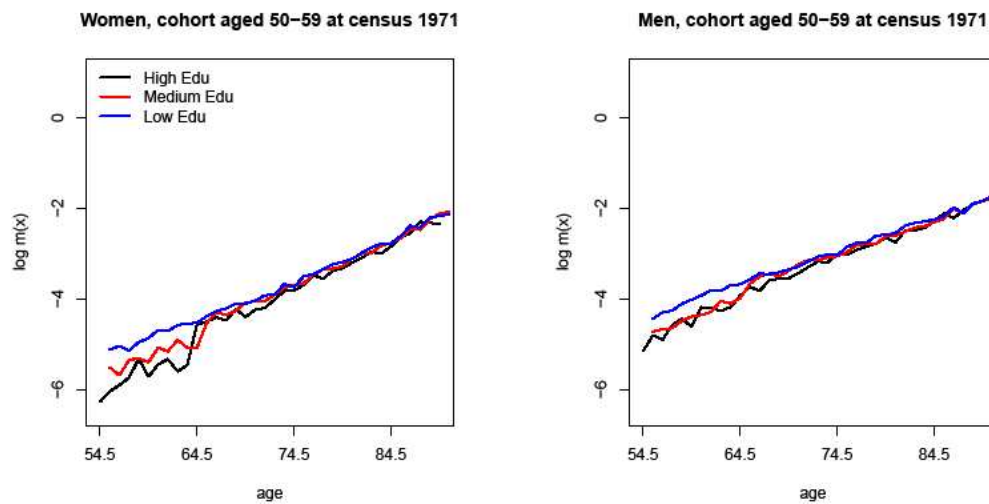
**Table B1. Mortality rate ratios between education groups and age groups estimated from an exponential survival hazard model with covariates education, age and their interaction. The table also reports the likelihood ratio test between this model and a model without an age-education interaction term.**

|  | 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.

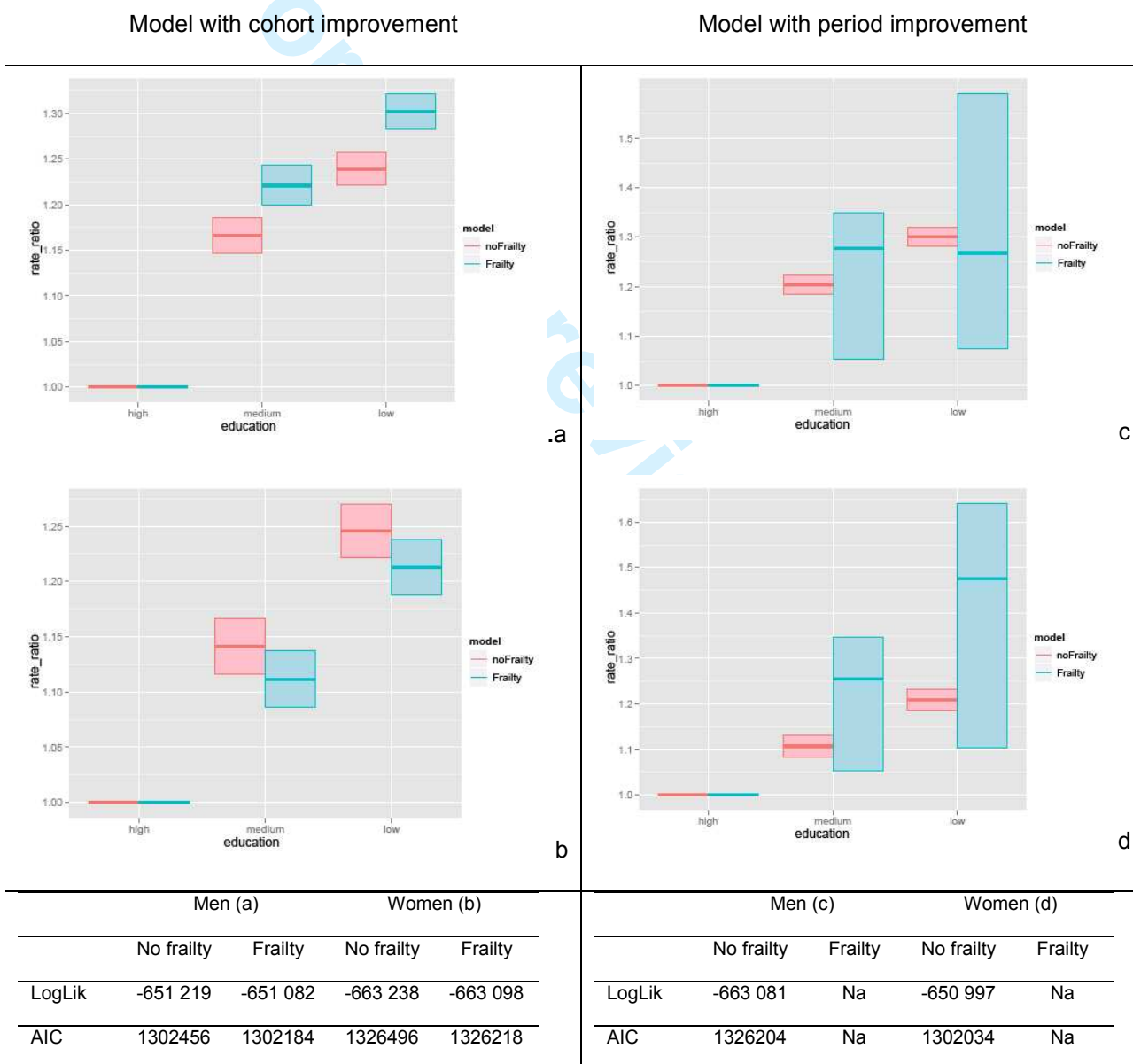
## Figures

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.**





**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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**Word count:** 3120

## 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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## 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 than 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

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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 24<sup>th</sup> 1971, official date of the census, to the end of July 2007, end of the linkage) during which the individuals were

1  
2 followed up until death, emigration from the city or end of observation period. The follow up  
3  
4 started at age 50. The study population contains 391 170 men and 456 216 women.

5  
6 Study information includes individual's date of birth, date of exit from the study, cause  
7  
8 of exit (death or emigration), sex, macro-region of birth and education level.

9  
10 Consistent with the literature (30-33) education level was used as an indicator of social  
11  
12 position.

13  
14 The study also controlled for the individual macro region of birth, as Turin is  
15  
16 characterized by a history of immigration from other regions of the country (34).

17  
18 To facilitate the comparison over a long follow up and different cohorts, we created  
19  
20 three broad educational groups: high (high school diploma or higher), medium (junior high  
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22 school) and low (primary school or lower).

23  
24 We estimated parametric survival models stratified by gender and as a function of  
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26 macro-region of birth and education level, with and without a parameter for the unobserved  
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28 heterogeneity component. The parametric choice is justified by the wide demographic  
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30 literature showing that human adult mortality can be accurately described by a Gompertz  
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32 function (35) or by some Gompertz-like variants, like Makeham. To identify the best  
33  
34 functional form for the baseline we compared the models with the AIC (36).

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36 The data are both right censored (due to emigration or end of follow up) and left  
37  
38 truncated (due to the different age at entry in the study of the individuals).

39  
40 The study includes many cohorts, each passing through the 36 years of observation at  
41  
42 different ages. However, from 1971 to 2007 a significant mortality improvement occurred and  
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44 younger cohorts experience lower age specific mortality than older cohorts.

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46 Time is a complex variable including three dimensions: age, period and cohort.  
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48 Controlling adequately for the effect of time would require to asses simultaneously the three  
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50 components but such models have been not identifiable for a long time because of linear  
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52 dependence between the three dimensions (37-39). Recently it has been showed that through  
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2 the introduction of the GLMM (generalized linear mixed models) framework, new estimation  
3 methods and model specifications can be used to tackle the identification problem (40).  
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6 However, this goes beyond the scope of our study.  
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9 We adopted two approaches for the control of time, corresponding to an age-cohort  
10 approach and an age-period approach, being aware that they represent two different  
11 dimensions of time.  
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15 First, we regarded the improvement as a cohort phenomenon, including a covariate for  
16 the cohort to which the individuals belong. In this setting, controlling for unobserved  
17 heterogeneity was implemented with univariate frailty models, which estimate the baseline  
18 parameters, the coefficients of the covariates and the variance of frailty (assumed to follow a  
19 gamma distribution with mean 1 and variance  $\sigma^2$  to be estimated).  
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27 We then considered the improvement as a period phenomenon and split the time into  
28 several calendar period covariates, as well as the survival spell of the individuals, according to  
29 which period they were passing through. This implied organizing the data into clusters, where  
30 each cluster represents one individual's survival spells. In this setting, to control for  
31 unobserved heterogeneity shared frailty models are needed, where the spells in each cluster  
32 pertain to the same individual and share the same hidden frailty. For computational reasons,  
33 the estimation of these highly complex models required the use of random subsampling (41-  
34 43). We repeated the estimation 250 times on a 1% sample of the dataset, randomly drawn  
35 without replacement and stratified by the major variables in analysis. The aim is to  
36 approximate the parameters estimates based on the empirical distribution of the repeated  
37 estimates.  
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51 In the model without frailty it was possible to include a finer calendar period division,  
52 12 period variables of 3 years each (1971-1973, 1974-1976...), while in the model with  
53 frailty, for computational reasons, the number of variables was reduced to 2 broader periods:  
54 1971-1990 and 1991-2007.  
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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   |
|           | $ae^{bx}$                             | $ae^{bx} + c$ | $\frac{ae^{bx}}{1 + \sigma^2 \frac{a}{b}(e^{bx} - 1)}$ | $\frac{ae^{bx} + c}{1 + \sigma^2 \frac{a}{b}(e^{bx} - 1) + cx}$ |
| 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 $\times 10^5$   | 5.237 $\times 10^5$ -<br>5.245 $\times 10^5$ | 4.495 $\times 10^5$ | 4.488 $\times 10^5$ -<br>4.501 $\times 10^5$ | 3.767 $\times 10^6$   | 3.755 $\times 10^6$ -<br>3.779 $\times 10^6$ | 1.605 $\times 10^6$ | 1.588 $\times 10^6$ -<br>1.623 $\times 10^6$ |
| 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 <sup>2</sup> | -                     | -  | 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 $\times 10^5$   | 3.196 $\times 10^5$ -<br>5.410 $\times 10^5$ | 0.004               | (0.000-0.010) | 8.031 $\times 10^5$   | 6.028 $\times 10^5$ -<br>1.070 $\times 10^6$ | 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 $\times 10^6$ | 8.610 $\times 10^7$ -<br>2.997 $\times 10^8$ |
| Sigma <sup>2</sup> | -                     | -  | 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

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2 and for the low education group, between 1.1 and 1.6, compared to 1.18 and 1.23. The same  
3  
4 pattern can be observed among men.  
5

6 The male difference between medium and low education group, on the contrary, was  
7  
8 not as clear as that among women.  
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#### 10 11 12 13 *Other results and the impact of the macro-region of birth on mortality* 14

15 As expected, the variance of frailty in the cohort models was smaller than in the period  
16  
17 models, since periods are more heterogeneous than cohorts.  
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19 Women were more heterogeneous than men: 0.09 (0.08-0.11) versus 0.04 (0.03-0.05)  
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21 in the age-cohort models and 0.29 (0.17-0.37) versus 0.27 (0.-0.36) in the age-period models.  
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23

24 This is consistent with the more pronounced convergence of the hazards by education  
25  
26 at old age found among women compared to the men. According to the framework of the  
27  
28 frailty models, converging hazards are the result of the effect of selection on the population  
29  
30 hazards, due to how much variance of unobserved frailty is present in the population at the  
31  
32 initial age of observation. The bigger the variance the stronger the convergence is. For more  
33  
34 information about frailty models, the process of selection and how they relate to narrowing  
35  
36 mortality differentials at old ages, please see appendix A.  
37  
38

39 In the age-cohort models the introduction of unobserved frailty affected the coefficient  
40  
41 for the macro-region of birth significantly. Among men, holding education equal, those born  
42  
43 in the South show a significant survival advantage over the natives of the North-West, while  
44  
45 in the model without frailty there was no such advantage. Among women, the model without  
46  
47 frailty showed a significant survival advantage for those born in the South but when frailty  
48  
49 was controlled for, this became not significant.  
50  
51

52 The pattern also resembles the regional mortality macro-dynamics that have  
53  
54 characterized Italy for most of the 20<sup>th</sup> century (although the two patterns refer to different  
55  
56 phenomena, the first one referring to mortality by region of birth), when male mortality in the  
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1  
2 South was lower than in the North (45-48). Cohort based analyses have highlighted that in  
3  
4 more recent cohorts (those born after WWII) there is a reversing trend (48, 49).  
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6

7 The models with age-period perspective did not identify any significant geographical  
8  
9 differences. This could be due to the utilization of random subsampling of a 1% sample.  
10  
11 Although 250 repetitions is considered by the literature a sufficient number for very complex  
12  
13 models (50-52), it is possible that it was inadequate to identify a clear pattern from the small  
14  
15 sample. For more detailed results see tables 1 and 2.  
16  
17

## 18 19 20 **Discussion**

21  
22 The interest in the role of unobserved heterogeneity in a life course approach to  
23  
24 socioeconomic mortality differences has recently increased. Most of the studies focus on  
25  
26 health outcomes (53-58) while fewer studies also analyze mortality (59-61). Their findings are  
27  
28 not consistent and fuel a still controversial debate.  
29  
30

31 In this study we investigated the role of unobserved individual heterogeneity on the  
32  
33 estimation of mortality differentials at adult-old ages by education level in a longitudinal  
34  
35 perspective. This study investigated if the estimates of the mortality differentials are affected  
36  
37 by the introduction of the unobserved heterogeneity component into the models.  
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39

40 We fitted survival analysis models with and without controlling for the unobserved  
41  
42 heterogeneity and we found that, when this component was included, the models gave a  
43  
44 significantly better fit.  
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46

47 We also found that in the majority of the cases, the educational gradient estimated by  
48  
49 the models with frailty was higher than the one estimated by the models without frailty. When  
50  
51 big uncertainty around the estimates did not allow assessing a precise value, the confidence  
52  
53 regions in the models with frailty spanned over higher values than those in the models without  
54  
55 frailty. It must be pointed out that, in the age-period approach, to the peculiar statistical  
56  
57 procedure used to estimate the frailty models did not allow obtaining a likelihood value  
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1  
2 comparable with the one of the model without frailty. Thus, the statistical comparison of the  
3  
4 models via the AIC was not possible, making this evidence weaker. Nevertheless, the results  
5  
6 seem to point to a direction that is consistent with the statistical literature about unobserved  
7  
8 heterogeneity (19-26).  
9

10  
11 Among men such a pattern was found in both the age-cohort and age-period  
12  
13 approaches. Among women, on the contrary, this pattern was less clear: in the age-cohort  
14  
15 model, controlling for hidden frailty resulted in a slight reduction of the mortality gradient.  
16  
17 Social determinants act on mortality also through risk factors that are known to affect more  
18  
19 men than women. Moreover, because of a lag in the smoking and fertility transitions, highly  
20  
21 educated women in Turin are more exposed to risk factors like cigarette smoking and smaller  
22  
23 number of children. Therefore, controlling for hidden frailty in the case of women might  
24  
25 reduce the educational gradient.  
26  
27

28  
29 In the models with age-cohort perspective controlling for the hidden frailty affected  
30  
31 also the estimates of the differentials by macro-region of birth, showing a survival advantage  
32  
33 of the men born in the South, but not of the women, for whom an advantage was instead  
34  
35 detected by the model that did not control for frailty.  
36  
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38  
39 The healthy migrant effect (62-67) could cause this pattern. Among the cohorts  
40  
41 involved in the migration women were likely to be more passive actors than men in the  
42  
43 migratory decision (68-70) and this might have selected them more than men. Frailty is a  
44  
45 general concept embedding all the hidden factors that affect the individual survival chances:  
46  
47 innate and acquired frailty, exposure to risk factors, life style factors and so on. Therefore,  
48  
49 controlling for frailty reduced the survival advantage of the women, who might have been less  
50  
51 health selected than men by the migration, while uncovered the advantage of the men.  
52  
53 However, another recent study on the impact of migration on all-cause mortality in Turin did  
54  
55 not find particularly strong gender differences in the so called healthy migrant effect (66) and  
56  
57 this point deserves future further investigation.  
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1  
2 The study spanned over a long observation window of 36 years. Therefore it was  
3 important to control for the general mortality improvement that took place during this time.  
4 We did so by adopting both an age-period and an age-cohort approach.  
5  
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8  
9 The age-period models, as expected, estimated higher heterogeneity than the age-  
10 cohort models. Periods aggregate different generations and are expected to be more  
11 heterogeneous than the cohorts themselves. In both period and cohort models the female  
12 variance of frailty was higher than for the males, indicating that men are more homogeneous  
13 than women. This could be attributed to a stronger selection process due to mortality that is  
14 usually observed to be higher among men than among women.  
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22 On the other hand, it is also possible that the industrialization process and the internal  
23 migration experienced by Italy after WWII (34) played a role. The vast majority of less  
24 educated individuals in Turin came from the South, seeking a job in the car factories of the  
25 city. As less educated men were mainly employed in heavier and riskier jobs and were  
26 exposed to higher mortality, it is possible that during their life they were selected at a faster  
27 pace than other educational groups and women. This might have reduced the differences in  
28 susceptibility to death among men, contributing to determining a lower level of heterogeneity  
29 than among women.  
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## 42 **Conclusion**

43  
44 This study found that neglecting selection effects due to unobserved heterogeneity in  
45 longitudinal analyses, could lead to underestimation of mortality differentials by social class.  
46 In the majority of the cases, the models that controlled for unobserved heterogeneity,  
47 estimated higher educational differences in mortality than the models that did not control for  
48 it.  
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55 Moreover, when compared with via the AIC, the models that controlled for  
56 unobserved heterogeneity gave a statistically significant better fit than the models that did not  
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1  
2 control for it. Although the best AIC shows just that the more complex model approximates  
3  
4 better the data and this does not represent an unequivocal proof of the selection hypothesis,  
5  
6 the results point to the possibility that the data could be better described by this hypothesis.  
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28  
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30  
31  
32

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36  
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41 interpretation of data and results, drafting the article and revising it; Graziella Caselli:  
42 interpretation of the results, drafting the article and revising it critically; Chiara Marinacci and  
43 Giuseppe Costa: revising the article for important intellectual content.  
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50  
51 *Data sharing.* No additional data available.  
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## References

1. Mackenbach JP, Kunst AE, Cavelaars AEJM, et al. Socioeconomic inequalities in morbidity and mortality in western Europe. *The Lancet*. 1997;349(9066):1655-9.
2. Mackenbach JP, Kunst AE, Groenhof F, et al. Socioeconomic inequalities in mortality among women and among men: an international study. *American Journal of Public Health*. 1999;89(12):1800-6.
3. Mackenbach JP, Stirbu I, Roskam AJR, et al. Socioeconomic inequalities in health in 22 European countries. *New England Journal of Medicine*. 2008;358(23):2468-81.
4. Antonovsky A. Social class, life expectancy and overall mortality. *The Milbank Memorial Fund Quarterly*. 1967;45(2):31-73.
5. Huisman M, Kunst AE, Mackenbach JP. Socioeconomic inequalities in morbidity among the elderly; a European overview. *Social Science & Medicine*. 2003;57(5):861-73.
6. Dalstra J, Kunst A, Mackenbach J, others. A comparative appraisal of the relationship of education, income and housing tenure with less than good health among the elderly in Europe. *Social Science & Medicine*. 2006;62(8):2046-60.
7. Martelin T. Mortality by indicators of socioeconomic status among the Finnish elderly. *Social Science & Medicine*. 1994;38(9):1257-78.
8. Huisman M, Kunst AE, Andersen O, et al. Socioeconomic inequalities in mortality among elderly people in 11 European populations. *Journal of Epidemiology and Community Health*. 2004;58(6):468-75.
9. House JS, Lepkowski JM, Kinney AM, et al. The social stratification of aging and health. *Journal of Health and Social Behavior*. 1994:213-34.
10. Decker S, Rapaport C. Medicare and disparities in women's health. National Bureau of Economic Research, 2002.
11. Dor A, Sudano J, Baker DW. The effect of private insurance on the health of older, working age adults: evidence from the Health and Retirement Study. *Health Services Research*. 2006;41(3p1):759-87.
12. Marmot MG, Shipley MJ. Do socioeconomic differences in mortality persist after retirement? 25 year follow up of civil servants from the first Whitehall study. *BMJ*. 1996;313(7066):1177-80.
13. Elo IT, Preston SH. Educational differentials in mortality: United States, 1979-1985. *Social Science & Medicine*. 1996;42(1):47-57.
14. Liang J, Bennett J, Krause N, et al. Old age mortality in Japan. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. 2002;57(5):S294.
15. Caselli G, Vaupel JW, Yashin AI. Explanation of the decline in mortality among the oldest-old: A demographic point of view. *Human Longevity, Individual Life Duration, and the Growth of the Oldest-Old Population*. 2006:395-413.
16. Manton KG, Stallard E, others. Methods for evaluating the heterogeneity of aging processes in human populations using vital statistics data: explaining the black/white mortality crossover by a model of mortality selection. *Human Biology*. 1981;53(1):47.
17. Vaupel JW, Manton KG, Stallard E. The impact of heterogeneity in individual frailty on the dynamics of mortality. *Demography*. 1979;16(3):439-54.
18. Vaupel JW, Yashin AI. Heterogeneity's ruses: some surprising effects of selection on population dynamics. *American Statistician*. 1985:176-85.
19. Aalen OO. Effects of frailty in survival analysis. *Statistical Methods in Medical Research*. 1994;3(3):227.
20. Aalen OO. Heterogeneity in survival analysis. *Statistics in Medicine*. 1988;7(11):1121-37.
21. Gail MH, Wieand S, Piantadosi S. Biased estimates of treatment effect in randomized experiments with nonlinear regressions and omitted covariates. *Biometrika*. 1984;71(3):431.

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22. Trussell J, Rodriguez G. Heterogeneity in demographic research. *Convergent issues in genetics and demography*: Oxford University Press, USA; 1990. p. 111-32.
23. Chamberlain G. Heterogeneity, omitted variable bias, and duration dependence. *Longitudinal Analysis of Labor Market Data*, ed JJ Heckman, B Singer. 1985:3-38.
24. Schumacher M, Olschewski M, Schmoor C. The impact of heterogeneity on the comparison of survival times. *Statistics in Medicine*. 1987;6(7):773-84.
25. Schmoor C, Schumacher M. Effects of covariate omission and categorization when analysing randomized trials with the Cox model. *Statistics in Medicine*. 1997;16(3):225-37.
26. Bretagnolle J, Huber-Carol C. Effects of omitting covariates in Cox's model for survival data. *Scandinavian Journal of Statistics*. 1988:125-38.
27. Wienke A. *Frailty models in survival analysis*: Chapman & Hall/CRC; 2010.
28. Marinacci C, Spadea T, Biggeri A, et al. The role of individual and contextual socioeconomic circumstances on mortality: analysis of time variations in a city of north west Italy. *Journal of Epidemiology and Community Health*. 2004;58(3):199-207.
29. Costa G, Cardano M, Demaria M. et al. *Storie di salute in una grande città. Città di Torino*, Ufficio di statistica, Osservatorio socioeconomico torinese. 1998.
30. Doblhammer G, Hoffmann R, Muth E, et al. A systematic literature review of studies analyzing the effect of sex, age, education, marital status, obesity, and smoking on health transitions. *Demographic Research*. 2009;20(5):37-64.
31. Krieger N, Williams DR, Moss NE. Measuring social class in US public health research: concepts, methodologies, and guidelines. *Annual Review of Public Health*. 1997;18(1):341-78.
32. Mirowsky J, Ross CE. *Education, social status, and health*: Aldine de Gruyter; 2003.
33. Galobardes B, Shaw M, Lawlor DA, et al. Indicators of socioeconomic position (part 1). *Journal of Epidemiology and Community Health*. 2006;60(1):7-12.
34. Bonifazi C, Heins F. Long-term trends of internal migration in Italy. *International Journal of Population Geography*. 2000;6(2):111-31.
35. Gompertz B. On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. *Philosophical Transactions of the Royal Society of London*. 1825;115:513-83.
36. Akaike H. A new look at the statistical model identification. *Automatic Control, IEEE Transactions on*. 1974;19(6):716-23.
37. Holford TR. Analysing the temporal effects of age, period and cohort. *Statistical Methods in Medical Research*. 1992;1(3):317-37.
38. Osmond C, Gardner M. Age, period, and cohort models. Non-overlapping cohorts don't resolve the identification problem. *American Journal of Epidemiology*. 1989;129(1):31.
39. Glenn ND. Cohort analysts' futile quest: Statistical attempts to separate age, period and cohort effects. *American Sociological Review*. 1976;41(5):900-4.
40. Yang Y, Land KC. *Age-period-cohort Analysis: New Models, Methods, and Empirical Applications*: Chapman & Hall; 2013.
41. Hartigan JA. Using subsample values as typical values. *Journal of the American Statistical Association*. 1969:1303-17.
42. Politis DN, Romano JP. Large sample confidence regions based on subsamples under minimal assumptions. *The Annals of Statistics*. 1994;22(4):2031-50.
43. Efron B. Bootstrap methods: another look at the jackknife. *The Annals of Statistics*. 1979;7(1):1-26.
44. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria 2011.
45. Barbi E, Caselli G. Selection effects on regional differences in survivorship in Italy. *Genus*. 2003:37-61.

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46. Caselli G, Egidi V. Le differenze territoriali di mortalità in Italia. Tavole di mortalità provinciali (1971-72). 1980.
47. Caselli G, Egidi V. L'analyse des données multidimensionnelles dan l'étude des relations entre mortalité et variable socio-économiques d' envirnment et de comportement individuel [Multivariate methods in the analysis of the relations between mortality and socio-economic, environmental and behavioural variables]. *Genus*. 1981;37(3/4):57-91.
48. Caselli G, Reale A. Does cohort analysis contribute to the study of the geography of mortality? *Genus*. 1999:27-59.
49. Biggeri A, Accetta G, Egidi V. Evoluzione del profilo di mortalita 30-74 anni per le coorti di nascita dal 1889 al 1968 nelle regioni italiane [Mortality Time Trends 30-74 years by Birth Cohorts 1889-1968 in the Italian Regions]. *Epidemiologia & Prevenzione*. 2011;35(5-6):50-67.
50. Efron B, Tibshirani R. An introduction to the bootstrap: Chapman & Hall/CRC; 1993.
51. Manly BFJ. Randomization, bootstrap and Monte Carlo methods in biology: Chapman & Hall/CRC; 1997.
52. Pattengale ND, Alipour M, Bininda-Emonds ORP, et al. How many bootstrap replicates are necessary? *Journal of Computational Biology*. 2010;17(3):337-54.
53. Beckett M. Converging health inequalities in later life-an artifact of mortality selection? *Journal of Health and Social Behavior*. 2000:106-19.
54. Ferraro KF, Farmer MM. Double jeopardy, aging as leveler, or persistent health inequality? A longitudinal analysis of white and black Americans. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. 1996;51(6):S319.
55. Herd P. Do functional health inequalities decrease in old age? *Research on Aging*. 2006;28(3):375-92.
56. Kim J, Durden E. Socioeconomic status and age trajectories of health. *Social Science & Medicine*. 2007;65(12):2489-502.
57. Lynch SM. Cohort and life-course patterns in the relationship between education and health: A hierarchical approach. *Demography*. 2003;40(2):309-31.
58. McMunn A, Nazroo J, Breeze E. Inequalities in health at older ages: a longitudinal investigation of the onset of illness and survival effects in England. *Age and Ageing*. 2009;38(2):181.
59. Dupre ME. Educational differences in age-related patterns of disease: Reconsidering the cumulative disadvantage and age-as-leveler hypotheses. *Journal of Health and Social Behavior*. 2007;48(1):1-15.
60. Hoffmann R. Do socioeconomic mortality differences decrease with rising age? *Demographic Research*. 2005;13(2):35-62.
61. Hoffmann R. Socioeconomic inequalities in old-age mortality: A comparison of Denmark and the USA. *Social Science & Medicine*. 2011;72(12):1986 - 92.
62. Anson J. The migrant mortality advantage: a 70 month follow-up of the Brussels population. *European Journal of Population/Revue Européenne de Démographie*. 2004;20(3):191-218.
63. Feinleib M, Lambert PM, Zeiner-Henriksen T, et al. The British-Norwegian migrant study--analysis of parameters of mortality differentials associated with angina. *Biometrics*. 1982:55-71.
64. Kington R, Carlisle D, McCaffrey D, et al. Racial differences in functional status among elderly US migrants from the south. *Social Science & Medicine*. 1998;47(6):831-40.
65. Norman P, Boyle P, Rees P. Selective migration, health and deprivation: a longitudinal analysis. *Social Science & Medicine*. 2005;60(12):2755-71.
66. Rasulo D, Spadea T, Onorati R, et al. The impact of migration in all-cause mortality: The Turin Longitudinal Study, 1971–2005. *Social Science & Medicine*. 2012.

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67. Singh GK, Siahpush M. All-cause and cause-specific mortality of immigrants and native born in the United States. *American Journal of Public Health*. 2001;91(3):392.
68. Bielby WT, Bielby DD. I will follow him: Family ties, gender-role beliefs, and reluctance to relocate for a better job. *American Journal of Sociology*. 1992:1241-67.
69. Cooke TJ. Gender role beliefs and family migration. *Population, Space and Place*. 2008;14(3):163-75.
70. Mincer J. Family Migration Decisions. *Journal of Political Economy*. 1978;86:749-75.

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3 **Mortality by education level at late-adult ages in Turin: a survival analysis**  
4  
5 **using frailty models with period and cohort approaches.**  
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9

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27

28 **Key words:** Mortality, inequality, education, frailty.  
29  
30

31 **Word count:** 3120  
32

33 **Abstract**  
34

35 Background. Unobserved heterogeneity of frailty can lead to biased estimates of coefficients  
36 in survival analysis models. This study investigated the role of unobserved frailty on the  
37 estimation of mortality differentials from age 50 on by education level.  
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39

40 Methods. We used data of a 36 years follow up from the Turin Longitudinal Study containing  
41 391 170 men and 456 216 women. As Turin underwent strong immigration flows during the  
42 post war industrialization, also the macro-region of birth was controlled for. We fitted  
43 survival analysis models with and without the unobserved heterogeneity component,  
44 controlling for mortality improvement from both cohort and period perspectives.  
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52 Results. We found that in the majority of the cases, the models without frailty estimated a  
53 smaller educational gradient than the models with frailty.  
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2 Conclusions. The results draw the attention on the potential underestimation of the mortality  
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4 inequalities by socioeconomic levels in survival models when not controlling for frailty.  
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## 8 **Introduction**

9  
10 An extensive literature shows significant differential mortality by socioeconomic condition  
11  
12 (1-3). Elderly show decreasing relative social inequalities in general mortality with increasing  
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14 age (4-8). The age-as-leveler hypothesis attributes this to factors that contribute to the  
15  
16 leveling-off of differences at old ages: governmental support to the elderly (9-11),  
17  
18 disengagement from systems of social stratification (12) and general vulnerability (13, 14).  
19  
20 However, this phenomenon could also be an artifact of selection due to unobserved  
21  
22 characteristics of the individuals: selective effects of earlier higher mortality, experienced by  
23  
24 the disadvantaged group, would leave more robust individuals at old ages, causing the  
25  
26 convergence with the risk of the lower mortality group, that is subject to weaker selection (15-  
27  
28 18). Neglecting these hidden differences in survival chances (called unobserved frailty), has  
29  
30 been shown to lead to biased estimates of the mortality hazard and of the effect of the  
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32 covariates on the survival probability (19-25).  
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37  
38 In longitudinal analyses on differential mortality it is important to control for hidden  
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40 frailty because, not controlling for it, **in models of survival analysis**, could lead to biased  
41  
42 estimates of the effect of the social position on the mortality risk. The statistical literature  
43  
44 shows that the bias is towards zero (24-26). This would lead to underestimation of the relative  
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46 differences in the mortality risks by socioeconomic group. To control for unobserved frailty  
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48 and to evaluate the impact on the observed mortality dynamics, frailty models have been  
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50 developed (27) . For more detailed explanations of the frailty models and how they relate to  
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52 differential mortality analyses, please, see appendix A.  
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56 This study investigated the presence of selection processes in the mortality patterns of  
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58 the Turin population (North-West Italy) from age 50 on. Adopting a longitudinal perspective,  
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2 this study aimed to investigate if the estimates of the mortality differentials are affected by the  
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4 introduction of the unobserved heterogeneity component into the models.  
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## 8 9 **Data and Methods**

10 We used high quality census linked data from the Turin Longitudinal Study (TLS), which  
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12 includes 1971, 1981, 1991 and 2001 census data for the Turin population. TLS records the  
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14 individual census socio-demographic information and, through record linkage with the local  
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16 population registry and other local health information systems, collects information on vital  
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18 status, cause of death and other health indicators (28, 29).  
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21  
22 For this study, the individuals registered in Turin during at least one of the four  
23  
24 censuses were selected. Their migration and vital status was followed up until the end of July  
25  
26 2007. The result is an observation window of 36 years (from October 24<sup>th</sup> 1971, official date  
27  
28 of the census, to the end of July 2007, end of the linkage) during which the individuals were  
29  
30 followed up until death, emigration from the city or end of observation period. The follow up  
31  
32 started at age 50. The study population contains 391 170 men and 456 216 women.  
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35  
36 Study information includes individual's date of birth, date of exit from the study, cause  
37  
38 of exit (death or emigration), sex, macro-region of birth and education level.  
39

40 Consistent with the literature (30-33) education level was used as an indicator of social  
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42 position.  
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44 The study also controlled for the individual macro region of birth, as Turin is  
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46 characterized by a history of immigration from other regions of the country (34).  
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49 To facilitate the comparison over a long follow up and different cohorts, we created  
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51 three broad educational groups: high (high school diploma or higher), medium (junior high  
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53 school) and low (primary school or lower).  
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55 We estimated parametric survival models stratified by gender and as a function of  
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57 macro-region of birth and education level, with and without a parameter for the unobserved  
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2 heterogeneity component. The parametric choice is justified by the wide demographic  
3 literature showing that human adult mortality can be accurately described by a Gompertz  
4 function (35) or by some Gompertz-like variants, like Makeham. To identify the best  
5 functional form for the baseline we compared the models with the AIC (36).  
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11 The data are both right censored (due to emigration or end of follow up) and left  
12 truncated (due to the different age at entry in the study of the individuals).  
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15 The study includes many cohorts, each passing through the 36 years of observation at  
16 different ages. However, from 1971 to 2007 a significant mortality improvement occurred and  
17 younger cohorts experience lower age specific mortality than older cohorts.  
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21 Time is a complex variable including three dimensions: age, period and cohort.  
22 Controlling adequately for the effect of time would require to assess simultaneously the three  
23 components but such models have been not identifiable for a long time because of linear  
24 dependence between the three dimensions (37-39). Recently it has been showed that through  
25 the introduction of the GLMM (generalized linear mixed models) framework, new estimation  
26 methods and model specifications can be used to tackle the identification problem (40).  
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36 However, this goes beyond the scope of our study.

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38 We adopted two approaches for the control of time, corresponding to an age-cohort  
39 approach and an age-period approach, being aware that they represent two different  
40 dimensions of time.  
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44 First, we regarded the improvement as a cohort phenomenon, including a covariate for  
45 the cohort to which the individuals belong. In this setting, controlling for unobserved  
46 heterogeneity was implemented with univariate frailty models, which estimate the baseline  
47 parameters, the coefficients of the covariates and the variance of frailty (assumed to follow a  
48 gamma distribution with mean 1 and variance  $\sigma^2$  to be estimated).  
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56 We then considered the improvement as a period phenomenon and split the time into  
57 several calendar period covariates, as well as the survival spell of the individuals, according to  
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1  
2 which period they were passing through. This implied organizing the data into clusters, where  
3 each cluster represents one individual's survival spells. In this setting, to control for  
4 unobserved heterogeneity shared frailty models are needed, where the spells in each cluster  
5 pertain to the same individual and share the same hidden frailty. For computational reasons,  
6 the estimation of these highly complex models required the use of random subsampling (41-  
7 43). We repeated the estimation 250 times on a 1% sample of the dataset, randomly drawn  
8 without replacement and stratified by the major variables in analysis. The aim is to  
9 approximate the parameters estimates based on the empirical distribution of the repeated  
10 estimates.  
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22 In the model without frailty it was possible to include a finer calendar period division,  
23 12 period variables of 3 years each (1971-1973, 1974-1976...), while in the model with  
24 frailty, for computational reasons, the number of variables was reduced to 2 broader periods:  
25 1971-1990 and 1991-2007.  
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30 Computations were realized with the software R (44). Formal details are in appendix  
31 A.  
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## 38 **Results**

39 Figure 1 shows that the log-death rates by education level and gender, for the cohort aged 50-  
40 59 in 1971, converge at old ages. Other cohorts showed very similar patterns.  
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44 A preliminary analysis found that the reduction of the gradient over age is statistically  
45 significant and more pronounced among women (results are reported in appendix B table B1).  
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49 Figure 1 here  
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### 51 *Frailty modeling*

52 Table 1 shows the AIC of the survival models, fitted to the all population mortality, with  
53 Gompertz and Makeham baselines. It also shows the results of the fit when unobserved frailty  
54 was controlled for. The comparison reveals that Gompertz baseline was a better fit for the  
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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   |
|           | $ae^{bx}$                             | $ae^{bx} + c$ | $\frac{ae^{bx}}{1 + \sigma^2 \frac{a}{b}(e^{bx} - 1)}$ | $\frac{ae^{bx} + c}{1 + \sigma^2 \frac{a}{b}(e^{bx} - 1) + cx}$ |
| 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 <sub>x10<sup>5</sup></sub> | <u>5.237<sub>x10<sup>5</sup>-</sub></u> | <u>4.495<sub>x10<sup>5</sup></sub></u> | <u>4.488<sub>x10<sup>5</sup>-</sub></u> | <u>3.767<sub>x10<sup>5</sup></sub></u> | <u>3.755<sub>x10<sup>5</sup>-</sub></u> | <u>1.605<sub>x10<sup>5</sup></sub></u> | <u>1.588<sub>x10<sup>5</sup>-</sub></u> |
|                    |                                  | <u>5.245<sub>x10<sup>5</sup></sub></u>  |  | <u>4.501<sub>x10<sup>5</sup></sub></u>  |  | <u>3.779<sub>x10<sup>5</sup></sub></u>  |  | <u>1.623<sub>x10<sup>5</sup></sub></u>  |
| 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 <sup>2</sup> | -                                | -                                       | 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 <sub>x10<sup>5</sup></sub> | 3.196 <sub>x10<sup>5</sup>-</sub> | 0.004               | (0.000-0.010) | 8.031 <sub>x10<sup>5</sup></sub> | 6.028 <sub>x10<sup>5</sup>-</sub> | 0.008                            | (0.000-0.016)                     |
|                    |                                  | 5.410 <sub>x10<sup>5</sup></sub>  |                     |               |                                  | 1.070 <sub>x10<sup>5</sup></sub>  |                                  |                                   |
| 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 <sub>x10<sup>6</sup></sub> | 8.610 <sub>x10<sup>7</sup>-</sub> |
|                    |                                  |                                   |                     |               |                                  |                                   | 2.997 <sub>x10<sup>5</sup></sub> |                                   |
| Sigma <sup>2</sup> | -                                | -                                 | 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

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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

1  
2 frailty models, converging hazards are the result of the effect of selection on the population  
3 hazards, due to how much variance of unobserved frailty is present in the population at the  
4 initial age of observation. The bigger the variance the stronger the convergence is. For more  
5 information about frailty models, the process of selection and how they relate to narrowing  
6 mortality differentials at old ages, please see appendix A.  
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13 In the age-cohort models the introduction of unobserved frailty affected the coefficient  
14 for the macro-region of birth significantly. Among men, holding education equal, those born  
15 in the South show a significant survival advantage over the natives of the North-West, while  
16 in the model without frailty there was no such advantage. Among women, the model without  
17 frailty showed a significant survival advantage for those born in the South but when frailty  
18 was controlled for, this became not significant.  
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27 The pattern also resembles the regional mortality macro-dynamics that have  
28 characterized Italy for most of the 20<sup>th</sup> century (although the two patterns refer to different  
29 phenomena, the first one referring to mortality by region of birth), when male mortality in the  
30 South was lower than in the North (45-48). Cohort based analyses have highlighted that in  
31 more recent cohorts (those born after WWII) there is a reversing trend (48, 49).  
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38 The models with age-period perspective did not identify any significant geographical  
39 differences. This could be due to the utilization of random subsampling of a 1% sample.  
40 Although 250 repetitions is considered by the literature a sufficient number for very complex  
41 models (50-52), it is possible that it was inadequate to identify a clear pattern from the small  
42 sample. For more detailed results see tables 1 and 2.  
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## 51 Discussion

52 The interest in the role of unobserved heterogeneity in a life course approach to  
53 socioeconomic mortality differences has recently increased. Most of the studies focus on  
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2 health outcomes (53-58) while fewer studies also analyze mortality (59-61). Their findings are  
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4 not consistent and fuel a still controversial debate.  
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7 In this study we investigated the role of unobserved individual heterogeneity on the  
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9 estimation of mortality differentials at adult-old ages by education level in a longitudinal  
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11 perspective. This study investigated if the estimates of the mortality differentials are affected  
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13 by the introduction of the unobserved heterogeneity component into the models.  
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16 We fitted survival analysis models with and without controlling for the unobserved  
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18 heterogeneity and we found that, when this component was included, the models gave a  
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20 significantly better fit.  
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23 We also found that in the majority of the cases, the educational gradient estimated by  
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25 the models with frailty was higher than the one estimated by the models without frailty. When  
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27 big uncertainty around the estimates did not allow assessing a precise value, the confidence  
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29 regions in the models with frailty spanned over higher values than those in the models without  
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31 frailty. It must be pointed out that, in the age-period approach, to the peculiar statistical  
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33 procedure used to estimate the frailty models did not allow obtaining a likelihood value  
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35 comparable with the one of the model without frailty. Thus, the statistical comparison of the  
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37 models via the AIC was not possible, making this evidence weaker. Nevertheless, the results  
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39 seem to point to a direction that is consistent with the statistical literature about unobserved  
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41 heterogeneity (19-26).  
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44  
45 Among men such a pattern was found in both the age-cohort and age-period  
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47 approaches. Among women, on the contrary, this pattern was less clear: in the age-cohort  
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49 model, controlling for hidden frailty resulted in a slight reduction of the mortality gradient.  
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51 Social determinants act on mortality also through risk factors that are known to affect more  
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53 men than women. Moreover, because of a lag in the smoking and fertility transitions, highly  
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55 educated women in Turin are more exposed to risk factors like cigarette smoking and smaller  
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2 number of children. Therefore, controlling for hidden frailty in the case of women might  
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4 reduce the educational gradient.  
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7 In the models with age-cohort perspective controlling for the hidden frailty affected  
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9 also the estimates of the differentials by macro-region of birth, showing a survival advantage  
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11 of the men born in the South, but not of the women, for whom an advantage was instead  
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13 detected by the model that did not control for frailty.  
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16 The healthy migrant effect (62-67) could cause this pattern. Among the cohorts  
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18 involved in the migration women were likely to be more passive actors than men in the  
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20 migratory decision (68-70) and this might have selected them more than men. Frailty is a  
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22 general concept embedding all the hidden factors that affect the individual survival chances:  
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24 innate and acquired frailty, exposure to risk factors, life style factors and so on. Therefore,  
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26 controlling for frailty reduced the survival advantage of the women, who might have been less  
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28 health selected than men by the migration, while uncovered the advantage of the men.  
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30 However, another recent study on the impact of migration on all-cause mortality in Turin did  
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32 not find particularly strong gender differences in the so called healthy migrant effect (66) and  
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34 this point deserves future further investigation.  
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38 The study spanned over a long observation window of 36 years. Therefore it was  
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40 important to control for the general mortality improvement that took place during this time.  
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42 We did so by adopting both an age-period and an age-cohort approach.  
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45 The age-period models, as expected, estimated higher heterogeneity than the age-  
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47 cohort models. Periods aggregate different generations and are expected to be more  
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49 heterogeneous than the cohorts themselves. In both period and cohort models the female  
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51 variance of frailty was higher than for the males, indicating that men are more homogeneous  
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53 than women. This could be attributed to a stronger selection process due to mortality that is  
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55 usually observed to be higher among men than among women.  
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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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## 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.

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- 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.

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11 Key messages

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- 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.

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21 Strengths and limitations

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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.

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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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*Competing Interest.* None to declare.

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*Data sharing.* There is no additional data available.

#### References

1. Mackenbach JP, Kunst AE, Cavelaars AEJM, Groenhouf F, Geurts JJM, others. Socioeconomic inequalities in morbidity and mortality in western Europe. *The Lancet*. 1997;349(9066):1655-9.
2. Mackenbach JP, Kunst AE, Groenhouf F, Borgan JK, Costa G, Faggiano F, et al. Socioeconomic inequalities in mortality among women and among men: an international study. *American Journal of Public Health*. 1999;89(12):1800-6.
3. Mackenbach JP, Stirbu I, Roskam AJR, Schaap MM, Menvielle G, Leinsalu M, et al. Socioeconomic inequalities in health in 22 European countries. *New England Journal of Medicine*. 2008;358(23):2468-81.
4. Antonovsky A. Social class, life expectancy and overall mortality. *The Milbank Memorial Fund Quarterly*. 1967;45(2):31-73.
5. Huisman M, Kunst AE, Mackenbach JP. Socioeconomic inequalities in morbidity among the elderly; a European overview. *Social Science & Medicine*. 2003;57(5):861-73.
6. Dalstra J, Kunst A, Mackenbach J, others. A comparative appraisal of the relationship of education, income and housing tenure with less than good health among the elderly in Europe. *Social Science & Medicine*. 2006;62(8):2046-60.
7. Martelin T. Mortality by indicators of socioeconomic status among the Finnish elderly. *Social Science & Medicine*. 1994;38(9):1257-78.
8. Huisman M, Kunst AE, Andersen O, Bopp M, Borgan JK, Borrell C, et al. Socioeconomic inequalities in mortality among elderly people in 11 European populations. *Journal of Epidemiology and Community Health*. 2004;58(6):468-75.
9. House JS, Lepkowski JM, Kinney AM, Mero RP, Kessler RC, Herzog AR. The social stratification of aging and health. *Journal of Health and Social Behavior*. 1994:213-34.
10. Decker S, Rapaport C. Medicare and disparities in women's health. *National Bureau of Economic Research*, 2002.
11. Dor A, Sudano J, Baker DW. The effect of private insurance on the health of older, working age adults: evidence from the Health and Retirement Study. *Health Services Research*. 2006;41(3p1):759-87.

12. Marmot MG, Shipley MJ. Do socioeconomic differences in mortality persist after retirement? 25 year follow up of civil servants from the first Whitehall study. *BMJ*. 1996;313(7066):1177-80.
13. Elo IT, Preston SH. Educational differentials in mortality: United States, 1979-1985. *Social Science & Medicine*. 1996;42(1):47-57.
14. Liang J, Bennett J, Krause N, Kobayashi E, Kim H, Brown JW, et al. Old age mortality in Japan. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. 2002;57(5):S294.
15. Caselli G, Vaupel JW, Yashin AI. Explanation of the decline in mortality among the oldest-old: A demographic point of view. *Human Longevity, Individual Life Duration, and the Growth of the Oldest-Old Population*. 2006:395-413.
16. Manton KG, Stallard E, others. Methods for evaluating the heterogeneity of aging processes in human populations using vital statistics data: explaining the black/white mortality crossover by a model of mortality selection. *Human Biology*. 1981;53(1):47.
17. Vaupel JW, Manton KG, Stallard E. The impact of heterogeneity in individual frailty on the dynamics of mortality. *Demography*. 1979;16(3):439-54.
18. Vaupel JW, Yashin AI. Heterogeneity's ruses: some surprising effects of selection on population dynamics. *American Statistician*. 1985:176-85.
19. Aalen OO. Effects of frailty in survival analysis. *Statistical Methods in Medical Research*. 1994;3(3):227.
20. Aalen OO. Heterogeneity in survival analysis. *Statistics in Medicine*. 1988;7(11):1121-37.
21. Gail MH, Wieand S, Piantadosi S. Biased estimates of treatment effect in randomized experiments with nonlinear regressions and omitted covariates. *Biometrika*. 1984;71(3):431.
22. Trussell J, Rodriguez G. Heterogeneity in demographic research. *Convergent issues in genetics and demography*: Oxford University Press, USA; 1990. p. 111-32.
23. Chamberlain G. Heterogeneity, omitted variable bias, and duration dependence. *Longitudinal Analysis of Labor Market Data*, ed JJ Heckman, B Singer. 1985:3-38.
24. Schumacher M, Olschewski M, Schmoor C. The impact of heterogeneity on the comparison of survival times. *Statistics in Medicine*. 1987;6(7):773-84.
25. Schmoor C, Schumacher M. Effects of covariate omission and categorization when analysing randomized trials with the Cox model. *Statistics in Medicine*. 1997;16(3):225-37.
26. Bretagnolle J, Huber-Carol C. Effects of omitting covariates in Cox's model for survival data. *Scandinavian Journal of Statistics*. 1988:125-38.
27. Wienke A. *Frailty models in survival analysis*: Chapman & Hall/CRC; 2010.
28. Marinacci C, Spadea T, Biggeri A, Demaria M, Caiazzo A, Costa G. The role of individual and contextual socioeconomic circumstances on mortality: analysis of time variations in a city of north west Italy. *Journal of Epidemiology and Community Health*. 2004;58(3):199-207.
29. Costa G, Cardano M, Demaria M. Torino. *Storie di salute in una grande città*. Città di Torino, Ufficio di statistica, Osservatorio socioeconomico torinese. 1998.
30. Doblhammer G, Hoffmann R, Muth E, Westphal C, Kruse A. A systematic literature review of studies analyzing the effect of sex, age, education, marital status, obesity, and smoking on health transitions. *Demographic Research*. 2009;20(5):37-64.
31. Krieger N, Williams DR, Moss NE. Measuring social class in US public health research: concepts, methodologies, and guidelines. *Annual Review of Public Health*. 1997;18(1):341-78.
32. Mirowsky J, Ross CE. *Education, social status, and health*: Aldine de Gruyter; 2003.
33. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Smith GD. Indicators of socioeconomic position (part 1). *Journal of Epidemiology and Community Health*. 2006;60(1):7-12.

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34. Bonifazi C, Heins F. Long-term trends of internal migration in Italy. *International Journal of Population Geography*. 2000;6(2):111-31.
35. Gompertz B. On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. *Philosophical Transactions of the Royal Society of London*. 1825;115:513-83.
36. Akaike H. A new look at the statistical model identification. *Automatic Control, IEEE Transactions on*. 1974;19(6):716-23.
37. Holford TR. Analysing the temporal effects of age, period and cohort. *Statistical Methods in Medical Research*. 1992;1(3):317-37.
38. Osmond C, Gardner M. Age, period, and cohort models. Non-overlapping cohorts don't resolve the identification problem. *American Journal of Epidemiology*. 1989;129(1):31.
39. Glenn ND. Cohort analysts' futile quest: Statistical attempts to separate age, period and cohort effects. *American Sociological Review*. 1976;41(5):900-4.
40. Yang Y, Land KC. *Age-period-cohort Analysis: New Models, Methods, and Empirical Applications*: Chapman & Hall; 2013.
41. Hartigan JA. Using subsample values as typical values. *Journal of the American Statistical Association*. 1969:1303-17.
42. Politis DN, Romano JP. Large sample confidence regions based on subsamples under minimal assumptions. *The Annals of Statistics*. 1994;22(4):2031-50.
43. Efron B. Bootstrap methods: another look at the jackknife. *The Annals of Statistics*. 1979;7(1):1-26.
44. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria 2011.
45. Barbi E, Caselli G. Selection effects on regional differences in survivorship in Italy. *Genus*. 2003:37-61.
46. Caselli G, Egidi V. Le differenze territoriali di mortalità in Italia. *Tavole di mortalità provinciali (1971-72)*. 1980.
47. Caselli G, Egidi V. L'analyse des données multidimensionnelles dan l'étude des relations entre mortalité et variable socio-économiques d' envirnment et de comportement individuel [Multivariate methods in the analysis of the relations between mortality and socio-economic, environmental and behavioural variables]. *Genus*. 1981;37(3/4):57-91.
48. Caselli G, Reale A. Does cohort analysis contribute to the study of the geography of mortality? *Genus*. 1999:27-59.
49. Biggeri A, Accetta G, Egidi V. Evoluzione del profilo di mortalita 30-74 anni per le coorti di nascita dal 1889 al 1968 nelle regioni italiane [Mortality Time Trends 30-74 years by Birth Cohorts 1889-1968 in the Italian Regions]. *Epidemiologia & Prevenzione*. 2011;35(5-6):50-67.
50. Efron B, Tibshirani R. *An introduction to the bootstrap*: Chapman & Hall/CRC; 1993.
51. Manly BFJ. *Randomization, bootstrap and Monte Carlo methods in biology*: Chapman & Hall/CRC; 1997.
52. Pattengale ND, Alipour M, Bininda-Emonds ORP, Moret BME, Stamatakis A. How many bootstrap replicates are necessary? *Journal of Computational Biology*. 2010;17(3):337-54.
53. Beckett M. Converging health inequalities in later life-an artifact of mortality selection? *Journal of Health and Social Behavior*. 2000:106-19.
54. Ferraro KF, Farmer MM. Double jeopardy, aging as leveler, or persistent health inequality? A longitudinal analysis of white and black Americans. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. 1996;51(6):S319.
55. Herd P. Do functional health inequalities decrease in old age? *Research on Aging*. 2006;28(3):375-92.



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56. Kim J, Durden E. Socioeconomic status and age trajectories of health. *Social Science & Medicine*. 2007;65(12):2489-502.
57. Lynch SM. Cohort and life-course patterns in the relationship between education and health: A hierarchical approach. *Demography*. 2003;40(2):309-31.
58. McMunn A, Nazroo J, Breeze E. Inequalities in health at older ages: a longitudinal investigation of the onset of illness and survival effects in England. *Age and Ageing*. 2009;38(2):181.
59. Dupre ME. Educational differences in age-related patterns of disease: Reconsidering the cumulative disadvantage and age-as-leveler hypotheses. *Journal of Health and Social Behavior*. 2007;48(1):1-15.
60. Hoffmann R. Do socioeconomic mortality differences decrease with rising age? *Demographic Research*. 2005;13(2):35-62.
61. Hoffmann R. Socioeconomic inequalities in old-age mortality: A comparison of Denmark and the USA. *Social Science & Medicine*. 2011;72(12):1986 - 92.
62. Anson J. The migrant mortality advantage: a 70 month follow-up of the Brussels population. *European Journal of Population/Revue Européenne de Démographie*. 2004;20(3):191-218.
63. Feinleib M, Lambert PM, Zeiner-Henriksen T, Rogot E, Hunt BM, Ingster-Moore L. The British-Norwegian migrant study--analysis of parameters of mortality differentials associated with angina. *Biometrics*. 1982:55-71.
64. Kington R, Carlisle D, McCaffrey D, Myers H, Allen W. Racial differences in functional status among elderly US migrants from the south. *Social Science & Medicine*. 1998;47(6):831-40.
65. Norman P, Boyle P, Rees P. Selective migration, health and deprivation: a longitudinal analysis. *Social Science & Medicine*. 2005;60(12):2755-71.
66. Rasulo D, Spadea T, Onorati R, Costa G. The impact of migration in all-cause mortality: The Turin Longitudinal Study, 1971–2005. *Social Science & Medicine*. 2012.
67. Singh GK, Siahpush M. All-cause and cause-specific mortality of immigrants and native born in the United States. *American Journal of Public Health*. 2001;91(3):392.
68. Bielby WT, Bielby DD. I will follow him: Family ties, gender-role beliefs, and reluctance to relocate for a better job. *American Journal of Sociology*. 1992:1241-67.
69. Cooke TJ. Gender role beliefs and family migration. *Population, Space and Place*. 2008;14(3):163-75.
70. Mincer J. Family Migration Decisions. *Journal of Political Economy*. 1978;86:749-75.

## 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:

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

where  $\sigma^2$  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:

$$\mu_i(x | u_i) = \mu_0(x) e^{\beta u_i} \quad (2)$$

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

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

Where for each individual  $i$ ,  $y_i$  is the entry time,  $x_i$  in the exit time,  $\delta_i$  is the status (1=dead, 0=right censored),  $u_i$  is the covariate profile with effect  $\beta$  and  $\mu(\cdot)$  denotes the hazard,  $S(\cdot)$  the survival function and  $\theta$  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:

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

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

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

Where for each individual  $i$ ,  $y_i$  is the entry time,  $x_i$  in the exit time,  $\delta_i$  is the status (1=dead, 0=right censored),  $u_i$  is the covariate profile with effect  $\beta$  and  $\mu(\cdot)$  denotes the hazard,  $M(\cdot)$  the cumulative hazard,  $\theta$  is the vector of parameters of the baseline hazard and  $\sigma^2$  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):

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

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):

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

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

The overall likelihood function is simply:

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

## 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.

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

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

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  $\lambda$  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.

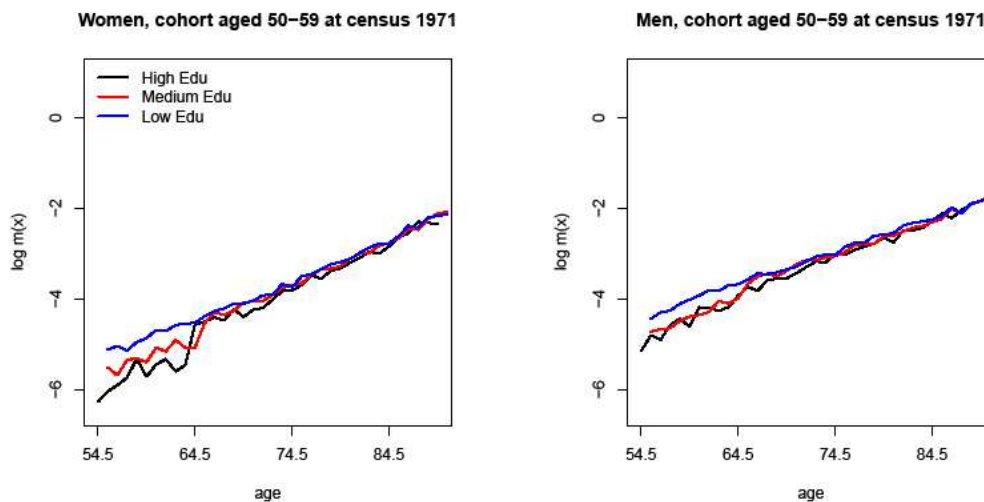
**Table B1. Mortality rate ratios between education groups and age groups estimated from an exponential survival hazard model with covariates education, age and their interaction. The table also reports the likelihood ratio test between this model and a model without an age-education interaction term.**

|  | 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-Fraily 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.



review only

**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.**

