# Why people survive to high advanced ages? Another look at the plasticity of ageing

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## Background

It has been shown that human longevity is extraordinarily plastic (Vaupel and Lundstrom, 1994; Burger et al., 2012). Burger et al. (2012) point out that the malleability of age-specific risk of death is attributed to environmental factors and that no other organism has ever experienced the type or magnitude or environmental improvement that humans have. We hypothesize that people surviving to older ages are highly adaptable to environmental changes and that the most resilient ones are capable to sustain their vitality and improve their survival. Robustness is therefore linked with the plasticity of longevity at a individual level such that most robust individuals exhibit greater malleability in their age at death. In this study, we analyse high-quality data from Danish registers and apply a quantile regression approach in order to reveal what are the characteristics that distinguish centenarians from people that have died much before. The aim of this study is to enhance current knowledge about the underlying dynamics of longevity and make strides on what are the determinants of the malleability of human longevity.

*Figure 1 and 2 about here*

The determinants of human longevity are little known. Previous research suggests that genetic factors play a substantial role in adult mortality patterns. In particular, genetic studies on Danish twins have shown that age at death in adulthood has a heritability (proportion of the total variance attributable to genetic factors) of approximately 25% (Herskind et al., 1996; Murabito et al., 2012). Ljungquist et al. (1998) studied Swedish twin cohorts and concluded that a maximum of around a third of the variance in longevity is attributable to genetic factors. Aplolipoprotein E (apoE) and the locus and the forkhead box 3A (FOXO3A) genes have been pointed out to be the genes that drive human longevity (Gerdes et al., 2000; Christensen and Murray, 2007; Flachsbart et al., 2009). However, the search for genes affecting good cognitive and physical function at high old ages is still ongoing.

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Studies on familial clustering of extreme longevity have also contributed to enhance our knowledge about the mechanisms behind deaths at old ages. Perls et al. (2002) pointed out that siblings of centenarians are four times more likely to survive at ages 80-94 in comparison with siblings of people who died at the age of 73. By analyzing Mormon genealogies, Kerber et al. (2001) found an increased recurrence risk for siblings for surviving to extreme ages. Gudmundsson et al. (2000) found that the first-degree relatives of individuals who live to an extreme old age 95 percentile, are twice as likely as the controls to survive to the same age. Schoenmaker et al. (2006) studied nonagenarian siblings pairs and their first-degree relatives (parents, brothers and sisters, offspring) as well as spouses. These longevous families shown a 30% survival benefit for first-degree family members of nonagenarians sibling individuals, but not for the spouses of nonagenarians. Male and female siblings of US centenarians were 17 and 18 times more likely to reach the age of 100 respectively (Perls et al., 2002). Hjelmborg et al. (2007) found that before age 60, twin pairs do not exhibit similar age at deaths, but after age 60 a co-twin age at death is significantly predictive of twin lifespan. This finding suggests that there are minimal genetic effects on lifespans less than 60 years, moderate effects on lifespans greater than 60 years and that genetic components are likely to have large contributions at highest ages.

The association between health and mortality at high advanced ages is less clear due to two main reasons. First, cause-of-death analyses at older ages require detailed and high-quality data which is rarely available (and reliable) at a population level. Second, identifying the underlying cause of death at old ages is problematic due to the many co-morbidities (Rosenberg, 1999). Some epidemiological and medical researches have approached this issue by looking at individual and high-quality data. Health analyses between centenarians from the Danish 1895 and 1905 cohorts suggest that although 50 per cent more people from the 1905 cohort reached age 100 years that did in the previous cohort, no increases in physical or cognitive disability level were reported (Christensen et al., 2009). In contrast, data from Japan suggest that more recent cohorts of centenarians have worse health than previous cohorts (Christensen et al., 2009). In recent years, cohort studies in the Netherlands have monitored diseases and phenotypic and genomic factors of the Dutch elderly. For instance, the *Leiden 85-plus Study* targets 85-year-old inhabitants of the city of Leiden. The *Rotterdam Study* is an ongoing study that since 1990 targets the health status of people above age 55 in the city of Rotterdam. The *LifeLines Cohort Study* is also a large population-based cohort study and biobank monitoring diseases from inhabitants of the northern part of The Netherlands and their families. Evidence from these studies suggests that frail elderly (frailty is here defined as the disability to compensate functional loss) are at an increased risk of death independent of co-morbidities.

During reproductive ages, natural selection plays an important role in determining the length of life of individuals since they are constantly making trade-offs between the reproductive output and improving the chances of survival in order to maximize their fitness (Baudisch and Vaupel, 2012; Wensink et al., 2014). As individuals age, the force of selection declines such that during post-reproductive ages there is no longer under any age specific pressure from evolution (Vaupel, 2003). However, the health conditions and vitality (ability to sustain life) of individuals at the onset of post-reproductive years of life are imposed by evolutionary forces operating at young ages. Centenarians have left far behind reproductive ages so in this sense, they have triumphed over the forces of evolution.

# Data and methods

For this study we propose to use high quality data from the Danish Civil Register System or *Centrale Person Register* in conjunction with survey data from select Danish cohort studies which are maintained by the Danish Aging Research Center, University of Southern Denmark.

Quantile regression is particularly useful when the rate of change in the conditional quantile, expressed by the regression coefficients, depends on the quantile. For a random variable Y with probability distribution function

$$F(y) = P(Y \leq y)$$

the $\tau$th quantile of Y is defined as the inverse function

$$Q_\tau(Y) = \inf\{y : F(y) \geq \tau\}$$

where $0 < \tau < 1$ is the quantile level. E.g. $Q_{0.5}$ is the median, $Q_{0.75}$ is the third quartile or 75th percentile

Suppose Y is the response variable, and X is the p-dimensional predictor. Let $F_Y(y|\mathbf{X} = x) = P(Y \leq y|\mathbf{X} = x)$ be the conditional cumulative distribution function (CDF) of $Y$ given $\mathbf{X} = x$. Then the $\tau$th conditional quantile of $Y$ is defined as the inverse of the CDF or mathematically,

$$Q_\tau(Y|\mathbf{X} = x) = \inf\{y : F(y) \geq \tau\}$$

This can be extended to the General Linear quantile regression model:

$$Q_\tau(Y|\mathbf{X} = x) = \mathbf{X}^T\boldsymbol{\beta}(\tau), \quad 0 < \tau < 1,$$

where $\boldsymbol{\beta}(\tau) = (\beta_1(\tau), \ldots, \beta_p(\tau))^T$ is the quantile coefficient that may depend on $\tau$ and represents the marginal change in the $\tau$th quantile due to the marginal change in $x$.

# Conclusion and ongoing work

In our particular context the predictor variables $\mathbf{X}$ will contain relevant information about available measures of health status, for example Activities of Daily Living and various measures of cognitive function. We expect to demonstrate a stronger association between lifespan and the various health measures for the longest lived individuals (i.e. the highest quantiles of lifespan) than for those with lower survival. In addition, we anticipate that over successive cohorts, any rate of improvement in health status over cohorts would be more pronounced at the highest quantiles. Previous work in the literature has shown that human longevity is extraordinarily plastic but the present understanding about the determinants of such plasticity are unknown. We expect that our work will contribute towards understanding the relationship between practical health measures and how they relate to lifespan extension.

# Figures and tables

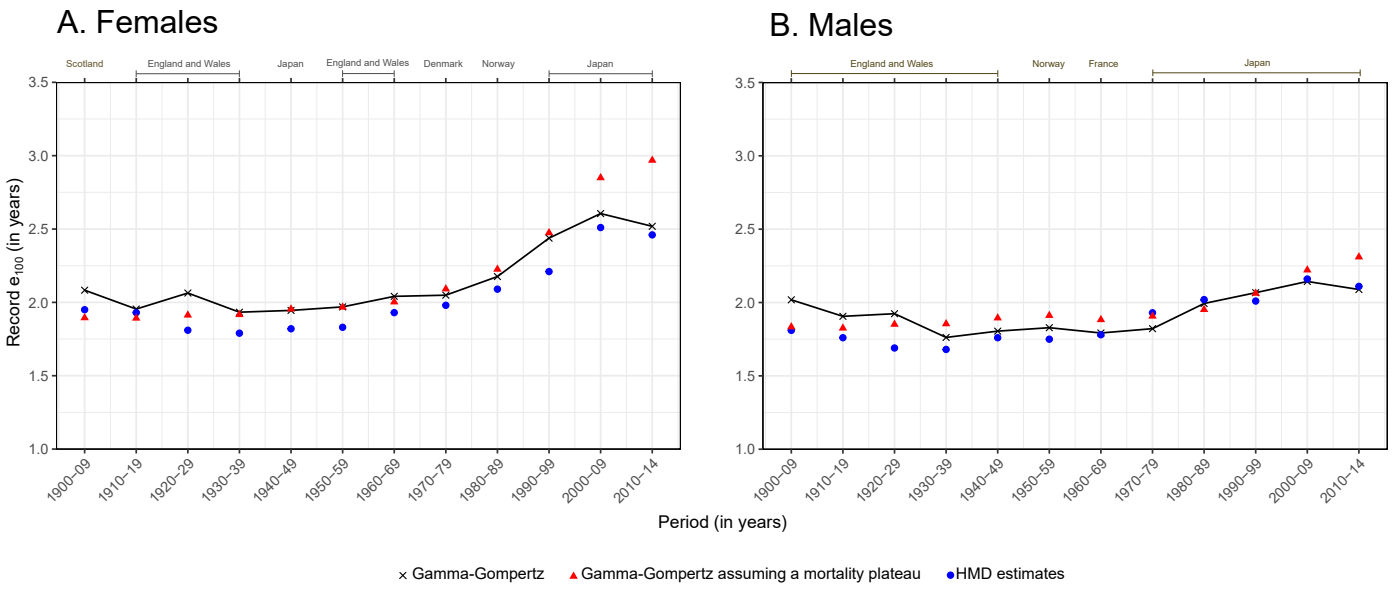


Figure 1: Record life expectancy at age 100 calculated under $\Gamma G$, $\Gamma G_p$ models and using Human Mortality Database (2017) estimates of $e_{100}$. Both sexes, 1900-2015.

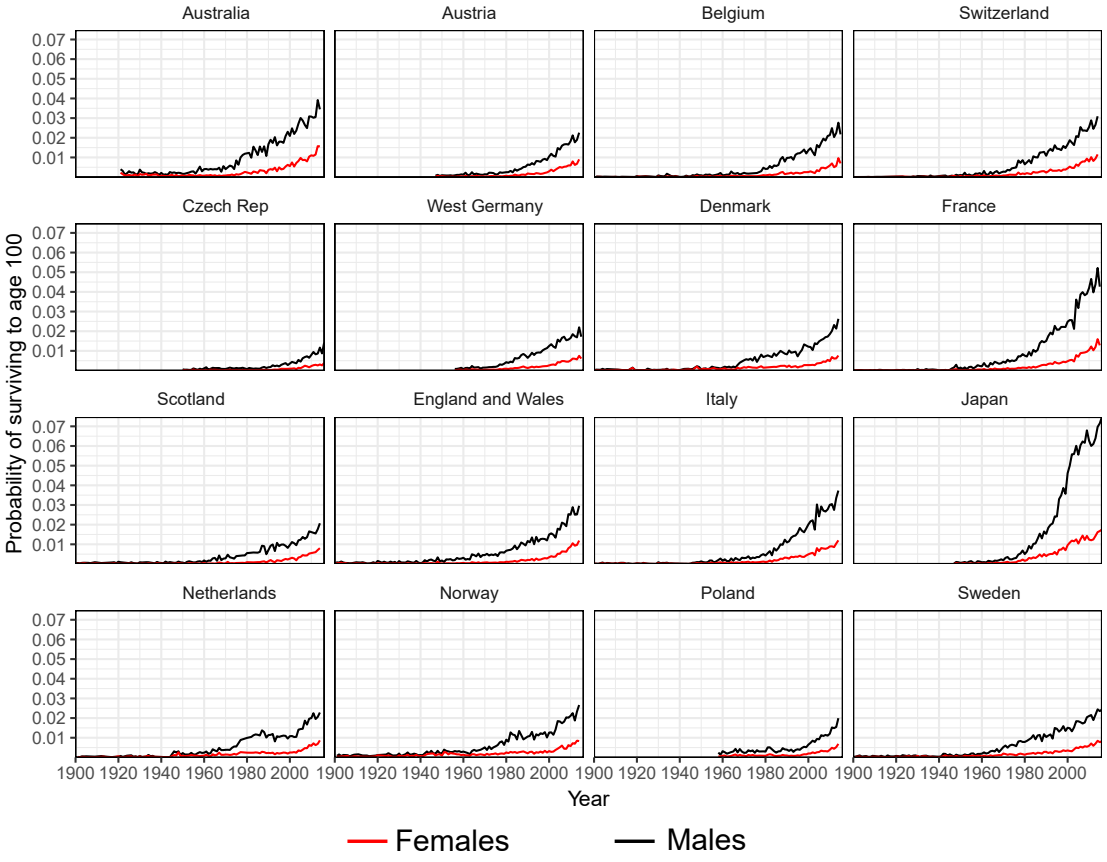


Figure 2: Probability that a newborn survives to age 100. Both sexes, 1900-2015.

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