Longevity Around the Turn of the 20th Century: Life-Long Sustained Survival Advantage for Parents of Today’s Nonagenarians

Niels van den Berg, MSc, Mar Rodríguez-Girondo, PhD, Anton J.M. de Craen, PhD, Jeanine J. Houwing-Duistermaat, PhD, Marian Beekman, PhD, and P. Eline Slagboom, PhD

1Department of Molecular Epidemiology, Leiden University, Albinusdreef, Leiden, The Netherlands. 2Department of Economic, Social, and Demographic History, Radboud University, Erasmusplein, Nijmegen, The Netherlands. 3Department of Medical Statistics, Leiden University, Albinusdreef, Leiden, The Netherlands. 4Department of Gerontology and Geriatrics, Leiden University, Albinusdreef, Leiden, The Netherlands

†Deceased.

Address correspondence to: Niels van den Berg, MSc, Department of Molecular Epidemiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands. E-mail: n.m.a.van_den_berg@lumc.nl

Received: November 16, 2017; Editorial Decision Date: March 8, 2018

Decision Editor: Rafael de Cabo, PhD

Abstract

Members of longevous families live longer than individuals from similar birth cohorts and delay/escape age-related diseases. Insight into this familial component of longevity can provide important knowledge about mechanisms protecting against age-related diseases. This familial component of longevity was studied in the Leiden Longevity Study which consists of 944 longevous siblings (participants), their parents (N = 842), siblings (N = 2,302), and spouses (N = 809). Family longevity scores were estimated to explore whether human longevity is transmitted preferentially through the maternal or paternal line. Standardized mortality ratios (SMRs) were estimated to investigate whether longevous siblings have a survival advantage compared with longevous singletons and we investigated whether parents of longevous siblings harbor a life-long sustained survival advantage compared with the general Dutch population by estimating lifetime SMRs (L-SMRs). We found that sibships with long-lived mothers and non-long-lived fathers had 0.41 (p = .024) less observed deaths than sibships with long-lived fathers and non-long-lived mothers and 0.48 (p = .008) less observed deaths than sibships with both parents non-long lived. Participants had 18.6 per cent less deaths compared with matched singletons and parents had a life-long sustained survival advantage (L-SMR = 0.510 and 0.688). In conclusion, genetic longevity studies may incorporate the maternal transmission pattern and genes influencing the entire life-course of individuals.

Keywords: Longevity, Biodemography, Inheritance, Human aging, Genetics

The average human life expectancy steadily increased over the last 200 years in industrialized countries, with record life expectancy increasing from 43/45 years in 1840 to 79/85 years in 2015 for males and females, respectively (1). Until 1950, the average increase in life expectancy could mainly be attributed to improved living conditions and better healthcare, causing a decrease in childhood and early life mortality (2). After 1950, the average life expectancy increased due to a delay of mid- and late-life mortality (3–6). Despite the average increase in life expectancy in the industrialized countries, significant individual differences in lifespan, defined as age at death, exist (7,8). In fact, a small group of individuals is able to survive into exceptionally old ages. This longevity capacity clusters within families (9–11) and on top of that, members of such long-lived families seem to delay or even escape age-related disease (12–15). Hence, research into long-lived families plays a key role in gaining knowledge about how to prevent age-related disease.

Previous research has focused on the survival of first-degree relatives and spouses of long-lived persons. Siblings of centenarians and siblings of nonagenarian descendants had a life-long sustained survival advantage compared with sex- and birth cohort–matched controls (9,10,16). In addition, siblings, parents, and offspring of...
nonagenarian siblings lived significantly longer than members of comparable birth cohorts (11). Multigenerational studies into the sex-specific inheritance pattern of lifespan and longevity showed inconsistent results however, with either paternal or maternal transmission patterns (Refs. 17–33, as reviewed in Ref. 34). Despite the generally observed survival advantage of first-degree relatives of longevous subjects, observations on the survival of their spouses and on longevity inheritance patterns remain inconclusive (11,35,36).

The limitations in current inheritance pattern studies are twofold. First, secular trends, such as the increase of life expectancy over time, are not taken into account. Second, parent-offspring analysis usually focuses on a single child per family, thereby omitting the potential of a complete sibship per family (37). Furthermore, studies have selected long-lived persons based on different criteria, focusing either on multiple siblings or singletons (9–11,16). It remains to be elucidated whether the stringency of long-lived case selection based on the presence or absence of a long-lived sibling provides a survival advantage in the selected persons compared with birth cohort- and sex-matched long-lived singletons. Apart from this, research into the survival of first-degree relatives and spouses of long-lived persons often struggles to obtain an accurate population-based control group, sometimes leading to the generalization of a single birth year control group to other birth years (16). It is also difficult to compare the survival of parents of long-lived persons to population-based sex- and birth cohort–matched controls because representative cohort lifetables preceding 1900 are often unavailable, except for the Netherlands and Sweden (38). Overall, research is still inconclusive about the following issues: sex-specific inheritance pattern of longevity, the survival advantage of long-lived sibships compared with long-lived singletons and about the question whether their parents already had a life-long sustained survival advantage.

To investigate these three issues, we used the data available in the Leiden Longevity Study (LLS). The LLS currently contains 421 complete three generational families, which we denote with filial 0 until 2 (F0–F2). First, we grouped complete F1 sibships to their parental longevity. We defined parental longevity as belonging to the top 1 per cent of their birth cohort (34,39) and constructed four parental groups: Group 1: both parents were long-lived (N = 1); group 2: mother long-lived and father not long-lived (N = 17); group 3: father long-lived and mother not long-lived (N = 21); group 4: both parents were not long-lived (N = 371). We subsequently compared the longevity Family Scores (LFS) of the different groups. Next, we investigated whether longevous siblings had a survival advantage over sex- and birth cohort–matched singletons using standardized mortality ratios (SMR). We compared the survival of spouses of longevous siblings to sex- and birth cohort–matched controls. Finally, we estimated lifetime SMRs (L-SMRs) to determine whether parents of longevous siblings had a life-long sustained survival advantage.

**Methods**

**Leiden Longevity Study**

The LLS was initiated in 2002 to study genetic determinants of human longevity. The LLS consists of 421 families and covers two generations of living subjects (F1 and F2) who were born between 1864 and 2017. Inclusion took place from 2002 until 2006. Men and women could participate if they were alive and aged ≥89 and ≥91, respectively. Both men and women were recruited to have a living sibling meeting the same criteria. Furthermore, the parents of the F1 participants had to be of Dutch Caucasian origin, and the siblings in one family had to descend from the same parents. The sex-specific age inclusion criteria represented individuals equal to or beyond the oldest 0.5 per cent of the Dutch population in 2001. There were no selection criteria on health or demographic characteristics. In total, 944 longevous F1 participants, who provided blood for research purposes, were included in the LLS (F1). In addition, their offspring and the spouses of their offspring were included (F2).

Relevant for the current study is that genealogical information was collected for the siblings (F1; N = 2,302), parents (F0; N = 842), and spouses (F1; N = 809) of the longevous F1 participants (henceforth referred to as siblings, parents, spouses, and participants). All genealogical information was verified by birth or marriage certificates and passports whenever possible. Additionally, verification took place via personal cards which were obtained from the Dutch Central Bureau of Genealogy in The Hague. In 2017, we updated the ages at death and last observation via the currently centralized municipal personal records database. For this study, we used two generations (F0 and F1) consisting of 4,807 individuals in all 421 families (Figure 1 and Table 1) because 86 per cent from the third generation (F2) were still alive.

**Lifetables**

In the Netherlands, population-based cohort lifetables are available from 1850 until 2017 (40,41). These lifetables contain, for each birth year and sex, an estimate of the hazard of dying between ages x and x + n (h_x) based on yearly intervals (N = 1) up to 99 years of age. Conditional cumulative hazards (H_x) and survival probabilities (S_x) can be derived using these hazards. In turn, we can determine to which sex- and birth year–based survival percentile each person of our study belonged to. For example, person “A” was born in 1876, was a female, and died at the age of 92. According to the lifetable information, this person belonged to the top 3 per cent survivors of her birth cohort, meaning that only 3 per cent of the women born in 1876 reached a higher age than person A. We used the lifetables to calculate the birth cohort and sex-specific survival percentiles for each individual in the LLS. Supplementary Figure A1 shows the ages at death corresponding to the top 10, 5, and 1 per cent survivors of their birth cohorts for the period 1850–1960.

**Statistical Analyses**

Statistical analyses were conducted using R statistics version 3.3.0 (42).

**Standardized mortality ratios**

To indicate excess mortality or excess survival of groups in the LLS compared with a reference population, we used SMRs. An SMR is...
estimated by dividing the observed number of deaths by the expected number of deaths. The expected number of deaths is given by the sum of all individual cumulative hazards based on the birth cohort and sex-specific lifetables of the Dutch population. An SMR between 1 and 0 indicates excess survival, an SMR of 1 indicates that the study population shows a similar survival to the reference population, and an SMR above 1 indicates excess mortality. The SMR can be estimated conditional on the specific age at which an individual starts to be observed in the study. This was necessary to avoid selection bias if individuals in a study population were not at risk of dying before a specific age of entry.

\[
SMR = \frac{\text{observed number of deaths}}{\text{expected number of deaths}} = \frac{\sum_{i=0}^{N} d_i}{\sum_{i=0}^{N} H_{0i}(t_{0i})},
\]

where \(d_i = \text{dead status (1 = dead, 0 = alive)}\), \(H_{0i} = \text{sex- and birth year–specific cumulative hazard based on lifetable, } t_{0i} = \text{timing, referring to age at death or last observation, } t_{0i} = \text{lifetable age conditioning, in this case from birth, } t_{0i} = 0, N = \text{group sample size}\).

SMRs were estimated for all first-degree relatives (F0 and F1) of the LLS participants (F1) to investigate their survival compared with the Dutch population. Direct or indirect selection effects were taken into account when estimating the SMR by conditioning the lifetable hazards to the age at first death of a specific group. SMRs were also estimated for participants by conditioning to age of inclusion, which varies between 89 and 102 years (see Supplementary Table A1 for an overview of conditioning criteria). Note that the lifetables do not contain yearly interval information beyond the age of 99. For this reason, the SMR estimations were truncated at 99 years.

To estimate the SMR at every possible starting age, we restricted age at death or last observation at yearly thresholds between 0 and 99 years for every group in the LLS, except for the participants because they were selected to have survived 289/91 years (men/women). We will refer to these age-conditioned SMRs as L-SMRs. These L-SMRs provided insight into the specific moment the first-death occurred. SMRs were also estimated by dividing the observed number of deaths by the expected number of deaths.

\[
LFS = \frac{\text{expected deaths} - \text{observed deaths}}{\text{siblings size}} = \frac{\sum_{j=1}^{n} (H_{mi}(t_{mi} - t_{0i}) - d_j)}{N_s},
\]

where \(d_j = \text{dead status (1 = dead, 0 = alive)}\) of individual \(j\), \(H_{mi} = \text{sex- and birth year–specific cumulative hazard based on lifetable, } t_{mi} = \text{timing, referring to age at death or last observation, } t_{0i} = \text{lifetable age conditioning, in this case from birth, } t_{0i} = 0, N_s = \text{siblings size}\).

To identify the presence of a sex-specific inheritance pattern, four groups of F1 sibships (participants + siblings) were constructed according to their parental longevity. We defined parental longevity as belonging to the top 1 per cent of their birth cohort. Group 1: both parents were long-lived (\(N = 1\)); group 2: mother long-lived and father not long-lived (\(N = 17\)); group 3: father long-lived and mother not long-lived (\(N = 21\)); group 4: both parents were not long-lived (\(N = 371\)). Group 1 was omitted from the analyses because the size was too small and 12 sibships could not be grouped due to missing ages at death of their parents. The LFS was used to summarize F1 sibship survival relative to the parental groups. F1 LFS differences between the groups were tested using the nonparametric Mann–Whitney U test and corresponding 95 per cent exact confidence intervals were reported (45).

**Results**

To investigate sex-specific inheritance and the presence of a life-long sustained survival advantage in the LLS, we used two generations covering longevous participants (F1; \(N = 944\)), their parents...
(F0; N = 842), siblings (F1; N = 2,302), and spouses (F1; N = 809) (Figure 1). The participants were born between 1900 and 1916, and 63 per cent were female (N = 595). The participants’ mean age at death or at last observation was 97 years and 22 (2%) participants are currently alive. The parents were born between 1850 and 1894 and they are all passed away with a mean age at death of 77 years. We were unable to retrieve the age at death of 22 parents (3%). The siblings were born between 1875 and 1941 and 47% were female (N = 1,082). The siblings mean age at death was 69 years and the median age at death was 80 years. Three hundred sixty-five (16%) siblings are currently still alive while we were unable to retrieve any information on the age at death for 33 (2%) siblings. The mean sibship size for F1 (participants-siblings) was 7.71 (SD = 3.4) with a minimum of 2 and a maximum of 17 siblings. The spouses were born between 1882 and 1950. Forty per cent of the spouses were female (N = 324) and their mean age at death was 75 years. Twenty-seven (3%) spouses are currently alive and for 119 (15%) spouses no age at death or last observation was available (Table 1).

Table 2. Sex-Specific Standardized Mortality Ratios (SMRs) For First-Degree Relatives and Spouses of LLS Participants

<table>
<thead>
<tr>
<th>Generation</th>
<th>Sample size</th>
<th>Observed deaths</th>
<th>Expected deaths</th>
<th>SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (F0)</td>
<td>842</td>
<td>820</td>
<td>1,190</td>
<td>0.688 (0.651–0.727)</td>
</tr>
<tr>
<td>Parents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siblings</td>
<td>2,302</td>
<td>1,867</td>
<td>2,816</td>
<td>0.663 (0.634–0.695)</td>
</tr>
<tr>
<td>Spouses</td>
<td>809</td>
<td>663</td>
<td>648</td>
<td>1.022 (0.966–1.093)</td>
</tr>
</tbody>
</table>

Notes: Confidence intervals have been estimated using bootstrapping with 500 cycles.

The LLS data are of high quality. We verified the observations as described by Schoenmaker and colleagues based on the first 100 LLS families by estimating SMRs for parents, spouses, and siblings of the complete enrolled LLS (Table 2). We estimated an SMR of 0.688 (95% CI = 0.651–0.727) for parents, indicating that we observed 31.2 per cent less deaths than would have been expected based on single individuals from a similar birth cohort and sex. The SMR for siblings was 0.662 (95% CI = 0.634–0.695), indicating that we observed 33.8 per cent less deaths than would have been expected based on single individuals from a similar birth cohort and sex. Spouses had an estimated SMR of 1.022 (95% CI = 0.966–1.093). This indicates that we have not found differences between the survival of spouses and single individuals from similar birth cohorts and sex.

Maternal Transmission of Longevity

To determine an inheritance pattern based on information of not just single individuals but an entire sibship, we used a LFS to summarize sibship survival. We grouped sibships (F1, participants + siblings) according to their parental (F0) longevity (parental longevity was defined as belonging to the top 1% survivors of their birth cohort) and compared the median group LFS of the complete sibships. Figure 2 shows that all F1 sibship groups, on average, had an excess survival compared with single individuals from the same birth cohorts and sex, as indicated by the median scores which were all above 0. Sibships with a long-lived (LL) father and a non-long-lived (NL) mother had a median LFS less observed deaths in reference to the Dutch population and a mean sibship size of 8.34 (SD = 3.4). Sibships with an LL mother and an NL father had a median LFS less observed deaths with a mean sibship size of 5 (SD = 1.9) and sibships with both parents NL had 1.1 less observed deaths with a mean sibship size of 7.95 (SD = 3.4). As a result, sibships with long-lived mothers and non-long-lived fathers showed larger LFSs than sibships with long-lived fathers and non-long-lived mothers (median difference in LFS of 0.41; 95% CI = 0.07–0.77; p = .024). Similarly, they showed larger LFSs than sibships with both parents non-long-lived (median difference in LFS = 0.48; 95% CI = 0.15–0.79; p = .008). We did not observe differential survival between sons and daughters with a long-lived mother (Supplementary Figure A2). In conclusion, we observed a maternal transmission pattern of human longevity with no evidence of a differential survival advantage for sons and daughters.

Last Life-Phase Survival Advantage of Siblings Over Singletones

To test if longevous F1 participants had a survival advantage over birth cohort-, sex-, and inclusion age-matched singletons, we estimated sex-specific SMRs for the participants (Figure 3A). An SMR of 0.814 (95% CI = 0.757–0.884) was estimated for the participants, indicating that as a group the participants had 18.6 per cent less deaths than expected based on single individuals from similar birth cohorts and sex. Female participants had a slightly larger survival advantage [0.804 (95% CI = 0.738–0.894)] than male participants [0.828 (95% CI = 0.742–0.943)] although this difference was not significant.

Life-Long Sustained Survival Advantage of Siblings and Parents But not For Spouses

Whether first-degree relatives and spouses of the participants had a survival advantage over their entire lifetime was studied by estimating L-SMRs. Figure 3B shows that siblings had a significant survival advantage compared with individuals from similar birth cohorts and sex at any point of their lifetime distribution until the threshold of 97 years, although the SMR at 98 years was again significant. The mean L-SMR was 0.680 and the median L-SMR was 0.660. No sex differences were identified at any age threshold. We observed that spouses had a nonsignificant L-SMR until age 74, indicating that…
we conclude that parents and siblings of the LLS participants had a life-long sustained survival advantage compared with individuals matched on birth cohorts and sex. Parents had a significant survival advantage compared with individuals from the same birth cohort and sex, regardless of their parental longevity, because we selected LLS participants to have lived ≥89 and 91 years for men and women, respectively. However, the median FLS for sibships with a long-lived father and a non-long-lived mother was 0.41 (p = .024) higher than for sibships with a long-lived father and a non-long-lived mother, and 0.48 (p = .008) higher than for sibships with both parents non-long-lived. This indicates that in the LLS longevity was transmitted preferentially via the maternal line. This maternal transmission of longevity is in concordance with the mitochondrial transmission hypothesis which posits that longevity may be transmitted through mitochondrial DNA from mothers to her offspring (8). Although this theory argues that because mitochondria are only maternally inherited, they are under selection pressure for optimized compatibility with only the female genome, we have no evidence that there is preferential transmission of longevity from mothers to daughters. Another explanation connects to Fogel’s theory of technophysio evolution which explains that in the turn of the 19th to the 20th century, childhood and early life mortality decreased significantly. This decrease was attributed to an increased birth weight and height of children and young adults, respectively (46). Since mothers are pivotal in this process it might be that the long-lived mothers were able to give birth to such healthy children whereas this may not have been the case for non-long-lived mothers, irrespective of the beneficial effect that 19th century long-lived fathers may have provided. The similarity in LFS for sibships with a long-lived father and a non-long-lived mother (LFS = 1.21) and sibships with both parents non-long-lived (LFS = 1.14) indicates the small influence of

Discussion

We investigated the survival of the longevous F1 LLS participants (who are longevous siblings) selected in the Leiden Longevity Study, and their F1 siblings, F0 parents, and F1 spouses. Based on the life-span data of entire sibships (F1, participants + siblings), we observed a maternal transmission pattern of longevity with equal probability to sons and daughters. Compared with inclusion age–matched singletons from similar birth cohorts and sex, LLS participants had 18.6 per cent less observed deaths than expected, and thus a survival advantage. In the LLS, the spouses of the participants had a life-long sustained survival pattern similar to the general population. Finally, we conclude that parents and siblings of the LLS participants had

Figure 3. Standardized mortality ratio (SMR) for participants and lifetime SMR for first-degree relatives + spouses. (A) SMR for the LLS participants, (B) all age SMR for sibs (F1) of participants, (C) all age SMR for spouses (F1) of participants, and (D) all age SMR for parents (F0) of participants. The horizontal dotted line illustrates the SMR threshold value of 1. The bars are SMR point estimates. The error bars represent the family bootstrapped confidence intervals. The colors in (B), (C), and (D) illustrate the sample size at every cutoff. The higher the age threshold, the lower the sample size, and hence, the lighter the color. The bars at the right side of the subfigures show the sample size associated with the colors of the SMRs.

Figure 2. Median longevity family score per sibship with one or none long-lived parent. Each gray dot represents a complete sibship. Green boxplot represents the group of sibships with long-lived father and a non-long-lived mother (N_sibships = 21; N_individuals = 177). Orange boxplot represents the group of sibships with a long-lived mother and a non-long-lived father (N_sibships = 17; N_individuals = 85). Light brown boxplot represents the group of sibships with both parents not long-lived (N_sibships = 371; N_individuals = 2,949).

Discussion

We investigated the survival of the longevous F1 LLS participants (who are longevous siblings) selected in the Leiden Longevity Study, and their F1 siblings, F0 parents, and F1 spouses. Based on the life-span data of entire sibships (F1, participants + siblings), we observed a maternal transmission pattern of longevity with equal probability to sons and daughters. Compared with inclusion age–matched singletons from similar birth cohorts and sex, LLS participants had
paternal effects compared with maternal effects. This absence may indicate that paternal socioeconomic status in the LLS is of marginal influence to the intergenerational transmission of longevity (47,48). Sibships with a long-lived mother and a non-long-lived father had not only had a higher LFS, but they also had a mean sibship size of 5, whereas the two other categories had a mean sibship size of 8.34 and 7.95. In general, the probability of finding long-lived families in families increases with sibship size (49). The finding of longevity among children in small sibships (with a long-lived mother) may therefore indicate that the longevity is less likely to be prominent by chance. The smaller sibship size of LL mothers may be explained by a trade-off in longevity families, either based on environmental (ie limited economic resources) or biological (ie reproductive capacity) factors. The discordant parental groups were quite small (Figure 2). We identified sibships with a long-lived father but not mother, and vice versa (N_sibships = 21; N_individuals = 177 and N_sibships = 17; N_individuals = 85) which interestingly shows that the maternal transmission effects are found not in all, but in a subset of LLS families.

To investigate familial clustering of longevity, studies selected long-lived subjects based on multiple siblings or singletons (9–11,16). So far it was unclear whether a sibling-based selection provides a survival advantage over singletons. We showed that long-lived sibships (F1 LLS participants) indeed had an 18.6 per cent survival advantage over inclusion age, birth cohort, and sex-matched longevous singletons. The effect can be considered large because the observational period focuses on the last stage of life (ages ≥89 and 91 for men and women), especially when taking into account that siblings of LLS participants, whose full-life course was observed, showed a 33.7 per cent survival advantage. It might even be expected that confining the sample to participants consisting of three or more longevous siblings increases the survival advantage. We did not, however, have the sample size to stratify our analyses to specific numbers of longevous participants within a family. Furthermore, we accounted for direct selection effects, although we could not directly account for the possibility that more healthy persons enrolled in the LLS than unhealthy persons or vice versa. We, however, did not expect that this has influenced our results since the first participants died only a few weeks after inclusion. We conclude that, when compiling a long-lived study after inclusion. We conclude that, when compiling a long-lived study cohort, selecting longevous siblings is a more stringent selection than longevous singletons of the same age.

Literature is inconclusive about the potential survival advantage of spouses of long-lived persons (10,11,35,36). We showed, in a large group, that spouses of longevous LLS participants (N = 809) had an equal survival to the general population until the age of 74. Beyond 74 years, we observed a small excess mortality. We have no other explanation for this finding than the fact that this excess mortality beyond 74 years may be a function of small sample size. Pedersen and colleagues observed a survival advantage in the long life family study for spouses of long-lived siblings when comparing them to a birth cohort and sex-matched control group. The authors point to assortative mating as a factor explaining the survival advantage for spouses of longevous participants (10). An earlier Quebec study also reported a survival advantage of spouses (35) and a study of Southern Italy found male nonagenarians to outlive their spouses, whereas this was not the case for female nonagenarians (36). Clearly, biological, environmental, and cultural factors influence survival to advanced ages in longevous families.

Because of unique Dutch lifetables dating back to 1850, we were able to show that parents of longevous LLS participants had a life-long sustained survival advantage compared with birth cohort and sex-matched controls, until at least the age of 93 years. Beyond 94 years the confidence intervals increased due to a limited sample size. The life-long sustained survival advantage of first-degree relatives indicates a familial clustering of human longevity, which may be the result of the absence of deleterious genetic mutations (50,51) or the presence of genetic mutations protecting from aging-related diseases (52). Genetic studies aimed at identifying longevity loci promoting a life-long survival advantage up to the highest ages requires a focus on extreme individuals: cases belonging to the top 1%–5% survivors with comparable parents. Recent genetic studies in the large UK Biobank (50,51) focused on subjects of 70 years on average without a parental selection (51) or selecting on parents belonging to the top 10 per cent survivors (50). This selection resulted in loci known to influence healthy aging and mortality in middle and older ages rather than exceptional longevity. As alternative to genetic influences, shared lifestyle or environmental factors may influence the longevity clustering in families. With the SMR analyses, we could not adjust for environmental and lifestyle factors. However, the fact that we found spouses to survive comparable to the general population and that first-degree relatives (siblings and parents) had a life-long sustained survival advantage suggests a familial/genetic influence on human longevity, possibly acting from early life onward.

Longevity clusters within specific families and insight into this familial clustering is important in gaining knowledge of factors involved in a life-long survival advantage up to the highest ages. Knowledge about the inheritance pattern of longevity may be useful for genetic studies trying to discover longevity-related genes. For example, effects of mitochondrial genes on human longevity should be investigated in those families with a history of maternal transmission of human longevity. Furthermore, research aiming to establish a study cohort of long-lived persons should ideally take family information into account, because we have demonstrated an enhanced survival for longevous siblings (LLS participants) over birth cohort— and sex-matched singletons. In the LLS, spouses seem comparable to the general population, making them a suitable comparison group for various health-related phenotypes as well as longevity. Lastly, compared with sex- and birth cohort–matched individuals, parents of the LLS participants at the turn of the 19th century have a life-long sustained survival advantage up to the highest ages which was previously reported for the 20th century survival of siblings of longevous singletons (9,10,16). This indicates that when studying the determinants of longevity factors involving the entire lifespan may contribute and emphasize the importance of longitudinal population–based studies in the search for protective factor for age-related disease.

**Informed Consent**

Informed consent was obtained from all Leiden Longevity Study participants.

**Supplementary Material**

Supplementary data is available at The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences online.

**Funding**

This work was supported by the Netherlands Organization for Scientific Research [360-53-180].
Conflict of interest
None declared.

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