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Research Article

The Survival of Spouses Marrying Into Longevity-Enriched Families

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Abstract

Background: Studies of longevity-enriched families are an important tool to gain insight into the mechanisms of exceptionally long and healthy lives. In the Long Life Family Study, the spouses of the members of the longevity-enriched families are often used as a control group. These spouses could be expected to have better health than the background population due to shared family environment with the longevity-enriched family members and due to assortative mating.

Methods: A Danish cohort study of 5,363 offspring of long-lived siblings, born 1917–1982, and 4,498 "first spouses" of these offspring. For each offspring and spouse, 10 controls were drawn from a 5% random sample of the Danish population matched on birth year and sex. Mortality was assessed for ages 20–69 years during 1968–2013 based on prospectively collected registry data.

Results: During the 45-year follow-up period, 437 offspring deaths and 502 offspring spouse deaths were observed. Compared with the background population, the hazard ratio for male offspring was 0.44 (95% confidence interval [CI]: 0.38–0.50) and for female offspring it was 0.57 (95% CI: 0.49–0.66). For male spouses, the hazard ratio was 0.66 (95% CI: 0.59–0.74), whereas for female spouses it was 0.64 (95% CI: 0.54–0.76). Sensitivity analyses in restricted samples gave similar results.

Conclusion: The mortality for ages 20–69 years of spouses marrying into longevity-enriched families is substantially lower than the mortality in the background population, although long-lived siblings participation bias may have contributed to the difference. This finding has implications for the use of spouses as controls in healthy aging and longevity studies, as environmental and/or genetic overmatching may occur.

Keywords: Long-lived families—Offspring—Mortality—Spousal overmatching

Although a rapidly increasing proportion of people in high-income countries are surviving into high ages, there is a very large variation in their health and functioning as well as their ages at death (1,2). Both genetic and environmental factors contribute to exceptional longevity (3), but the specific mechanisms are complex and are not well understood. A very large cohort study with a very long follow-up is required to study directly the causes and predictors of an exceptionally long life. Case–control studies with younger controls acting as comparison groups are confounded by both age and cohort differences (4,5), except for fixed traits (eg, genotype or sex) in stable populations (6). Studies of longevity-enriched families are thus a valuable tool that can shed light on the mechanisms related to longevity by assessing the characteristics and the health profile of the family members compared with nonfamily members (7–9).

When using offspring of long-lived families to shed light on these mechanisms, it is a challenge to select a proper comparison

group that may adequately represent the general population, perhaps adjusted for confounders. The spouses of the offspring have been used as a comparison group in a number of studies, such as the Long Life Family Study (LLFS), the Leiden Longevity Study, and the Amish Family Longevity Study (9–14). There are several advantages in this approach: The spouses are expected to be matched on age/birth cohort (14), adult environment (9), and socioeconomic and geographical background (10–12), but otherwise be representative of the general population, and differences between offspring and their spouses may be attributed to genetic factors or to early life environmental factors (that are unrelated to later environmental factors). Moreover, when recruiting study participants, it is often convenient to recruit spouses as contact has already been established with the family in question. There is, however, a concern that spouse controls are more similar to the offspring than what can be attributed to shared adult environment, and that this similarity perhaps extends both to early life socioeconomic environment, as well as to genetic factors due to assortative mating, where spouses are matched on physical attributes or behaviors, some of which have substantial genetic components (15). There may also be a postmarriage "spillover" effect of behaviors from each spouse to the other, which could attenuate differences in their health profiles to a greater extent than would be justified by the "external" shared environment (16,17). To correctly interpret the health profiles of offspring in contrast to their spouses, it is therefore important to assess how the health profiles of the spouses of the offspring in long-lived families differ from those observed in the general population.

The aim of this study is to assess the unified impact on survival of all factors (implicitly) matched on in the offspring versus offspring' spouse design. The findings will therefore provide insight on how important it is to know more about the role of the different factors involved in the spousal matching. The study objectives are to estimate the relative difference in mortality rates between spouses of offspring of Danish long-lived families and the general Danish population matched on sex and birth year, and to compare this difference with the corresponding estimated difference in mortality between offspring of Danish long-lived families and the general Danish population. We hypothesize that the survival of the spouses of the offspring in long-lived families is better than that of the background Danish population, due to the reasons mentioned earlier such as assortative mating and shared adult environment that influence the behavior and health of both spouses.

Methods

Study Population

Identification of long-lived families in Denmark

Initially, all individuals born before April 2, 1918, and alive in 2004 were identified in the Danish Civil Registration System, which covers all persons alive and living in Denmark on or after April 2, 1968, when the registry was established (18) and has continuously updated information on vital status and emigration status. By matching on birth parish and surname and subsequently looking up the parents of the matches in church records, 3,638 families with at least two siblings alive were identified (Figure 1). In the subsequent recruitment to one of three consecutive nationwide studies in Denmark—the Danish Oldest Siblings Study (a pilot study), the Genetics of Healthy Aging Study, and the LLFS—eligibility was conditional on having at least two siblings reaching age 88+ years, although the age criterion for the Genetics of Healthy Aging Study was that both siblings should reach 90+ years, and LLFS recruited only families with a Family Longevity Selection Score above 7, and at least one of the recruited siblings' living offspring willing to participate (8). The recruitment for each of these studies took place during 2004–2009 until the required number of participating families was reached and resulted in the enrollment overall of 1,511 siblings from 659 families. In a structured interview in the homes of the participants, information on the names and birth dates of their siblings as well as their offspring and their siblings' offspring was gathered, resulting in the identification of 3,972 siblings and 5,377 offspring of siblings in all three studies combined. A more detailed description of the method is found in the Supplementary Material, and further information on identification and inclusion of offspring from long-lived families can be found elsewhere (19).

Identification of spouses

Information on spouse identity was obtained from the Danish Civil Registration System. For each offspring, the spouse included was the spouse on April 2, 1968, or, if unmarried on that date, the first spouse registered after that date. Of the 5,377 offspring, 4,712 (88%) had a spouse according to these criteria, but missing spousal id (n = 206), spouse overlap (n = 1), or emigration (n = 1) meant that 4,504 spouses (95.6%) were included.

Selection of controls

For each of the 5,377 offspring and the 4,504 spouses, we selected 10 random controls from a 5% random sample of the entire Danish population. These controls were matched on birth year, sex, and on being alive on April 2, 1968, if born before that date.

Sensitivity Analyses

In the sampling procedure, it is possible that unidentified offspring in participating families may have had poorer health profiles than those identified. To limit this potential source of selection bias, we performed a subanalysis restricted to offspring of those siblings who were recruited and interviewed, considering it very unlikely that they or the family were not able to recall that the participant had an offspring who died as an adult (that is, after 1968). Moreover, in order to consider a more homogeneous sample with respect to enrichment

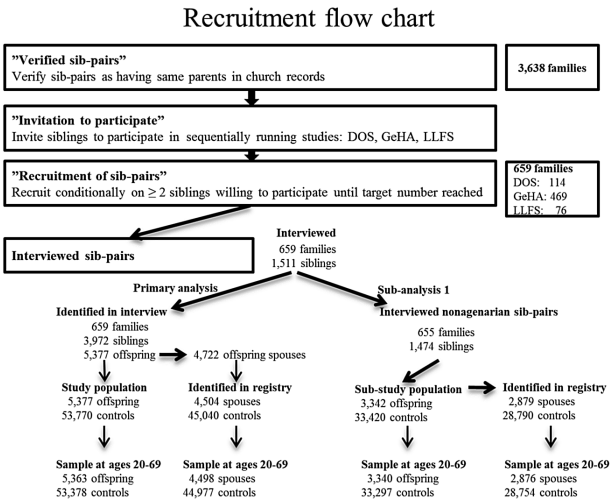

Figure 1. Flow chart indicating the sampling procedure from identification of Danish long-lived sibpairs to recruitment of sibpairs, identification of offspring and offspring spouses, and selection of controls.

for longevity, we restricted this analysis to sets of siblings with an attained age of 90 years or older by June 30, 2013. From the 659 interviewed families, 1,474 siblings from 655 families fulfilled these criteria, resulting in 3,342 offspring from 616 families with 2,879 spouses in this subanalysis sample.

In a second set of subanalyses, the study sample was restricted to families recruited in LLFS, which had particular emphasis on obtaining the entire pedigree of each family (8,10). Because LLFS participants have been extensively phenotyped, both at time of inclusion and in yearly follow-ups since 2009 (20), it is of particular interest to know whether this subsample is different from the other Danish longevity-enriched families. From 76 LLFS families, 265 siblings were included, resulting in 1,412 offspring and 1,212 spouses.

The choice of selecting the first spouse of the offspring was made to permit assessment of mortality at as early an age as possible in the spouse group. However, this could lead to a different sampling of spouses compared with other studies (eg, Leiden Longevity Study and LLFS), where offspring are recruited at around the age of 60 years, and their current wife/partner is included as control, depending on the marital history (21). We assessed this possibility through subanalyses.

Finally, because the recruitment of offspring entailed having parents/uncles/aunts alive and living in Denmark at an old age who themselves were born in the late 19th or early 20th century in a Danish parish, there was a potential higher tendency to recruit offspring who were themselves born in Denmark and had never migrated with their parents. To assess a possible bias toward the null association due to fewer healthy migrants (22) in the offspring sample compared with the general population, we performed a sensitivity analysis restricting offspring and controls to individuals born in Denmark.

Subanalysis—General Marriage Association Versus Specific Marriage Into Long-Lived Family Association

To quantify the extent to which an advantageous survival in offspring spouses reflected a possible difference between survival in the general population and survival in the subpopulation of married individuals, we also compared survival of spouses to matched, married controls in the general Danish population, where one control was selected for each spouse matched on birth year, sex, and year of marriage. Furthermore, we compared married offspring to the general population as well as the general married population, matching controls on sex, birth year, and, respectively, survival at date of marriage, or marriage within 1 calendar year from the offspring.

Statistical Methods

The mortality comparison of the offspring and the spouses to their respective matched controls were done by comparing survival curves as well as estimating hazard ratios (HRs) using a stratified Cox regression with strata defined by the individual matches and using robust standard error estimates (23,24) to adjust for the family clusters. Time scale was age, and mortality was studied between April 2, 1968, and June 30, 2013, constituting a 45-year follow-up period. Individuals with a status of emigrant at the end of follow-up were censored at time of outmigration. Because the observation time accumulated outside the age interval from 20 to 69 years was limited (Supplementary Table 2), we restricted the estimation of HRs in the Cox regression analyses to this age interval. As nine offspring died and five emigrated before the age of 20 years, whereas six spouses married for the first time after the age of 70 years, the estimated HRs were based on 5,363 offspring and 4,498 spouses.

Ethical Approval

The study has been approved by The Regional Scientific Ethical Committees for Southern Denmark (S-VF-20030227) and The Danish Data Protection Agency (J.nr. 2008-41-1753).

Results

In the 45-year follow-up period, the average follow-up time was 43.3 person-years for each offspring and 35.6 person-years for each spouse. For offspring, about 90% of the observation time occurred at ages 20–69 years, whereas this number was about 95% for the spouses. The male and female offspring had very similar birth cohort distribution with 90% of both study populations from the 1934–1962 birth cohorts (Supplementary Table 1). The birth cohorts of male and female spouses differed slightly from the offspring: Male spouses were born earlier with 90% from the birth cohorts 1927–1959 and female spouses were born later with 90% from the birth cohorts 1936–1964. In this age interval, the offspring sample observed 239 (8.7%) male deaths and 198 (7.5%) female deaths, whereas the spouse sample observed 332 (14.9%) male and 170 (7.5%) female deaths.

Figures 2 and 3 show the Kaplan–Meier estimates of the survival curves for men and women, respectively. These curves are all conditional on survival to age 20 years. Both figures show a markedly higher survival when (a) comparing offspring to the matched offspring controls and (b) comparing offspring spouses to their matched controls. For both men and women, the survival benefit of the offspring is somewhat better than for the spouses, and for both offspring and spouses, the survival advantage is more pronounced among men than among women. The age-specific mortality HRs in Supplementary Tables 4 and 5 show no violation of proportional hazard across ages in the age interval 20 to 69 years. At ages 70–79, there is an indication of relatively less survival advantage among male offspring and male spouses, but not for women who maintain the same degree of relatively lower mortality, both among offspring and spouses.

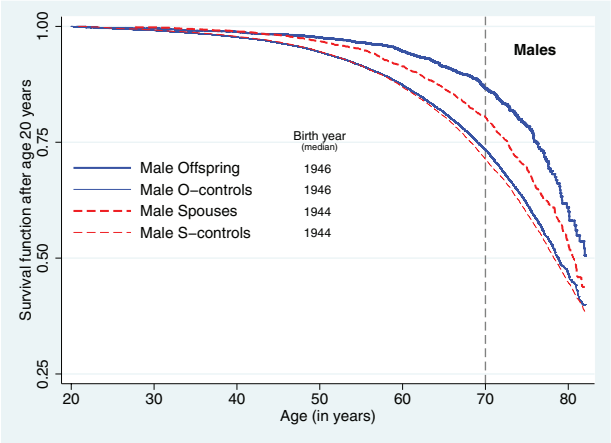

Figure 2. Kaplan–Meier survival curves for male offspring of Danish long-lived families, male spouses to female offspring, and their sex- and age-matched controls, conditional on survival to age 20 years.

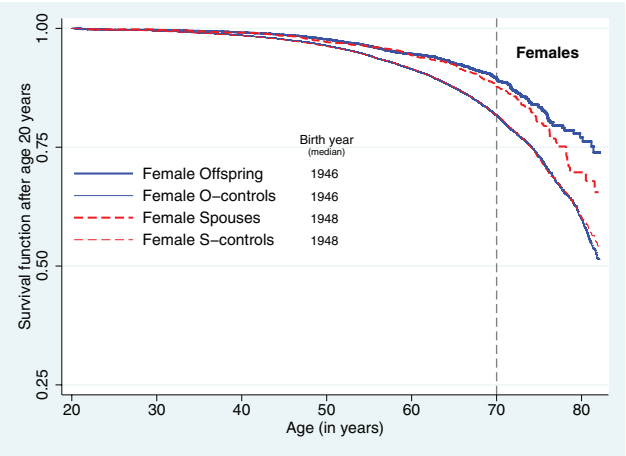

Figure 3. Kaplan–Meier survival curves for female offspring of Danish long-lived families, female spouses to male offspring, and their sex- and age-matched controls, conditional on survival to age 20 years.

Compared with the matched control groups, the HR for male offspring was 0.44 (95% confidence interval [CI]: 0.38–0.50), and for female offspring it was 0.57 (95% CI: 0.49–0.66). For spouses, the HR for men was 0.66 (95% CI: 0.59–0.74), and for women it was 0.64 (95% CI: 0.54–0.76) (Supplementary Table 3).

Sensitivity Analyses

For the subanalysis of 3,340 offspring of nonagenarian siblings and 2,876 offspring spouses observed between ages 20 and 69 years, the HRs changed slightly, so that for male offspring it was 0.41 (95% CI: 0.35–0.48) compared with 0.63 (95% CI: 0.55–0.73) for male spouses, and for female offspring it was 0.57 (95% CI: 0.47–0.68) compared with 0.65 (95% CI: 0.54–0.79) for female spouses. For the 1,410 LLFS offspring and 1,211 LLFS offspring spouses in the analysis restricted to ages 20 to 69 years, the male offspring HR was 0.47 (95% CI: 0.35–0.62) as compared with 0.67 (95% CI: 0.54–0.84) for the male spouses, whereas for the female offspring the HR was 0.57 (95% CI: 0.42–0.77) compared with 0.54 (95% CI: 0.37–0.78) for the female spouses.

At the offspring's age of 60 years, there were 2,854 spouses of offspring alive in Denmark. Of these spouses, 2,484 (87.0%) were the offspring's first spouses. The mortality risks of these 2,854 spouses at age 60–69 were quite similar to those in Supplementary Tables 4 and 5 for the same age interval. Finally, when the analyses were restricted to individuals born in Denmark, the HRs in all samples changed no more than 0.02.

Subanalysis—General Marriage Association Versus Specific Marriage Into Long-Lived Family Association

In the comparison of spouses to married controls, the survival advantage in spouses attenuated slightly with a HR of 0.79 (95% CI: 0.67–0.93) for men and 0.73 (95% CI: 0.59–0.90) for women. When restricting the offspring sample to married offspring and comparing with the general Danish population controls, the HR was 0.35 (95% CI: 0.30–0.41) for men and 0.50 (95% CI: 0.43–0.59) for women. Further restricting the selection of controls to the married Danish population, the HR for men was 0.37 (95% CI: 0.30–0.45), and for women it was 0.55 (95% CI: 0.44–0.67).

Discussion

This study found marked survival advantages among spouses to offspring of long-lived families of a magnitude corresponding approximately to halfway between the mortality among offspring and the general population, with a tendency in the point estimates of being slightly more similar to the offspring. Among male offspring of long-lived families, we found a markedly lower all-cause mortality between ages 20 and 70 years corresponding to about half the mortality rate when compared with sex- and age-matched controls from the general Danish population. For male spouses of female offspring of long-lived families, there was a large survival benefit with mortality rates of about three fourths of the mortality rates among age- and sex-matched controls. For female offspring, the survival benefit was almost as good as for male offspring on a relative scale with mortality rates at about 60% of age- and sex-matched controls, and for female spouses, the benefit was almost as good with mortality rates of about 70% when compared with age- and sex-matched controls.

The inclusion of offspring of long-lived families in the study base is not related to the survival status of the offspring. The only "advantage" of the offspring in relation to survival is that they had a parent and an uncle/aunt, or two of the latter, who lived a long time and participated in a longevity study. The only exception was for LLFS offspring for whom the inclusion criteria for a family required that one of the two long-lived siblings willing to participate had a living offspring also willing to participate. As the ages of most of the recruited siblings in LLFS were 90+ years, the criteria entailed that one offspring per LLFS sibship by selection would survive at least to an age of about 50 to 70 years.

Contrary to the offspring study base, the offspring spouses were selected conditional on having obtained a marriage (ie, to an offspring of a long-lived family). As the successful entry into marriage may in itself relate to better health and higher longevity potential (25–28), the better survival in offspring spouses compared with the general population could perhaps be attributed to the spouses representing the population of ever-married Danes. The survival benefit of the offspring spouses in comparison with age- and sex-matched married controls was still substantial and significant, but it was slightly smaller than that in the comparison between offspring spouses and the general age- and sex-matched controls. This indicates that the selection of married individuals may partially explain the improved survival in offspring spouses compared with the general population but that the main part of the survival benefit of being married to a long-lived offspring must be influenced by other factors not attributed to marriage itself. Also worth noting is that despite the selection of spouses through having successfully entered marriage, the offspring still had a larger survival benefit relative to the offspring spouses.

Given the relatively young age period of observation of mortality (<70) in this study, the most likely factor contributing to the observed survival advantage of spouses of offspring is shared lack of unhealthy behaviors and environments known to be by far the most common causes of death at these ages, such as smoking, clinically significant obesity (eg, with associated diabetes and coronary artery disease), and socioeconomic disparities. Perhaps as this sample is followed over time and survival to much older ages (or not) can be observed, genetic factors may be inferred as potential differentiating factors in survival.

Contrary to our findings, in a subsample of the Leiden Longevity Study, no difference was found between mortality in 178 partners of long-lived siblings and the expected mortality based on rates in the

general Dutch population, whereas 500 siblings of long-lived proband siblings in the same study had a markedly lower mortality than the partners of the proband siblings (12). The smaller partner sample size may be the reason that no survival advantage could be detected. In a comparison of 500 siblings of nonagenarian probands with 300 siblings' spouses in a study of from Calabria, Italy, the results were somewhat mixed with substantial survival advantage of male siblings compared with male spouses, but no differences for women (29). However, the survival curves comparing siblings to spouses as well as the average birth cohort of the probands suggest that both for men and women, the survival advantage of siblings is larger compared with the general Italian population. Finally, a study from Quebec, Canada, of almost 3,000 siblings of centenarians and 400 spouses of centenarians found better survival both in siblings and spouses than in a random sample of French Canadians from the 1901 Canadian Census sample, with similar survival advantages in male siblings and spouses (30). The particular advantage of male Quebecois centenarian spouses may be related to the sampling, where centenarian spouses by design do not experience increased mortality associated with the loss of a spouse, as this association is more pronounced with the loss of a female spouse. In our study, however, we do not have the same restriction to offspring spouses with long-lived partners.

The members of the longevity-enriched families in LLFS have previously been found to have a number of positive health characteristic such as delayed onset of functional decline, slower rate of change, and/or higher baseline functional reserve (31). Our finding is in line with a recent study of the U.S. participants in LLFS based on the 2008–2010 Beneficiary Annual Summary Files from the Centers for Medicare & Medicaid Services (32). In our study, all the sensitivity analyses revealed very similar patterns except in the small group of LLFS female offspring/spouses where the spouse had slightly better survival than the offspring. However, the CI of the estimates all included the overall estimates, and it is therefore probably a chance finding.

Strengths and Limitations

Strengths in the present study include large sample size, follow-up study over a 45-year period, random selection of population controls including random married controls to spouses, high quality data on vital status, and low information bias due to minimal loss to follow-up. Another strength of this study is that the study population of offspring and offspring spouses is based solely on their identification in population registries. It is well established that study volunteers tend to be healthier, be better educated, and have better lifestyles than nonresponders, but because all identified offspring are included in the analyses, this potential bias is avoided. However, the recruitment of the long-lived siblings is subject to this selection mechanism, and to the extent that the participating sibpairs do not represent the general population of all long-lived families with respect to these aspects, the same could be said about their offspring. If the selection is primarily through healthier participants, then the result is recruitment of families with even stronger longevity enrichment. But it cannot be ruled out that participating sibpairs are better educated and have healthier lifestyles than nonparticipating sibpairs who are otherwise equally healthy at the time of recruitment. Unfortunately, we have no access to information on nonparticipants and their reasons for not participating, so we cannot quantify the potential size of this bias. Another weakness is possible missing information on offspring, but the analysis restricted to offspring from interviewed siblings gave similar results. In LLFS, recruitment was conditional on one offspring being alive, but LLFS participants were only a small fraction of the families included, and analysis restricted to LLFS gave similar results. We have limited follow-up time after age 70 and therefore we cannot reliably assess survival after that age. The included spouses entailed marriage or registered partnership which could differ from international studies, where the offspring comparison group consists of the offspring's "partner,", which presumably could also include unmarried partners (12).

The present study of survival patterns among longevity-enriched families in Denmark and the study by Ash and colleagues (32) on the morbidity patterns among longevity-enriched LLFS families in the United States both suggest that spouses who marry into long-lived families are healthier than the general population with a sex and age distribution equal to the spouses. Hence, findings of no differences between offspring and spouses may reflect that they share common advantageous characteristics or health profiles compared with the general population, and findings of a better health profile in offspring than in spouses may reflect an even better health profile in these offspring when compared with the general population. However, it is possible that participation bias in the recruitment of long-lived siblings may have contributed to the observed differences between the offspring/spouses and the general population.

The underlying mechanism for more similar characteristics and health profiles could be both environmental, for example, similar educational level, and genetic due to assortative mating on characteristics such as anthropometric measures, cognitive abilities, and lifestyle factors, which all have substantial genetic components (15,33–35). Further studies of morbidity patterns and life course health characteristics of the spouses in this study are required to understand why there is a survival advantage associated not only with being a member of a long-lived family but also with being married into one.

Supplementary Material

Please visit the article online at http://biomedgerontology.oxfordjournals.org/ to view supplementary material.

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