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Increasing Sibling Relative Risk of Survival to Older and Older Ages and the Importance of Precise Definitions of "Aging," "Life Span," and "Longevity"

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Abstract

The lack of a formal definition of human longevity continues to generate confusion about its genetic and nongenetic determinants. In order to characterize how differences in birth year cohorts and percentiles of survival are associated with familial contribution to variation in survival, we estimated sibling relative risk of living to increasingly rare percentiles of survival based on a dataset of 1,917 validated sibships each containing at least one individual living to age 90 years. About 1,042 of the sibships included at least one individual who survived to age 100 and 511 included at least one individual who survived to age 105 and older. We show that sibling relative risk increases with older ages, sex, and earlier birth year cohorts of the proband and siblings of male 90-year-olds (5th percentile of survival) have 1.73 (95% CI: 1.5; 2.0) times the chance of living to age 90, while siblings of both male and female probands who survived to age 105 years (~0.01 percentile of survival) have 35.6 (95%CI: 15.1; 67.7) times the chance of living to age 105 compared with population controls. These results emphasize the importance of consistently defining the longevity phenotype in terms of rarity of survival for appropriate comparisons across studies.

Key Words: Longevity—Heritability—Centenarian—Demographic selection—Sibling relative risk.

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There is considerable inconsistency in the gerontological literature concerning phenotypic definitions of aging, oldest old, longevity, and life span. The casual use of these terms leads to confusing claims regarding heredity and nonreplicated genetic associations and linkages (1). Many researchers equate the term "longevity" with "old age" and neither term is adequately specific. In the 1980s, "oldest old" commonly referred to people surviving to age 85+ years, and now the oldest old participants in the New England Centenarian Study are 110+ years old. "Life span" has two common meanings. On an individual basis, life span simply refers to an individual's age at death. On a species level, life span or maximum life span are defined by the reliably substantiated oldest ever member of the species. Calment (2) established the current record for human life span in 1997, when she died at the age of 122 years and 167 days.

In 1980, Fries (3) hypothesized that as humans approach the limit of life span, they compress the time in which they experience age-related morbidities into a shorter and shorter period prior to death. Fries posited that this compression occurs at about age 100 years. However, even at 100 years, centenarians are heterogeneous in their ages of onset of age-related diseases and environmental exposures (4). It was not until we analyzed longitudinal morbidity data from

people living to 110+ years, who much better approximate human life span, that we generated results supportive of Fries' compression of morbidity hypothesis. We showed that on average people surviving to age 110+ years spend only the last 5 years of their extremely long lives with age-related diseases that are associated with increased mortality risk (5). Such individuals also markedly compress the period of their lives spent with disability. Consistent with the compression of morbidity hypothesis, people surviving beyond age 105 years are also phenotypically much more similar to one another than younger individuals dying in their 1980s and 1990s.

From a demographic selection point of view, there are exponential differences and therefore likely important genetic differences between members of a birth cohort who live to, eg, 90, 100, 105 and 110+ years. For example according to the U.S. Social Security Agency's 1900 cohort life table (http://www.ssa.gov/oact/NOTES/as120/LifeTables_Tbl_7.html), males alive at age 90 years constituted the top 5th percentile and females at age 90 constituted the top 15th percentile. The top 1 percentile was composed of men age 96 years and older and females aged 100 years and older. Males surviving to at least age 101 years and females surviving to age 104 years were in the top 0.1 percentile of survival for their birth cohort. And finally, males surviving to age 106 and females to age 109 were in the top 0.01 percentile. Thus over a difference of just 5, 10, and 15 years of survival beyond age approximately 95, there are 10, 100, and 1,000-fold differences, respectively, in the rarity of these individuals. We hypothesize that these dramatic differences in risks of survival reflect an equally dramatic force of demographic selection and increasing phenotypic homogeneity at the extreme tail of survival. We further hypothesize that an increasing genetic influence underlies these rarer rates of survival and greater phenotypic homogeneity.

That is not to say that just a few genetic variants are necessary for survival to very rare ages. Instead, we posit that many genetic variants (mostly common, some rare) with individually modest effects, in specific combinations with one another, are particularly influential in the variation of survival to extreme ages. Supporting this hypothesis, we discovered that different genetic signatures or combinations of longevity-associated genotypes of a set of 281 single nucleotide polymorphisms (SNPs) are associated with different median ages of survival ranging from 103 to 105 years of age (6).

Given the dramatic degree of demographic selection that occurs beyond age 90, it is critical to precisely define the birth cohort and percentile of survival of the subjects in a study of "longevity." For example, the lax use of the term longevity has led to many studies continuing to cite Scandinavian twin studies from the 1990s as supportive of the claim that heritability of "longevity" is 25% and therefore genetic variation explains a minor component of this trait. In a 1993 article titled "Longevity is moderately heritable in a sample of Danish Twins born 1870–1880", the authors calculated heritability of age at death among a sample of monozygotic and dizygotic twins surviving beyond the age of 15 years. The mean ages of death were 73 (*SD* = 16) and 71 (*SD* = 17) years that correspond to the 36th and 40th percentiles of survival respectively in the 1870–1880 Danish birth year cohort (7). A 1996 follow-up study of a larger sample of Danish twins born between 1870 and 1900 and with similar mean ages of death produced slightly lower heritability estimates of "longevity" of 26% and 23% for males and females (8). A 1998 Swedish study of twins born between 1886 and 1925 reported the genetic component of "longevity" to be about 33%. The study used the terms "life span" and "longevity" interchangeably, and no men in the sample lived past the age of 89 years, and about 2% of the female sample lived to age 90+ years (9). Finally, in a 2001 study titled, "Heritability of life span in the Old Order Amish," the authors investigated Amish pedigrees for parental and offspring ages of death for subjects born prior to 1890 who survived to at least age 30 years. The mean age of death was 71 ± 16 years, and about 7% of the sample was age 90+ years with only a few subjects age 95+ years. The authors interchangeably used the terms "longevity" and "life span" and estimated the heritability of both to be 25 ± 5% (10).

These twin and pedigree studies represent important contributions to the estimation of the relative genetic influence upon the variation in survival, but the ages of death are approximately those of what most people should be able to achieve in the presence of good health behaviors. Therefore, it makes sense that the vast majority of the variation in how old the people in these studies lived to be is explained by their health-related habits and environments rather than genetic differences. The Seventh Day Adventist Health Study, suggests that average people can, in the setting of specific healthy behaviors, achieve an average life expectancy of 86 years (11). Note that Seventh Day Adventists are an ethnically and geographically heterogeneous sample that, by virtue of their religious beliefs, are generally vegetarian and eat in moderation, don't smoke tobacco or drink alcohol, regularly exercise, and regularly participate in religious and family activities. Thus, this study suggests that such a heterogeneous sample of people have the average genetic makeup to facilitate survival to almost ninety years in the setting of healthy behaviors.

The casual use of the term "longevity" has also generated confusion in molecular genetic studies of human longevity. For example, in a meta-analysis of genome-wide association studies of what the authors called "longevity" (12), the largest sample in the analysis, the deCode sample from Iceland (*n* = 4,272), had a mean age of 90 years (*SD* = 4). The lead study in the analysis, the Leiden 85-plus Study I (*n* = 245) and II (*n* = 551, replication sample) had mean ages of 93 years (*SD* = 3) and 92 years (*SD* = 5), respectively. The Genetics of Healthy Aging (GEHA) sample, a consortium of European studies, had mean ages ranging from 94 to 96 years. Many of these studies had relatively few subjects achieving even the top 1 percentile of survival, and one sample, the French CEPH centenarian cohort, was the only sample with a mean age that fell within the top 1 percentile of survival for women. Furthermore, no samples with ages older than the top 1 percentile of survival were used in the replication phase of the study. Despite the relatively common ages of the subjects in their analysis (~15th percentile for women and 5th percentile for men), the authors claimed that because their study could not replicate a genetic study led by the New England Centenarian Study (6), the latter study must be invalid. This work shows that the Leiden-led study and the New England Centenarian Study investigate the familial and genetic bases of two significantly different phenotypes with very different degrees of demographic selection and therefore without proper power calculations, the lack of replication in a study of largely nonagenarians does not invalidate the findings from a study of centenarians. Supporting this claim, Tan and coauthors (13) suggest that the power of case–control studies to detect associations with longevity increases with increasing heritability of the phenotype and therefore the power to detect associations is much greater for centenarian versus nonagenarian samples.

In order to detail the importance of clearly defining the longevity phenotype when carrying out and comparing studies meant to discover underlying determinants, we set out to determine sibling relative risks for rarer percentiles of survival using an unprecedentedly large sample of centenarians (ages 100–104 years) and semi-supercentenarians (ages 105–109 years). Directly related to percentile

of survival, we also explore the impact of birth year cohort upon heritability of these small percentiles of survival.

Methods

Participants

1,522 multigenerational pedigrees of participants enrolled in the New England Centenarian Study were manually validated using U.S. federal and state census data, state and local birth, marriage and death registries, the U.S. Social Security Death Index, obituaries, and gravestone records that were queried through Ancestry.com. Additional details are in (14). The 1,522 pedigrees included 5,008 sibships, and 1,914 sibships included at least one individual who lived to age 90 years and older.

Statistics

Let A^* denote the age of the longest lived individual in a sibship. The relative risk that an additional sibling lives past age A, given that the longest lived sibling survived to age A^* was estimated by the ratio

$$\lambda(A \mid A^*) = pr(Sib > A \mid A^*, B) \,/\, pr(Sib > A \mid B)$$

where $pr(Sib > A \mid A^*, B)$ is the conditional probability that one sibling survives to age A given that the longest lived sibling survived to age A^*, and is the marginal probability that the sibling survives to age A, given birth year cohort B (15,16). Note that, by definition, the age A can only be at most as old as A^*. We assumed for simplicity that the siblings were from the same birth year cohort. The birth year-specific probabilities, $pr(Sib > A \mid B)$, were estimated using cohort life tables from the Social Security Administration (SSA) for birth year cohorts 1900 and later, for males and females combined (17). For birth year 1890–1899, we used cohort life tables from Sweden (http://www.mortality.org/hmd/SWE/STATS/) as an approximation of the survival experience in the United States. Four analyses were conducted based on the attained age of the longest lived sibling $A^* > 90, 95, 100, 105$. In each analysis, the number N of additional siblings who survived to age $A > 90, 95, 100, 105$ was modeled by a Poisson distribution with expected value μ that was parameterized using the log-linear model:

$$\log(\mu) = \beta_0 + \sum\nolimits_k \beta_k x_k + \alpha$$

The parametric model included birth year, attained age, and sex of the proband, and a random effect α that modeled the correlation of sibships from the same pedigree. Age was centered at the mean age of the proband, sex, and birth year were coded as dummy variable. Bayesian estimates of the probability $pr(Sib > A \mid A^*, B) = pr(N = 1 \mid A^*) = \mu e^{-\mu}$ for different sex-specific birth year cohorts, and 95% intervals were computed using Markov Chain Monte Carlo methods in Openbugs (http://www.openbugs.info/w/), with an initial burn-in of 1,000 iterations. An additional 4,000 iterations were used to estimate parameters and intervals by the median and the 2.5 and 97.5 percentiles. The prior distributions of the parameters β were assumed to be Normal with variance 100, and the prior distributions of the random effects were assumed to be Normal with variance that followed a Gamma distribution. Interaction between proband attained age and birth year cohort, and quadratic effects of proband age were tested but did not reach statistical significance. To assess the goodness-of-fit of the Poisson log-linear model, the mean number of siblings $\bar{x}$ who survived to ages $A > 90, 95, 100, 105$ were calculated for each proband age $A^* = 90, 91, 92, \ldots, 100$. These sample means were used to compute the "observed" conditional probabilities as $\bar{x}e^{-\bar{x}}$ that were plotted with the model-based fitted probabilities.

Results

The pedigrees furnished data for 1,917 sibships with at least one individual who survived to age 90. The 1,917 sibships included 1,391 sibships with at least one individual who survived to age 95. About 1,042 of the 1,391 sibships included at least one individual who survived to age 100, and 511 of these included at least one individual who survived to age 105 and older. Bayesian mixed effects Poisson regression was used to estimate the conditional distribution of the number of additional siblings who survived to ages 90, 95, 100, and 105, as a function of the age of the longest lived sibling in a sibship (proband), adjusting for the sex and birth year cohort of the longest lived sibling.

Table 1 provides the estimates of the regression coefficients for the four analyses. The positive sign of the regression coefficient for age indicates that older age of the proband is associated with an increased chance of long-lived siblings. This effect, however, becomes nonsignificant for very extreme ages of the proband (older than 105), which is likely due to insufficient power because only 19 sibships had an additional sibling who lived past age 105. Sex of the proband failed to reach statistical significance (thus, credible intervals contained 0), and the posterior distribution of the parameter representing the sex effect became more symmetrical on either side of 0 for older ages 100 and 105 (Figure 1), suggesting that the lack of significance is more consistent with a true negative effect rather than a lack of statistical power. This result agrees with other studies showing a convergence of phenotypes of males and females at extreme ages (5,18). The birth year cohort of the proband had a substantial effect that increased with the older and older age of the proband. For example, having a sibling who was born before 1895 and survived to age 100 increased the expected number of centenarian siblings by more than 50% compared to having the longest lived sibling who survived to age 100 and was born after 1895.

Table 2 shows the relative risk that an individual survived to ages A= 90, 95, 100, 105 given that the longest lived sibling survived to ages $A^* > 90, 95, 100, 105$ for the 1900 birth year cohort. The relative risk ranged between a less than a twofold increase ($A = 90, A^* = 90$) to more than a 35-fold increase for very extreme survival ages ($A = 105, A^* = 105$). The relatively small increase in the chance of living to age 90 or 95 given the existence of a sibling who lived to these ages is consistent with the results from the Utah (19) and Iceland (20) studies and confirms the limited heritability of surviving to the early to mid-nineties for the 1900 birth cohort. However, living to older ages yields much higher sibling relative risks (eg, 35 for survival to age 105 years).

The plot in the left top panel of Figure 2 shows the estimated trend of these conditional probabilities for a wider range of probands' ages. The pattern of observed data scatters around the fitted lines suggesting that the models provide a good fit, particularly for older ages A, A^*. The plot in the right panel of Figure 2 shows the estimated trend of the relative risk of surviving to age 90, 95, and 100 as a function of the survival age of the longest lived sibling. Note the substantial increase in relative risk of surviving to age 100, given an additional sibling who lives to ages 100–110, which is consistent with previous estimates from the New England Centenarian Study

Table 1. Estimates and Standard Deviation (*SD*) of Regression Coefficients of Age, Sex, and Birth Year Cohort (BYC) of the Longest Lived Sibling ("proband") in the Mixed Effect Poisson Regression

	Proband	Estimate	*SD*	95% CI
$A = 90$	Intercept	**−0.62**	**0.061**	**(−0.744; −0.506)**
$A^* \geq 90$	Age (A^* −99.88)	**0.086**	**0.005**	**(0.076; 0.097)**
	Sex (male)	−0.07	0.07	(−0.210; 0.070)
	BYC (>1,895)	−0.043	0.07	(−0.175; 0.082)
$A = 95$	Intercept	**−0.98**	**0.098**	**(−1.168; −0.803)**
$A^* \geq 95$	Age (A^* −102.89)	**0.096**	**0.009**	**(0.078; 0.115)**
	Sex (male)	−0.05	0.112	(−0.279; 0.167)
	BYC (>1,895)	−0.159	0.1	(−0.357; 0.0367)
$A = 100$	Intercept	**−1.66**	**0.103**	**(−2.025; −1.355)**
$A^* \geq 100$	Age (A^* −104.89)	**0.096**	**0.0229**	**(0.056; 0.139)**
	Sex (male)	−0.069	0.206	(−0.488; 0.320)
	BYC (>1,895)	**−0.456**	**0.693**	**(−0.814; −0.079)**
$A = 105$	Intercept	**−2.65**	**0.36**	**(−3.436; −1.975)**
$A^* \geq 105$	Age (A^* −107.89)	0.001	0.087	(−0.174; 0.172)
	Sex (male)	−0.028	3.147	(−6.167; 6.107)
	BYC (>1,895)	**−0.995**	**0.499**	**(−1.976; −0.011)**

A is the age of survival of siblings of the proband, and A^* is the age of the proband. Highlighted in bold face are the significant parameters with 95% credible intervals that do not contain 0. Ages of probands were centered at the mean ages: 99.88 for $A^* \geq 90$; 102.89 for $A^* \geq 95$; 104.89 for $A^* > 100$ and 107.89 for $A^* > 105$ so that the exponential value of the intercept terms represents the expected number of siblings of age A, given a proband living to the mean age.

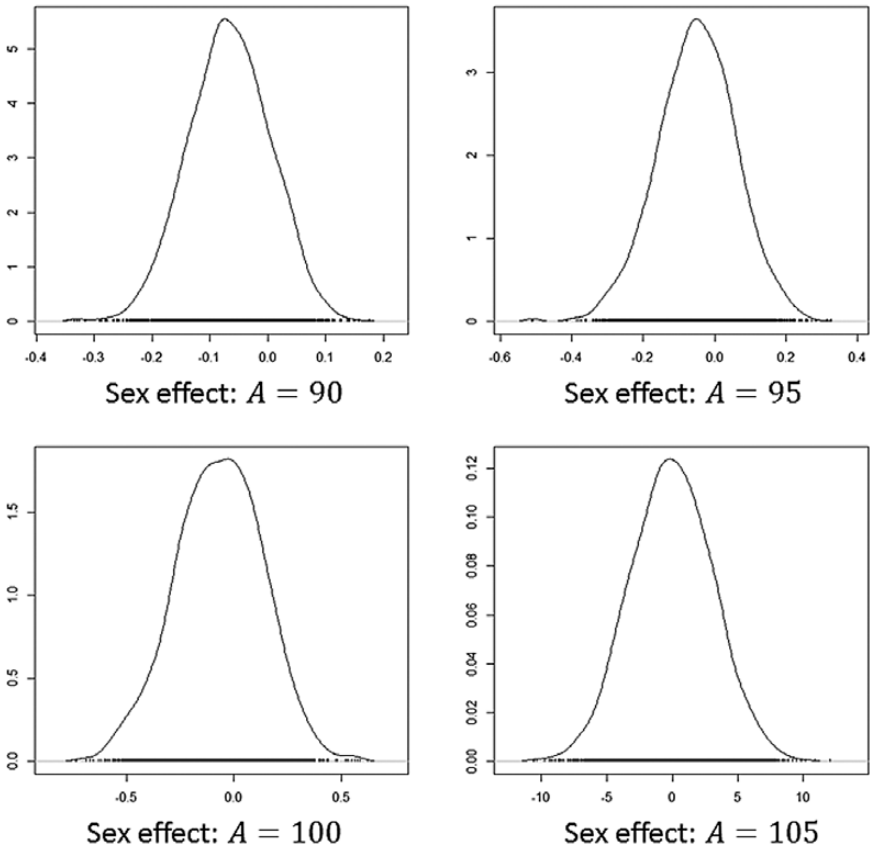

Figure 1. Posterior density of the parameter representing the sex effect, for ages $A = 90$, 95, 100, and 105. The increasing symmetry of the posterior distribution for older ages suggests that sex of the longest lived sibling does not affect the chance of living to very old ages of the siblings.

calculated by a different method and a smaller sample (21). Table 3 shows the same relative risk for siblings of probands born before 1895. The relative risks are all larger, but of note is the larger conditional probability of living to older ages and the larger uncertainty of the estimates shown by the wider interval estimates (Figure 2). The increased conditional probability combined with the greater rarity of centenarians in the 1890–1899 Swedish birth cohort life table (www.lifetable.de) results in very large sibling relative risks. Unfortunately, U.S. birth cohort life tables are not available for birth year cohorts earlier than 1900. Insufficient data were available to estimate the

Table 2. Estimated Relative Risk that an Individual Survived to Age *A*, Given that the Longest Lived Sibling (proband) Survived to Age *A**, for the 1900 Birth Year Cohort

Relative Risk of a Sibling Surviving Age $A = 90$, Given the Longest Lived Sibling reached age A^*				
Proband age (A^*)	90	95	100	105
Male proband	1.73 (1.5; 2.01)	2.39 (2.15; 2.65)	3.11 (2.89; 3.31)	3.69 (3.54; 3.78)
Female proband	1.83 (1.59; 2.1)	2.50 (2.29; 2.73)	3.21 (3.06; 3.36)	3.74 (3.67; 3.79)
Relative risk of a sibling living past age $A = 95$, given the longest lived sibling reached age A^*				
Proband age (A^*)		95	100	105
Male proband		3.38 (2.68; 4.15)	5.02 (4.23; 5.81)	7.04 (6.13; 7.89)
Female proband		3.52 (2.85; 4.23)	5.2 (4.59; 5.82)	7.27 (6.76; 7.76)
Relative risk of a sibling living past age $A = 100$, given the longest lived sibling reached age A^*				
Proband age (A^*)			100	105
Male proband			8.61 (5.53; 12.81)	13.38 (9.42; 18.28)
Female proband			9.2 (6.53; 12.2)	14.17 (11.59; 16.9)
Relative risk of a sibling living past age $A = 105$, given the longest lived sibling reached age A^*				
Proband age (A^*)				105
Male and female proband†				35.64 (15.11; 67.67)

Notes: †These are merged data for males and females because there is no significant sex effect at these extreme ages

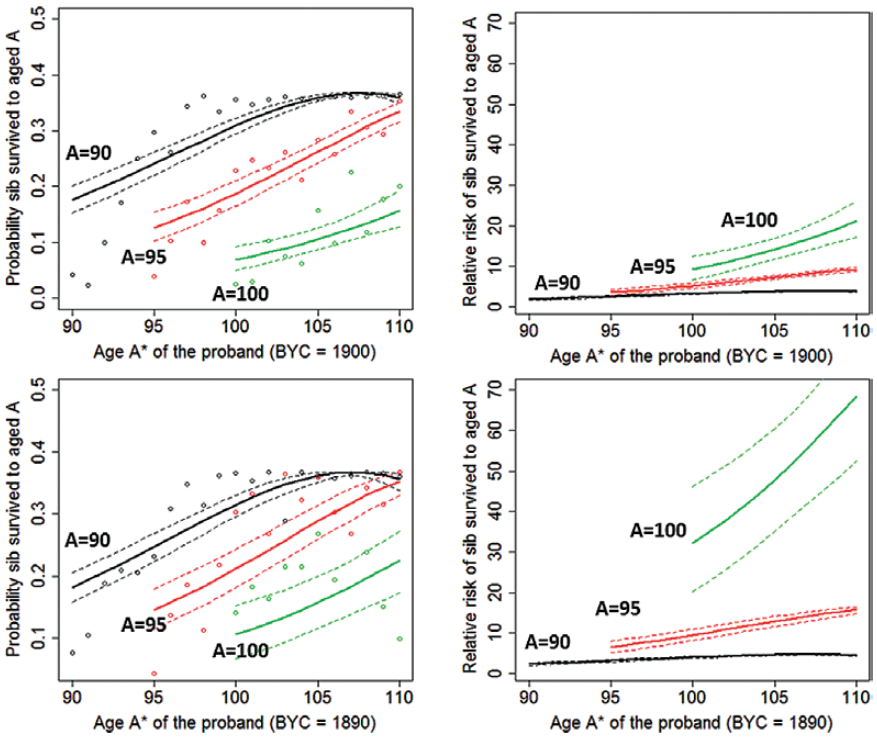

Figure 2. Top panel: estimated conditional probability (left panel, solid lines) and relative risk (right panel, solid lines) and 95% credible interval (dashed lines) that an individual survived to age *A*, given that the longest lived sibling (proband) survived to age *A** and was born in the 1900 birth year cohort. Black: age $A = 90$, red: age $A = 95$, green: age $A = 100$. The U.S. 1900 cohort life table was used to estimate the population risk of living to ages 90, 95, and 100 for the generation of the top panels. Dots in the left panels represent the conditional probabilities estimated from the observed frequencies. Bottom panel: Conditional probabilities and estimated relative risks for siblings born in the 1890 birth year cohort. The Swedish 1890–1899 cohort life table was used to estimate the population risk of living to ages 90, 95, and 100. The increased conditional probability combined with the greater rarity of centenarians in the 1890 Swedish birth cohort life table (www.lifetable.de) results in very large sibling relative risks.

conditional probability of a sibling surviving to 105 years, given the proband's age at death > 105 years for this birth year cohort.

Discussion

Our analysis of over 1,900 sibships that contain at least one sibling achieving the age of 90 years clearly demonstrates that if one limits themselves to the study of people surviving to approximately the age of 90 years (5th percentile of survival for men, 15th percentile for women), the relative risk of their siblings achieving age 90 years is relatively small (1.7–1.8). For probands who survived to age 95 (1st percentile for males, 5th percentile for females), the relative risk for their siblings achieving the same age goes up to about 3.5. The relative risks are very different for probands living to age 100 (0.1

Table 3. Estimated Relative Risk that an Individual Survived to Age *A*, Given that the Longest Lived Sibling (proband) Survived to Age *A** for the 1890 Birth Year Cohort

Relative risk of a sibling living past age 90, given the longest lived sibling reached age *A**				
Proband age (*A**)	90	95	100	105
Male proband	2.19 (1.89; 2.51)	3 (2.68; 3.32)	3.87 (3.57; 4.14)	4.53 (4.33; 4.64)
Female proband	2.3 (2.01; 2.62)	3.13 (2.85; 3.43)	3.99 (3.76; 4.2)	4.59 (4.47; 4.65)
Relative risk of a sibling living past age 95, given the longest lived sibling reached age *A**				
Proband age (*A**)		95	100	105
Male proband		6.18 (4.87; 7.8)	9.06 (7.5; 10.71)	12.47 (10.72; 14.04)
Female proband		6.46 (5.1; 7.96)	9.41 (7.99; 10.82)	12.82 (11.47; 14.04)
Relative risk of a sibling living past age 100, given the longest lived sibling reached age *A**				
Proband age (*A**)			100	105
Male proband			29.74 (17.32; 45.86)	44.77 (29.41; 62.6)
Female proband			31.32 (20.33; 46.45)	47.1 (35.2; 61.12)

percentile for males, 1st percentile for females), where the relative risk of their siblings living to that age is 8.6 and 9.2 in the case of male and female probands, respectively. Finally, for both male and female probands surviving to age 105 years (0.01 percentile for males and 0.1 percentile for females), the relative risk of siblings surviving to 105 years is 35. Sibling relative risk is one of several possible measures of heritability or familiality (16). These much higher relative risks likely reflect different and more potent genetic contributions to the rarity of survival being studied, and strongly suggest that survival to age 90 and survival to age 105 are dramatically different phenotypes with very different underlying genetic influences.

We also hypothesized that these relative risks would be higher for members of earlier birth cohorts achieving the same ages because they experienced a greater degree of demographic selection. For example, according to the Swedish cohort life tables, of 100,000 women born between 1890–1899, 537 survived to 100, while among 100,000 women born in 1900, 881 survived to 100. In fact, we did find a significant effect due to the proband birth year cohort, particularly for ages 100 and older (Table 1) and also showed that the relative risks for survival of siblings of centenarians born before 1895 were substantially higher than those of sibships belonging to the 1900 birth cohort. Although a limitation of this analysis is that we had to use Swedish instead of U.S. cohort tables for the calculation of the sibling relative risk for the 1890–1899 birth year cohort, the significant effect of the proband's birth year cohort is not affected by the selection of this different referent group and reinforces the importance of taking into account the birth cohort when considering survival to extreme ages. Particularly, extreme longevity should be defined based on birth cohort-specific percentile survival ages rather than chronological ages.

While these relative risks become quite high for siblings of probands living beyond 100 years relative to those observed in other complex phenotypic traits, it is important to recognize that we are discussing a rare phenotype. In the case of survival to the top 0.1 percentile, having a marked increased relative risk for a rare phenotype can still translate into low probability of achieving the phenotype because of how generally rare that phenotype is. This is apparent in our calculation of the estimated conditional probabilities of siblings of centenarians also living to very old age. For example, as Figure 2 illustrates, in the case of a proband born in 1900 who survives to age 100 years, the conditional probability of an additional sibling living to 100 is approximately 0.05. In other words, out of 100 sibships with an individual who lives to 100 years, about five sibships will include an additional centenarian. If the proband lived to 105 years, this conditional probability doubles to approximately 0.1 (or 10 out of 100 sibships of 105 year olds include an additional centenarian). Note that in our analysis we intentionally limited attention to ages of younger siblings in a sibship ($A \leq A^*$) to evaluate the effect of the most extreme age in a sibship on the longevity of the remaining siblings. Therefore, in our analysis, we only looked at four age groups for siblings ($A = 90$, 95, 100, and 105), and let the proband age A^* vary continuously, with $A \leq A^*$. We were unable to design the study without the restriction $A \leq A^*$ and also allow the proband age A^* to vary continuously.

The sibling relative risks of survival to age 100 years that are observed in this study are similar to those that the New England Centenarian Study noted with a substantially smaller sample of sibships and a different analytic approach (21). In this study, we did not analyze the impact of a sibling's sex upon their own relative risk of survival to very old age. Instead, we focused on the impact of the sex of the proband upon their siblings' risk of survival to much older ages. We found that the sex of the proband did not affect the sibling's relative risk of also achieving the rarest percentile of survival. This finding is consistent with our noting a convergence of phenotypic characteristics between men and women as they approach ages like 105 years and older (again, of the 1891–1900 birth cohort) (5).

The increase of sibling relative risk with increasing older ages of the proband is consistent with the studies noted in the introduction, indicating that the genetic influence upon survival increases with older and older ages, particularly beyond the one percentile of survival (6). The important implication of this finding for genetic studies of human longevity is that the genetic basis of surviving to the 5th and 15th percentiles for men and women (age 90 for the 1900 birth cohort) is likely to be weaker and different from the genetic basis of surviving to the one percentile which in turn is different from the 0.1 percentile of survival. For example, in a genome-wide association study of human extreme longevity comprising 801 centenarians with median age 104 years and 914 genetically matched controls, we discovered a group of 281 independent SNPs that were associated with human extreme longevity. We then generated a Bayesian model that can differentiate centenarians from healthy younger controls based on the genetic profile of these SNPs. Consistent with the increasing sibling relative risk for older ages, when this model was tested in independent data sets it had only 61% sensitivity in picking out the 95 year olds, but it reached 85% sensitivity to identify the 105 year olds (6). We also showed that different combinations of these 281 SNPs (signatures)

were jointly associated with significantly different median ages of death. These findings are also consistent with the hypothesis that the very strong genetic influence upon survival to the top 0.01 percentile of age is the result of specific combinations of many common and rare genetic variants, and that these combinations can vary according to different ethnicities, exposures and subphenotypes of exceptional longevity. Carrying a subset of these longevity-associated variants may result in people living longer than average but not likely to exceptional ages. Survival to much older ages likely entails an enrichment of the longevity variants and therefore samples of participants surviving to more extreme percentiles of survival are much more powerful for the discovery of such variants than younger samples.

Recently, the authors of a meta-analysis of largely nonagenarians (12) were unable to reproduce the associations of the 281 SNPs in (6) and used their negative result to assert that our findings were false positive associations. However, what our analysis of sibling relative risk of extreme longevity indicates is that one should not be surprised by the lack of consistent results between genetic studies of "longevity" that use samples with marked differences in percentiles of survival and therefore substantially different statistical power. Reinforcing this point, when studies are similar in terms of a rare percentile of survival, a large number of the associated SNPs are actually replicated (22).

In summary, we present a careful analysis of the increasing sibling relative risk of surviving to rarer percentiles (15–0.1) of survival based on a large dataset of manually curated multigenerational pedigrees. The results confirm that heritability of living to extreme old ages increases with older ages so that tenth, hundredth, and thousandth differences in percentiles of survival have likely dramatic effects on the findings of genetic and epidemiology studies of very and extreme old ages. Therein lies the critical importance of carefully and consistently defining the rarity of survival when asserting associated genetic and/or environmental factors or comparing one's findings against other studies (1). Furthermore, stating age is not sufficient, because the rarity of the age is highly dependent upon the birth cohort. Therefore, we advocate that percentile of survival for the cohort in question be provided in all studies of "longevity" so that the phenotype, at least in terms of rarity of survival, is clearly defined.

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Conflict of Interest

The authors have no potential conflicts of interest to report.

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