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Familial Risk for Exceptional Longevity

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Abstract

One of the most glaring deficiencies in the current assessment of mortality risk is the lack of information concerning the impact of familial longevity. In this work, we update estimates of sibling relative risk of living to extreme ages using data from more than 1,700 sibships, and we begin to examine the trend for heritability for different birth-year cohorts. We also build a network model that can be used to compute the increased chance for exceptional longevity of a subject, conditional on his family history of longevity. The network includes familial longevity from three generations and can be used to understand the effects of paternal and maternal longevity on an individual's chance to live to an extreme age.

Introduction

The prevalence of centenarians continues to increase, due in part to dramatic and persistent decreases in infant mortality beginning in the late 1800s, increased years of education, and major improvements in socioeconomic conditions, public health interventions and medical care that enabled average life expectancy to nearly double over the past century (Vaupel, Carey et al. 1998). As a result, many more people predisposed to achieving extreme old age have a greater opportunity to achieve these ages and there is not a clear answer to what the nature of this predisposition is.

The Seventh-Day Adventist Health Study, which took place in California from 1976 to 1988, suggests that average humans can achieve an average life expectancy of 86 years, in the setting of specific healthy behaviors that include vegetarian diet, no tobacco or alcohol use, regular exercise and significant time devoted to family and religion (Fraser and Shavlik 2001). Supporting this observation, Scandinavian twin studies indicate that the vast majority of variation in survival to mid to late octogenarian years can be explained by differences in environment and behaviors (Herskind, McGue et al. 1996, McClearn, Johansson et al. 1997, Iachine, Holm et al. 1998, Christensen, McGue et al. 2000, Hjelmberg, Iachine et al. 2006). Heritability is generally regarded as the proportion of the variation of the expression of a

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phenotype controlled by genes as opposed to environmental factors (Visscher PM, Hill WG et al. 2008). Thus, based on these twin studies, various authors and many in the lay press erroneously state that the heritability of aging and even longevity is approximately 25 percent. But more precisely, these studies and the Seventh-Day Adventist Study suggest this heritability applies to survival average people should be able to achieve in the absence of environmental factors that predispose to premature mortality and the presence of behaviors conducive to good health.

There is growing evidence, however, that heritability, or the genetic component of survival, becomes higher with survival to much older ages beyond the age of 90 (Tan, Zhao et al. 2008, Gogele, Pattaro et al. 2010, Sebastiani P, Solovieff N et al. 2012). For example, analyses of data from about 20,000 monozygotic and dizygotic twins born in Nordic countries between 1870 and 1910 show that the genetic influence on survival is minimal prior to age 60 but increases sharply at least to the late 90s (Christensen, Johnson et al. 2006, Hjelmborg, Iachine et al. 2006). We have published several articles demonstrating a strong familial influence upon survival to extreme old age. Siblings of centenarians have markedly increased risk (relative risk $RR = 18$ for brothers and $RR = 7$ for sisters) of achieving age 100 relative to their birth cohort (Perls, Bubrick et al. 1998, Perls, Wilmoth et al. 2002). The Okinawan Centenarian Study has also noted an increased risk of survival to extreme old age among siblings of centenarians (Willcox BJ 2006). Moreover, we noted that by their late 70s, children with at least one centenarian parent have a 60 percent reduced mortality rate compared to their birth cohort (Terry, Wilcox et al. 2004).

Because of our large enrolled sample of centenarians, family members and their accompanying biodemographic data, the New England Centenarian Study (NECS) (Sebastiani and Perls 2012) is in a unique position to address numerous questions about environmental and genetic factors that may contribute to living to age 100 and beyond. In this manuscript, we report updated estimates of sibling relative risks of living to extreme longevity based on more than 1,700 sibships. We also measure the contribution of familial longevity to living to old ages and propose a network-based approach to examine the joint contributions of different patterns of familial longevity. The model can be used to estimate the increased odds for longevity given family history in first- and second-order relatives and provides the first comprehensive approach to combine different types of familial longevity into a single measure of risk.

Materials and Methods

Sample

The New England Centenarian Study sample consists of approximately 2,000 centenarian probands (oldest alive in a sibship) with an age range of 95–119. Pedigree data have been obtained for more than 1,500 subjects, providing data for more than 49,000 individuals born after 1645. The pedigrees were reported from study participants, and about 250 were checked for consistency using census data, the Social Security Death Index and additional sources available through Ancestry.com. Many pedigrees have been age-validated at least for the probands and their siblings noted to survive to age 90. There are missing data, particularly for the subjects' grandparents and earlier generations, while data on their

parents, siblings and offspring are more complete. Additional quality control and completion of the data is ongoing. Figure 1 shows an example of a pedigree that spans four generations.

Sibling relative risk

For ages $A = 90, 95, 100$, we estimated the sibling relative risk of living past age A by the ratio $\lambda(A|A^*) = pr(Sib > A|A^*) / pr(S > A|B, S)$ where $pr(Sib > A|A^*)$ is the probability that a sibling of a proband who lived past age A^* lives past age A , and $pr(S > A|B, S)$ is the probability that a subject in the population lives past age A (Olson JM and Cordell HJ 2000). The symbols B and S denote birth year and sex. The birth-year and sex-specific probabilities $pr(S > A|B, S)$ were estimated using cohort life tables from the Social Security Administration (SSA) for birth-year cohorts 1900 and later (Bell and Miller 2005). For earlier birth-year cohorts, we used cohort life tables from Sweden (<http://www.lifetable.de>) as an approximation of the survival experience in the United States. Eligible sibships were selected from the data based on the age of the oldest sibling, and only those sibships in which the attained age of the oldest sibling exceeded age $A^* > 90, 95, 100$ were included in the analysis. As we described in (Sebastiani, Nussbaum et al. 2015), the number N of additional affected siblings in each sibship was modeled by a Poisson distribution with expected value μ that was parameterized using the log-linear model:

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

This model is commonly used to estimate relative risk (Jewell 2003). The parametric model included covariates x_k to estimate the effects of factors such as birth cohort, age at death, sex of the proband, proportion of females in the N siblings and sibship size. The parameter α denoted a random effect that modeled the correlation of sibships from the same pedigree. (For example, the pedigree in Figure 1 would contribute two sibships). Bayesian estimates of the probability $pr(Sib > A|A^*) = pr(N = 1) = \mu e^{-\mu}$ for different sex-specific birth-year cohorts and 95 percent intervals were computed using Markov chain Monte Carlo methods in Openbugs (<http://www.openbugs.info/w/>). The advantage of the Bayesian analysis is that the significance of the parameters can be tested by marginalizing out the random effects, and estimates of the predicted probabilities can be computed with the correct intervals of uncertainty.

Network analysis

To simultaneously analyze age at death in different generations, we recoded ages at death A of all subjects in the data set by the probability of surviving past age A , say $pr(S > A|B, S)$, using sex and birth-year cohort-specific survival probabilities as noted above. We will refer to these probabilities as percentile survival, and the smaller the percentile survival, the more extreme the longevity. This transformation adjusts the ages at death by the trend in increasing lifespan. For example, while the percentile survival of a male born in the 1900 cohort who survived past age 95 is 1.4 percent, the percentile survival of a male born in 1850 who survived past the same age is 0.4 percent. The longest-lived individual in each sibship was selected ($N = 5,488$), and his/her percentile survival was used in a joint network model including these additional covariates: his/her sex, maternal and paternal ages at

his/her birth, number of older and younger siblings, and percentile survival of second longest-lived sibling, of the parents, of the maternal and paternal uncles and aunts, and of the maternal and paternal grandparents. These variables were categorized into at most four categories. The percentile survival of the longest-lived subject in each sibship was categorized into four groups defined as

- (1) S_1 : the percentile survival was $> 10^{\text{th}}$ using sex/birth-year matched cohort tables;
- (2) S_2 : the percentile survival was between 10 percent and 5 percent;
- (3) S_3 : the percentile survival was between 5 percent and 1 percent;
- (4) S_4 : the percentile survival was less than 1 percent.

Details for the other variables are shown in table A.1 in the appendix. These variables were used to generate a Bayesian classification model, shown in Figure 2, which can be used to compute the posterior probability of survival into one of the four groups, S_1, S_2, S_3, S_4 , based on evidence of familial longevity. The posterior probability that an individual survival is in one of the four groups S_l is given by the formula:

$$p(S=S_l | F_1, F_2, F_3, \dots, F_k) = \frac{\prod_j p(F_j | S=S_l, \pi(F_j)) p(S=S_l)}{\sum_{i=1}^4 \prod_j p(F_j | S=S_i, \pi(F_j)) p(S=S_i)} \quad (1)$$

where $F_1, F_2, \dots, F_k$, are values of the covariates such as maternal age at death, paternal age at death, and number of younger or older siblings. Formula (1) for the calculation of the posterior probability uses assumptions of conditional independence between the variables in the model that are displayed by the directed graphical model displayed in Figure 2 (Sebastiani, Abad et al. 2005). The node Age.P in the model represents the event where an individual's survival is in one of the four groups S_l while the other nodes are the covariates that describe different types of familial longevity. The probabilities $p(F_j | S=S_l, \pi(F_j))$ are estimated from the contingency tables that cross-classify each covariate, the percentile survival to one of the four groups S_l , and additional dependencies represented by the symbol $\pi(F_j)$, using standard Bayesian conjugate analysis for multinomial distributions with Dirichlet priors (Cowell, Dawid et al. 1999). The additional dependencies represent known relations between the variables in the network. The advantage of this modeling approach is that the different conditional probabilities can be estimated using the largest sample size available. This feature is important here because the amount of missing data is large for some variables, particularly in the grandparents' generations, but much smaller for data about siblings and parents of subjects. A possible limitation of this approach is to rely on a set of conditional independence assumptions that are used to simplify the calculations of the posterior probability $p(S=S_l | F_1, F_2, F_3, \dots, F_k)$. The adoption of conditional independence assumptions to build risk prediction models is common for example in genetic epidemiology (Sebastiani, Solovieff et al. 2012), but the validity of these assumptions was not tested in the current data and additional work is needed to assess the adequacy of the assumptions.

The program Bayesware Discoverer (<http://dcommon.bu.edu/xmlui/handle/2144/1288>) was used to estimate the conditional probabilities $p(F_j | S_l, \pi(F_j))$ from the dataset of 5,487

sibships. The program was also used to compute the posterior probability of survival into one of the four groups given any combination of covariates $F_1, F_2, F_3, \dots, F_k$ using Formula (1). These posterior probabilities were used to predict the survival group of each proband in the data set using the most likely outcome, and boxplots of the true percentile survival in each of the 4 survival groups stratified by the predicted ages at death are displayed in Figure 3.

Results

Sibling relative risk

We generated estimates for sibling relative risk using 1,714 sibships obtained from 1,505 NECS pedigrees in which the oldest sibling attained an age of at least 90 years, and the age range was 90–116. Pedigrees of centenarians enrolled for a sib-pair genetic linkage study (Geesaman, Benson et al. 2003) were not included in this analysis. We used Poisson regression with a log-linear model of the mean to estimate the probability $pr(Sib > A | A^*)$ that one additional sibling in each sibship lived past age A , given that the longest-lived sibling reached age A^* , as detailed in methods. Covariates in the regression model included the age at death of the proband, sex and birth-year cohort coded as a binary variable (1895–1905 or <1895). We repeated the analysis for probands who lived past ages $A^* = 90, 95$ and 100. The relative risk for varying combinations of A and A^* were computed using the formula for $\lambda(A | A^*)$ described in the methods, and the birth-year and sex-specific probabilities $pr(S > A | B, S)$ were estimated using cohort life tables from the Social Security Administration (SSA) for birth-year cohorts 1900 and later (Bell and Miller 2005) and cohort life tables from Sweden (<http://www.lifetable.de>) for 1890.

Results in Table 1 show that sibling relative risk increases with increasing ages of the proband, increasing age of the sibling and earlier birth-year cohort of the probands. For example, male siblings of centenarians born in the 1900 birth-year cohort had a 3.35 times greater chance of living past age 90, compared to people born in the 1900 birth-year cohort, and 8.21 times greater chance of living past age 100. The estimates agree with sibling relative risks for nonagenarians reported from Utah (Kerber, O'Brien et al. 2001) and Iceland studies of longevity (Gudmundsson, Gudbjartsson et al. 2000), and show that the risk increases noticeably for ages 100 and older. The estimates of sibling relative risks for the 1900 birth-year cohort of the probands are smaller than results previously published (Perls, Wilmoth et al. 2002), but those results pulled together a wider range of birth-year cohorts that are associated with larger risks. This analysis was recently extended to include a larger set of pedigrees and confirms the results in Table 1 (Sebastiani, Nussbaum et al. 2015).

Network analysis

Figure 2 displays the network implemented in the program Bayesware Discoverer with a sample of 4 of the 21 the conditional probability tables associated with each of the 21 nodes of the network. Table a) in Figure 4 shows the distribution of the 4 survival groups in the data, while table b) shows the distribution of the sex of the proband, in each of the 4 survival groups. Tables c) and d) show the distribution of the maternal and paternal longevity in each of the 4 survival groups. The conditional probability tables were estimated from the database

of 5487 sibships as described in the method section and they can be used to calculate the probabilities of some events of interest using Formula (1). As shown in table a, 27% of the sibships had the longest-lived individual surviving past the top 1 percent survival and 13 percent of the sibships had the longest-lived individual surviving between the 5th percent and 1st percent survival. Therefore, the contribution of different types of familial longevity needs to be compared to these prior probabilities for correct interpretation.

Some selected vignettes from the results of the network model include the following findings. NECS subjects who survived past the fifth percentile survival were more likely to be female. This is shown in table b) that describes the conditional probability of sex of the proband, conditionally on the proband's age at death (Figure 2). The table shows that 56% of probands who survived between the 5th and 1st percentile survival age were females, and the proportion of females increases to 68% in probands who survived past the 1st percentile survival age.

In addition long lived probands appeared to have some type of familial longevity. For example, 23% of probands who survived to an age between the 5th and 1st percentile survival age had a father who survived past the 5th percentile survival of his birth year cohort, and 20% of probands who survived past the 1st percentile survival age had a father who survived past the 5th percentile. In contrast, only 17% of probands who did not survive past the 5th percentile survival had a father who survived past the 5th percentile.

By using Formula (1) and the conditional probability tables in the network, one can compute the odds for survival past say the 1st percentile survival given family longevity. For example, the calculations show that the odds of survival past the 1st percentile survival age are 0.422 if the father survived past the 5th percentile age, compared to 0.366 if the father did not survive past the fifth percentile age. Having a paternal grand-mother who survived past the 10 percent survival age, in addition to a long lived father, increases the odds for longevity to 0.47. Ages of parents at a subject's birth have an effect that changes with the number of siblings: being born from older parents seems to have a detrimental effect on an individual's longevity in small sibships but not in large sibships. Although the results are preliminary, they suggest that a history of familial longevity contributes to increasing the odds for an individual's longevity, and that the different components of familial longevity can be combined to estimate an individual's odds for living to extreme ages.

Figure 3 shows the distribution of $-\log_{10}(\text{percentile survival})$ of the individuals in the original data set stratified in the four groups predicted by the network model. The more extreme the observed survival age, the smaller the percentile survival and the larger the value in $-\log_{10}$ scale. Therefore, a well calibrated prediction should assign individuals with the largest $-\log_{10}(\text{percentile survival})$ to the group representing survival past the 1st percentile survival (LT.01 in Figure 3), and should assign individuals with less extreme survival to the other groups. The figure shows that subjects assigned to the group LT.01 tend to have the largest $-\log_{10}(\text{percentile survival})$, while the median $-\log_{10}(\text{percentile survival})$ of subjects assigned to the group BTW.05.01 was greater than the median $-\log_{10}(\text{percentile survival})$ of subjects assigned to the group BTW.10.05. The difference in $-\log_{10}(\text{percentile survival})$ for subjects assigned to the groups LT.01 and BTW.05.01 was statistically

significant (p-value from t-test $< 10^{-15}$), while the difference in $-\log_{10}(\text{percentile survival})$ for subjects assigned to the groups BTW.05.01 and BTW.10.05 was almost statistically significant (p-value from t-test 0.06).

When the model was used to classify the subjects of the study into the most likely groups of survival based on the predicted probabilities and assuming uniform prior probabilities, 41 percent of subjects were correctly classified, which is more than 1.4 times the rate expected by a random classification. Although the initial validation of the probability computed with the network model is positive, additional validation of the model using independent data is needed.

Conclusions

Analysis of this large number of sibships from families of centenarians in the New England Centenarian Study validated previous estimates of the sibling relative risk of living past extreme ages. The increasing relative risks of survival to very old age that is associated with older and older ages of the relative is consistent with the conjecture that the heritability of longevity is substantial only when we start looking at the oldest fifth and smaller percentiles of survival. In addition, we used network modeling to begin combining different contributions of familial longevity into a single risk measure. As we obtain more complete pedigree data, we anticipate conducting more sophisticated network analyses and possibly more accurate models will be generated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Bibliography

- Bell F, Miller M. Life Tables for the United States Social Security Area 1900-2100. Actuarial Study No. 116. 2005
- Christensen K, Johnson TE, Vaupel JW. The quest for genetic determinants of human longevity: challenges and insights. *Nat Rev Genet.* 2006; 7(6):436–448. [PubMed: 16708071]
- Christensen K, McGue M, Yashin A, Iachine I, Holm NV, Vaupel JW. Genetic and environmental influences on functional abilities in Danish twins aged 75 years and older. *J Gerontol A Biol Sci Med Sci.* 2000; 55(8):M446–452. [PubMed: 10952367]
- Cowell, RG.; Dawid, AP.; Lauritzen, SL.; and Spiegelhalter, DJ. Probabilistic Networks and Expert Systems. Springer Verlag; New York: 1999.
- Fraser GE, Shavlik DJ. Ten years of life: Is it a matter of choice? *Arch Intern Med.* 2001; 161(13): 1645–1652. [PubMed: 11434797]
- Geesaman BJ, Benson E, Brewster SJ, Kunkel LM, Blanche H, Thomas G, Perls TT, Daly MJ, Puca AA. Haplotype-based identification of a microsomal transfer protein marker associated with the human lifespan. *Proc Natl Acad Sci U S A.* 2003; 100(24):14115–14120. [PubMed: 14615589]

- Gogele M, Pattaro C, Fuchsberger C, Minelli C, Pramstaller PP, Wjst M. Heritability Analysis of Life Span in a Semi-isolated Population Followed Across Four Centuries Reveals the Presence of Pleiotropy Between Life Span and Reproduction. *J Gerontol A Biol Sci Med Sci*. 2010
- Gudmundsson H, Gudbjartsson DF, Frigge M, Gulcher JR, Stefansson K. Inheritance of human longevity in Iceland. *Eur J Hum Genet*. 2000; 8(10):743–749. [PubMed: 11039573]
- Herskind AM, McGue M, Holm NV, Sorensen TI, Harvald B, Vaupel JW. The heritability of human longevity: a population-based study of 2872 Danish twin pairs born 1870-1900. *Hum Genet*. 1996; 97(3):319–323. [PubMed: 8786073]
- Hjelmborg JV, Iachine I, Skytthe A, Vaupel JW, McGue M, Koskenvuo M, Kaprio J, Pedersen NL, Christensen K. Genetic influence on human lifespan and longevity. *Hum Genet*. 2006; 119(3): 312–321. [PubMed: 16463022]
- Hjelmborg, v. B. J.; Iachine, I.; Skytthe, A.; Vaupel, JW.; McGue, M.; Koskenvuo, M.; Kaprio, J.; Pedersen, NL.; Christensen, K. Genetic influence on human lifespan and longevity. *Hum Genet*. 2006; 119(3):312–321. [PubMed: 16463022]
- Iachine IA, Holm NV, Harris JR, Begun AZ, Iachina MK, Laitinen M, Kaprio J, Yashin AI. How heritable is individual susceptibility to death? The results of an analysis of survival data on Danish, Swedish and Finnish twins. *Twin Res*. 1998; 1(4):196–205. [PubMed: 10100811]
- Jewell, R. *Statistics for Epidemiology*. CRC/Chapman and Hall; Boca Raton: 2003.
- Kerber RA, O'Brien E, Smith KR, Cawthon RM. Familial excess longevity in Utah genealogies. *J Gerontol A Biol Sci Med Sci*. 2001; 56(3):B130–139. [PubMed: 11253150]
- McClearn GE, Johansson B, Berg S, Pedersen NL, Ahern F, Petrill SA, Plomin R. Substantial genetic influence on cognitive abilities in twins 80 or more years old. *Science*. 1997; 276(5318):1560–1563. [PubMed: 9171059]
- Olson JM, Cordell HJ. Ascertainment bias in the estimation of sibling genetic risk parameters. *Genet Epidemiol*. 2000; 18:217–235. [PubMed: 10723107]
- Perls TT, Bubrick E, Wager CG, Vijg J, Kruglyak L. Siblings of centenarians live longer. *Lancet*. 1998; 351(9115):1560. [PubMed: 10326548]
- Perls TT, Wilmoth J, Levenson R, Drinkwater M, Cohen M, Bogan H, Joyce E, Brewster S, Kunkel L, Puca A. Life-long sustained mortality advantage of siblings of centenarians. *Proc Natl Acad Sci U S A*. 2002; 99(12):8442–8447. [PubMed: 12060785]
- Sebastiani P, Solovieff N, DeWan AT, Walsh KM, Puca A, Hartley SA, Melista E, Andersen S, Dworkis DA, Wilk JB, Myers RM, Steinberg MH, Montano M, Baldwin CT, Hoh J, Perls TT. Genetic signatures of exceptional longevity in humans. *PLoS ONE*. 2012; 7(1):e29848. doi: 10.1371/journal.pone.0029848. URL: <http://dx.plos.org/10.1371/journal.pone.0029848>. [PubMed: 22279548]
- Sebastiani, P.; Abad, M.; Ramoni, MF. *The Data Mining and Knowledge Discovery Handbook*. Morgan Kaufmann; 2005. Bayesian networks.; p. 193-230.
- Sebastiani P, Nussbaum L, Andersen SL, Black MJ, Perls TT. Increasing Sibling Relative Risk of Survival to Older and Older Ages and the Importance of Precise Definitions of “Aging,” “Life Span,” and “Longevity. *J Gerontol A Biol Sci Med Sci*. 2015 2015 in press. PMID 25814633.
- Sebastiani P, Perls TT. The genetics of extreme longevity: lessons from the new England centenarian study. *Front Genet*. 2012; 3:277. [PubMed: 23226160]
- Sebastiani P, Solovieff N, Sun JX. Naive Bayesian Classifier and Genetic Risk Score for Genetic Risk Prediction of a Categorical Trait: Not so Different after all! *Front Genet*. 2012; 3:26. [PubMed: 22393331]
- Tan Q, Zhao JH, Zhang D, Kruse TA, Christensen K. Power for genetic association study of human longevity using the case-control design. *Am J Epidemiol*. 2008; 168(8):890–896. [PubMed: 18756013]
- Terry DF, Wilcox MA, McCormick MA, Pennington JY, Schoenhofen EA, Andersen SL, Perls TT. Lower all-cause, cardiovascular, and cancer mortality in centenarians' offspring. *J Am Geriatr Soc*. 2004; 52(12):2074–2076. [PubMed: 15571545]
- Vaupel JW, Carey JR, Christensen K, Johnson TE, Yashin AI, Holm NV, Iachine IA, Kannisto V, Khazaeli AA, Liedo P, Longo VD, Zeng Y, Manton KG, Curtsinger JW. Bideographic trajectories of longevity. *Science*. 1998; 280(5365):855–860. [PubMed: 9599158]

- Visscher PM, Hill WG, Wray NR. Heritability in the genomics era-concepts and misconceptions. *Nature Rev. Genet.* 2008; 9:255–266. [PubMed: 18319743]
- Willcox BJ, Willcox DC, He Q, Curb JD, Suzuki M. Siblings of Okinawan centenarians share lifelong mortality advantages. *J Gerontol A Biol Sci Med Sci.* 2006; 61:345–354. [PubMed: 16611700]

Figure 1.

Example of pedigree included in the analysis. Labels under each node denote the individual identifier in the pedigree, the age at death, birth year and death year. Missing data are denoted by NA. Circles denote females and squares denote males. This pedigree includes four generations and three sibships.

Figure 2. Display of the Bayesian classification model used to estimate the contribution of familial longevity of an individual's chance for extreme survival.

Figure 3.

Boxplots of $-\log_{10}(\text{percentile survival})$ for the subjects stratified in the four groups predicted by the network model. The four groups are: GT.10: if the age at death of a person is $>10^{\text{th}}$ percentile survival; BTW.10.05: if the age at death is between the 10^{th} and the fifth percentile survival; BTW.05.01: if the age at death is between the fifth and the first percentile survival; and LT.01 if the age at death is older than the first percentile survival. The four boxplots show that subjects allocated to the group with the most extreme survival reached extreme percentile survival. For example, the median percentile survival for subjects classified as GT.10 was 13%, while the median percentile survival for subjects allocated to group LT.01 was 1%.

Table 1

Estimates of relative risk that a male or female sibling lives past age A, given that the proband lived past age 90, 95 and 100, respectively, and was born between 1895 and 1905 (row 1/2) or before 1895 (row 3/4). Data were insufficient to estimate risk in cases of probands born before 1895 who lived past age 100.

Probands	Sex	2 nd sib A = 90+			2 nd sib A = 95+		2 nd sib A = 100+
		90+	95+	100+	95+	100+	100+
1895–1905	M	2.11	2.74	3.35	3.98	5.49	8.21
	F	2.32	2.95	3.52	4.23	5.79	12.42
Before 1895	M	4.88	6.39	7.95	18.16	24.80	//
	F	5.36	6.92	8.43	19.29	26.15	//