North American Actuarial Journal

ISSN: 1092-0277 (Print) 2325-0453 (Online) Journal homepage: http://www.tandfonline.com/loi/uaaj20

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To cite this article: Leonid A. Gavrilov & Natalia S. Gavrilova (2015) Predictors of Exceptional Longevity: Effects of Early-Life and Midlife Conditions, and Familial Longevity, North American Actuarial Journal, 19:3, 174-186, DOI: 10.1080/10920277.2015.1018390

To link to this article: http://dx.doi.org/10.1080/10920277.2015.1018390

Published online: 09 Jul 2015.

North American Actuarial Journal, 19(3), 174–186, 2015

ISSN: 1092-0277 print / 2325-0453 online
DOI: 10.1080/10920277.2015.1018390

Predictors of Exceptional Longevity: Effects of Early-Life and Midlife Conditions, and Familial Longevity

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Knowledge of strong predictors of mortality and longevity is very important for actuarial science and practice. Earlier studies found that parental characteristics as well as early-life conditions and midlife environment play a significant role in survival to advanced ages. However, little is known about the simultaneous effects of these three factors on longevity. This ongoing study attempts to fill this gap by comparing centenarians born in the United States in 1890–1891 with peers born in the same years who died at age 65. The records for centenarians and controls were taken from computerized family histories, which were then linked to 1900 and 1930 U.S. censuses. As a result of this linkage procedure, 765 records of confirmed centenarians and 783 records of controls were obtained. Analysis with multivariate logistic regression found the existence of both general and gender-specific predictors of human longevity. General predictors common for men and women are paternal and maternal longevity. Gender-specific predictors of male longevity are occupation as a farmer at age 40, Northeastern region of birth in the United States, and birth in the second half of year. A gender-specific predictor of female longevity is the availability of radio in the household according to the 1930 U.S. census. Given the importance of familial longevity as an independent predictor of survival to advanced ages, we conducted a comparative study of biological and nonbiological relatives of centenarians using a larger sample of 1,945 validated U.S. centenarians born in 1880–1895. We found that male gender of centenarian has a significant positive effect on survival of adult male relatives (brothers and fathers) but not female blood relatives. Life span of centenarian siblings-in-law is lower compared to life span of centenarian siblings and does not depend on centenarian gender. Wives of male centenarians (who share lifestyle and living conditions) have a significantly better survival compared to wives of centenarians' brothers. This finding demonstrates an important role of shared familial environment and lifestyle in human longevity. The results of this study suggest that familial background, some early-life conditions and midlife characteristics play an important role in longevity.

1. INTRODUCTION

Studies of centenarians (people living to 100 and older) could be useful in identifying factors leading to long life and avoidance of fatal diseases. Even if some individual characteristics have a moderate protective effect on risk of death, people with this trait or condition should be accumulated among long-lived individuals because of cumulative survival advantage. Thus, study of centenarians may be a sensitive way to find genetic, familial, environmental, and life-course factors associated with lower mortality and better survival.

Most studies of centenarians in the United States are focused on either genetic (Hadley et al. 2000; Perls and Terry 2003; Zeng et al. 2010; Murabito et al. 2012; Sebastiani et al. 2012) or psychological (Adkins et al. 1996; Hagberg et al. 2001; Margrett et al. 2010; Martin et al. 2010; Murabito et al. 2012) aspects of survival to advanced ages. On the other hand, several theoretical concepts suggest that early-life events and conditions may have significant long-lasting effect on survival to advanced ages. These concepts include (but are not limited to) the reliability theory of aging and the high initial damage load (HIDL) hypothesis in particular (Gavrilov and Gavrilova 2001a, 2003b, 2006); the theory of technophysio evolution (Fogel and Costa 1997; Fogel 2004); the idea of fetal origin of adult diseases (Kuh and Ben-Shlomo 1997; Barker 1998); and a related idea of early-life programming of aging and longevity (Gavrilov and Gavrilova 2004). These ideas are supported by studies suggesting significant effects of early-life conditions on late-life mortality (Elo and Preston 1992; Fogel and Costa 1997; Kuh and Ben-Shlomo 1997; Barker 1998; Gavrilov and Gavrilova 2003a; Finch and Crimmins 2004; Hayward and Gorman 2004; Costa and Lahey 2005; Smith et al. 2009b). The

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role of early-life conditions in shaping late-life mortality is now well recognized, and studies of centenarians can contribute to this area of research.

Our search for appropriate data resources for centenarian studies revealed an enormous amount of life span data that could be made readily available for subsequent full-scale studies (Gavrilova and Gavrilov 1999; Gavrilov et al. 2002). Millions of genealogical records are already computerized and, after their strict validation, could be used for the study of familial and other predictors of human longevity. Computerized genealogies provide more information on the life span of centenarians' relatives when compared to other sources such as death certificates, census data, and the U.S. Medicare database.

Studies of centenarians require serious work on age validation (Jeune and Vaupel 1999; Poulain 2010, 2011) and careful design including the choice of an appropriate control group. Taking general population as a control group is one of the most popular approaches in centenarian studies. Preston et al. (1998) suggested an original methodology to study longevity in the United States. The researchers collected individual death certificates for people who died at age 85 or above between January 1 and 14, 1985. Death certificate data were then linked to the 1900 U.S. census. Individual data from the 1900 U.S. census were used as a control group. Population-based census data are available as a part of the Integrated Public Use Microdata Series (IPUMS) project at the University of Minnesota (Ruggles et al. 2004). We applied the method suggested in Preston et al. (1998) in our earlier study of centenarians taken from computerized family histories and compared that to the IPUMS dataset (Gavrilova and Gavrilov 2007).

The results of this study demonstrate that the region of childhood residence and the household property status were the two most significant variables that affect the chances of a household producing a future centenarian (for both sons and daughters). Spending a childhood in the Mountain Pacific and West Pacific regions in the United States were found to increase chances of long life (by a factor of three) compared to the Northeastern part of the country (Gavrilova and Gavrilov 2007). Also a farm (particularly an owned farm) residence in childhood was associated with better survival to advanced ages. These findings are consistent with the hypothesis that lower burden of infectious diseases during childhood expressed as lower child mortality in families of farm owners and families living in the West (Preston and Haines 1991) may have far-reaching consequences for survival to extreme old ages. Some of these results are consistent with earlier studies of childhood conditions and survival to age 85+ (Preston et al. 1998; Hill et al. 2000). These studies, also based on linkage to early censuses, demonstrated a significant advantage in survival to age 85 for children living on farms for both African Americans (Preston et al. 1998) and native-born Caucasians (Hill et al. 2000). On the other hand, the Northeast and Midwest were found to be the best regions of childhood residence for subsequent survival to age 85+ (Hill et al. 2000).

Although the use of population-based controls facilitates the research and often helps to obtain reproducible results, it has a serious limitation. If centenarians and controls are sampled differently, then the results of the longevity study may be biased by factors unrelated to differential survival. For instance, genetic composition of centenarians and younger controls (often used in gene association studies) may be differently affected by migration. Centenarians in the New England Centenarian Study were found to be better educated compared to the general population (Perls et al. 2002). Nevertheless, the researchers compared survival of siblings of centenarians in this study to the general population. Although researchers adjusted their calculations for educational status, there is a possibility the relative survival of siblings of centenarians could be overstated because of residual confounding. In our earlier study, we made an assumption that people in computerized family histories do not differ from the general population (Gavrilova and Gavrilov 2007) and found some agreement with other studies (Preston et al. 1998; Hill et al. 2000). However, there is a possibility of biased results if this assumption is not true. For this reason, better research approaches to centenarian studies, as are considered in this article, should be developed.

In this article we consider more correct approaches to choosing a control population in centenarian studies: (1) selection of centenarians and controls from the same population universe and (2) use of nonbiological relatives as a control group. These approaches are illustrated using data on American centenarians, their relatives, and unrelated shorter-lived controls obtained from the same online genealogies.

2. THE BETWEEN-FAMILY APPROACH: SAMPLING CENTENARIANS AND GENETICALLY UNRELATED CONTROLS FROM THE SAME POPULATION UNIVERSE

In this study, we compare centenarians born in the United States to their peers in the same birth cohort who were also born in the United States but died at age 65. Both cases and controls were randomly sampled from the same population universe (computerized family histories) and had the same birth year window (1890–1891). These records were then linked to historical U.S. censuses (1900 1910, 1930). The main focus of the study is on the 1900 and 1930 censuses that correspond to the childhood and adulthood periods of their individual lives. The age at death for controls is selected assuming that the majority of deaths at age 65 occur due to chronic age-related diseases rather than injuries or infectious diseases (Gavrilov and Gavrilova 2013). This design does not suffer from so-called immortal time bias (Ferrie and Ebrahim 2014) because we analyzed past events and conditions when both cases and controls were alive (and of the same age) and did not analyze variables collected at time of death for centenarians and shorter-lived controls.

Sample sizes of male centenarians are small in the majority of longevity studies, and to resolve this problem and have a sample balanced in regard to gender, males are oversampled in this study. This oversampling does not affect the analyses because male and female data are studied separately, taking into account that men and women may respond differently to the same set of risk factors. To obtain a more homogeneous birth cohort regarding the secular changes in mortality and life course events, a narrow birth-date window was used: 1890–1891.

Prevalence of centenarians in modern populations is very low: about 1 per 10,000 population (Hadley et al. 2000), and therefore traditional methods of population sampling are difficult and not feasible for obtaining large samples of centenarians. Case-control design proved to be the most appropriate and cost-effective approach for studies of rare conditions (Breslow and Day 1993; Woodward 2005) and hence is extremely useful for centenarian studies. Breslow and Day (1993) suggested the classic case-control design can be expanded in a variety of ways. One such expansion is a design suggested in Preston et al. (1998). According to this design, a survival to advanced ages (rather than disease or death) is considered to be a case, and relative survival probabilities are used instead of odds ratios. In this study, we draw centenarians and controls randomly from the same universe of online family histories to ensure comparability and avoid possible selection bias when centenarians and controls are drawn from different populations. Also, we used data from historical sources collected when centenarians and controls were children or young adults, thereby avoiding a limitation related to self-report or recall bias. Only records from genealogies of presumably good quality with available information on exact (day, month, year) birth dates and death dates (for centenarians) as well as information on birth and death dates of both parents are used in the sampling procedure for both cases and controls.

Individuals born in 1890–1891 represent an interesting birth cohort to study. These people experienced high exposure to infections during childhood and decreasing infectious disease load later in life. It is important to note that nonagenarians and centenarians living now in the United States have very similar experiences as those born at the end of the 19th century. Therefore, more detailed analysis of past history and life course of this birth cohort may be important for understanding the underlying factors and causes of mortality among the currently living old age cohorts.

Centenarians represent a group with a really rare condition of successful survival (only two men and 14 women out of 1,000 from the 1900 U.S. birth cohort survived to age 100; Bell et al. 1992) but common enough for obtaining samples of sufficient size. In this study, we analyzed early-life and adulthood effects that operate throughout life by comparing centenarians of each gender to the respective control groups.

Data quality control procedure in this study included (1) preliminary quality control of computerized family histories (data consistency checks), (2) verification of the centenarian's death date, (3) verification of the birth date (for centenarians and controls), and (4) verification of family information (parents, spouses, and siblings). These methods of age validation were based on the approaches proposed by the experts in this area (Jeune and Vaupel 1999; Poulain 2010) and our own research experience. All records (for centenarians and controls) were subjected to verification and quality control using several independent data sources. Our primary concern was the possibility of incorrect dates reported in family histories. Previous studies demonstrated that age misreporting and age exaggeration in particular are more common among long-lived individuals (Elo et al. 1996; Shrestha and Rosenwaike 1996; Hill et al. 2000; Rosenwaike and Stone 2003). Therefore, the primary focus in this study was on the age verification for long-lived individuals, which involved death-date verification using the U.S. Social Security Administration Death Master File (DMF) and birth-date verification using early U.S. censuses.

According to our experience, the linkage to DMF selects out the majority of incorrect records for alleged centenarians (Gavrilova and Gavrilov 2007). A definite match was established when information on first and last names (spouse's last name for women); day, month, and year of birth matches in DMF; and family history (Sesso et al. 2000) was verified. In the case of disagreement in day, month, or year of birth, the validity of the match is verified on the basis of additional agreement between place of the last residence and place of death.

The procedure of death-date verification using DMF is not feasible for validating death dates of controls because data completeness of DMF is not very high for deaths before the 1970s. We found that approximately 30% of deaths in the control group could be confirmed through the U.S. state death indexes, cemetery records, and obituaries, which cover longer periods. Taking into account that exact ages of death for controls are not particularly important for the study design, it is possible to rely on death-date information recorded in family histories for controls not found in external sources, as was done in the Utah Population Database for individuals who died before 1932 (Kerber et al. 2001).

Verification of birth dates was accomplished through a linkage to the 1900 U.S. census data recorded when the person was a child (when age exaggeration is less common compared to claims of exceptional longevity made at old age). The preference is given to the 1900 census because it is more complete and detailed in regard to birth-date verification (it contains information on month and year of birth) compared to the 1910 and 1920 censuses. If a person cannot be found in the 1900 census, then he or she was searched in the 1910 census. We obtained a good linkage success rate (92–95%) in our study because of the availability of

TABLE 1
Information Available in Early U.S. Censuses for the Search of Longevity Predictors

	Early U.S. census						
Variables	1860	1870	1880	1900	1910	1920	1930
Age, sex, color/race	+	+	+	+	+	+	+
Month and year of birth				+			
Marital status			+	+	+	+	+
Marriage duration (for married)				+	+		+
Literacy	+	+	+	+	+	+	+
School attendance (for children)	+	+	+	+	+	+	+
Place of birth	+	+	+	+	+	+	+
Places of birth for parents			+	+	+	+	+
Parental nativity		+	+	+	+	+	+
Mother tongue						+	+
Home ownership				+	+	+	+
Farm status				+	+		+
Value of real and personal estate	+	+					+
Number of children born and surviving (for women)				+	+		
Whether speech or hearing impaired					+		
Radio in household							+
Occupation	+	+	+	+	+	+	+
Employment			+	+	+	+	+
Citizenship		+		+	+	+	+
Year of immigration				+	+	+	+
Veteran status					+		+

powerful online indexes provided by the Ancestry.com service and supplemental information in family histories (Gavrilova and Gavrilov 2007). These indexes allowed us to conduct searches on the following variables: first and last names (including Soundex), state, county, township, birthplace, birth year (estimated from census), immigration year, and relation to head-of-household. Data on birth dates, birth places, and names of siblings produced unambiguous matches in an overwhelming majority of cases.

Ancestry.com has a powerful search engine, which helps researchers find a person in multiple historical sources simultaneously (including all historical U.S. censuses up to 1940) based on all information available in computerized genealogies. Use of this service greatly facilitates the linkage procedure and helps to obtain unambiguous links in practically all studied cases. After the linkage to early censuses, the final database on centenarians and controls combined information on family characteristics (taken from family histories), data on the early-life conditions taken from the 1900–1910 U.S. censuses, and adult socioeconomic status taken from the 1930 census. Early U.S. censuses contain a rich set of variables, which can be used to study the effects of both childhood and adulthood living conditions on human longevity (see Table 1).

Below we summarize the core topical domains of the variables analyzed in this study.

Childhood living conditions at household level: This information was obtained from the 1900 and 1910 censuses. Selection of variables was guided by the results obtained in previous studies on child mortality at the turn of the 20th century (Preston and Haines 1991). These studies demonstrated that child mortality is negatively affected by household structure (presence of a boarder in household) and positively affected by maternal and paternal literacy, paternal farmer occupation, and family structure (when the proband lived with both parents) (Preston and Haines 1991). An important factor of survival to advanced age is childhood farm residence—a result found in our earlier study (Gavrilova and Gavrilov 2007) as well as in other studies (Preston et al. 1998; Hill et al. 2000).

Infectious burden: The main hypothesis we studied here is that early exposure to infections decreases chances of survival to advanced ages, affecting mortality later in life. Infectious burden is estimated as the within-family infectious burden. Information on all children born and children surviving allowed us to estimate proportion of surviving children for each family where the biological mother is present. Child mortality served as a proxy of infectious disease burden in the family, characterizing the living environment, as suggested by other researchers (Preston and Haines 1991; Bengtsson and Lindstrom 2000, 2003; Finch and Crimmins 2004). We based our estimates of child mortality on information available in the 1910 census whenever possible because by this time the majority of studied mothers had finished their reproductive period.

Seasonal early-life conditions: Effects of seasonal conditions on survival to extreme ages are studied using month of birth as an integral proxy for environmental seasonal conditions (e.g., seasonal infections) before and shortly after the birth. Existing literature on U.S. mortality and our own results based on the within-family approach show that month of birth may be a significant predictor of mortality not only during childhood but also in later life (Gavrilov and Gavrilova 1999, 2011; Doblhammer and Vaupel 2001; Doblhammer 2004; Costa and Lahey 2005).

Adulthood social conditions: Socioeconomic achievement at adult ages for men was estimated using occupation status and dwelling ownership status (measured as in the 1900 census). In particular, we tested a hypothesis that farm background is particularly favorable for male survival because sons of farmers also become farmers (Preston et al. 1998). In this case, the farm status in both 1900 and 1930 should bring a significant advantage for survival to 100. In the case of females, estimation of socioeconomic achievements through their occupation is not feasible because in 1930 the proportion of women in the labor force was relatively small in the United States. A reasonable proxy variable describing social status of nonworking adult women is an occupation of husband (for married women) or occupation of the head of household for single, widowed, or divorced women. Urban/rural residence in 1930 is another variable used in the study. Preston and Haines (1991) found that child mortality in 1900 was significantly higher in urban areas than in rural areas. Urban adults in the contemporary United States also have higher mortality despite better infrastructure and access to health services (Hayward et al. 1997).

Familial longevity and other family characteristics: Family histories allow us to obtain information on life span of biological and nonbiological relatives. For this particular study, the most important variables are life spans of mother and father. As yet, no studies have simultaneously examined the net effects of parental longevity and early-life conditions. Studies suggest that effects of parental longevity on longevity of the offspring may be substantial (Pearl and Pearl 1934; Kerber et al. 2001; Gavrilov et al. 2002) and heritability of life span estimates increase dramatically when parents live longer than 80 years (Gavrilova et al. 1998). Therefore, we believe that parental longevity (measured as paternal and maternal life span 80 years and over) may have significant moderating influence on the effects of childhood conditions and can be used as a proxy for genetic influences on life span. Other family variables of interest are paternal and maternal ages at person's birth, sibship size, and birth order.

In this ongoing study, we have identified 838 centenarians born in 1890–1891 in the United States and 910 controls born in the United States in 1890–1891 who died at age 65. Further linkage to the 1900 census resulted in a 98.2% success rate for centenarians and 98.6% success rate for controls. For the 1930 census, 94.9% of centenarian records and 96.4% of control records were successfully linked. Linkage to the 1900 census revealed that 95.6% of centenarians and 96.0% of controls lived with one or both biological parents. According to the 1900 census, 67% of fathers of studied individuals were farmers. Centenarians and controls had approximately equal sibship sizes (7.6 and 7.8, respectively), which are higher compared to the general population in the 1900 census (5.6), suggesting larger sizes of families presented in computerized genealogies. In further analyses, we restricted our sample with records where information was available for both the 1900 and 1930 census. To study effects of marriage history on survival to age 100, only records for individuals married in 1930 were taken into account. Finally, data for 765 centenarians and 783 shorter-lived controls were used in our analyses.

Multivariate logistic regression model was used to study survival to age 100. Our main focus was on the following three types of variables:

1. Early-life conditions drawn from the 1900 census (type of parental household: farm or nonfarm, owned or rented, parental literacy, parental immigration status, paternal occupation, number of children born/survived by mother, size of parental household in 1900, places of birth for household members)
2. Midlife conditions drawn from the 1930 census (type of person's household, availability of radio in household, person's age at first marriage, person's occupation or husband's occupation in the case of women, industry of occupation, number of children in household, veteran status) and
3. Family characteristics drawn from computerized genealogies (paternal and maternal life span, paternal and maternal age at person's birth, number of siblings).

In the first step, we studied familial, childhood, and adulthood variables separately using univariate analyses. Study of familial characteristics taken from genealogies revealed that paternal and maternal longevity was significantly associated with survival to age 100 for both men and women. Being born in the second half of the year was significantly associated with male longevity. However, loss of parents early in life (before 1910) had no effect on the chances of becoming a centenarian. Childhood conditions recorded in the 1900 census included paternal and maternal literacy and immigration status, paternal occupation, status of dwelling (owned or rented farm, owned or rented house), household size, grandparent or boarder in household, proportion of surviving children reported by mother, and region of birth. Larger household size and having a farmer father were found to be significant predictors of male (but not female) longevity in univariate analyses. Birth in the Northeast region is also predictive for survival to

TABLE 2
Predictors of Male Survival to Age 100: Effects of Parental Longevity, Early-Life and Midlife Conditions, Results of Multivariate Logistic Regression

Variable	Odds ratio	95% CI	*p* value
Father lived to 80+	1.84	1.35–2.51	< 0.001
Mother lived to 80+	1.70	1.25–2.32	0.001
Farmer in 1930	1.67	1.21–2.31	0.002
Born in the Northeast region	2.08	1.27–3.40	0.004
Born in the second half of year	1.36	1.00–1.84	0.050
Radio in household, 1930	0.87	0.63–1.19	0.374

Note: $N = 723$. Farm childhood in 1900 was found to be nonsignificant predictor for males. Calculated using the Stata 11 statistical package (procedure logistic).

advanced ages in men. This result agrees with findings by (Hill et al. 2000) for people who survived to age 85, but does not agree with the results of our earlier study, which compared centenarians drawn from computerized family histories with population-based controls (Gavrilova and Gavrilov 2007). This contradictory finding may indicate that the earlier use of population-based control could produce biased results if the studied sample of genealogical records does not represent the general population. Female longevity revealed no significant associations with any of the 1900 census variables. Adulthood conditions in the 1930 census included dwelling status, occupation of self (husband or head of household for females), radio in household, veteran status of self (or husband), marital status, age at first marriage, and availability of children (composite variable based on information taken from the 1930 census and genealogies). Univariate analyses showed that farmer occupation in 1930 was a very strong predictor of longevity for men. In the case of women, having a husband-farmer had no effect on the chances of survival to age 100. For women, availability of a radio in the household was the strongest predictor of longevity among the studied midlife variables.

In multivariate analyses, when familial, early-life, and midlife characteristics are combined, having a farmer father is no longer associated with longevity of men. Parental longevity turned out to be one of the strongest predictors of survival to age 100. Table 2 presents the results of multivariate analyses for men. Note that occupation as a farmer in 1930 is one of the strongest predictors of survival to age 100, which agrees with results of other studies, including our own study of centenarians based on a population-based sample of survivors to age 100 from the 1887 birth cohort (Gavrilov and Gavrilova 2012).

Table 3 presents results of multivariate analyses for women. For women, having a farmer husband has no effect on survival to age 100. Interestingly, having a radio in the household in 1930 has a positive effect on longevity for women but not for men (Table 3). This finding can be explained by the fact that women in 1930 spent most of their time at home and were much more exposed to radio (as an educational and entertainment source) compared to men. Listening to radio improves people's feelings of happiness and energy, and an electro-encephalographic (EEG) study found that listening to radio creates high levels of positive engagement in the brain, according to the findings of the "Media and the Mood of the Nation" research project conducted by Sparkler Research in spring 2011 (Redican and Barber 2012).

Finally, we tested our previous results that season of birth may be predictive for survival to long life and compared season-of-birth among centenarians and shorter-lived controls in this database. Figure 1 shows proportion of people born in the first and

TABLE 3
Predictors of Female Survival to Age 100: Effects of Parental Longevity, Early-Life and Midlife Conditions, Results of Multivariate Logistic Regression

Variable	Odds ratio	95% CI	*p* value
Father lived to 80+	2.19	1.61–2.98	< 0.001
Mother lived to 80+	2.23	1.66–2.99	< 0.001
Husband (or head of household) farmer in 1930	1.15	0.84–1.56	0.383
Radio in household, 1930	1.61	1.18–2.20	0.003
Born in the second half of year	1.18	0.89–1.58	0.256
Born in the Northeast region	1.04	0.65–1.67	0.857

Note: $N = 815$. Calculated using the Stata 11 statistical package (procedure logistic).

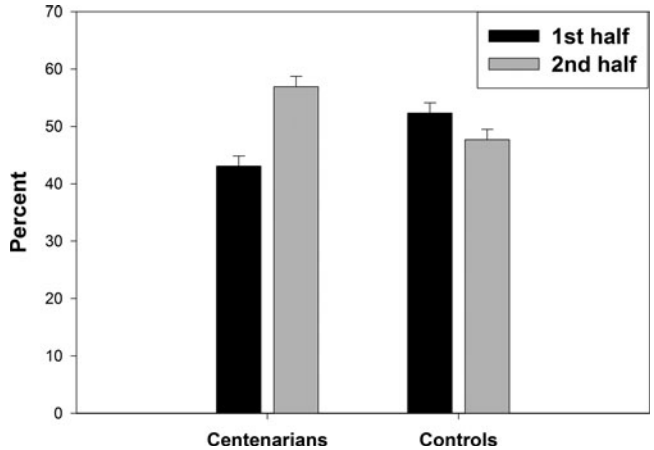

FIGURE 1. Season of Birth and Survival to 100: Proportion (Percent) of People Born in the First Half and the Second Half of the Calendar Year among Centenarians and Controls (Who Died at Age 65). Error Bars Correspond to Standard Errors.

the second halves of the calendar year for centenarians and controls. Note that more centenarians than controls were born in the second half of the year, and this difference is statistically significant ($p = 0.008$, chi-square test). This result confirms our findings obtained using the within-family analysis (Gavrilov and Gavrilova 2011), which showed that centenarians were born more often in September to November.

These findings are also consistent with our previous results as well as results of other studies, which found positive effects of farming and farm background on late-life survival (Gavrilova and Gavrilov 2007; Preston et al. 1998). Farm childhood background turned out to be particularly favorable for men who usually continue to work on a farm.

This study demonstrated that both midlife and early-life conditions affect survival to age 100 with some gender specificity. At the same time, we found no effects of higher child mortality in the household (a proxy of infectious burden) on longevity as suggested by the inflammatory hypothesis of aging (Finch and Crimmins 2004). Parental longevity is one of the most important predictors of survival to age 100 for both men and women.

3. COMPARATIVE STUDY OF BIOLOGICAL AND NONBIOLOGICAL RELATIVES

Numerous studies found that biological relatives of long-lived individuals have a substantial survival advantage compared to relatives of shorter-lived individuals (Pearl and Pearl 1934; Gavrilov and Gavrilova 2001b, 2014; Kerber et al. 2001; Gavrilov et al. 2002; Willcox et al. 2006; Perls et al. 2007; Smith et al. 2009a), while relatively few studies analyze life span of nonbiological relatives (Schoenmaker et al. 2006; Mazan and Gagnon 2007; Westendorp et al. 2009; Montesanto et al. 2011). At the same time, nonbiological relatives may serve as a nonbiased environmental control group in contrast to the general population control. Information about biological relatives may be useful in another type of design called "within-family-analysis" where siblings of centenarians serve as a control group (Gavrilov and Gavrilova 2011, 2012). Family histories (genealogies) proved to be a good source of information for different types of relatives and were successfully used in historical demography (Adams and Kasakoff 1984; Anderton et al. 1987; Bean et al. 1992) and biodemography (Gavrilova et al. 1998; Gavrilov et al. 2002; Caselli et al. 2006; Smith et al. 2009a, 2009b).

Studies of biological and nonbiological relatives usually deal with relatively small numbers of relatives. In our study, we intended to create a large sample of centenarians and their relatives, so we conducted a large-scale search in many hundreds of online family histories using a technique known as web automation (Sklar and Trachtenberg 2002). This technique allowed us to search online databases on a large-scale basis for people with exceptional longevity (and some other traits). In particular, a technique has been developed to scan more than 300,000 online databases in the Rootsweb WorldConnect project (http://wc.rootsweb.ancestry.com), a publicly available data source. Application of web-automation techniques to this online source identified more than 40,000 records of alleged centenarians born between 1880 and 1895 with known information about their parents.

After collecting data on centenarians, the next step was to collect detailed data on their parents from computerized genealogies using the same web-automation technique. After this procedure, we selected the most detailed genealogies where information on birth and death dates for both parents was available. Our prior experience working with computerized genealogies suggests that this procedure selects out the majority of genealogies with poor quality. As a result of this procedure, the total number of centenarian records slightly decreased from 25,451 to 23,127 (see Table 4). In the next step, we collected data on siblings for those centenarians who had detailed data on parental birth and death dates. Using this procedure, we collected 172,091 records

TABLE 4
Number of Centenarians and Their Siblings at Different Stages of Data Collection and Cleaning

	Number of centenarians			
Type of records	Males	Females	Total	Number of siblings
All initial nonduplicate records for centenarians born in 1880–1895 with names of parents available	7,174	18,277	25,451	
Centenarians having detailed information on birth and death dates of their parents	6,370	16,757	23,127	172,091
Centenarians having detailed information on birth and death dates of their parents and siblings	707	2,127	2,834	21,893
Centenarians after data cleaning with confirmed death dates through the linkage to U.S. Social Security Death Master File	398	1,313	1,711	13,419

for siblings of centenarians. However, a significant proportion of these records did not contain information about the death dates of siblings, which created some difficulties for the within-family study of human longevity. So the next step was to identify the most detailed data on families with complete information on birth and death dates for siblings. As a result of this identification procedure, we found 2,834 families for whom information on birth and death dates was known for more than 80% of siblings. Finally, the age at death of centenarians in our sample was verified using the U.S Social Security Administration Death Master File. This file contains information about birth and death dates as well as first and last names and residence for people who died in the United States. This procedure confirmed the age for 1,711 centenarians in our sample. Our previous study found that the ages of centenarians confirmed through the linkage to DMF are then usually confirmed through the linkage to early U.S. censuses (Gavrilova and Gavrilov 2007), so there is no strong need to make an additional verification with the early census records. Table 4 shows the number of records obtained in each stage of data collection.

Finally, 1,711 validated centenarians born in 1880–1895 with their death dates verified with the Social Security Death Index are used for further analyses. The database of centenarians and their relatives contains information on life span for 398 male and 1,313 female centenarians, and their 13,419 siblings, 1,307 spouses, and 7,924 siblings-in-law. This database is used for comparative analysis of longevity in different types of biological and nonbiological relatives.

Each centenarian has 7.8 siblings on average. The total sibship size (nine siblings on average) in the studied centenarian families is higher than the average number of children in American families reported by the 1900 U.S. census: 5.12 ± 0.01; data are obtained from the 5% sample of the U.S. 1900 census from the IPUMS (Ruggles et al. 2010). Larger sibship size in the centenarian families compared to the general population can be explained by the fact that genealogies are more likely to be compiled for larger families and that longer-lived individuals in the United States were born more often in rural areas with higher fertility (Preston et al. 1998; Gavrilova and Gavrilov 2007). This difference in sibship size compared to the general population is not critical when an appropriate control group (biological and nonbiological relatives of centenarians) is selected.

Spouses of male centenarians are 5.07 years younger, and spouses of female centenarians are 3.37 years older, on average than their long-lived mates. This asymmetry in spousal age gap between male and female centenarians is statistically significant: The 95% confidence interval for mean spousal age gap is 4.40–5.74 years in male centenarian couples and only 3.01–3.73 years in female centenarian couples. Such asymmetry in spousal age gap could happen if, during their marriage ages, the future centenarians were perceived at the marriage market as younger than they really were, thus obtaining a younger mate than typically expected.

Comparison of mean life span for relatives survived to age 50 reveals a survival advantage of brothers and sisters of centenarians compared to the same-sex siblings-in-law: Brothers lived 2.6 and sisters lived 2.9 years longer on average compared to siblings-in-law of corresponding sex (Table 5) with differences in life span being statistically significant ($p < 0.001$).

Wives of centenarians tend to live 0.8 year less on average than married sisters of centenarians, although this difference is not statistically significant. Husbands of centenarians live 2.3 years less on average than married brothers of centenarians (the difference is statistically significant, $p < 0.001$). Although fathers of centenarians are born about 30 years earlier than brothers-in-law of centenarians, they still have higher life spans conditional on survival to age 50 than later-born nonbiological relatives such as siblings-in-law ($p < 0.001$) and husbands of centenarians ($p = 0.04$). On the other hand, mothers of centenarians survived to age 50 have the shortest life span among all relatives—77.2 years on average. Overall, siblings-in-law have the lowest life span

TABLE 5
Mean Life Span Conditional on Survival to Age 50 (LS50) with 95% Confidence Intervals for Relatives of Centenarians (Compared to the 1900 U.S. Birth Cohort)

	Men		Women	
Relatives of centenarians	Sample size, *N*	LS50 (95% CI), years	Sample size, *N*	LS50 (95% CI), years
Parents	1,590	76.2 (75.7–76.8)	1,557	77.2 (76.7–77.8)
All siblings	5,324	77.6 (77.3–77.9)	4,877	82.4 (82.0–82.7)
Married siblings	3,221	77.7 (77.3–78.1)	3,028	82.2 (81.8–82.6)
Spouses	876	75.4 (74.6–76.1)	283	81.4 (80.1–82.7)
Siblings-in-law	2,349	75.0 (74.6–75.5)	2,407	79.5 (79.0–79.9)
1900 U.S. birth cohort		73.3		79.4

compared to biological relatives and spouses born in a similar period. At the same time, life span of siblings-in-law is still higher than mean life span of the general population (1900 U.S. birth cohort). This difference is particularly high for men, 1.7 years ($p < 0.001$), while for women this difference is not statistically significant (Table 5). This finding is particularly important because it indicates that use of general population as a control group to compare survival of siblings of centenarians or other biological relatives may overstate survival advantage of biological relatives and hence overstate the genetic effect on life span. Thus, the use of general population to compare survival of relatives of long-lived individuals may be inappropriate, particularly for males. Therefore, siblings-in-law is a better control group for comparison than the general population.

Although the positive association of a person's longevity with better survival of biological relatives is well documented, little is known about the effects of centenarian's gender on longevity of biological and nonbiological relatives. In this article, we use the effects of centenarian's gender to explore genetic and environmental effects on longevity. We found that fathers of male centenarians lived significantly longer than fathers of female centenarians: Mean life span conditional on survival to age 50 was 77.22 years versus 75.93 years ($p = 0.023$; see Table 6). This effect is gender specific and is observed for fathers of male centenarians but not for mothers of male centenarians (who have similar survival as mothers of female centenarians). Brothers of male centenarians also lived significantly longer compared to brothers of female centenarians: Mean life span conditional on survival to age 50 is 79.25 and 77.09 years, respectively ($p < 0.001$; Table 6). Again, this effect is gender specific: Sisters of female centenarians have no statistically significant survival advantage over sisters of male centenarians (82.45 vs. 82.06 years, $p = 0.836$; Table 6). This finding is also supported by comparison of siblings' sex ratio in families of male and female centenarians. The sex ratio for siblings surviving to age 50 is higher (more males) in families with a male centenarian (sex ratio = 1.22), when compared to the sex ratio in families with a female centenarian (sex ratio = 1.10).

TABLE 6
Mean Life Span Conditional on Survival to Age 50 (LS50) for Biological and Nonbiological Relatives of Centenarians, by Gender of Centenarian

	Male centenarians		Female centenarians		
Relatives of centenarians	Sample size, *N*	LS50, years	Sample size, *N*	LS50, years	*p* value[a]
Parents:					
Fathers	374	77.22	1,216	75.93	0.023
Mothers	362	77.96	1,195	77.03	0.087
Siblings:					
Brothers	1,268	79.25	4,056	77.09	<0.001
Sisters	1,071	82.06	3,806	82.45	0.836
Siblings-in-law:					
Brothers-in-law	492	74.00	1,857	74.55	0.577
Sisters-in-law	611	79.22	1,796	79.55	0.730

[a]*P* values are related to the difference between life spans of corresponding relatives of male versus female centenarians.

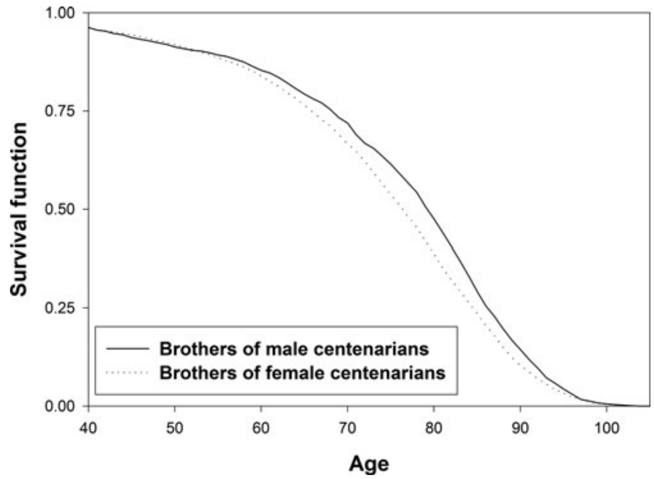

FIGURE 2. Survival of Male Siblings (Brothers) of Centenarians, by Centenarian Gender.

Figure 2 shows survival curves after age 40 for male siblings of centenarians depending on centenarian gender. Note that brothers of male centenarians have substantially better survival than brothers of female centenarians, and this difference in survival is highly statistically significant ($p < 0.001$) according to the generalized Wilcoxon test (Breslow 1970). This survival advantage is particularly strong after age 65, while, before age 50, the differences in survival are not observed. Thus, having a centenarian brother is associated with better late-life survival for males.

Taking into account that female gender of centenarian has a much weaker effect on survival of sisters compared to the effect of male gender of centenarian on the survival of brothers, we may hypothesize that male centenarians and their brothers share living conditions and lifestyle favorable for men. To test this hypothesis, we used data on mean life span for siblings-in-law of centenarians as a control group. Siblings-in-law do not share specific genes and family environment with centenarians, but they usually come from a similar socioeconomic background (because of assortative mating). Table 6 shows mean life span conditional on survival to age 50 years for siblings and siblings-in-law of centenarians depending on centenarian gender. If survival advantage of brothers of male centenarians is related to better socioeconomic status of their families compared to families of brothers of female centenarians, then it may be expected that wives of brothers of male centenarians (siblings-in-law) would also have better survival than siblings-in law of female centenarians. Note that centenarian gender has no effect on life expectancy of siblings-in-law (Table 6). This result suggests that survival advantage of brothers of centenarians is not related to better socioeconomic status of families of male centenarians and their brothers compared to brothers of female centenarians.

One hypothesis explaining the survival advantage of brothers of male centenarians may suggest stronger genetic influence on male longevity. This hypothesis of stronger heritability of longevity among males was recently suggested by Italian researchers who studied 202 nonagenarians born around 1910 and their relatives in the province of Calabria, Italy (Montesanto et al. 2011). The researchers found that brothers and sisters of male nonagenarians have better survival compared to siblings-in-law of male nonagenarians. On the other hand, only brothers of female nonagenarians have reduced mortality compared to same-sex siblings-in-law. The authors made a conclusion that genetic factors in males have a higher impact than in females on attaining longevity. In our study, we found that both brothers and sisters have higher longevity compared to siblings-in law regardless of centenarian gender. Only male biological relatives of male centenarians demonstrated survival advantage compared to biological relatives of female centenarians. These differences between the earlier study and our results may be explained by the relatively small sample in the Italian study (202 nonagenarians with only 76 males) and largely rural and underdeveloped Calabrian society with strong social differences. Although our results may point to genetic factors as an explanation of the observed effects of male centenarian gender, we need to consider alternative nongenetic explanations as well.

One possible nongenetic explanation of the observed phenomenon comes from the family traditions. In the past, men often continued to live in the place of their childhood while women more often left the parental household after marriage. Favorable living conditions and/or lifestyle of male centenarians could be more likely shared by their brothers (rather than sisters) as well as by their spouses. If this hypothesis is correct, then spouses of male centenarians (wives) should have higher life expectancy compared to wives of brothers of centenarians. Results presented in Table 7 confirm this hypothesis. Thus, we may suggest that living in a household with a male centenarian has a positive effect on survival of wives (presumably because of better environment and healthier lifestyle determined by the head of household in the past). To illustrate this point, consider, for example, that smoking and binge drinking in households in the past were driven more often by husbands' habits than wives'.

TABLE 7
Mean Life Span Conditional on Survival to Age 50 (LS50) for Spouses of Centenarians and Spouses of Siblings of Centenarians, by Gender

	Spouses of centenarians		Spouses of siblings of centenarians		
Relatives	Sample size, *N*	LS50, years	Sample size, *N*	LS50, years	*p* value[a]
Husbands	876	75.38	2,349	75.04	0.221
Wives	283	81.40	2,407	79.46	0.004

[a]*P* value is related to difference between mean life span of spouses of centenarians versus spouses of siblings of centenarians.

4. CONCLUDING REMARKS

This study demonstrated that both midlife and early-life conditions affect survival to age 100 with some gender specificity. It is also important to note that parental longevity turned out to be one of the strongest predictors of survival to age 100. Thus, we may conclude that information about such an important predictor as parental longevity cannot be ignored and should be collected in contemporary longitudinal studies. This study also suggests that a significant portion of life span advantage for siblings of centenarians may be related to better lifestyle and living conditions rather than pure genetic effects only (otherwise, wives of centenarians would not benefit much from husbands' longevity).

Some cases of exceptional longevity may represent particularly interesting outcomes of successful natural experiments on delaying human aging and preventing age-related diseases. Therefore, studies on centenarians could become a gold mine for unraveling the secrets of human longevity through careful epidemiological analysis of fortunate and unintended natural experiments on life extension and disease prevention. A comparison with the gold mine is appropriate here not only in terms of high expected gains for possible dramatic extension of healthy human life but also in terms of required effort: We had to scan more than 300,000 online family histories and then do tedious work on data validation and cleaning to obtain just a few hundred reliable records and some meaningful findings. Therefore we consider the results of this study the beginning of a subsequent large-scale research effort with the potential for breathtaking future findings.

ACKNOWLEDGMENTS

We are most grateful to discussant of our presentation and participants of 2014 Living to 100 Symposium for useful comments and suggestions and to anonymous reviewers of this article for constructive criticism.

FUNDING

This study was supported by U.S. National Institutes of Health (NIH) grant R01 AG028620.

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