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Early Life Biodemographic Influences on Exceptional Longevity: Parental Age at Person's Birth and the Month of Birth are Important Predictors

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Abstract

This study explores effects of parental age at person's birth and the month of birth on chances of survival to age 100. We have developed and analyzed a new computerized database on 1,711 validated centenarians from the United States, as well as their shorter-lived siblings (5,778) as controls. Comparison of siblings' characteristics was made within families (rather than between families) using method of conditional logistic regression. We found significant effects of young maternal age at person's birth on survival to age 100 with particularly strong positive influence at maternal age 20-24 years. Effect of young mother is particularly prominent in smaller families, which is important taking into account a smaller family size in contemporary population. Persons born in September-November had higher chances to become a centenarian, compared to their siblings born in other months. The study was supported by NIA (grant AG028620).

Introduction

Studies of centenarians (persons living to age 100 and over) could be useful in identifying factors leading to long life and avoidance of fatal diseases. Even if some middle-life factors have a moderate protective effect on risk of death, persons with this trait/condition would be accumulated among long-lived individuals. 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 *et al.* 2000; Perls 2001; Puca *et al.* 2001; Perls *et al.* 2002; Perls & Terry 2003; Christensen *et al.* 2006; Pawlikowska *et al.* 2009; Testa *et al.* 2009) or psychological (Adkins *et al.* 1996; Hagberg *et al.* 2001; Jang *et al.* 2004; Martin *et al.* 2008) 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 & Gavrilova 2004b; Gavrilov & Gavrilova 2004a; Gavrilov & Gavrilova 2006); the theory of technophysio evolution (Fogel & Costa 1997; Fogel 2004), the idea of fetal origin of adult diseases (Kuh & Ben-Shlomo 1997; Barker 1998) and the related idea of early-life programming of aging and longevity. These ideas are supported by studies suggesting significant effects of early-life conditions on late-life mortality (Elo & Preston 1992; Fogel & Costa 1997; Kuh & Ben-Shlomo 1997; Barker 1998; Preston *et al.* 1998; Gavrilov & Gavrilova 2003; Hayward & Gorman 2004; Costa & Lahey 2005). The existence of correlations between early growth patterns and subsequent fitness is now well established not only for human beings but for some other mammalian species as well (Lummaa & Clutton-Brock 2002).

In this study we analyze effects of early-life characteristics (parental age at birth and month of birth) on survival to age 100 years using a large set of centenarians and their shorter-lived siblings.

Data and Methods

<u>Data</u>

This study compares centenarians to their shorter-lived siblings who share the same childhood conditions and genetic background using a large set of computerized family histories.

1.1. Collecting Data on Centenarians

Family histories (genealogies) proved to be a useful source of information for studies in historical demography (Adams & Kasakoff 1984; Anderton *et al.* 1984; Anderton *et al.* 1987; Adams & Kasakoff 1991; Bean *et al.* 1992; Kasakoff & Adams 2000) and biodemography (Gavrilov & Gavrilova 2001; Kerber *et al.* 2001b; Gavrilov *et al.* 2002). I this study, we conducted a large scale search in many hundreds of online family histories using an innovative technique known as web-automation (Sklar & Trachtenberg 2002). This technique allowed us to search online databases on a large-scale basis for persons with exceptional longevity (or other traits). In particular, a technique was developed to scan over 300,000 online databases in Rootsweb WorldConnect (*http://worldconnect.rootsweb.com*) publicly available data source. Application of web automation techniques to this online source identified over 40,000 records of centenarians born in 1880-1895 with known information about parents (see Table 1).

1.2. Collecting Data on Centenarian Relatives

After collecting data on centenarians, the next step was to collect detailed data on their parents from computerized genealogies using the web automation technique. After this procedure we selected the most detailed genealogies where information on birth and death dates of both parents was available. As a result of this procedure the total number of centenarian records slightly decreased from 24,451 to 23,127.

In the next step of data collection, we collected data by web automation technique on centenarian siblings (brothers and sisters) for those centenarians who had detailed data on parental birth and death dates. As a result of this procedure, we collected 172,091 records for centenarian siblings. However, significant proportion of these records did not contain information about death dates of siblings, which created some difficulties for within-family study of human longevity. So, the next step was to indentify 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 1,711 families where information on birth and death dates was known for more than 80 percent of siblings. Table 1 shows the number of records obtained in each stage of data collection.

Table 1. Number of centenarians at different stages of data collection and cleaning

Type of records	Centenarians			Number of Siblings
	Males	Females	Total	
All initial records for centenarians born in 1880-1895	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 siblings	707	2,127	2,834	21,893
Centenarians after data cleaning with confirmed death dates	398	1,313	1,711	13,654
Centenarians used in data analyses (including additional centenarian siblings)	450	1,495	1,945	13,392

Because of data overlapping some centenarians were found in more than one genealogy, so we removed duplicate records leaving the most informative ones in the database. Also note that the proportion of males (23.0%) found in genealogies (see Table 1) is close to the official estimates (20-25%) of male/female ratio of centenarians in the United States based on the census data (Krach & Velkoff 1999), which somewhat mollifies concerns about quality of genealogies and male overrepresentation in them.

1.3 Validation of Centenarians' Age

Data quality control is an important part of all centenarian studies and in our case it 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 dates for centenarians and their siblings for a sample of centenarian families. All records (for centenarians and controls) were subjected to verification and quality control using several independent data sources. The study's primary concern was about 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; Rosenwaike & Hill 1996; Shrestha & Rosenwaike 1996; Rosenwaike *et al.* 1998; Hill *et al.* 2000; Rosenwaike & Stone 2003). Therefore, the primary focus in our study was on the age verification for long-lived individuals. We followed the approach of age verification and data linkage developed by a team of demographers at the University of Pennsylvania (Elo *et al.* 1996; Preston *et al.* 1996; Rosenwaike & Hill 1996; Rosenwaike *et al.* 1998; Hill *et al.* 2000; Rosenwaike & Stone 2003). This approach involves death date verification using Social Security Administration Death Master File and birth date verification using early U.S. censuses. In order to validate the age of the centenarians, these records were linked to the Social Security Administration

Death Master File records for death date validation. More details about this procedure were published elsewhere (Gavrilova & Gavrilov 2007).

Data consistency checks used information about paternal, maternal and centenarian/sibling birth dates. This procedure helped us to remove about 100 records with incorrect information about parents or their children. Also it was checked whether parents died before the person's birth, which helped us to remove several more erroneous records.

Table 2. Distribution of centenarians by age at death

Age at death	Centenarians born in 1880-1895	Centenarians born in 1880-1889 used in the analyses		
	Both sexes	Males	Females	Total
99	339	58	145	203
100	536	82	287	287
101	365	59	200	200
102	273	33	137	137
103	186	24	110	110
104	89	12	50	50
105	77	11	48	48
106	47	8	26	26
107	18	2	11	11
108	5	0	3	3
109	5	2	4	4
110	3	0	1	1
111		0	0	0
112	2	0	1	1
Total:	1,945	291	790	1,081

Verification of death dates was accomplished through a linkage of family history data to the Social Security Administration Death Master File (DMF). This is a publicly available data source (available at the Rootsweb.com) that allows a search for individuals using various criteria: birth date, death date, first and last names, Social Security number and place of last residence. This resource covers deaths that occurred in the period 1937-2010 (Faig 2001) and captures about 95% of deaths recorded by the National Death Index (Sesso *et al.* 2000). Many researchers suggest that the quality of SSA/Medicare data for older persons is superior to vital statistics records because of strict evidentiary requirements in application for Medicare, whereas age reporting in death certificates is made by proxy informant (Kestenbaum 1992; Faig 2001; Kestenbaum & Ferguson 2001; Rosenwaike & Stone 2003). Definite match was established when information on first and last names (spouse last name for women), day, month and year of birth matched in DMF and family history (Sesso *et al.* 2000). In the case of disagreement in day, month or year of birth, the validity of match was verified on the basis of additional agreement between place of the last residence and place of death. DMF covers about 90 percent of all deaths for which death certificates are issued (see Faig, 2001) and about 92-96 percent of deaths for persons older than 65 years (Hill, Rosenwaike, 2001).

In this study we left only those records of centenarians that were found in DMF with the same birth and death years with a few cases when death year was different (however, in these cases the individual still had a centenarian status). Our previous work with centenarian data cleaning revealed that incorrect death dates was the main source of errors in this data. At the same time, birth dates were correctly reported in almost 100% of all cases with correct death dates. For this reason, in this study we made sample check of birth dates for approximately 15% of cases and in all cases birth years of centenarians agreed with information reported in 1880, 1900 or 1910 censuses (as well as information about siblings). In addition to that, verification of centenarian birth dates was accomplished through the DMF.

As a result of data quality checks, we found 1,711 records of centenarians born in 1880-1895 with verified birth and death dates. Given the fact that longevity is often clustered in families we found other centenarians in our families so that the total number of centenarians become equal to 1,945. Distribution of centenarians by their lifespan is presented in Table 2. Note that some centenarians did not live exactly 100 years. This is because we used broader definition of centenarians assuming that these are individuals whose birth and death years differ by 100. This definition does not take into account months and days of birth and death.

1.4 Data Collection and Validation for Siblings of Centenarians

Further study was done for the records of 1711 previously validated centenarians born in 1880-1895 with confirmed birth and death dates. All birth dates of centenarian siblings were reconstructed using information available in computerized genealogies and early censuses. The procedure of death date verification using DMF is not feasible for validating death dates of shorter-lived siblings (used as controls), because data completeness of DMF is not very high for deaths occurred before the 1970s. State death indexes, cemetery records and obituaries cover longer periods of time. Taking into account that exact ages of death for controls (siblings) are not particularly important for comparison we relied on death date information recorded in family histories for siblings not found in external sources. This approach was used in the Utah Population Database study for individuals died before 1932 (Kerber *et al.* 2001a). Death dates were reconstructed for 99.99% of siblings using the Social Security Death Master File, state death indexes and online genealogies (only 124 out of 13,392 cases were left unresolved). As a result, each case (centenarian) had 7 control siblings on average. Overall, this procedure allowed us to reconstruct information for 13,654 siblings of centenarians.

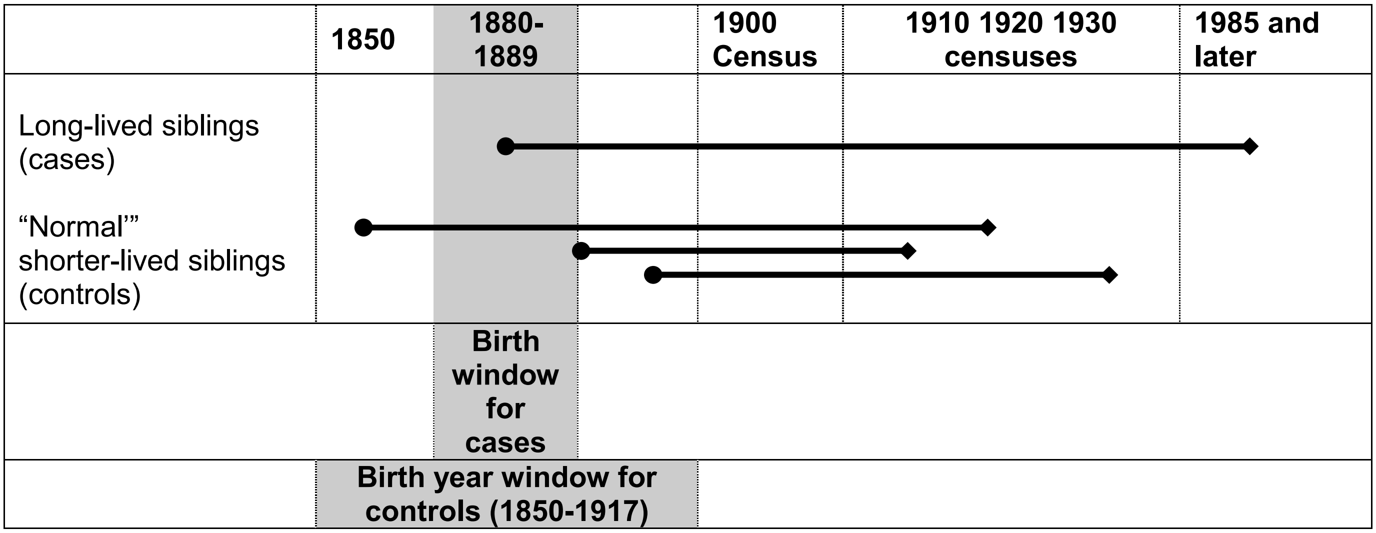
Research Design and Statistical Methods

This study explored the effects of early-life factors (birth order, paternal age, maternal age, month of birth) on the likelihood of survival to advanced ages. Centenarians (cases) were compared to their “normal” shorter-lived siblings (controls) using a within-family approach. During the process of data inspection, we found that some siblings were born after 1910 and their death dates were not indicated (hence they potentially could become centenarians). In order to decrease this kind of data truncation, we used data for our index centenarians who were born in 1880-1889 rather than 1880-1895. For this subgroup of centenarians, no siblings born after 1910 with unknown death dates were found.

The study applied a case-sibling design (see Figure 1), a variant of a matched case-control design in which siblings of cases (long-lived individuals) are used as controls (Woodward 2005). This approach allows investigators to study within-family differences, not being confounded by between-family variation. Long-lived persons born mostly in 1880-1889 were used as cases. Siblings were born in 1850-1910 time window.

Taking into account relatively high child mortality in the 19th century, in our analyses we used data only for siblings who survived to adult ages (age 50 and over) and did not analyze child and young adult mortality.

The main approach used in this study is based on comparison of children within rather than across families. Within a family, children are born to parents at different ages and this variation may be used to estimate the net effect of parental age more conclusively (Kalmijn & Kraaykamp 2005). Similarly we can estimate the net effects of months of birth.



Circles indicate birth, diamonds indicate death.

Figure 1. Description of Case-Sibling Design in this study

The statistical analyses of within-family effects were performed using a conditional multiple logistic regression model (fixed-effect model) to investigate the relationship between an outcome of being a case (long-lived person) and a set of prognostic factors (Breslow & Day 1993; Hosmer & Lemeshow 2001). Only within-family variation is taken to influence the uncertainty of results (as reflected in the confidence interval) of a within-family study using a fixed effect model. Variation between the estimates of effect from each family (heterogeneity) does not affect the confidence interval in a fixed effect model. The fixed-effects logit model can be written as (StataCorp 2005):

$Pr(y_{it} = 1|x_{it}) = F(\alpha_i + \mathbf{x_{it}}\beta)$ where $F(z) = \exp(z)/(1 + \exp(z))$ is a cumulative logistic function.

and $i = 1,2, \ldots n$ denotes the families (independent units) and $t=1,2,\ldots T_i$ denotes the children for the ith family; x_{it} denotes vector of within-family covariates including maternal age, birth order and month of birth. The likelihood to survive to advanced ages (to be in the long-lived group) is used as a dependent variable. Computations were performed using Stata (release 11) procedure *clogit*. The following variables were included in the model: birth order, paternal age, maternal age, sex (male or female) and month of birth.

Results

<u>Month of birth</u>

First we studied effects of person's month of birth on survival to age 100 after the age of 50 years. We found that being born in spring months was associated with decreased chances of survival to age 100 while birth in autumn months increases chances to become a centenarian. Table 3 shows the odds ratios for becoming a centenarian by month of birth. It should be noted that this approach enables us to estimate net effects of months of birth independent of any between families variation.

Table 3. Odds ratios (with p-values) to become a centenarian as predicted by conditional logistic regression (fixed effects) for different subgroups. Effects of month of birth.

Variable	Siblings survived to age 50	Siblings survived to age 70	Siblings survived to age 50, small and medium family size (<9)	Siblings survived to age 50, large family size (9+)
Month of birth:				
January	1.05 (0.817)	1.08 (0.715)	0.97 (0.912)	1.13 (0.652)
February	1.28 (0.187)	1.21 (0.325)	1.12 (0.696)	1.43 (0.161)
March	Reference	Reference	Reference	Reference
April	1.18 (0.393)	1.18 (0.406)	0.94 (0.852)	1.41 (0.196)
May	1.38 (0.107)	1.36 (0.127)	1.04 (0.899)	1.67 (0.049)
June	1.15 (0.480)	1.14 (0.537)	1.37 (0.259)	0.91 (0.739)
July	1.26 (0.238)	1.27 (0.235)	1.33 (0.335)	1.26 (0.399)
August	1.38 (0.089)	1.34 (0.133)	1.26 (0.397)	1.49 (0.127)
September	1.51 (0.026)	1.48 (0.040)	1.12 (0.698)	1.85 (0.012)
October	1.80 (0.001)	1.70 (0.004)	1.39 (0.230)	2.17 (0.001)
November	2.03 (<0.001)	2.00 (<0.001)	2.23 (0.003)	1.93 (0.009)
December	1.60 (0.009)	1.57 (0.015)	1.53 (0.108)	1.68 (0.035)
Female sex	3.23 (<0.001)	2.90 (<0.001)	3.26 (<0.001)	3.21 (<0.001)
Pseudo R^2	0.0759	0.0661	0.0868	0.0742
Number of observations	5698	4747	2107	3591

Taking into account that month of birth have significant effect on survival to age 100, we included month-of-birth variable in our further analyses.

Parental age at birth

First of all, we were interested in the effects of such variables as parental ages at birth and birth order. We found no statistically significant effects of birth order on the chances to survive to advanced ages on this data sample.

Then, we explored the role of the father's age as a potential predictor for survival to age 100. When the first child is born, the father is younger and can provide resources for this child for a longer period of time than for his later-born children. We found that indeed siblings born to fathers younger than age 40 had higher chances to survive to 100 than siblings born to older fathers (aged 50 and over). However, control for maternal age decreased this dependence and made it statistically insignificant. Thus, it is possible that the effects of young father's age may be related to effects of young mother in predicting the chances of exceptional longevity. Comparing male centenarians with their shorter-lived brothers increased effects of young father on longevity although this effect remained statistically not significant due to reduction in the sample size. For daughters, effects of paternal age are non-significant and do not depend on paternal age (data not shown).

Another question studied was related to the family size. Families in our dataset were rather large with median size of nine children and with some families having up to 18 children. So we divided families of centenarians into ones with less than nine children ever born and families with nine children and more. It should be noted that in many large families some siblings died in infancy or early childhood.

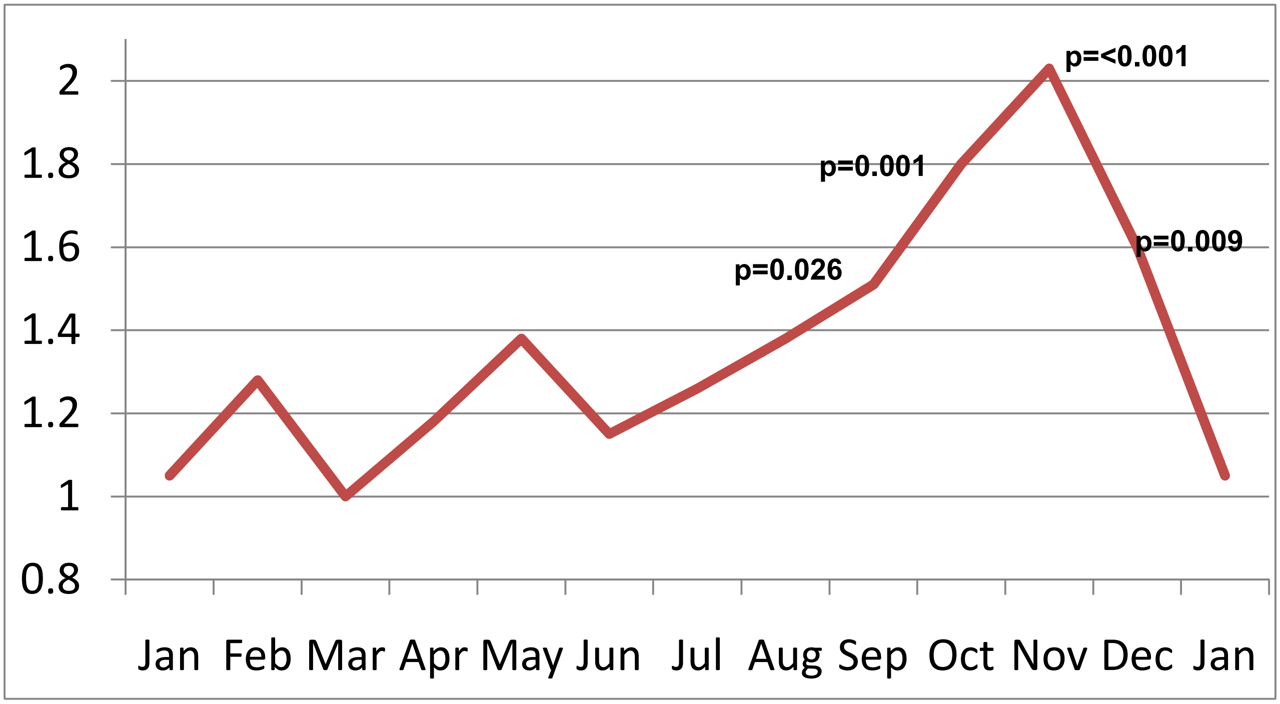


Figure 1. Month of birth and odds to become a centenarian. Within-family-study of 5,698 centenarians and their siblings survived to age 50.

In the next step, we included into analysis maternal age at birth, and it turned out that the young maternal age at childbirth was the most important predictor of exceptional survival, while the effects of paternal age at birth have become statistically insignificant (Table 4). We found that the odds to become a centenarian are 1.5-1.6 times higher for children born to younger mothers compared to siblings (brothers and sisters) born to mothers older than age 30 in the same families and even after controlling for paternal age (see Table 4).

It was found that for persons over age 50 the odds to live to 100 are 1.5 times higher for those born to mothers younger than 25 years compared to siblings born to 40-years old mothers (Table 4). Moreover, even at age 75 it still helps to be born to young mother -- the odds to celebrate the 100th birthday are 1.6 times higher for siblings born to mothers younger than 20 compared to those born to 40-years old mothers (Table 4).

Study of survival to 100 in medium and large families showed that effect of maternal age on survival significantly increases in medium families compared to large families. In medium families, siblings born to mothers younger than 20 years had more than twice chances to survive to age 100 compared to their brothers and sisters born to 40-years old mothers (Table 5).

Thus, within-family analysis of the paternal and maternal age effects on human longevity revealed that it is young age of mother that increases chances of siblings to reach longevity. Within-family approach has great advantages over other methods, because it is free of confounding caused by between-family differences.

Table 4. Odds ratios (with p-values) to become a centenarian as predicted by conditional logistic regression (fixed effects). Effects of maternal age.

Variable	Model 1 Siblings survived to age 50	Model 2 Siblings survived to age 50	Model 1 Siblings survived to age 70
Maternal age:			
<20	1.59 (0.025)	1.65 (0.034)	1.65 (0.019)
20-24	1.53 (0.005)	1.55 (0.010)	1.55 (0.005)
25-29	1.49 (0.007)	1.48 (0.013)	1.52 (0.006)
30-34	1.16 (0.339)	1.15 (0.388)	1.15 (0.373)
35-39	1.06 (0.712)	1.06 (0.741)	1.06 (0.711)
40+	Reference	Reference	Reference
Paternal age:			
<25		0.92 (0.621)	
50+		0.98 (0.935)	
Female sex	3.24 (<0.001)	3.25 (<0.001)	2.95 (<0.001)
Born in October-November	1.52 (<0.001)	1.52 (<0.001)	1.50 (<0.001)
Pseudo R^2	0.0787	0.0788	0.0701
Number of observations	5778	5778	4813

Table 5. Odds ratios (with p-values) to become a centenarian as predicted by conditional logistic regression (fixed effects) for different subgroups. Effects of maternal age and family size.

Variable	Siblings survived to age 50	Siblings survived to age 50, small and medium family size (<9)	Siblings survived to age 50, large family size (9+)
Maternal age:			
<20	1.59 (0.025)	2.51 (0.003)	1.24 (0.423)
20-24	1.53 (0.005)	2.16 (0.007)	1.26 (0.213)
25-29	1.49 (0.007)	1.72 (0.032)	1.42 (0.049)
30-34	1.16 (0.339)	1.23 (0.423)	1.15 (0.447)
35-39	1.06 (0.712)	1.31 (0.306)	0.94 (0.757)
40+	Reference	Reference	Reference
Female sex	3.24 (<0.001)	3.36 (<0.001)	3.18 (<0.001)
Born in October-November	1.52 (<0.001)	1.56 (0.003)	1.50 (9,001)
Pseudo R^2	0.0787	0.0941	0.0719
Number of observations	5778	2153	3625

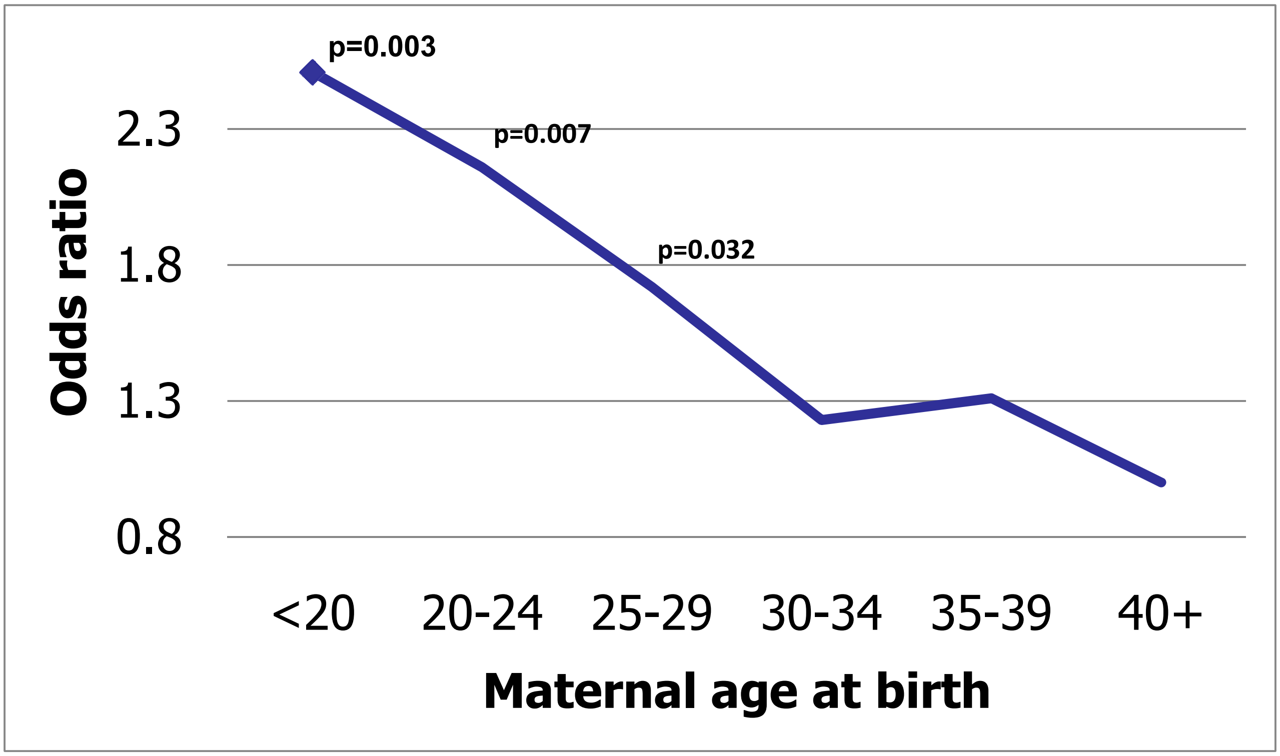


Figure 2. Maternal age at person's birth and odds to become a centenarian. Within-family-study of 2,153 centenarians and their siblings survived to age 50. Small and medium families.

Discussion

In this study we used large sample of centenarians and their siblings to study early-life effects on human longevity.

We found significant effects of month of birth on survival to age 100. Month-of-birth effects on mortality at older ages were reported in previous studies (Doblhammer 1999; Gavrilov & Gavrilova 1999; Doblhammer & Vaupel 2001; Doblhammer 2003). For the United States, Doblhammer (2003) showed that mean age at death estimated using the U.S. death certificates was higher for persons born in October-November. These results were obtained for persons died after age 50 years. Our previous study used data on mortality in single-year birth cohorts in the United States and found that mortality at very old ages (after age 80) is dependent on month of birth: persons born in October-December have the highest life expectancy at age 80 (Gavrilov & Gavrilova 2008).

The results obtained in this study, which are in a good agreement with previous publications on the effects of month-of-birth on longevity in the United States (Doblhammer 2003; Gavrilov & Gavrilova 2008). However these results are obtained using principally different approach and they demonstrate that month-of-birth has a strong independent effect on human longevity.

This study of parental age effects shows good agreement with our previous results obtained using significantly smaller sample size (Gavrilova & Gavrilov 2007; Gavrilova & Gavrilov 2010). We found significant effects of young maternal age on survival to age 100 with maximum effect observed predominantly at age 20-24 years. Paternal age effects were also observed but they were mainly driven by young maternal age. Effect of young mother is particularly prominent in small and medium families, which is important taking into account smaller family size in contemporary population.

The finding of beneficial effect of maternal age on offspring survival to age 100 in humans may have biological explanation. There is empirical evidence that the quality of female eggs in human beings rapidly declines with age (Bickel 2005; Pellestor *et al.* 2005) and this deterioration starts rather early—before age 30 (Heffner 2004). Maternal age influences the biology of the mother-fetus relationship, with a negative effect on fetal development and predisposition to severe diseases such as type I diabetes (Gloria-Bottini *et al.* 2005).

Experiments on laboratory mice found that the offspring born to younger mothers live longer (Tarin *et al.* 2005). This study also demonstrated that the largest effect is observed at later life. Animal studies have also found that hormonal profiles in pregnant mice are different depending on maternal age (Wang & vom Saal 2000). This may explain why adult offspring of adolescent and middle-aged mothers have lower body weight and delayed puberty and male offspring have smaller reproductive organs than those born to young adult mothers (Wang & vom Saal 2000). Female offspring produce progeny whose birth weight depended on the age at pregnancy of their grandmothers, demonstrating a transgenerational effect of maternal age (Wang & vom Saal 2000). Delayed motherhood in mice has also been demonstrated to have negative effects on behavioral traits of young adult offspring (Tarin *et al.* 2003). Data on the long-term effects of maternal age in human beings are scarce. One study showed that the lifespan of children decreased with increasing maternal age (Kemkes-Grottenthaler 2004). Our earlier studies have not detected an association of maternal age with offspring mortality in historical populations of European aristocracy (Gavrilov & Gavrilova 1997; Gavrilov & Gavrilova 2000), but the we believe that this might be due to limitations in the data or the tools to analyze them.

The fact that lifespan of offspring depends on mother's age at their birth even in laboratory animals indicates that some fundamental biological mechanisms may be involved. Such possible epigenetic mechanisms as changes in genomic imprinting in oocytes of aging females may be a plausible hypothesis (Comings & Macmurray 2001; Comings & MacMurray 2006). Another plausible biological hypothesis is the “telomere theory of reproductive senescence" in females (Keefe *et al.* 2005), which posits that eggs ovulating from older females have shorter telomeres because of late exit from the oogonial “production line” (Polani & Crolla 1991) during fetal life, with incomplete restoration by telomerase (Keefe *et al.* 2005). Telomeres are DNA repeats which cap and protect chromosome ends, so that longer telomeres in eggs of younger females may be beneficial for offspring lifespan. However, in human beings some additional sociobehavioral mechanisms may be also involved, on top of more general biological mechanisms.

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