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Search for Mechanisms of Exceptional Human Longevity

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Abstract

This study presents initial findings of a new ongoing research project aimed to identify important predictors and mechanisms of exceptional human longevity. For this purpose the detailed data on long-lived people surviving to 100 years in the Unites States are collected, validated, and analyzed. The study found that being born to a young mother is an important predictor of person's longevity. The study also found that the "stout" body build at age 30 years (being in the heaviest 15% of population) significantly decreases chances of survival to 100 years. These findings demonstrate that early-life and mid-life personal characteristics play an important role in human longevity.

Studies of exceptional human longevity may provide important clues on possible factors and mechanisms that delay human aging and promote healthy life span. This epidemiological approach to unraveling the mechanisms of human aging and longevity is applied in two studies using two different datasets on centenarians.

The first study explored the determinants of exceptional survival to age 100 and beyond using genealogical data on American centenarians with detailed information on their parents and siblings. Using a conditional logistic regression model, we applied a method of within-family analysis to investigate the occurrence patterns for centenarians among siblings, which allows researchers to avoid confounding caused by between-family variation (command *clogit* in Stata 10 statistical package). For this analysis, the 198 validated centenarians born in United States in 1890–1893 were identified, and their family histories were reconstructed using the U.S. censuses, Social Security Administration Death Master File (SSA DMF), state death indexes, family histories, and other supplementary data resources. The following predictor variables were explored: Sex, birth order, paternal age at person's birth, and maternal age at person's birth. The study found that first-born siblings are more likely to survive to 100 years when compared to later-born siblings (odds ratio [OR] = 1.77, 95% confidence interval [CI] = 1.18–2.66, $p = 0.006$). To find out the mechanism of the birth-order effect, a multivariate analysis, which included parental age variables, was performed. This analysis found that the protective effect of being first-born is driven mostly by the young maternal age at person's birth (being born to a mother younger than 25 years). Being born to a young mother is the major predictor of human longevity (OR = 2.03, 95% CI = 1.33–3.11, $p = 0.001$; see also Fig. 1). Moreover, even at age 75 it is still important to be born to young mother to survive to 100 years (OR = 1.87, 95% CI = 1.15–3.05, $p = 0.01$).

This finding may have a biological explanation. There is an empirical evidence that the quality of female eggs in human beings rapidly declines with age,[1,2] and this deterioration starts rather early—before age 30.[3] 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.[4] Experiments on laboratory mice found that the offspring born to younger mothers live longer.[5] Animal studies have also found that hormonal profiles in pregnant mice are different depending on maternal age.[6] 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.[6] Female offspring produce progeny whose birth weight depended on the age at pregnancy of their grandmothers, demonstrating a transgenerational effect of maternal age.[6] Delayed motherhood in mice has also been demonstrated to have negative effects on behavioral traits of young adult offspring.[7]

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.[8] Our earlier studies have not detected an association of maternal age with offspring mortality in historical populations of European aristocracy,[9,10] but we believe that this might be due to limitations in the data or the tools to analyze them. On the other hand, our findings presented here suggest that in American families siblings born to younger mothers (before age 25) have almost twice the odds to live to 100 years, even after age 75. This corresponds well with the earlier findings on laboratory mice.[5]

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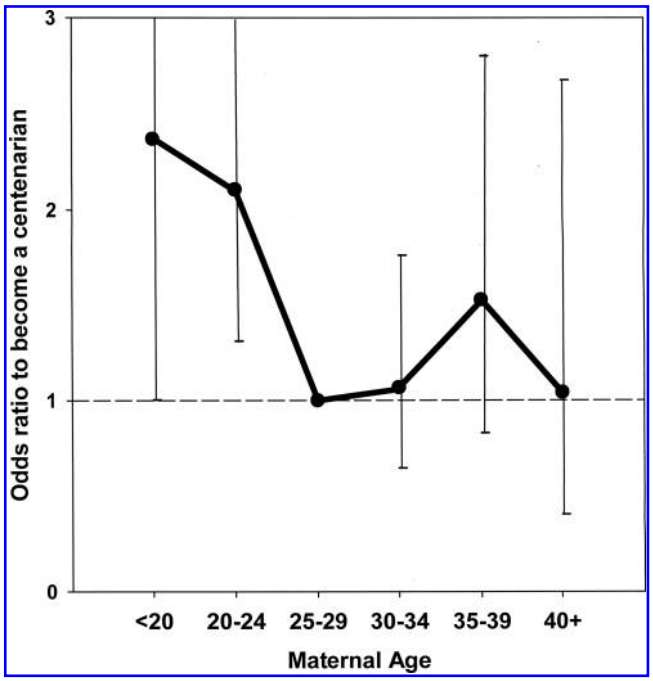

FIG. 1. Odds ratio to survive to 100 years as a function of maternal age at person's birth. Data for persons born to mother at 25–29 years are treated as a reference category.

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.[11,12] Another plausible biological hypothesis is the "telomere theory of reproductive senescence" in females,[13] which posits that eggs ovulating from older females have shorter telomeres because of late exit from the oogonial "production line"[14] during fetal life, with incomplete restoration by telomerase.[13] Telomeres are DNA repeats that 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.

The second study explored whether people living to 100 and beyond were any different in physical characteristics from their peers at their middle age (30 years). To this aim, a random sample of 240 males surviving to age 100 and born in 1887 was selected from the SSA DMF and linked to the World War I civil draft registration cards collected in 1917–1918. The linkage was based on person's first and last names and three components of complete date of birth (date, month, year), with additional supporting information on the state of social security number issuance. Overall linkage rate to the draft registration card data was 72.5% (174 linked records). It should be noted that not all centenarians found in the DMF could participate in the World War I draft registration. Study of additional data sources revealed that 2 persons in DMF sample served in the regular army during the draft registration, 7 persons had their Social Security number (SSN) issued after 1955 (suggesting late immigration), and in 6 cases we found misprints in SSA DMF (persons in fact were born in 1987 according to their death certificates). Elimination of these noneligible cases increased the linkage success to 77.3%. A total of 72% of records were successfully matched to the draft registration cards and classified as "very confident"[15] (exact match by name and birth date) and the match of 11% was considered as "somewhat confident" and required additional study (when day, month or year of birth did not match). The proportion of immigrants was similar among centenarians (20%) and controls (22%) and close to the officially reported proportion in 1920 census for age group 20–44 years (18%),[16] demonstrating the external validity for our centenarian sample. The proportion of African Americans (5%) was lower than in 1920 census (9%),[16] which can be explained by higher mortality of blacks compared to whites at middle ages and hence lower survival of blacks to extremely old ages. Thus, the linkage of centenarian records to World War I draft registration cards was not subjected to significant biases regarding foreign-born status or race. Randomly selected shorter-lived men matched by birth year, race, and county of draft registration were used as controls. We used a method of conditional regression model to compare future centenarians with their matched shorter-lived control individuals (command *clogit* in Stata 10 statistical package).

It was found that the "stout" body build (being in the heaviest 15% of control population) was negatively associated with longevity and persons with slender and medium body build had higher chances of survival to 100 ($OR = 2.63$, $p = 0.025$). Both farming occupation and having large number of children (4+) at age 30 significantly increased the chances of exceptional longevity ($OR = 2.20$, $p = 0.016$ and $OR = 2.71$, $p = 0.051$, respectively). The effects of immigration status, marital status, and body height on longevity were less important, and they were statistically insignificant in the studied data set. This study provides new estimates of height, body build, and other vital characteristics for the future centenarians at their young adult ages, and shows that detrimental effects of obesity may have an exceptionally long time range, and that obesity at young adult age (30 years) is predictive for almost three times lower chances of survival to age 100 years.

These two studies demonstrate that early-life and mid-life living conditions play an important role in exceptional longevity. More detailed description of research methodology, including data collection, validation, and analysis, can be found in our earlier publications on related topics.[17–19]

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