Childhood Exposure to Infections and Exceptional Longevity

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Earlier studies suggest that childhood exposure to infections may increase adult risk of cardiovascular diseases. However, little is known about effects of early-life exposure to infections on exceptional longevity. This study attempts to fill this gap by comparing American centenarians born in 1890-1891 with their shorter-lived peers who died at age 65 years. Data were taken from computerized family histories, which were then linked to 1900 and 1930 U.S. censuses. Infectious load was measured as household child mortality index (CMI) in 1900 using information on children ever born and survived by mothers of studied individuals. It was found that CMI in families of centenarians is not significantly different from CMI in control families suggesting that infectious load during childhood does not influence mortality after age 65. The results of this study suggest that parental longevity and mid-life characteristics rather than childhood infections play an important role in exceptional longevity.

Introduction

Early exposure to infections may be related to chronic diseases later in life

Childhood exposure to infections (as a factor of elevated mortality later in life) deserves special attention. Finch and Crimmins (Finch and Crimmins 2004) proposed a hypothesis that historical decline in chronic inflammation (due to decreasing exposure to early-life infections) has led to a decrease in morbidity and mortality resulting from chronic conditions in old age. Studies of rural 18th century Sweden (Bengtsson and Lindstrom 2000, 2003), U.S. Civil War veterans (Costa 2000, 2002), and Americans in their 50s (Blackwell, Hayward and Crimmins 2001) demonstrated that exposure to infections early in life is associated with elevated mortality from chronic diseases at older ages.

Childhood exposure to infections may be particularly important in explaining differential mortality later in life for cohorts of American oldest old (85+). These individuals, born in 1895 through 1920, experienced high exposure to infections during childhood and decreasing infectious disease load later in life. The United States is in a unique position in this regard. While at the end of the 19th century children from European countries suffered from poor nutrition and overcrowding, their American counterparts were relatively well fed and had better housing conditions (Preston and Haines 1991). On the other hand, existing historical evidence suggests that disease load in the early 20th century United States was high (Preston and Haines 1991). Many factors related to child mortality in 1900 were found to be significant predictors of survival to advanced ages (Hill et al. 2000; Preston, Hill and Drevenstedt 1998; Stone 2003). This suggests that early childhood infections in the late 19th and early 20th century represent a significant health hazard with potential harmful effects later in life.

The publication by Finch and Crimmins (Finch and Crimmins 2004) on early-life exposure to infections as a cause of late-life chronic diseases generated a flurry of criticisms and responses (Barbi and Vaupel 2005; Caruso et al. 2004; Gavrilov and Gavrilova 2004; Hein and Jongbloet 2004; Payne 2004). Some authors argued that current living conditions are far more important in mortality determination than early-life events and factors (Barbi and Vaupel 2005). Also there is an alternative view on the role of early infections in development of chronic diseases later in life (so-called “hygiene hypothesis”). This hypothesis suggests that reduced microbial exposure because of improved sanitation and cleaner lifestyles has facilitated the rise in asthma, allergic disease, and multiple sclerosis in the Western world (Wills-Karp, Santeliz and Karp 2001). It was found that individuals exposed to infant siblings had lower incidence of multiple sclerosis

(Ponsonby et al. 2005). The "hygiene hypothesis" has been linked to the development of heart disease (lower risk of heart disease was associated with more childhood infections) (Pesonen et al. 2007).

Genetic factors play an important role in exceptional longevity.
Scientific studies of familial longevity have deep historic roots. In 1899 the founder of biometrics, Karl Pearson and his student Mary Beeton analyzed the correlation of parent/child ages at death based on English genealogies dating back to the 17th century (Beeton and Pearson 1899). This pioneer work was followed by dozens of other studies that addressed the same issue (see review in (Gavrilov et al. 2002)). These studies demonstrated statistically significant associations between lifespans of blood relatives. For example, Raymond Pearl discovered that the ancestors of long-living persons (nonagenarians) had a substantially higher lifespan compared to a control population (Pearl and Pearl 1934).

The study of heritability in European aristocratic families demonstrated that narrow-sense heritability of lifespan is relatively small (0.25) when data are analyzed for the whole range of parental lifespans, while for parents living more than 75 years heritability estimates are significantly higher: 0.50 and more (Gavrilova et al. 1998). These results demonstrate that some traditional assumptions underlying methods of quantitative genetics may need to be revised in view of a special position of lifespan among other quantitative traits. Summarizing this brief overview of longevity studies we may conclude that effects of familial longevity are significant and should not be ignored when other factors of exceptional longevity and late-life mortality are analyzed.

Another problem receiving little attention in the scientific literature is a possibility of interactions between environmental (including social environment) and genetic factors (measured through the exceptional longevity of relatives) in determination of lifespan. Studies of early-life conditions commonly ignore the possibility of moderating genetic effects on longevity (Costa and Lahey 2005), while biologists and medical scientists focus their research on genetic traits (Atmon et al. 2005; Barzilai et al. 2001; Perls 2002; Perls, Kunkel and Puca 2002) often overlooking interactions with environmental effects.

Reconciling both approaches and simultaneous study of both familial and environmental factors of longevity was applied in this study.

Infectious burden. The main hypothesis we studied is that the early exposure to infections decreases chances of survival to advanced ages affecting mortality later in life. Infectious burden was estimated as within-family child mortality. Information on children ever born and children survived by mothers of centenarians and controls allowed us to estimate child mortality index for each family, where biological mother is present. Child mortality index served as a proxy of infectious disease burden in the particular family characterizing the living environment, as suggested by other researchers (Bengtsson and Lindstrom 2000, 2003; Bengtsson and Mineau 2009; Finch and Crimmins 2004; Preston and Haines 1991).

Data and Methods
Data.
In this study we compare centenarians born in the United States to their peers born in the United States in the same year and died at age 65 years. Both cases and controls were randomly sampled from the same population universe (computerized family histories) and had the same birth year window (1890-91). 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.

Sample sizes of male centenarians are small in the majority of longevity studies, and in order to resolve this problem and to 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. In order to obtain a more homogeneous birth cohort

regarding the secular changes in mortality and life course events, a narrow birth date window was used: 1890-91.

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 that the classic case-control design can be expanded in a variety of ways. One such expansion is a design suggested by Samuel H. Preston (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 in order to ensure comparability and avoid possible selection bias when centenarians and controls are drawn from different populations. Also we use data from the 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. Thus, the sampling procedure was the same for both centenarians and their shorter-lived controls.

Persons born in 1890-91 represent an interesting birth cohort to study. These individuals 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 persons born in 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 really rare condition of successful survival (only two men and 14 women out of 1000 from 1900 US birth cohort survived to age 100) but common enough for obtaining samples of sufficient size. In this study we analyzed early-life and adulthood effects that operate throughout the 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); (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; Hill et al. 2000; Rosenwaike and Stone 2003; Shrestha and Rosenwaike 1996). 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). Definite match was established when information on first and last names (spouse last name for women), day, month and year of birth matches in DMF and family history (Sesso, Paffenbarger and Lee 2000). In the case of disagreement in day, month or year of birth, the validity of 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 occurred before the 1970s. We found that approximately 30 percent of deaths in the control group could be confirmed through the US state death indexes, cemetery records and obituaries, which cover longer periods of time. 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 it was done in the Utah Population Database for individuals 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 (contains information on month and year of birth) compared to the 1910 and 1920 censuses. If person cannot be found in 1900 census, then he/she was searched in 1910 census. We obtained a good linkage success rate (92-95%) in our study, because of availability of 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 search on the following variables: first, last names (including Soundex), state, county, township, birthplace, birth year (estimated from census), immigration year, relation to head-of-household. Data on birth dates, birth places and names of siblings produced unambiguous matches in overwhelming majority of cases.

Ancestry.com has a powerful search engine, which helps researchers to find a person in multiple historical sources simultaneously (including all historical U.S. censuses, up to 1940 census) based on all information available in computerized genealogies. Use of this service greatly facilitates the linkage procedure and helps to obtain unambiguous link 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 socio-economic 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 (including effects of childhood infections) on human longevity.

Methods

Estimation of child mortality index from census data. Child mortality index is defined as the ratio of actual child deaths to expected child deaths for individual women or groups of women (Preston and Haines 1991; Preston, Heuveline and Guillot 2001). It is usually reported for currently married parous women with marriage duration less than 25 years. We extended this duration to 35 years in our study. The index assumes that a child's risk is proportional to a standard mortality schedule (taken from a model life table) faced by other children.

Obtaining child mortality index is based on the indirect method of child mortality estimation from census data developed by William Brass (Brass 1975), which applies information available in censuses about the total number of children that woman has borne and the number of surviving children (questions asked in the 1900 and 1910 U.S. censuses) as well as cumulative fertility estimates for women of different ages. Preston and Palloni modified this technique by adding information on the ages of surviving children to the general equation used for child mortality estimation, which relaxed an assumption of unchanging fertility over time and improved technique of indirect mortality estimation (Preston and Palloni 1977).

The number of child deaths (D_i) that has occurred to woman *i* is computed by subtracting her reported number of surviving children (S_i) from reported children ever born (B_i). The expected number of dead children for the *i*th woman in marital duration group *j*, ED_{ij}, is given by

$$ED_{ij} = B_i\, EPD_j, = B_i \times q(a)/K_j$$

where EPD_j is the expected proportion of children who died among women in marital-duration group j under the standard mortality schedule, $q(a)$ is the probability of dying from birth to age "*a*" and K_j is a multiplier for this marital duration category (taken from the United Nations Manual X, see Preston and Haines 1991). The values of probabilities of dying, $q(a)$, are taken from the model life table (model West life table, level 13.0 with males and females combined). The West level 13.0 corresponds to under-five mortality, q(5), of 0.191, the infant mortality rate of 0.129, and life expectancy at birth equal to 48.5 years. It was shown that this level provides a good fit to historical data on the U.S. mortality (Preston and Haines 1991).

Using this procedure, we assigned a child mortality index (before age 5) to each mother of cases and controls, which allowed us to estimate within-family effects of child mortality. Preston and Haines (1991) recommended to use under-five probability of death, *q(5)*, because it proved to be more robust to time trends or an error in the choice of model life table.

Results

In this study we have identified 836 centenarians born in 1890-91 in the United States and 841 shorter-lived controls born in the United States and died at age 65 years. Further linkage to 1900 census resulted in 98.2% success rate for centenarians and 98.6% success rate for controls. 94.9% of centenarian records and 96.4% of control records were successfully linked to the 1930 census. Linkage to the 1900 census revealed that 95.6% centenarians and 96.0% controls lived with one or both biological parents. 67% of fathers were farmers according to the 1900 census. Centenarians and controls had approximately equal sibship sizes on average (7.6 and 7.8 respectively), which are higher compared to the general population in 1900 census (5.6) suggesting larger sizes of families presented in computerized genealogies. In further analyses we restricted our sample to records where information was available for both 1900 and 1930 census. To study effects of marriage history on survival to age 100 years, only records for individuals being 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) Child mortality index measured using data from the 1900 census.
(2) Other characteristics of childhood conditions drawn from the 1900 census (type of parental household - farm or non-farm, own or rented, parental literacy, parental immigration status, paternal occupation, size of parental household in 1900, places of birth for household members),
(3) 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),
(4) family characteristics drawn from computerized genealogies (paternal and maternal lifespan, 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 year was significantly associated with male longevity. However loss of parents early in life (before 1910) had no effect on the chances to become a centenarian. Childhood conditions recorded in the 1900 census included: child mortality index, 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, region of birth. Larger household size, birth in the North East or Midwest regions and having farmer father were found to be significant predictors of male (but not female) longevity in univariate analyses. Birth in the North-East region is predictive for survival to advanced ages in men and this result agrees with findings by Hill and colleagues for persons survived to age 85 (Hill et al. 2000). However, this result does not agree with the results of our earlier study, which compared centenarians drawn from computerized family histories to population-based controls (Gavrilova and Gavrilov 2007). Female longevity revealed no significant associations with any of 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, availability of children (composite variable based on information taken from 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 husband-farmer had no

effect on the chances of survival to age 100. For women, availability of radio in household was the strongest predictor of longevity among the studied midlife variables.

Mean Child Mortality Index (CMI) in 1900 for families of centenarians is equal to 0.532 (95% CI = 0.480-0.585). Mean CMI in 1900 for control families is equal to 0.565 (0.508-0.622). Although mean CMI in families of shorter-lived individuals is slightly lower than CMI of centenarian families this difference is not statistically significant. On the other hand, CMI for families of both centenarians and controls shows much lower child mortality as it is predicted by model life tables suggested for describing mortality pattern in the U.S. in 1900 (Preston and Haines 1991). This finding demonstrates that child mortality in families described by computerized family histories and especially families with individuals surviving past age 60 may be lower compared to the general population.

When CMI was included into multivariate logistic regression model with familial, early-life and middle-life characteristics it was not a significant predictor of longevity for both men (Table 1) and women (Table 2). In multivariate analyses, when familial, early-life and midlife chanracteristics are combined the region of birth and having farmer father are no longer associated with longevity of men. Parental longevity turned out to be one of the strongest predictors of survival to age 100. Note that the farmer occupation in 1930 is one of the strongest predictors of survival to age 100 for men, which agrees with the results of other studies including our own study of centenarians based on population-based sample of survivors to age 100 from the 1887 birth cohort (Gavrilov and Gavrilova 2012).

Table 1. 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 80+	1.73	1.25-2.41	0.001
Mother lived 80+	1.70	1.22-2.37	0.002
Farmer in 1930	1.84	1.30-2.61	0.001
Born in the North-East region	2.00	1.16-3.43	0.012
Born in the second half of year	1.25	0.91-1.74	0.174
Radio in household, 1930	0.85	0.60-1.20	0.352
Child Mortality Index	0.53	0.81-1.26	0.934
Pseudo R^2 = 0.0499			

N=634. Calculated using Stata 11 statistical package (procedure logistic).

Table 9. 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 80+	2.17	1.57-3.00	<0.001
Mother lived 80+	2.13	1.56-2.91	<0.001
Husband (or head of household) farmer in 1930	1.25	0.90-1.73	0.177
Radio in household, 1930	1.71	1.23-2.37	0.001
Born in the second half of year	1.27	0.93-1.73	0.127
Born in the North-East region	0.99	0.60-1.64	0.979
Child Mortality Index	0.89	0.72-1.11	0.306
Pseudo R^2 = 0.0631			

N=727. Calculated using Stata 11 statistical package (procedure logistic).

Discussion

This study found no statistically significant effects of higher child mortality in household (a proxy of infectious burden) on longevity as suggested by inflammatory hypothesis of aging (Finch and Crimmins 2004).

Several studies also showed no association between child mortality and adult survival in the same birth cohorts. For example study of French-Canadians born in the 17th and 18th centuries showed that increasing infant mortality rate did not translate into survival prospects in late life (Gagnon and Mazan 2009). Analysis of mortality data for Sweden, Finland, Denmark, Netherlands and England and Wales found that early-life shocks in cohorts' mortality have little effect on later mortality. However, this study found strong period effects on mortality (Myrskyla 2010).

Some studies found that survival to age 85 years is associated with lower CMI in families of both African-American (Preston et al. 1998) and white (Hill et al. 2000) individuals. It should be noted that in these studies survival was studied over the entire life span rather than over late-life portion of life duration. It may well happen that childhood infections do affect mortality in late childhood and early adulthood. The advantage of our study is that it compares individuals who already reached late adulthood ages. Also unlike previous studies, which analyzed mortality in demographic cohorts, our study compares one and the same individuals at different stages of their life course. Thus, information about child mortality in the families of studied individuals is linked to their chances of become a centenarian.

Our results demonstrate that childhood exposure to infections seems to be not a significant predictor of exceptional longevity for persons survived to late adulthood ages.

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