

Human Longevity and Reproduction

An Evolutionary Perspective

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Evolutionary considerations of the significance of grandmaternal effects discussed in this book bring us to a more general question: What does evolutionary theory tell us about the links between human longevity and reproduction? The purpose of this chapter is to review the ideas and facts on longevity-reproduction studies in evolutionary context and to present some new findings on this issue. The idea that human longevity and reproduction are linked to each other, and that this relationship could have a fundamental evolutionary explanation, has deep historical roots (Beeton, Yule, and Pearson 1900). Dozens of comprehensive studies on this topic have been published in the past (to mention a few, see Powys 1905; Bell 1918; Freeman 1935; Henry 1956; Gautier and Henry 1958; Bideau 1986; Knodel 1988). Yet the topic continues to be a matter of intensive study (Le Bourg et al. 1993; Westendorp and Kirkwood 1998; Korpelainen 2000, 2003; Lycett, Dunbar, and Volland 2000; Gavrilov and Gavrilova 2002; Müller et al. 2002; Doblhammer and Oeppen 2003) and debate (Ligtenberg and Brand 1998; Gavrilov and Gavrilova 1999; Westendorp and Kirkwood 1999).

The nature of the longevity-reproduction relationship is not just one scientific problem but a set of problems (which have used an identical terminology), and how longevity and reproduction will interact depends on the context of a particular study. For example, studies of human populations practicing birth control and family planning address fundamentally different question(s) on the link between longevity and reproduction than studies of populations with natural fertility. The studies of modern contraceptive-using populations address questions about modulating effects of socioeconomic status and personal health/reproductive choices, while the studies of natural fertility populations come closer to addressing fundamentals of human biology and evolution. Such a distinction may sound trivial, but these two very different types of studies are often confused with each other because they use an identical terminology (terms "reproduction" and "longevity").

The next issue of critical importance is related to how human longevity is defined. Those studies that include deaths at reproductive ages into analysis address fundamentally different question(s) than studies focused

on postreproductive survival only. The former studies consider anticipated effects of premature deaths on reproductive output, while the latter studies are more relevant to the studies of human longevity and its possible non-trivial link to reproduction. Again these two very different research approaches are often confused with each other because they use a similar terminology.

Finally it is particularly important to distinguish how reproductive success is measured. Straightforward studies on the numbers of children will reveal the "direct costs" of reproduction related to the potentially debilitating effects of excessive childbearing in natural fertility populations. Although this research approach addresses an important problem of the physiological and economic costs of reproduction, this ecological problem is different from a genetic problem posed by evolutionary theory, which is focused on heritable genetic components of reproductive costs, not just trivial environmental trade-offs.

Specifically, some evolutionary theories predict that genes enhancing human longevity should impair human reproduction because they divert resources from reproduction to body maintenance and repair (Kirkwood and Holliday 1979; Westendorp and Kirkwood 1998). If this theory is correct, then people with exceptional longevity should be infertile more frequently because they have a higher frequency of longevity gene(s) suppressing reproduction. Indeed, one study found that almost a half of long-lived women were allegedly childless (Westendorp and Kirkwood 1998). Moreover, it was found that this reported effect of exceptional longevity on reproductive output (numbers of children) was determined exclusively by increased proportion of childless women (Ligtenberg and Brand 1998). Thus the dependence of infertility rate instead of number of children on human life span at extremely old post-reproductive ages could be more informative for testing specific predictions of evolutionary theories on the links between longevity and reproduction.

Surprisingly, such an important and informative variable as childlessness/infertility rate has not received much attention in the studies of longevity-reproduction links. Most studies continue to operate with the numbers of children, a variable whose causes may have a trivial explanation (health exhaustion through excessive childbearing). Also, the number of children is strongly affected by family planning and reproductive habits (by frequency of sexual intercourse, for example). In contrast to the numbers of children, the childlessness rate is a more robust variable, because only a few couples remain childless voluntarily (Glass 1963; Toulemon 1996). Thus studies of childlessness rates among long-lived people may be particularly interesting and informative for testing evolutionary theories of aging. In this study, we try to fill this gap and present new findings regarding a pos-

sible link between human longevity and childlessness rate. We also provide a historical review of the relevant studies and discuss methodological issues related to the longevity-reproduction problem.

Historical Review of the Studies on Fertility and Longevity

Studies of the relationship between reproduction and longevity have a long and interesting history with many useful lessons to learn.

One of the first systematic studies on this topic was conducted by famous statisticians Karl Pearson and George Yule with the assistance of Mary Beeton in 1900 (Beeton, Yule, and Pearson 1900). The authors tried to test one of predictions of the Darwinian evolutionary theory that the fittest individuals should leave more offspring. These researchers studied the dependence of the number of children on parental life span after age fifty (at postreproductive ages). The authors found a slightly *positive* relationship between life span of both mothers and fathers and the number of offspring in four different sets of genealogical data (English Quaker records and Whitney family of Connecticut records for females and American Whitney family and Burke's *Landed Gentry* for males). Interestingly, this positive relationship was stronger when American data were analyzed. They also tried to use data on the British peerage but had to discard them because the data for women proved to be incomplete (many birth dates were missing) and because of indications that British peerage practiced some artificial restriction of births. They came to the conclusions that "fertility is correlated with longevity even after the fecund period is passed" (Beeton, Yule, and Pearson 1900, 163) and that "selective mortality reduces the numbers of the offspring of the less fit relatively to the fitter" (1900, 170). They also suggested that "in the case of life under wild conditions, the correlation between fertility and power of surviving would probably be far greater." (1900, 170).

Powys (1905) analyzed longevity of married women in post-reproductive period using vital statistics of the New South Wales for the years 1898 to 1902. He found that mothers of "moderate" sized families of about six children live on the average longer than those with smaller or larger families, and that extreme fecundity is unfavorable to extreme longevity in females but not males. The author explained the latter observation by "incessant strain upon the physique of women who bear large families during the periods of gestation, parturition and lactation" (Powys 1905, 244). It should be noted, however, that these results were obtained using cross-sectional data subjected to biases due to population structure and secular effects.

Another important study of fertility and longevity was conducted by the famous telephone inventor, Alexander Graham Bell, who analyzed genealo-

gies of the Hyde family in New England. He found that "*The longer lived parents were the most fertile*" (Bell 1918, 52; emphasis added).

In 1935 Bettie Freeman conducted a thorough study on the fertility and longevity of married women living beyond the reproductive period. She correctly criticized previous studies on this topic for not taking into account such important confounding variables as the age at marriage, and she emphasized the importance of avoiding right truncation of life span data, which occurs when data for nonextinct birth cohorts are used in the analysis. Freeman carefully selected for analysis eleven of the most complete and accurate American genealogies with data on 2,614 married women born from 1625 to 1825, who lived beyond age forty-five and had living husbands at the end of their reproductive period. The advantage of this study is the use of nontruncated data for the extinct birth cohort. The author also took into account calendar years of birth (control for changes over time), duration of marriage (control for exposure to childbirth) and the woman's age at marriage using a stratification approach. As a result of this careful study, the author found weak *positive* correlations between the duration of postreproductive life in women and the number of offspring borne, although this dependence was statistically significant only for women married before age twenty (Freeman 1935). This is an interesting observation, because the early-married women have the longest exposure to childbearing "risk." These early-married women also start to reproduce earlier, which may be protective against certain diseases like breast cancer (Bernier et al. 2000; Meister and Morgan 2000). Freeman came to the following conclusion on the link between reproduction and longevity: "this study gives no evidence that the association between the two variables is of sufficient moment to play a significant part in affecting population movements" (1935, 418).

After Freeman's comprehensive analyses, researchers of human evolution apparently considered this topic to be completely explored and left further studies of longevity and reproduction to historical demographers. Studies of historical populations revealed either no relationship (Henry 1956; Gautier and Henry 1958; Knodel 1988) or a positive relationship (Bideau 1986) between reproduction and longevity.

In 1993 Eric Le Bourg and colleagues returned to evolutionary studies of human longevity and reproduction using historical data for Québec. The authors tried to test Williams' (1957) evolutionary theory of senescence (antagonistic pleiotropy theory), which predicts the existence of a trade-off between early fecundity and longevity. They used population registers of French immigrants to Québec in the seventeenth century and of the first Canadians in the seventeenth and eighteenth centuries, a noncontraceptive human population living at a time when longevity had not been extended by advanced medical care and was not artificially shortened by wars, epi-

demics, or other external causes. The authors did not find any trade-off between longevity and reproduction in this historical population (Le Bourg et al. 1993).

In 1998 Westendorp and Kirkwood tested the predictions of the antagonistic pleiotropy theory in general and a disposable soma theory in particular (Kirkwood and Holliday 1979). Using genealogical data for British (actually European) aristocracy for a historical period when it was believed no birth control was practiced, the authors of this study reported that long-lived women are especially unsuccessful in reproduction. In particular, as many as 50 percent of the married long-lived women were reported to be childless. The long-lived women had, according to this study, less than two children on average, and they had their first child at a later age—by the age of twenty-seven years. The authors came to the conclusion that human longevity is achieved at the cost of reproductive success because of a genetic trade-off between longevity and reproduction predicted by the disposable soma theory of aging (Westendorp and Kirkwood 1998).

The authors apparently were not aware that their conclusions were in conflict with many previous findings on the relationship between reproduction and longevity. They did not quote and discuss the inconsistency of their results with findings from numerous previous studies on the same topic, where not only were any strong trade-offs between human longevity and fertility *not* observed, but even the opposite trend was often found (Beeton, Yule, and Pearson 1900; Freeman 1935; Henry 1956, 1963; Bideau 1986; Knodel 1988; Le Bourg et al. 1993). Thus an impression was created that their strong trade-off between longevity and reproduction is a well-documented observation, consistent with previous research. Now an impaired fertility of long-lived women is often presented in the scientific literature and mass media as an established fact (Kirkwood 2002; Westendorp 2002; Glannon 2002; Perls et al. 2002). Confirmation of this trade-off has become an appealing task for subsequent researchers because it seemed to be endorsed both by evolutionary theory and by publication in the prestigious scientific journal *Nature* (Westendorp and Kirkwood 1998). As a result, subsequent researchers began to seek trade-offs between fertility and longevity and report them, even though these trade-offs were not directly observable from their data (Lycett, Dunbar, and Voland 2000; Doblhammer and Oeppen 2003).

For example, Lycett, Dunbar, and Voland studied a historical population of northwest Germany (1720–1870) and found no difference in life span between married childless and parous women. Then the authors studied the relationship between residual longevity and residual number of children and found a *positive* correlation between these variables for farmers and smallholders, which is opposite to Westendorp and Kirkwood's findings but

is consistent with many earlier publications. The authors also found a weak negative relationship for particularly poor landless persons. The authors concluded, "while our data do not at first appear to provide support for the disposable soma theory for the evolution of human ageing, our subsequent analyses of social groups within the Krummhörn suggest that, at least for the poorest social group, there is a trade-off between reproduction and longevity" (Lycett, Dunbar, and Voland 2000). Ironically, this study, published 100 years after Karl Pearson's paper (Beeton, Yule, and Pearson 1900) in the same journal (*Proceedings of the Royal Society of London*), came to the opposite conclusion, but somehow each of these studies reported support for the evolutionary theory. Recently Dribe (2004) found a positive relationship between mortality and number of children among poor landless women but not among women from other social groups in preindustrial Sweden, which he believes is caused by economic rather than biological factors.

Doblhammer and Oeppen also sought a trade-off between reproduction and longevity using Hollingsworth's database on British peerage. This database is more complete compared to the Bloore's database used by Westendorp and Kirkwood (1998), although it represents a British peerage that seemed to practice artificial restriction of births as noted by Karl Pearson and coauthors (Beeton, Yule, and Pearson 1900). Initially, Doblhammer and Oeppen did not find any trade-off between postreproductive life span and fertility when they analyzed the data in a conventional way. Then they introduced an additional unobserved variable (without any justification) into the analysis, which was interpreted as "unobserved health"—and after excluding childless women and women with one child from the analysis, they finally got the anticipated trade-off: a positive correlation between relative mortality risk and parity (Doblhammer and Oeppen 2003). It is not clear, however, why the important and informative cases of childless women have to be excluded from the analysis in order to get a statistically significant trade-off between reproduction and longevity.

There was one more study that reported a diminished fertility among long-lived women (Korpelainen 2000). The author studied historical data on European aristocrats and rural Finns and did not find any significant increase in the childlessness among long-lived women (80+ years). She explained this apparent contradiction with the trade-off paradigm by insufficient data quality: "childless families are more easily overlooked in historical genealogical data" (Korpelainen 2000, 1769). The author, however, surmised lower number of progeny among long-lived women, although this observation was not statistically significant. This conclusion is likely to be an artifact of not taking into account a dramatic historical increase in life span accompanied by significant historical decline in fertility (the data were not controlled for time changes over two centuries).

Thus the studies of reproduction and longevity produced controversial conclusions on the relationship between number of offspring and postreproductive life span. It looks like in populations with natural fertility there is a positive relation between postreproductive longevity and number of offspring. This relationship was observed for some historical populations with natural fertility (Beeton, Yule, and Pearson 1900; Freeman 1935; Bideau 1986), supporting the idea of Karl Pearson that the fittest individuals leave more offspring. It appears that in the same context we may interpret the results that demonstrated higher longevity of women who had late children (Perls et al. 1997; Müller et al. 2003). It was shown that age at menopause is negatively correlated with mortality (Jacobsen, Heuch, and Kvale 2003), so women that have late children and reproduce longer are healthier than women who stop reproducing earlier because of early menopause.

In populations practicing birth control, a positive relationship between reproduction and longevity is replaced by a curve with the optimum when the lowest risk of death is observed for women having three (Kumle and Lund 2000) to six (Powys 1905) children. It seems that European aristocrats started to use birth control relatively early in history, as noted by Karl Pearson and colleagues more than a century ago. Interestingly, these researchers found strong *positive* correlation between life span and reproduction for American women, which continued up to ninety years of age at death (Beeton, Yule, and Pearson 1900). However, for the English data the positive relationship between life span and number of offspring only holds until age seventy-five years, and beyond this age at death there appeared to be a slight decrease in numbers of children. One possible explanation of this phenomenon may be that more educated English women started taking measures for birth control earlier in history than Americans, thereby decreasing the debilitating effects of excessive childbearing on health. In populations with natural fertility, most married women achieve their reproductive potential, so both the longevity and the number of offspring reflect an organism's fitness. In populations practicing birth control, the number of children is no longer related to fitness alone, so physically robust women having fewer children may live longer due to smaller exposure to the debilitating effects of excessive childbearing.

It is known that number of children borne is modulated by the age of marriage, which was particularly late among the British aristocracy (Hollingsworth 1964). As a result, the observed number of offspring is not a good measure of their biological reproductive potential. The situation becomes even more complicated if we take into account artificial restriction of fertility, which British aristocrats started to practice after the eighteenth century (Hollingsworth 1964). For example, the mean number of children among the British peerage (4.84, see Doblhammer and Oeppen 2003) is much

lower than among the early New England settlers (5.7 to 7.2, see Freeman 1935). The most likely explanation of this difference is the late age at marriage and partial birth control among the British peerage (Hollingsworth 1964). On the other hand, childlessness is much less affected by restrictions of birth control because the majority of married couples agree to have at least one child; voluntary childlessness is extremely rare (Glass 1963; Toulemon 1996). This makes studies on links between childlessness and longevity particularly promising. In our study, we present data on the relationship between reproduction and longevity using childlessness as a proxy for biological infertility (there is further justification of this assumption below). Another reason for studying childlessness comes from an observation published by Ligtenberg and Brand (1998) that alleges that an inverse relationship between longevity and reproduction was caused by changes in the proportions of reported childless women. As those authors concluded, "it is not a matter of reduced fertility, but a case of 'to have or have not'" (Ligtenberg and Brand 1998). Still, a study of childlessness using genealogical data requires a high quality and completeness of the data set to be used in the analyses.

There is no question that genealogical data and historical demographic data might be of great interest for evolutionary studies on human longevity and reproduction. However, this specific area of research requires extremely careful data handling (data quality control and adjustment for important predictor variables) described in the classical books on historical demography (Knodel 1988). We believe, therefore, that the relationship between human longevity and childlessness should be explored again with these methodological caveats in mind.

Are Longevous Women Infertile? Validation Study of Infertility Rates as a Function of Life Span

Data and Methods

MAIN DATA SOURCE

This study applies the database on European royal and noble families that was developed and used in our previous studies. This family-linked database was developed as a result of more than ten years of continued efforts that proved to be both labor-intensive and time-consuming because of extensive data cross-checking and data quality control. We used earlier intermediate versions of this database in previous studies (Gavrilov and Gavrilova 1997, 1999b, 2000, 2001, 2003, 2004; Gavrilov et al. 1997, 2002; Gavrilova and Gavrilov 2001; Gavrilova et al. 1998, 2003, 2004). To develop this database, we have chosen one of the best professional sources of genealogical data

available: the famous German edition of the *Genealogisches Handbuch des Adels* (called also the *New Gotha Almanac*), edited by W. Van Hueck, as well as several other reputable data sources described elsewhere (Gavrilova and Gavrilov 1999).

A detailed description of this database and issues of quality control for this historical dataset are available in previous publications (Gavrilov and Gavrilova 2001; Gavrilova and Gavrilov 2001). The main feature of this data source (compared to other genealogical resources) is its very high quality achieved through cross-checking of each record with multiple data sources. Also, this wealthy population is reasonably homogeneous regarding socio-economic characteristics, and it did not suffer from undernutrition, starvation, or poor living conditions. Thus, although the sample analyzed in this study does not represent the whole human population (as laboratory animals do not represent species in the wild), it is one of the best possible samples to test biological hypotheses because the effects of population heterogeneity are minimized with regard to social status.

Data quality control was an important part of our effort to develop a high-quality family-linked database and use it for scientific research. In particular, we checked data for completeness, accuracy, and representativeness.

The *completeness* in birth and death dates reporting in the *New Gotha Almanac* was very high: dates of all vital events were reported for nearly 95 percent of all persons. Such high completeness is not common for other genealogical data sources. For example, the British peerage data published by Burke's almanac often lack information on birth dates for women, making the calculation of female life span impossible. This problem with British aristocratic women was first noticed by Karl Pearson and Mary Beeton a century ago (Beeton and Pearson 1899, 1901). The authors used British peerage data to study longevity inheritance and had to exclude women from their consideration for the following reason: "The limitation to the male line was enforced upon us partly by the practice of tracing pedigrees only through the male line, partly by the habitual reticence as to the age of women, even at death, observed by the compilers of peerages and family histories" (Beeton and Pearson 1901, 50–51). Our own experience revealed much lower quality of British genealogies compared to German and Scandinavian genealogies, particularly in the case of female birth-date recording. For example, the proportion of female birth dates with an unknown month of birth was 16 percent in British genealogies versus 1.6 percent in German genealogies.

The accuracy of data published in the *New Gotha Almanac* is also very high: the frequency of inconsistent records is less than 1 per 1,000 records while for many other genealogical data sources it falls within 1 per 300 to 400 records.

As for representativeness, the comparison of our data with Hollingsworth's analysis of the British peerage (Hollingsworth 1964) revealed close agreement between his findings and ours on mortality patterns, including the male/female gap in life expectancy (seven to ten years of female advantage in life span).

Another important advantage of this dataset is that the data are not spoiled by selective emigration (a common problem for data collected through local registers) because in this dataset every person is traced until his or her death. It was possible to trace the destiny of almost every person, including even those relatively rare cases when a person left Europe and eventually died in another part of the world (United States, Canada, Australia, South Africa, India, Latin America, and so on).

We also used extinct (noncensored) birth cohorts in our study. For this purpose, only those birth cohorts were used in the study that were born at least 100 years before the year of data publication (to be sure that the birth cohort under study is almost extinct).

CHARACTERISTICS OF THE DATA SAMPLE USED FOR THE CHILDLESSNESS STUDY

Selection of data for this particular study was conditioned by the necessity of obtaining reliable information on women's fertility, date of marriage, and husband characteristics. Therefore, data on 3,723 married women born from 1500 to 1875 and belonging to the upper European nobility were used for the analysis. Although data for women born before 1500 were also available, we found that completeness of these old data is not satisfactory because of obvious underreporting of children who died in infancy and underreporting of family size compared to post-1500 data (even for royal lines). Thus we decided to discard these data in order to ensure a high quality of data selected for the analyses. Also, the most accurate information on the number of children is available in genealogies compiled for upper European nobility: royal, princely, and ducal lines as well as German mediated houses. To ensure higher accuracy of the data, we excluded all non-royal lines of Russian nobility since they have lower quality compared to other European upper nobility genealogies. We would like to emphasize the importance of selecting upper nobility genealogies for studying fertility with genealogical data. It turned out that in published genealogies, the number of reported children and proportion of childless women often are inversely related to the nobility rank of the studied family. For example, in the Bloore's database used by Westendorp and Kirkwood (1998), the percentage of allegedly childless long-lived women (life span above 80 years, born before 1800) dropped from 43 percent in poorly documented families of low nobility rank to 23 percent in better-studied families (where husbands

belonged to nobility ranks higher than barons and baronets). Note that the latter estimate of childlessness better agrees with published data (Knodel 1988; Lycett, Dunbar, and Volland 2000) while the former estimate looks unrealistically high. To avoid this problem, we excluded families with low nobility rank from the analyses.

Women with two or more marriages (5 percent) were excluded from the analysis in order to simplify the interpretation of results (to ensure continuity of exposure to childbearing).

The most difficult issue was to prove that women with no recorded children were really childless. To ensure the accuracy of this judgment, every case of childlessness has been checked using at least two different genealogical sources. Although most records in our dataset belong to continental European nobility, it has approximately 65 percent overlap with Bloore's dataset used by Westendorp and Kirkwood (1998) regarding the studied families. This significant data overlap occurred because a considerable number of records for the British peerage in Bloore's database lacked information about female birth dates and therefore were useless for further analysis. As a result, 60 to 65 percent of the records with a known female life span in Bloore's database belonged to the continental European (mostly German) ruling lines rather than to the British peerage.

ANALYTICAL METHODS

The statistical analyses were performed using the multivariate logistic regression model (Breslow and Day 1980; Aldrich and Nelson 1984; Hosmer and Lemeshow 1989).

Suppose Y is a binary variable indicating the fact of being childless and x is a vector of explanatory variables. Then probability $p = Pr(Y = 1|x)$ of being childless can be modeled by linear logistic regression:

$$\log\left(\frac{p}{1-p}\right) = \alpha + \beta x$$

where α is the intercept parameter, β is the vector of slope parameters, and x is a vector of predictor variables.

Childlessness was considered as a dependent outcome variable in multivariate logistic regression with dummy (0-1) predictor variables using the SAS statistical package (procedure LOGISTIC). The independent predictor variables included six sets of binary variables:

1. calendar year of birth (to control for historical increase in life expectancy as well as for fluctuations in life span over time). The whole birth-year period of 1500 to 1875 was split into four fifty-year intervals

- (for 1500 to 1700), five twenty-five-year intervals (1700 to 1825) and ten five-year intervals (after 1825) presented by binary (0–1) variables with the reference level set at 1870–1874 birth years.
2. female life span (the key variable of this study aimed to explore the effects of female life span on childlessness). The female life span data were grouped into eight ten-year intervals with the exception of the first (< 20 years) and the last (≥ 90 years) intervals, which had a small number of observations. The data were coded as dummy variables with the reference level set at 50 to 59 years for female life span.
 3. female (wife's) age at marriage. This variable is used to control for possible confounding effects of female age on probability of being childless. Age at marriage is the most important explanatory variable both for the number of progeny and for the age at first childbirth (Knodel 1988). For example, it is well known in historical demography that the mean number of progeny in the past was about eight children for women married at age 20 to 24, and only two children for women married at age 35 to 39 (Knodel 1988). For this reason, if the data are not adjusted for the age at marriage (age when the births of legitimate children start), the analysis of the number of progeny in humans can be seriously compromised. In our study, the female age-at-marriage data were grouped into six five-year intervals with the exception of the first (< 20 years) and the last (≥ 40 years) intervals, which had a small number of observations. The data were coded as dummy variables with the reference level set at 20 to 24 years old for wife's age at marriage.
 4. male (husband's) age at marriage. This is a second fundamental predictor variable for the number of offspring (a proxy for husband's fertility). If the husband is ten or more years older than the wife, the number of births may be twice as low compared to a situation where the husband is younger than the wife (Knodel 1988). This variable is used to control for possible confounding effects of the husband's age on the probability of being childless. The husband's age-at-marriage data were grouped into seven five-year intervals with the exception of the first (< 20 years) and the last (≥ 45 years) intervals, which had a small number of observations. The data were coded as dummy variables with the reference level set at 20 to 24 years old for husband's age at marriage.
 5. male (husband's) life span. This variable controls for duration of marriage dependent on spousal death. The data were grouped and coded in the same way as female (wife's) life span.
 6. nationality. The nationality of the individual is represented by three categories: British, French, and other European nationalities. The group of "other" nationalities (mostly Germans) was the reference group.

Results and Discussion

The results of the univariate analyses of childlessness are presented in tables 3.1 and 3.2. Table 3.1 shows the historical distribution of childless women in our sample of women belonging to the European upper nobility. The data demonstrate a gradual decline of childlessness over time among aristocratic women. Similar trends were observed in the eighteenth and nineteenth century for the British peerage (Hollingsworth 1957, 1964) and during the first half of the twentieth century in France (Toulemon 1996); these trends may reflect an improvement of reproductive health over time.

Table 3.2 presents the distribution of childlessness as a function of female life span. Data obtained by other researchers are presented in the same table for comparison. Note the unrealistically high proportion of childless women in the data published by Westendorp and Kirkwood (1998). On the other hand, data by Lycett, Dunbar, and Volland (2000) as well as our data for aristocratic women are consistent with each other and do not demonstrate any increase in childlessness for long-lived women.

The results presented so far were obtained using univariate analyses, which do not take into account important confounding variables described earlier. In order to study the "true" relationship between childlessness and longevity, we need to take into account these other confounding variables. We applied multivariate logistic regression with childlessness as a dependent

Table 3.1 Reproductive and lifespan characteristics of married women in a historical dataset used in this study. Data on European aristocratic women with high nobility rank born in 1500–1875.

Birth cohort (Birth-year range)	Average number of progeny	Proportion of childless women	Mean age at death, years	Sample size, number of cases
1501–1550	6.00 ± 0.48	0.24	52.58 ± 1.62	111
1551–1600	5.21 ± 0.34	0.21	51.10 ± 1.21	185
1601–1650	5.19 ± 0.33	0.16	52.52 ± 1.11	220
1651–1700	4.53 ± 0.25	0.20	53.21 ± 1.09	302
1701–1725	5.07 ± 0.33	0.13	53.21 ± 1.41	165
1726–1750	5.07 ± 0.31	0.13	57.85 ± 1.52	171
1751–1775	4.50 ± 0.23	0.13	56.23 ± 1.23	234
1776–1800	4.12 ± 0.17	0.14	60.41 ± 1.09	346
1801–1825	3.88 ± 0.14	0.11	63.52 ± 0.89	475
1826–1850	3.85 ± 0.11	0.07	66.50 ± 0.71	666
1851–1875	3.48 ± 0.09	0.10	69.80 ± 0.61	848
Total	4.25 ± 0.06	0.13	61.59 ± 0.32	3,723

Table 3.2 Proportion of childlessness by women's age at death. Comparison of our data set with similar data for the historical German population (Lycett et al. 2000) and data for the British aristocracy (Westendorp and Kirkwood 1998).

Age at death, years	Proportion of childless women in different datasets		
	Gavrilovs dataset on European upper nobility	Lycett et al. (2000), German data	Westendorp and Kirkwood (1998), British aristocracy
20–29	0.17	0.15	0.39
30–39	0.10	0.08	0.26
40–49	0.14	0.08	0.31
50–59	0.13	0.11	0.28
60–69	0.12	0.09	0.33
70–79	0.10	0.09	0.31
80–89	0.15	0.10	0.45
90+	0.12	—	0.49

binary variable and calendar year of birth, female age at marriage, male age at marriage, female life span, and male life span as predictor variables.

The main result of our study is shown in figure 3.1. This figure presents the odds of being childless as a function of female life span, adjusted for other important confounding variables. The odds of childlessness are particularly high when women's life span is short (< 30 years), which is not surprising. What is important is that the chances of being childless do not demonstrate a statistically significant increase among long-lived women (life span > 90 years). This result confirms the findings from our univariate analyses (table 3.2) as well as from other studies (Lycett, Dunbar, and Voland 2000; Korpelainen 2000) that demonstrated that long-lived women do not have a higher rate of childlessness even when controlling for other important confounding variables.

Figure 3.2 demonstrates the chances of a married couple being childless as a function of the husband's life span. As in the previous case, the chances for a couple to be childless are particularly high when husband's life span is short (< 40 years), which again is not surprising. What is interesting is that the odds of childlessness do not increase for longer-lived males, including nonagenarians (life span > 90 years). Thus, both males and females with high longevity do not demonstrate any signs of impaired fertility, contrary to some previous reports (Westendorp and Kirkwood 1998).

We also found the women's age at marriage to be a significant predictor of childlessness. The odds ratio for childlessness is five times higher for women married at ages 35 to 40 years compared to early-married women

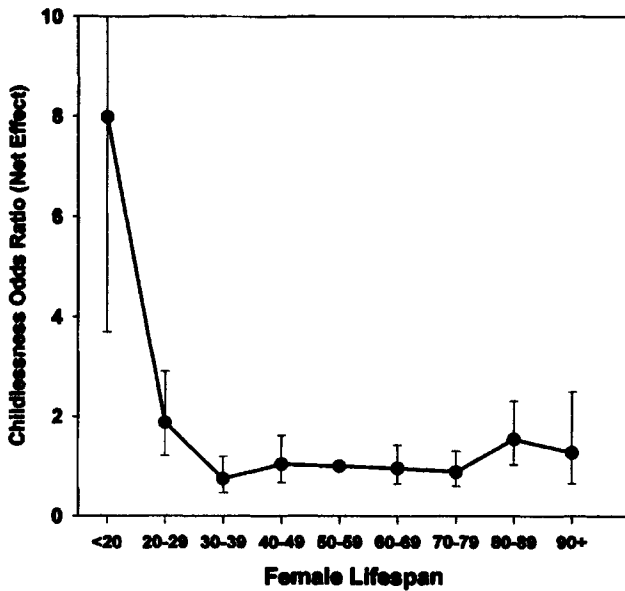


Figure 3.1 Childlessness odds ratio as a function of female life span. Net effects are adjusted for female calendar year of birth, female age at marriage, husband's life span, and husband's age at marriage. Multivariate regression analysis of 3,723 European aristocratic families.

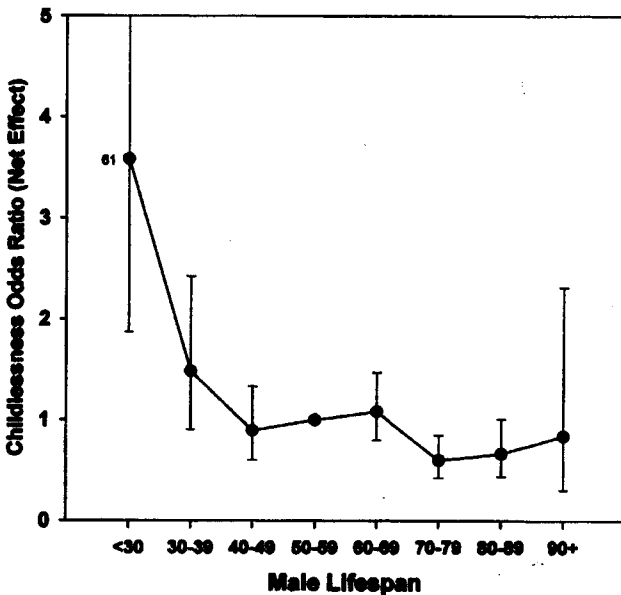


Figure 3.2 Childlessness odds ratio as a function of husband's life span. Net effects are adjusted for female calendar year of birth, female life span, female age at marriage, and husband's age at marriage. Multivariate regression analysis of 3,723 European aristocratic families.

(ages 20 to 25 years). Our results also demonstrate the importance of the husband's age at marriage as a significant predictor of couple childlessness. In particular, the trend of rising infertility with age of husband starts as early as at 25 years old for men. The odds ratio for childlessness is twice as high when the husband's age at marriage is 35 to 40 years compared to early-married husbands (at ages 20 to 25 years). These data demonstrate that a husband's age of marriage cannot be ignored in studies of human fertility.

The finding that a woman's age at marriage has a tremendous effect on the chances of being childless is in accord with common sense and many other observations. The importance of a husband's age at marriage is less obvious, and it is particularly intriguing that some loss of fertility starts so early in men's life—at age 25 years. In early studies of human reproduction, the husband's age at marriage was considered an unimportant variable in fertility determination (Freeman 1935). However, our results demonstrate that a decline in fertility with husband's age starts very early and progresses rapidly. It is known that mutation rates in male germ cells are much higher than in female ova cells (Crow 1997, 2000; Gavrilov and Gavrilova 2000), and this rapid accumulation of mutation load with age may contribute to an age-related increase in male infertility. It is clear that ignoring such important variables as the age at marriage for each spouse would compromise any scientific study of human fertility no matter how carefully planned and analyzed are other aspects of the study.

Our study does not support the concept that human longevity comes at the cost of infertility. This conclusion may have both theoretical significance (testing some evolutionary theories of aging) as well as practical implications for the future of life extension. It helps relax concerns over the question of whether it is morally acceptable to extend human longevity at the cost of infertility. Specifically, our findings do not support the prediction that “the next generations of *Homo sapiens* will have even longer life spans but at the cost of impaired fertility” (Westendorp 2004). Some authors have already raised concerns on the unintended consequences of life span extension: “increasing longevity through genetic manipulation of the mechanisms of aging raises deep biological and moral questions. These questions should give us pause before we embark on the enterprise of extending our lives” (Glannon 2002). This study helps alleviate some concerns on these issues.

Conclusions

We have tested the prediction of some evolutionary theories of aging that exceptional human longevity should come with a high cost of infertility. To this aim, we collected particularly accurate genealogical data for the upper

European nobility that were cross-checked against multiple data sources. We found no increase in the proportion of childlessness among long-lived women and men. Thus our study does not support the concept that human longevity comes at a high cost of infertility. Previous reports of high rates of childlessness among long-lived women (Westendorp and Kirkwood 1998) are likely to be an artifact of data incompleteness caused by underreporting of children in the analyzed data set, as revealed in previous studies (see Gavrilova and Gavrilov 1999; Gavrilov and Gavrilova 2002; Doblhammer and Oeppen 2003; Gavrilova et al. 2004). Our finding is also consistent with the results of earlier studies (Beeton, Yule, and Pearson 1900; Freeman 1935; Henry 1956, 1963; Bideau 1986; Knodel 1988; Le Bourg et al. 1993) as well as recent publications (Costa, Luzzza, and Mattace 2000; Gudmundsson et al. 2000; Müller et al. 2002) that demonstrated that exceptional human longevity is not associated with impaired fertility.

It is important now to revise a highly publicized scientific concept of heavy reproductive costs for human longevity and to make corrections in related teaching curriculums for students. It is also important to disavow the concerns over further extension of human life span that were recently voiced in biomedical ethics because of acceptance of the idea of harmful side effects of life span extension, including infertility (Glannon 2002).

There is little doubt that the number of children can affect human longevity through complications of pregnancy and childbearing, through economic costs of childbearing and changes in socioeconomic status, and so forth. However, the concept of heavy infertility cost in exchange for human longevity is not supported by data, when these data are carefully cleaned and cross-checked to ensure their completeness and accuracy. Our finding that there is no infertility cost for human longevity makes it easier to study and interpret the grandmaternal effects on offspring survival and reproduction because these effects are not confounded by longevity-infertility relationships for individuals. This helps to straighten out the interpretation of numerous important studies on the effects of grandmothers on grandchildren survival and reproductive success (Volland 1998; Hawkes 1998, 2004; Sear, Mace, and McGregor 2000; Volland and Beise 2002; Lahdenperä et al. 2004).

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GRANDMOTHERHOOD

The Evolutionary Significance of
the Second Half of Female Life



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