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Human Longevity and Parental Age at Conception

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Abstract

Childbearing at older ages has become increasingly common in modern societies because of demographic changes (population aging), medical progress (e.g., in vitro fertilization in older women) and personal choice. Therefore, the following question has become particularly important: What will be the health and longevity of the children born to older parents? While the detriment effects of late reproduction on infant mortality and genetic diseases have been well documented, little is known about the long-term postponed effects of delayed parenting on the mortality and longevity of adult offspring. The purpose of this study is to fill the gap that exists in our knowledge about the possible postponed detrimental effects of late parenting.

Individuals born to older parents may suffer from a load of deleterious mutations. The human spontaneous mutation rate for DNA base substitutions is reported to be very high, presumably more than one new mutation per zygote (Crow 1997). The mutation rate is much higher in male sperm cells than in female ovaries and increases with paternal age due to the large number of cell divisions in the male germ line (Crow 1997). In this study we checked whether human longevity is affected by the increased mutation load expected for the progeny of older fathers. For this purpose the high quality data (more than 15,000 records) on European royal and noble families were collected, computerized and analyzed. The data on offspring life span were adjusted for historical trends and fluctuations in life expectancy of human birth cohorts. Also, to avoid bias in estimating the offspring life span, only extinct cohorts were analyzed (born in 1800–1899).

We found (after controlling for maternal age at reproduction, paternal and maternal longevity and sex-specific cohort life expectancy) that adult daughters (30+ years) born to older fathers (45–55 years) lived shorter lives, and for each additional year of paternal age the daughters lost about 0.5 ± 0.2 years of their life span. In contrast to daughters, the sons were not significantly affected by delayed paternal parenting. This result was also confirmed after taking into account additional confounding variables (nationality, birth order, cause of death and loss of parents before age 20) using multiple regression on nominal variables. Since only daughters inherit the paternal X chromosome, this sex-specific life span shortening for daughters born to older fathers might indicate that the

Robine et al. (Eds.)
Sex and Longevity: Sexuality, Gender,
Reproduction, Parenthood

genes affecting longevity and sensitive to mutation load are probably concentrated in the X chromosome.

The mutation theory of life span predicts that those individuals who have a low mutation rate in their somatic and germ cells will live longer lives and will be able to produce normal offspring even in old age. This prediction was tested in this study for the first time and proved to be correct. Daughters born to old fathers lived shorter lives but those daughters who were born to longer-lived fathers (81+ years) were not affected by the late paternal age at conception.

Another new finding of this study is that daughters born to particularly young fathers (below 25 years) also tended to live shorter lives. This finding is consistent with existing epidemiological data on the increased risk of congenital diseases and impaired behavioral performance among children born to particularly young fathers, as well as with similar animal studies. Thus, the age constraints for the donors of sperm cells (used for in vitro fertilization) should be carefully revised.

Why Studies of Parental-Age Effects Are so Important

Practical Importance of the Studies

Childbearing at older ages has become increasingly common in modern societies because of demographic changes (population aging), medical progress [e.g., in vitro fertilization (IVF) in older women] and personal choice (Kuliev and Modell 1990). For example, in the United States the number of births to older mothers (35–39 years and 40+ years) more than doubled since 1980, whereas the number of births to younger mothers (below age 30) did not increase (see Table 1).

Birth rates for older fathers (ages 45–49 and 50–54) are also increasing (US Monthly Vital Statistics Report 1997), and this trend may even accelerate in the future due to medical progress (Viagra, for example). Moreover, it has become possible to enjoy fatherhood at an older age through an assisted reproduction technique called intracytoplasmic sperm injection (ICSI). A few spermatozoa are

Table 1. American mothers are becoming older. Increasing number of births to older mothers

Age of mother	Total number of births in thousands in the United States, by year										
	1980	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
<20	562	478	472	473	489	518	533	532	518	501	518
20–24	1,226	1,141	1,102	1,076	1,067	1,078	1,094	1,090	1,070	1,038	1,001
25–29	1,108	1,201	1,200	1,216	1,239	1,263	1,277	1,220	1,179	1,129	1,089
30–34	550	696	721	761	804	842	886	885	895	901	906
35–39	**141**	**214**	**230**	**248**	**270**	**294**	**318**	**331**	**345**	**357**	**372**
40 and more	**24**	**29**	**31**	**36**	**41**	**46**	**50**	**54**	**58**	**61**	**66**

Source: US Bureau of the Census (1997)

extracted either from the semen or testis of old men, and each sperm is then injected into an individual egg that is implanted in the fallopian tube. Thus, old age and even clinical death are not obstacles to fatherhood any longer.

However, one important concern remains: What will be the health and longevity of the children born to older parents? While the detrimental effects of late reproduction on infant mortality and genetic diseases have been well documented (see below), little is known about the long-term postponed effects of delayed parenting on the mortality and longevity of adult offspring. The purpose of this study is to fill the gap that exists in our knowledge about the possible postponed detrimental effects of late parenting.

Scientific Significance of Studies of Parental-Age Effects

Despite their practical and scientific importance, the fundamental mechanisms that determine human longevity are still unknown. In particular, it is not yet known whether genomic damage is the most critically important force influencing human longevity (mutation theory of aging; see Vijg and Gossen 1993). One approach to resolving this problem is to study the life span of offspring born to parents at different ages and to determine whether the established, age-related accumulation of the DNA damage in parental germ cells is important for the longevity of the offspring. The scientific credibility of such an approach is supported by the recent findings that paternal age at reproduction is the major determinant of the level of mutation load in humans (Crow 1993, 1995, 1997).

According to existing evidence, parental age has many detrimental influences on the longevity of offspring (for an exhaustive review of this topic, see Finch 1990). The major maternal age-related changes in humans are increases in fetal aneuploidy later in reproductive life such as:

- Down's syndrome (trisomy 21) (Hook 1986; Carothers et al. 1978; Bocciolone et al. 1989; Erickson 1978; Saxen 1983)
- Klinefelter's syndrome (XXY) (Carothers et al. 1978; Carothers and Filippi 1988)
- Edward's syndrome (trisomy 18) and Patau's syndrome (trisomy 13) (Hook 1986; Carothers et al. 1978).

Advanced maternal age also remains an important independent risk factor for fetal death (Parazzini et al. 1990; Resseguie 1976; Fretts et al. 1995).

The detrimental effect of late paternal reproduction is also well known: advanced paternal age has been associated with an increase in new dominant mutations in offspring that result in congenital anomalies (Auroux 1993a, b, 1983; Risch et al. 1987; Lian et al. 1986; McIntosh et al. 1995; Meacham and Murray 1994; Savitz et al. 1991; Friedman 1981; Bordson and Leonardo 1991; Vogel 1983; Carothers et al. 1986; Young et al. 1987). In particular, paternal age is responsible for new dominant autosomal mutations that cause different malformations, including:

- achondroplasia (Auroux 1993a, b; Lian et al. 1986)
- Apert syndrome (Auroux 1993a, b)
- Marfan syndrome (Auroux 1993a, b)
- osteogenesis imperfecta (Carothers et al. 1986; Young et al. 1987) and other inherited diseases.

Older paternal age was observed among patients with Costello syndrome (Lurie 1994), chondrodysplasia punctata (Sheffield et al. 1976), fibrodysplasia ossificans progressiva (Connor and Evans 1982; Rogers and Chase 1979), and thanatophoric displasia (Martinez-Frias et al. 1988). Advanced paternal age at reproduction is also associated with increased risk of preauricular cyst, nasal aplasia, cleft palate, hydrocephalus, pulmonic stenosis, urethral stenosis, and hemangioma (Savitz et al. 1991). Increased paternal age at childbirth is also an important independent risk factor for neonatal and infant mortality (Gourbin and Wunsch 1999).

There is, however, one very important question that has yet to be addressed: does parental age at birth (or conception) influence the longevity of the vast majority of the population of so-called "normal healthy people" who do not suffer from aneuploidy and other obvious genetic conditions that tend to appear early in life? In other words, are aging-related diseases associated with paternal and maternal age at conception or birth? It is possible to address this question by examining the life expectancy of adults (say, at age 30 and older) as a function of parental age at reproduction. By adult age a substantial portion of the subpopulation suffering from early-acting deleterious mutations has already died (i.e., selected out). The information on potential life-shortening effects of late parental reproduction on adult offspring is notable because it addresses a possibly important gap in knowledge about the mechanisms of human longevity, the aging process itself, and of the possible role of accumulated genetic damage in the germ line on aging and longevity.

Historical Background

The first mention in the historical literature suggesting a possible life-shortening effect on offspring of delayed parenting was made by the French naturalist Buffon (1826), who noted that when old men procreate "they often engender monsters, deformed children, still more defective than their father" (see Robine and Allard 1997).

Later, intensive studies of human genealogical data were initiated by Karl Pearson (Beeton and Pearson 1901) and Raymond Pearl (Pearl 1931; Pearl and Dewitt 1934) and developed further by other researchers (Hawkins et al. 1965; Abbott et al. 1974; Murphy 1978; Wyshak 1978; Desjardins and Charbonneau 1990; Bocquet-Appel and Jakobi 1991). However, these empirical studies were focused specifically on inheritance of human longevity rather than on the question of parental age effects at birth on offspring longevity, as proposed here.

Before our early preliminary studies on this topic (Gavrilov et al. 1995a, b), other researchers partially addressed the same issue (Jalavisto 1950; Philippe

1980). Jalavisto (1950) analyzed 12,786 published family records of the Finnish and Swedish middle class and nobility born in 1500–1829. Unfortunately, in this interesting study the secular changes in human life span during this long historical period (1500–1829) were not taken into account, and the investigator did not attempt to control for the possible effects of other confounding factors. Jalavisto (1950) concluded that offspring born to older mothers live significantly shorter lives, and the age of the father was of no importance. These observations deserve to be replicated in future studies by controlling for the effects of other confounding factors and historical changes in the life expectancy of birth cohorts.

In 1980 Pierre Philippe studied five birth cohorts (1800-29, 1830–49, 1850–69, 1870–79, 1880–99) from a small rural population of Isle-aux-Coudres, Quebec, Canada. Multiple discriminant analysis was used to study the effects of different familial characteristics (such as parental consanguinity, maternal and paternal age at time of childbirth, birth order, the interval since the previous birth, months of birth, viability of the preceding infant, etc.) on offspring age at death, broken into 10 age groups (from age 0 through 90 years and over). Surprisingly, possibly the most evident and important predictors of offspring longevity (paternal and maternal life spans) were not included in the analysis. Also, the author noted the following: "taking into consideration the possibility of differential emigration" from this small rural area (Isle-aux-Coudres), the results of analysis "must certainly be regarded cautiously" (Philippe 1980, p. 215). Indeed, in many cases the results of this analysis were not statistically significant, perhaps because of the small size of the birth cohorts (105–298 cases only in each cohort), and also because of possible overloading of the analysis by too many variables (up to 26 binary variables were included in the analysis). In spite of these problems, the author of this study made an intriguing observation that increased maternal age at time of childbirth (35 years and above) is the main factor common to both early (0–5 years) and late (70 years and above) death (Philippe 1980). By contrast, increased father's age was uncommon for long-lived offspring (Philippe 1980).

These important and contradictory observations deserve to be tested in future studies by using larger sample sizes and controlling for parental longevity. Control for parental longevity is important since recent studies have demonstrated that among long-lived women the proportion of those able to become mothers after 40 years is four times higher compared to "normal" women (Perls et al. 1997). Thus, increased offspring longevity might not be due to the older age of mother at childbirth per se, but due to higher longevity of such mothers and the inheritance of the longevity by the offspring. This hypothesis deserves to be tested in future studies.

Recent Preliminary Studies

Our first preliminary studies on long-term effects of parental age at reproduction on offspring longevity in humans were based on the statistical analysis of human genealogical data on European royal and noble families. We demonstrated that

paternal age at reproduction has a specific threshold life-shortening effect on daughters rather than on sons (Gavrilov et al. 1995a, b, 1997a–c; Gavrilov and Gavrilova 1997a, b). Attempts to reproduce these results were made recently by other authors (Robine and Allard 1997) using archives in Arles, France, but in this study both sexes (daughters and sons) were mixed and analyzed together, so the results are not comparable. Since paternal and maternal ages at reproduction are correlated (older mothers tend to have older spouses), it is important to study the effect of maternal age on offspring longevity. It was found that for mothers in the reproductive age range of 20–39 there was no observed effect of maternal age on the longevity of adult children (Gavrilov et al. 1997b). Since the reproductive life span of females is shorter than in males because of menopause, the sample size for children of very old mothers (more than 40 years old) has so far been too small to draw any conclusions on this issue. Further studies designed to increase sample sizes are therefore important in order to assess the independent effects of both paternal and maternal ages at reproduction on offspring longevity.

Biological Ideas Related to Studies of Parental Age Effects

Two preliminary observations were made in the above-mentioned studies (Gavrilov et al. 1995a, b, 1997a, c; Gavrilov and Gavrilova 1997a, b).

First, the effect of parental reproductive age on longevity of adult children was observed for fathers only (specific paternal effect).

Second, paternal age is detrimental for longevity of daughters only (specific sex-linked effect on daughters).

Both observations may have biological explanations. It has already been established that the mutation rate in human paternal germ cells is much higher than in maternal ones (Crow 1993, 1995, 1997), with the age of the father demonstrated to be the main factor determining the spontaneous mutation rate of nuclear DNA (Crow 1993, 1995, 1997). Thus, there is good reason to expect the presence of a paternal rather than a maternal influence on offspring longevity, since mutational load in germ cells is mainly of paternal origin. The reason for this specific paternal effect is that the mutation rate is largely determined by the number of cell divisions and DNA replications, a time when errors are introduced into the DNA of the germ cells. Since the number of cell divisions between zygote and sperm (in males) is much larger than between zygote and egg (in females), much higher accumulation of DNA damage in paternal germ cells should be expected. In humans, the estimated number of cell divisions in females between zygote and egg is 24, which is largely independent of age (Vogel and Motulsky 1997). In males the number of cell divisions between zygote and sperm is much larger. The number of divisions prior to a sperm produced at puberty (e.g., age 13) is estimated at 36, and thereafter the number increases by 23 divisions per year (Vogel and Motulsky 1997). So, at age 20 the number of cell divisions is about 200 and has increased by age 50 to about 890 cell divisions Thus, there is reason to hypothesize specific paternal effects on mutational load and longevity in the offspring.

The second observation from our previous work is that high paternal reproductive age is detrimental for daughters only. Since the paternal X chromosome is inherited by daughters rather than sons, this observation might indicate that critical genes (critical targets for mutational damage) important for longevity are located on the X chromosome. This suggested explanation is valid for both dominant and recessive mutations, since only one X chromosome is active in each particular human female cell and the second X chromosome is inactivated after the first 48 hours of the zygote's development.

It is important to note that there is a good evolutionary reason for mother Nature to hide critical genes on the X chromosome, since it is one of the safest locations in the human genome. The reason is that the level of DNA damage in a particular chromosome is determined by its exposure to the "male environment." For example, the most unfavorable situation is observed for Y chromosomes that are male-specific. Since the Y chromosome is always in males whereas an autosome is in males only half of the time, the level of DNA damage for this chromosome should be especially high. Indeed, it has already been demonstrated that the primate evolution rates (that are correlated to mutation rates) of the Y-linked argininosuccinate synthetase pseudogene are about two times higher than those of its autosomal counterpart (Miyata et al. 1990). Thus, in a sense the Y chromosome is the most "dangerous" place in the human genome, which might be the reason why so few genes are associated with that chromosome. Contrary to the Y chromosome, the X chromosome is less exposed to the "male environment" since females have two copies of it whereas males have only one copy. Since one-third of all human X chromosomes are in males, the X chromosome should have a mutation rate that is two-thirds that of the autosomes (2/3 = 0.67). Miyata et al. (1990) demonstrated that the X/autosome ratio for silent changes in DNA during primate evolution (that is proportional to mutation rates) is in fact 0.69 (very close to the expected 0.67 ratio).

Recent studies on rodents have also demonstrated that the rate of substitution of synonymous mutations in X-linked genes to that in autosomal ones is 0.62 $\pm$ 0.04, which is consistent with X-linked genes having a reduced mutation rate (McVean and Hurst 1997). Thus, the X chromosome is in a sense the "safest" place in the human genome, implying that there is a good evolutionary reason to hide the most critical genes in this particular chromosome. One such critical gene located in the X chromosome is the gene for DNA polymerase alpha, an enzyme involved in DNA replication (Wang et al. 1985). Mutations of this critical enzyme may result in a decrease in the accuracy of DNA replication and thus a catastrophic increase in mutation rates (Orgel 1963, 1970). Other critical genes located on the X chromosome are genes for glucose-6-phosphate dehydrogenase (important for protection against oxidative damage of DNA and other structures) and plasma membrane Ca^{++} transporting ATPase.

Another possible explanation for the critical importance of mutation load on the X chromosome is related to the special status of this chromosome in females. As already noted, in each particular female cell only one X chromosome is active, and the second one is inactivated. Thus, at the intracellular level there is no

genetic redundancy for genes located on the X chromosome compared to genes located on autosomes (two active copies are there). For this reason, deleterious recessive mutations could be completely complemented if they are heterozygous and are located in autosomes, but they **cannot** be complemented at the intracellular level if they are located on the X chromosome. Complementation of these mutations is possible at the intercellular level only. Mutations on X chromosomes may therefore be more "visible" through their effects on mortality compared to mutations on other chromosomes.

The specific, life-shortening effect of paternal age on daughters' longevity might also be caused by the specific increase of mutation rates on the paternal X chromosome. The X is methylated in the male germ line and for this reason should be more prone to mutations than maternal X, as both X chromosomes are unmethylated in the female germ line (Driscoll and Migeon 1990).

The X chromosome hypothesis provides a very specific prediction that we propose to test in future studies. Since the grandfather's X chromosome is inherited through the mother's side only, one might expect a specific effect of the reproductive age of the maternal grandfather. Specifically, this hypothesis predicts that grandchildren (grandsons in particular) should live shorter lives if their mother was born to an older grandfather (Gavrilov and Gavrilova 1997a). This specific age effect of the maternal grandfather has already been demonstrated for some X-linked genetic diseases, such as Duchenne muscular dystrophy (caused by mutation in locus on Xp21; Bucher et al. 1980), hemophilia A and Lesch-Nyhan disease (reviewed by Vogel and Motulsky 1997). However, this hypothesis has never been tested for the duration of human life; we plan to test it in our future studies.

Possible Implications from Studies of Parental-Age Effects

The following important implications may be expected from future studies of parental age effects on offspring longevity:

1) If future studies confirm significant parental age effects in humans, these findings will have a profound effect on the concepts and methods of genetic, epidemiologic longevity studies. In particular, all previous epidemiological and genetic studies of human aging and life span will have to be revised, controlling for the confounding effects of the parental age variables.

2) Physicians will become aware whether potential patients born to older parents represent a risk group that should be screened more carefully for health problems at older ages. For example, it was recently found that older paternal age is a risk factor for a sporadic form of Alzheimer's disease, whereas maternal age has no prognostic importance (Bertram et al. 1998). If parental age effects prove to be as important as the effects of smoking habits, the implications for life insurance practice could become obvious.

3) Potential older parents (and physicians involved in new reproductive technologies) will receive important new knowledge about health risks associated

with parenting in later life. In the case of IVF, the age constraints for donors of sperm and ova cells will be more carefully considered.

4) On the other hand, if parental age effects prove to be insignificant in future studies, this would be a great relief for older parents and their children. This is a particularly relevant issue today given trends in delaying childbearing in the United States and other developed nations. This outcome of the study will also become a scientific challenge for biologists, who have to explain how the human species manages to cope with high mutation rates. This problem has already received increasing attention from the scientific community (see recent discussions on this problem in scientific literature; Crow 1997, 1999; Eyre-Walker and Keightley 1999; Gavrilov and Gavrilova 1999a).

Research Findings and Discussion

The First Wave of Exploratory Studies: Analysis of Cross-Tabulations

In our first study of parental age effects for 8,518 persons from European aristocratic families with well-known genealogy (Van Hueck 1977–1997; Gavrilova and Gavrilov 1999), we found a strong inverse relationship between father's age at reproduction and daughter's (not son's) longevity (Gavrilov and Gavrilova 1997a; Gavrilov et al. 1997a). The results of this study are summarized in Table 2.

Note that daughters born to old fathers lose about 4.4 years of their life and these losses are statistically significant ($p < 0.01$; Student's test, $t = 3.1$), whereas sons are not significantly affected. This finding is in accord with the mutation theory of aging (Vijg and Gossen 1993), since paternal age at reproduction is

Table 2. Human longevity and sex differential in longevity as a function of father's age at reproduction

Paternal age at reproduction[a] (years)	Mean age at death[b] ± standard error (years) Daughters (sample size)	Sons (sample size)	Sex differential in life span (years)
20–29	66.5 ± 0.7 (592)	61.3 ± 0.4 (1,238)	5.2 ± 0.8
30–39	65.9 ± 0.5 (1,214)	60.8 ± 0.3 (2,580)	5.1 ± 0.6
40–49	64.4 ± 0.7 (694)	60.5 ± 0.4 (1,543)	3.9 ± 0.8
50–59	62.1 ± 1.2 (206)	60.3 ± 0.7 (451)	1.8 ± 1.4

[a] Data are controlled for father's longevity (all fathers lived 50 years and more) to eliminate bias caused by correlation between father's and offspring life span.

[b] Human longevity was calculated for adults (those who survived to age 30) born in the 18th and 19th centuries. The data for those born in the 20th century were excluded from the analysis to have unbiased estimates of longevity for extinct birth cohorts.

considered to be the main factor determining human spontaneous mutation rate (Crow 1993, 1995, 1997). Also, since only daughters inherit the paternal X chromosome, this sex-specific decrease in longevity of daughters born to old fathers might indicate that human longevity genes (crucial, housekeeping genes) sensitive to mutational load might be located in this chromosome (Gavrilov and Gavrilova 1997a; Gavrilov et al. 1997a).

Another interesting observation is that sex differences in human longevity are a function of paternal age at reproduction. The data presented in Table 2 show that females live longer than males when fathers are young, whereas in the case of old fathers sex differences are very small and statistically insignificant (Gavrilova et al. 1995; Gavrilov et al. 1995b, 1997a). This preliminary observation may also have a biological explanation. Since females have two X chromosomes, they are genetically more redundant than males, who have only one X chromosome. However, when the father is older and the X chromosome transferred to his daughter has a higher mutational load, there is no longer a difference in genetic redundancy between males and females, since both have only one intact (maternal) X chromosome. Thus, there is every reason to expect that with increases in paternal reproductive age the sex differences in offspring longevity should decrease (see Table 2, the column for the sex differential in longevity, supporting this hypothesis).

It should be noted, however, that in these first studies (Gavrilov and Gavrilova 1997a; Gavrilov et al. 1997a) some possibly important covariates and confounding factors were not controlled for, such as maternal age at reproduction (which is strongly correlated with paternal age), historical trends and fluctuations in life expectancy of birth cohorts, and parental longevity (age at death). Thus, the next logical step in this line of inquiry is to fill this gap and examine the previous observations on the life-shortening effects of late paternal reproduction, taking into account the other important covariates mentioned above.

The Second Wave of Exploratory Studies: Multiple Linear Regression

In this next step of our study we increased the sample size and re-analyzed the data for the offspring born to older fathers at age 35–55. Offspring life span was analyzed for adults (those who survived by age 30) to study the long-term, postponed effects of late reproduction of the parents. The data for offspring born in the 20th century were excluded from the analysis in order to have unbiased estimates of longevity for extinct birth cohorts. The data for offspring born before the 19th century were also excluded in order to minimize the heterogeneity of the sample.

For each birth cohort the mean sex-specific expectation of life at age 30 was calculated and used as an independent variable in a multiple linear regression model to control for cohort and secular trends and fluctuations in human longevity. Offspring longevity for each particular sex (4,566 records for males and 2,068 records for females) was considered as a dependent variable in the multiple

Table 3. Parental predictors of human longevity. Coefficients (slopes) of multiple linear regression ± standard error

Variable	Sons	Daughters
Paternal age at reproduction	−0.06 ± 0.05	**−0.16 ± 0.07**
Maternal age at reproduction	0.03 ± 0.04	0.02 ± 0.06
Paternal age at death	0.13 ± 0.02	0.09 ± 0.03
Maternal age at death	0.03 ± 0.01	0.04 ± 0.02
Cohort life expectancy	1.07 ± 0.10	1.04 ± 0.05
Other characteristics of regression		
Sample size	4,566	2,068
Multiple R	0.2	0.4
F ratio	37.2	86.3

regression model (program 1R in BMDP statistical package) and a function of five independent predictors: paternal age at reproduction in the range of 35–55 years (where the life-shortening effect was previously detected; Gavrilov and Gavrilova 1997b), maternal age at reproduction (control for maternal age is important since it is correlated with paternal age), paternal age at death, maternal age at death (to control for heritability of human longevity), and sex-specific cohort life expectancy (control for cohort and secular trends and fluctuations).

The results of this study are presented in Table 3. The regression slope (b) for daughter's longevity as a function of paternal age at reproduction is negative ($b = -0.16 \pm 0.07$) and this inverse relationship is statistically significant (Student test, $t = -2.35$, $P = 0.02$) even when the effects of the other important four covariates are taken into account. In the case of sons the association with paternal age at reproduction is much weaker (regression slope, $b = -0.06 \pm 0.05$) and statistically insignificant (Student test, $t = -1.20$, $P = 0.23$).

Thus, this study lends support to the previous preliminary observations (Gavrilov and Gavrilova 1997a; Gavrilov et al. 1995b, 1997a) on the sex-specific, life-shortening effect of late paternal reproduction on daughters' longevity. It would be interesting to continue these studies and to check the prediction of the X chromosome hypothesis: the expected specific life-shortening effect of late grandpaternal reproduction from the mother's side only.

The results described above were based on the assumption that the dependence between offspring longevity and paternal age at reproduction could be considered approximately linear for paternal ages in the range of 35–55 years. The next step of the study was to check whether this assumption was valid. For this reason we re-analyzed the data for different ranges of paternal age at reproduction. It turned out that for the subgroup of younger fathers (35–45 years), the mean loss of daughters' life span is very small (0.02 ± 0.12 years lost per each additional year of paternal age) and statistically insignificant (sample size, $n = 1651$; Student test, $t = 0.16$; $p = 0.87$), whereas for older fathers (45–55 years) this loss is particularly high (0.48 ± 0.21 years lost per each additional year of paternal age) and statistically significant ($n = 598$; $t = 2.34$; $p = 0.02$). These results are

consistent with the general conclusion of Professor James Crow on the non-linear accelerating increase of mutation rates with paternal age (Crow 1993, 1995, 1997).

One possible explanation for this threshold effect of paternal age might be the competition among sperm cells. Since only one of a huge number of sperm cells succeeds in fertilization in each particular case, damaged sperm cells with a high mutational load may not withstand this strong competition. Only at very old ages, when the proportion of damaged sperm cells becomes higher than some threshold level, does the selection mechanism finally fail and accumulation of mutational load becomes evident (Gavrilov et al. 1997a).

There may be another explanation for the threshold nature of paternal effect on offspring longevity. Since short-lived fathers can participate in reproduction at young ages only, the detrimental effect of age-related accumulation of mutational load in paternal germ cells might be compensated for by selection effects (i.e., the population of old fathers is also the population of survivors compared to young fathers). In other words, the threshold behavior might be an artifact caused by the heterogeneity of the population. It is therefore important to study the effect of paternal age on a more homogeneous population of longer-lived fathers.

The results of our cohort study of the genealogical records of 8,518 persons from European aristocratic families presented in Table 2 have shown that the life-shortening effect of paternal age is more gradual (as opposed to operating under a threshold) if it is studied in a relatively homogeneous population of long-lived fathers (with life span of more than 50 years; Gavrilov et al. 1997a). This conclusion might be of practical importance since the effect of paternal age is not restricted by relatively rare cases of old fathers (50 years and above) but might be important in developed nations where a significantly larger portion of offspring are likely to be born to middle-aged fathers.

It is important to continue these studies to try to resolve the controversy between threshold and gradual parental age effects observed in different types of data analysis.

The Third Wave of Exploratory Studies: Analysis of Contour Maps for Life span

In this next stage of our study we increased the sample size (up to 17,215 computerized genealogical records) and applied the methods of contour maps to study parental age effects on offspring life span.

The idea behind this method is quite simple: the levels of life span are mapped in a way similar to the mapping of surface altitude in geographical maps. The horizontal, X axis corresponds to paternal age at childbirth (20–60 years), similar to the "West-East" dimension used in geographical maps. The vertical, Y axis corresponds to the maternal age at childbirth (15–45 years), similar to the "South-North" dimension used in geographical maps. Data for each person are plotted as points with X and Y coordinates corresponding to paternal and maternal ages when the person was born. The third dimension in this map is the per-

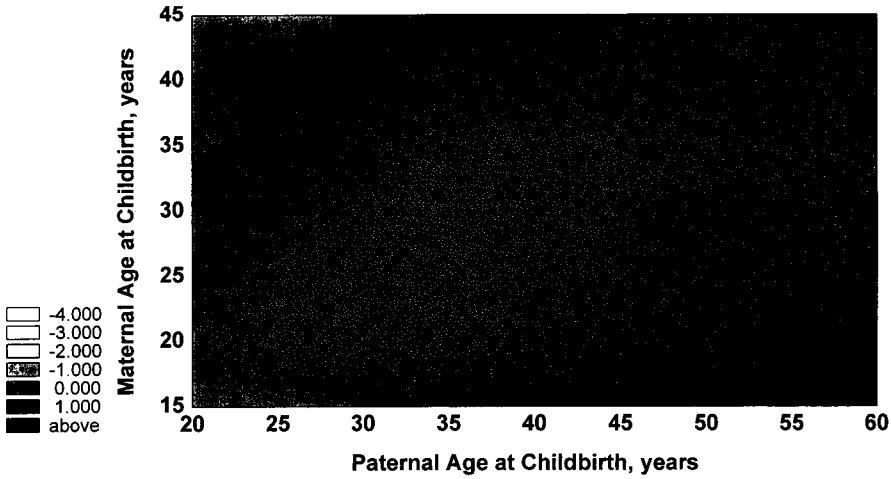

Fig. 1. Contour plot for levels of sons' life span (deviation from cohort mean) as a function of paternal (X axis) and maternal (Y axis) ages at childbirth. European noble families: 1800–1880 birth cohorts. Spline smooth. 12,015 cases

son's life span (expressed in normalized form as a deviation from control level: the mean life span of persons of the same sex, born in the same calendar year).

These life span residuals form the surface that is some years above or below the control life span level (similar to the sea level used in geographical maps). The surface is colored, like in geographical maps, depending on the direction and the extent of the deviation from the control life span level. In our study we used white for the lowest level of life span, grays of different intensities for intermediate life span levels and black for the highest level of life span.

As a result of such data presentation, contour life span maps are produced that allow one to visualize the large amounts of data in the form of colored contours. The data for men (sons) and women (daughters) are analyzed separately, producing two different maps (Fig. 1 and 2) with the same scales to allow their comparison.

The contour life span map for sons (Fig. 1) supports our previous findings that neither the father's nor the mother's age at childbirth has a significant effect on the son's life span. The whole map area is covered by intermediate grays, which indicate a very flat landscape ("life span prairie") and nothing interesting to study.

In contrast, the contour life span map for daughters (Fig. 2) has a very interesting and contrasting landscape ("life span precipice"). The lowest levels of daughters' life span (white areas) are observed for daughters born to young mothers (15–20 years) and to fathers of extreme ages (either below 25 years or above 55 years). In these two extreme cases the daughters' life span is three to four years below the reference level.

The highest levels of daughters' life span (black area) are observed for daughters born to older mothers (above 30–35 years) and middle-aged fathers (35–45

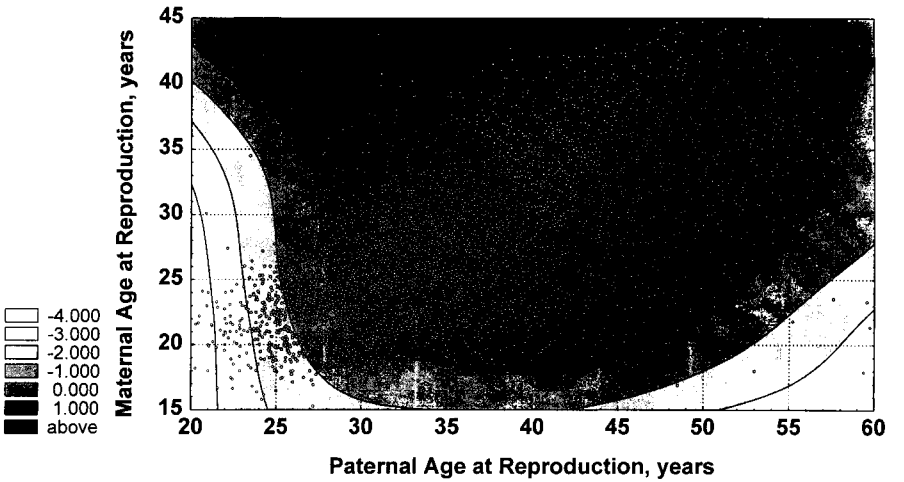

Fig. 2. Contour plot for levels of daughters' life span (deviation from cohort mean) as a function of paternal (X axis) and maternal (Y axis) ages at childbirth. European noble families: 1800–1880 birth cohorts. Spline smooth. 5,200 cases

years). In this case the daughters' life span is more than one year above the reference life span level. The black area observed for daughters of younger fathers ("Northwestern" part of the map; Fig. 2) should not be considered seriously, since there are no real data there (no couples composed of 20–30-year-old fathers and 40- to 45-year-old mothers).

If one fixes the mother's age at some level (say, age 30) and studies the paternal age effect (moving horizontally from the "West" to the "East"; Fig. 2), the daughters' life span first increases, reaching the maximum at a paternal age of 40–45 years. After that age the daughters' life span starts to decline. The decline in life span of daughters born to older fathers (above 40–45 years) is consistent with our previous findings (see earlier). However, the paradoxical increase in daughters' life span with paternal age for younger fathers (20–40 years) is a new finding that deserves to be studied in more detail.

One possible explanation of the "young father-short daughters' life span" paradox is that short-lived fathers cannot be old! Thus, the proportion of short-lived fathers with genetic diseases should be higher among younger fathers. Since human life span is heritable (Gavrilova et al. 1998), this may explain the observed paradox.

To test this hypothesis, we studied the contour life span maps, where the paternal life span variable is included in the analysis (Fig. 3–4). In these maps the horizontal, X axis corresponds to paternal life span (40–95 years, "West-East" dimension). The vertical, Y axis corresponds to paternal age at childbirth (20–60 years, "South-North" dimension). The maps for sons (Fig. 3) and daughters (Fig. 4) have the same scale of gradations and colors, allowing their comparison.

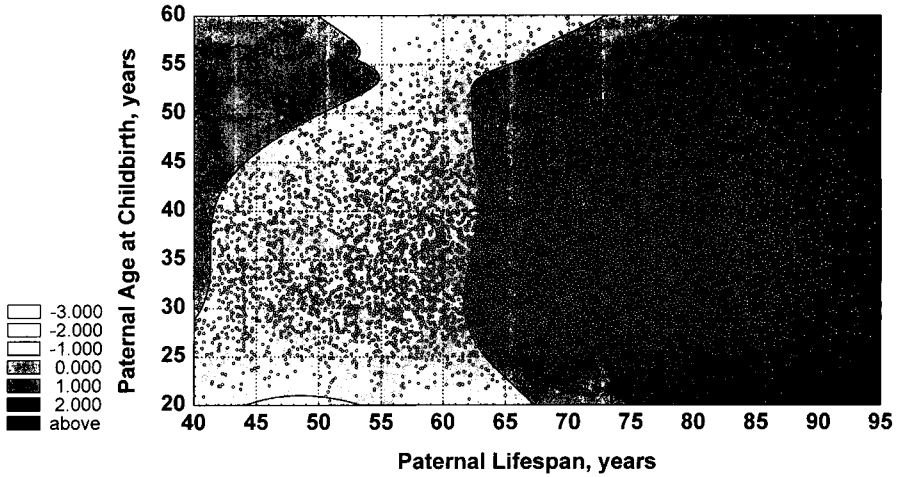

Fig. 3. Contour plot for levels of sons' life span (deviation from cohort mean) as a function of paternal life span (X axis) and age at childbirth (Y axis). European noble families: 1800–1880 birth cohorts. Spline smooth. 12,015 cases

The contour life span map for sons (Fig. 3) has vertical orientation of isolines, with the highest life span levels in the right, "Eastern" part of the map, corresponding to long-lived fathers (85–95 years). This pattern ("life span uphill") is consistent with our prior knowledge that sons' life span is determined by fathers' life span and does not depend on fathers' age at childbirth (no "South-North" differences).

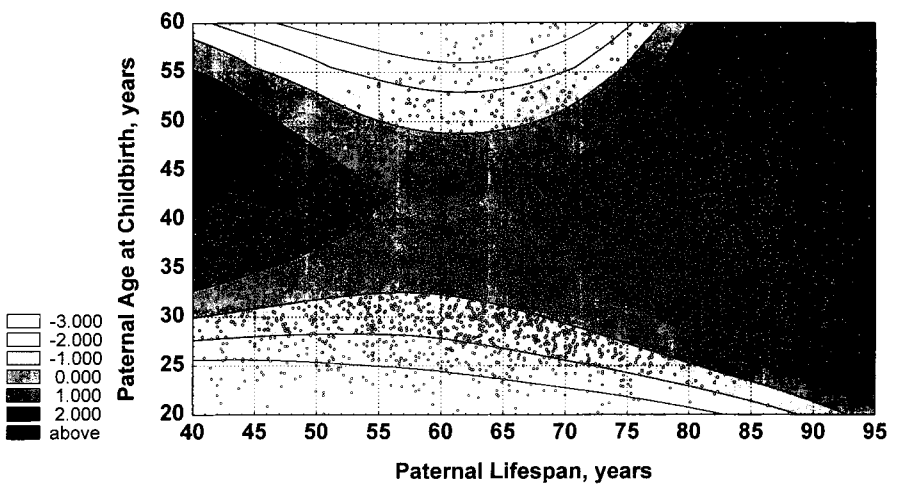

Fig. 4. Contour plot for levels of daughters' life span (deviation from cohort mean) as a function of paternal life span (X axis) and age at childbirth (Y axis). European noble families: 1800–1880 birth cohorts. Spline smooth. 5,200 cases

The contour life span map for daughters (Fig. 4) is particularly interesting: it looks like a "life span col." In addition to the paternal life span effects ("West-East" differences) there is also an effect of paternal age at childbirth ("South-North" differences). What is important is that, at any level of paternal life span, there is an optimal level of paternal age at childbirth (35–45 years), where daughters have the highest life span (horizontal "West-East life span ridge").

Thus, the shorter life span of the daughters born to particularly young fathers (20–25 years) is not an artifact caused by the shorter life span of young fathers. In fact, the phenomenon of short life span of early daughters is observed at any level of paternal life span (see the bottom of Fig. 4).

Analysis of the scientific literature suggests that there may be a fundamental biological explanation of the "young father – short daughters' life span" paradox. The risk of congenital heart defects (ventricular septal defects and atrial septal defects) is increased among the offspring of older fathers (over 35 years) and also among the offspring of particularly young fathers (under 20 years; Olshan et al. 1994). Children born to younger fathers (under 20 years) have increased risk of neural tube defects, hypospadias, cystic kidney, and Down syndrome (McIntosh et al. 1995).

In the mouse, offspring born to mature fathers exhibit better behavioral performances (for spontaneous activity in both sexes and learning capacity in males) than those born to particularly young, post-pubescent fathers (Auroux et al. 1998). Similar results were obtained for humans in a study that involved the distribution of scores obtained in psychometric tests by 18-year-old male subjects, according to their father's age at the time of their birth. This distribution indicated not only that increased paternal age is accompanied by effects similar to those observed in animals, but also that very young paternal age was also related to these effects. Thus, the curve of such scores produced an inverted U-shape, with maximum scores obtained when the father was about 30 years of age. Maternal age did not appear to play a part in this event. These results pose the problem of identifying genetic and/or psychosocial factors that might have an impact on the quality of the conceptus (Auroux et al. 1989).

The practical importance of these findings is obvious: the age constraints for the donors of sperm cells in IVF should probably be revised to exclude not only the old donors but also those donors who are too young (under 25 years).

Another interesting observation that comes from the analysis of the data in Figure 4 (large black spot in the "North-Eastern" part of the map) is that longer-lived fathers (over 80–85 years) produce longer-lived daughters, even when they are old (55–60 years). In other words, daughters born to older fathers live shorter lives only in those cases when their fathers die before the age of 80–85 years. The importance of this finding and its possible explanation are discussed in the next section of this chapter.

Coming to Understand the Parental Age Effects on Human Life span

In this final stage of data analysis we applied a multiple regression analysis with nominal variables, which is a very flexible tool to control for effects of both quantitative and qualitative (categorized) variables. This method also allows one to accommodate for complex non-linear and non-monotonic effects of predictor variables. We used the data for extinct birth cohorts (born in 1800–1880) free of censored observations and tested a long list of explanatory and potentially confounding variables (see below) to consider all possible artifacts.

Life span of adult (30+) progeny (sons and daughters separately) was considered as a dependent outcome variable in multivariate regression with dummy (0–1) variables using a SPSS statistical package. The independent predictor variables included 12 types of binary variables:

1) calendar year of birth (to control for historical increase in life expectancy as well as for complex secular fluctuations in life span). The whole birth year period of 1800–1880 was split into five-year intervals (16 intervals) presented by 15 binary (0–1) variables with the reference level set at 1875–1880 birth years.

2) maternal life span (to control for maternal influence through combined genetic effects and shared environment). The maternal life span data were grouped into five-year intervals (15 intervals) with the exception of the first (15–29 years) and the last (95–110 years) longer intervals with small numbers of observations. The data were coded with 14 dummy variables with the reference level set at 75–80 years for maternal life span.

3) paternal life span (to control for paternal influence through combined genetic effects and shared environment). The data were grouped and coded in a way similar to maternal life span (see above).

4) maternal age when a person (proband) was born. This is the key explanatory variable to study maternal age effects on offspring life span. The data for mother's age were grouped in five-year intervals (seven intervals to cover the age range of 15–60 years) with the exception of the last, longer interval of 45–59 years with small numbers of observations. Maternal age of 25–29 years was selected as a reference.

5) father's age when a person was born. This is the key explanatory variable to study paternal age effects on offspring life span. The data were grouped and coded in five-year intervals (nine intervals to cover the age range of 15–80 years) with the exception of the first (15–24 years) and the last (60–79 years) longer intervals with small numbers of observations. Paternal age of 40–44 years was selected as a reference.

6) birth order. This variable is represented by binary variable coded as 1 when the individual was a first born child and coded as 0 otherwise.

7) nationality. The nationality of the individual is represented by a set of four categories – Germans, British, Russians and others. Germans (the largest group in our sample) is selected as a reference group.

8) cause of death (violent versus non-violent). This variable is represented as a set of four dummy variables: 1) violent cause of death (war losses, accidents,

etc.), 2) death in prison and other unfavorable conditions (concentration camp, etc.), 3) death from acute infections (cholera, etc.) and 4) maternal death (for women only). Deaths from all other causes combined were considered as a reference outcome.

9) loss of the father in the formative years of life (before age 20). This is a binary variable coded as 1 when father was lost before the age of 20 and coded as 0 otherwise.

10) loss of the mother before age 20. This binary variable is coded as 1 in those cases when mother was lost before the age of 20 and coded as 0 otherwise.

11) loss of both parents (orphanhood) before the age of 20. This binary variable is coded as 1 in those cases when both parents were lost before the age of 20 and coded as 0 otherwise.

12) month of birth. This variable was included in the analysis because previous studies have found that month of birth is an important predictor of adult life span (Gavrilov and Gavrilova 1999b; Doblhammer 1999), particularly for daughters (Gavrilov and Gavrilova 1999b). This variable was represented as a set of 11 dummy variables, with those born in August considered as a reference group.

The results of data analysis are presented in Figures 5–10. Figure 5 depicts the net (adjusted) effects of paternal age at reproduction on daughters' life span when the effects of other variables (listed above) are controlled for. Daughters born to older fathers (55–59 years, 72 cases) live shorter lives compared to daughters born to middle-aged fathers (40–44 years): a difference in life expectancy at adult ages (30+) is 4.52 ± 1.94 years, which is statistically significant (t-ratio = −2.33, p = 0.02).

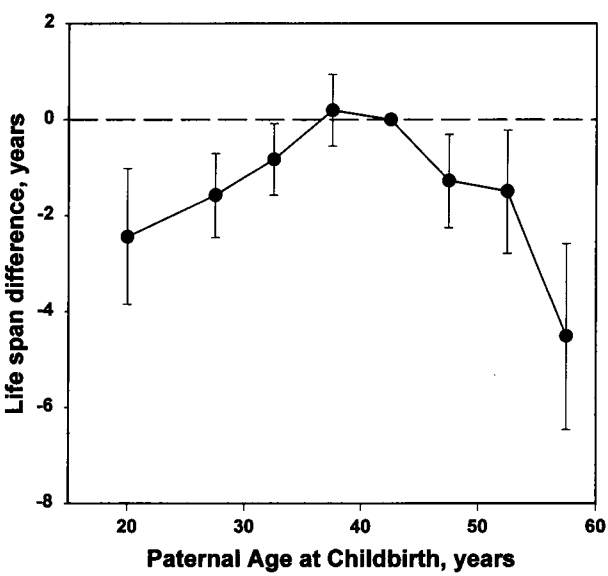

Fig. 5. Effect of paternal age at childbirth on daughters' life span based on 4,369 daughters from European aristocratic families born from 1800–1880. Life expectancy of adult women (30+) as a function of father's age when these women were born (expressed as a difference from the reference level for those born to fathers aged 40–44 years). The data are point estimates (with standard errors) of the differential intercept coefficients adjusted for other explanatory variables using multiple regression with nominal variables. Daughters of long-lived fathers (81+) are excluded from the analysis

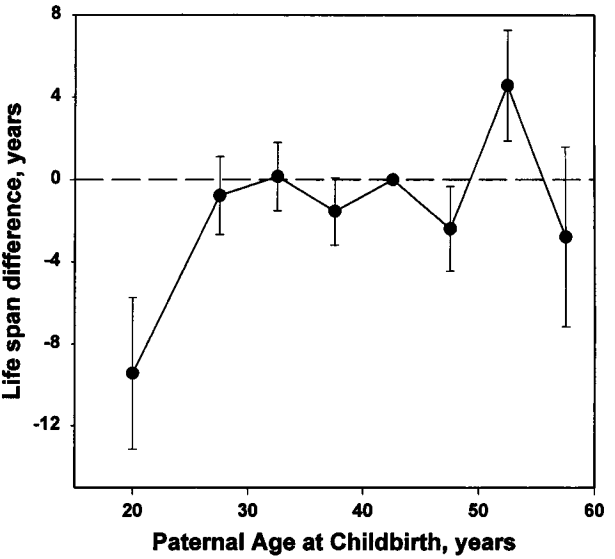

Fig. 6. Effect of paternal age at childbirth on daughters' life span based on 831 daughters from European aristocratic families born from 1800–1880. Daughters of longer-lived fathers (81+). Life expectancy of adult women (30+) as a function of father's age when these women were born (expressed as a difference from the reference level for those born to fathers aged 40–44 years). The data are point estimates (with standard errors) of the differential intercept coefficients adjusted for other explanatory variables using multiple regression with nominal variables

The data presented in Figure 5 are for daughters born to shorter-lived fathers (life span below 81 years). It is tempting to analyze the data for longer-lived fathers and to see whether the devastating effects of late reproduction will disappear. The rationale for such a prediction is based on the idea that mutations rates in both germ and soma cells depend on many common factors, including life style (exposure to carcinogens due to smoking, alcohol abuse, etc.) and genetic

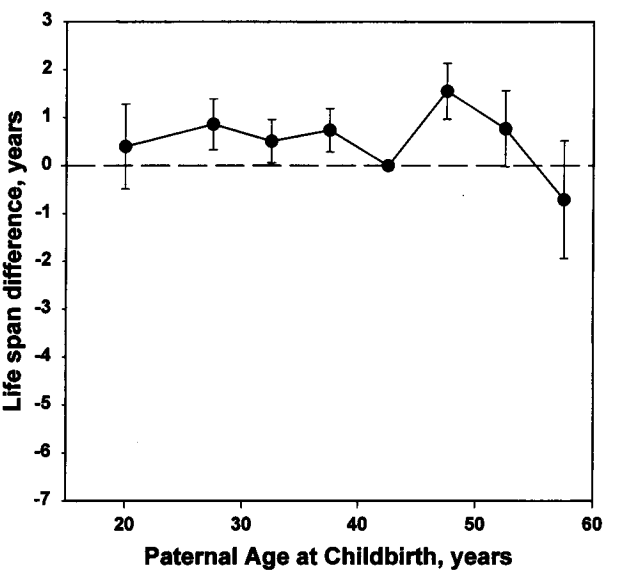

Fig. 7. Effect of paternal age at childbirth on sons' life span based on 10,103 sons from European aristocratic families born from 1800–1880. Life expectancy of adult men (30+) as a function of father's age when these men were born (expressed as a difference from the reference level for those born to fathers of 40–44 years). The data are point estimates (with standard errors) of the differential intercept coefficients adjusted for other explanatory variables using multiple regression with nominal variables. Sons of long-lived fathers (81+) are excluded from the analysis

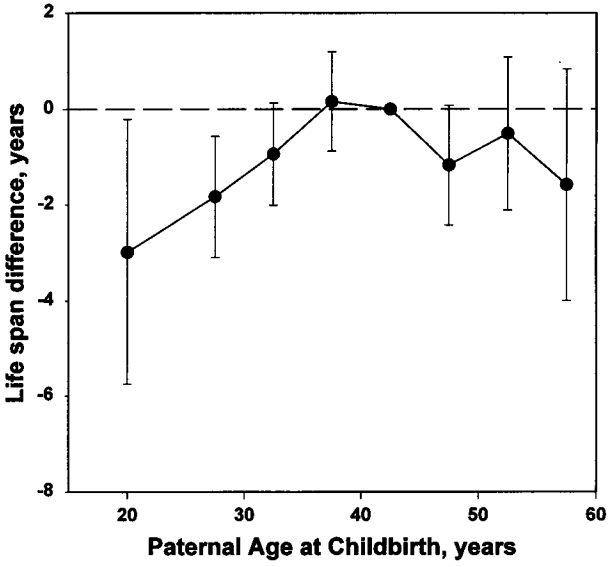

Fig. 8. Effect of paternal age at childbirth on sons' life span based on 1,912 sons from European aristocratic families born from 1800–1880. Sons of longer-lived fathers (81+). Life expectancy of adult men (30+) as a function of father's age when these men were born (expressed as a difference from the reference level for those born to fathers aged 40–44 years). The data are point estimates (with standard errors) of the differential intercept coefficients adjusted for other explanatory variables using multiple regression with nominal variables

predisposition. It is known that deficiency of vitamins B_{12}, folic acid, B_6, niacin, C, or E, appears to mimic radiation in damaging DNA by causing single- and double-strand breaks, oxidative lesions, or both, and may contribute to premature aging (Ames 1998). Therefore, those fathers who are fortunate for some reason to have low mutation rates are expected to live longer lives (because of less damage to their somatic cells) and also to produce healthy offspring with a normal life span in later life (because of less damage to their germ cells).

The results of data analysis for longer-lived fathers (81+) support the prediction that their progeny have normal life spans, even if conceived in old age (see Fig. 6).

Data for sons (Figs. 7, 8) demonstrate that a son's life span is not affected significantly by late conception, either by shorter-lived fathers (Fig. 7) or by longer-lived fathers (Fig. 8). This observation supports the previous finding that the life-shortening effect of late reproduction on offspring life span is in fact sex-specific (only daughters are affected). Possible explanations for this sex-specific phenomenon were discussed earlier.

As for maternal age effects on offspring life span, they are negligible for sons (Fig. 9) and suggestive (slightly positive) for daughters (Fig. 10). These results are consistent with the previous findings obtained by analysis of contour life span maps (see earlier). Further studies on larger sample sizes are required to have enough life span data for those born to particularly old mothers (over 45 years).

One of the new intriguing findings of this study is the paradoxical observation that children born to particularly young fathers (under 25 years) live shorter lives. To explain this paradox we suggest a hypothesis that life span shortening is caused by the residual genomic imprinting of the germ cell DNA in particularly young males. Specifically, we hypothesize that the DNA of young males is hyper-

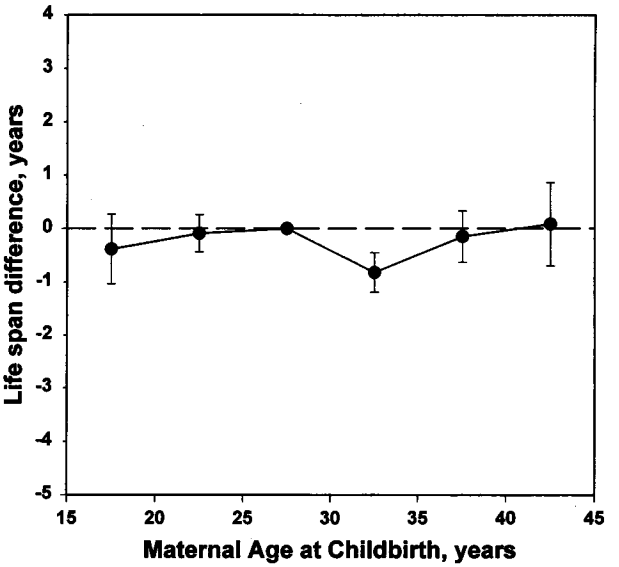

Fig. 9. Effect of maternal age at childbirth on sons' life span based on 12,015 sons from European aristocratic families born from 1800–1880. Life expectancy of adult men (30+) as a function of mother's age when these men were born (expressed as a difference from the reference level for those born to mothers aged 25–29 years). The data are point estimates (with standard errors) of the differential intercept coefficients adjusted for other explanatory variables using multiple regression with nominal variables

methylated and, for this reason, is more prone to mutations. Later in life, as males become more mature, their DNA is partially demethylated, so the risk of mutations may decline provisionally with age (25–30 years). After that time the mutation rate may start to increase again because of copy errors. It is known that the X chromosome is indeed methylated in the male germ line, whereas both X chromosomes are unmethylated in the female germ line (Driscoll and Migeon

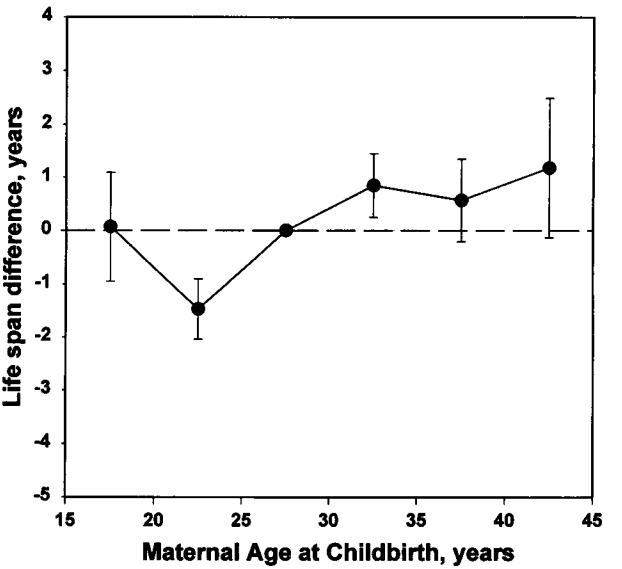

Fig. 10. Effect of maternal age at childbirth on daughters' life span based on 5,200 daughters from European aristocratic families born from 1800–1880. Life expectancy of adult women (30+) as a function of mother's age when these women were born (expressed as a difference from the reference level for those born to mothers aged 25–29 years). The data are point estimates (with standard errors) of the differential intercept coefficients adjusted for other explanatory variables using multiple regression with nominal variables

1990). This finding may explain why parental age effect on offspring life span is sex-specific: only paternal age is important, whereas maternal age effects are quite small, and also the affected sex is daughters only (who inherit paternal X chromosome). Further studies along these lines are required to allow us to test the proposed hypothesis as well as many other possible biological and social explanations. Collaboration in this area with other researchers and the IPSEN Foundation could shed light on the mechanisms of parental age effects that are of significant scientific and practical importance.

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