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Section 10 “Biodemography of Aging”

Biodemographic Study of Parental Age Effects on Human Longevity

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Abstract. The purpose of this paper is to find out whether persons born to older parents live shorter (expected as a result of age-related accumulation of spontaneous mutations in parental germ cells). We have also tested on a larger sample size our previous finding (Science, 1997, 277: 17-18; Mutation Research, 1997, 377: 61-62) that only daughters born to older fathers have a shorter life expectancy (consistent with critical importance of mutation load on paternal X-chromosome inherited by daughters only). For this purpose the most reliable genealogical data on longevity for more than 800 European noble families were analyzed. Offspring longevity for each particular sex was considered as a dependent variable in multiple regression model and a function of 5 independent predictors: 2 parental ages at reproduction, 2 parental ages at death and sex-specific cohort life expectancy (control for cohort and secular trends and fluctuations). The new results support our previous findings.

1. Introduction.

Despite its practical and scientific importance, many of the mechanisms that influence human longevity are still unknown. In particular, it is not yet known with certainty whether DNA damage and repair is a critically important force that influences human longevity. One approach to resolving this problem is to study the longevity of the offspring born to parents at different ages and to determine, as an indirect measure, whether the age-related accumulation of the DNA damage in parental germ cells is important for longevity of the offspring. The scientific credibility of such 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; Nazer et al., 1991; 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 affect of paternal age effect is also well known: advanced paternal age has been associated with an increase in new dominant mutations that result in congenital anomalies (Auroux, 1993a; 1993b; 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 aging is responsible for new dominant autosomic mutations that cause different malformations, including achondroplasia (Auroux, 1993a; 1993b; Lian et al., 1986), Apert or Recklinghausen disease (Auroux, 1993a; 1993b), Marfan syndrome (Auroux, 1993a; 1993b), osteogenesis imperfecta (Carothers et al., 1986; Young et al., 1987) and other inherited diseases. Increased paternal age at birth was observed among patients with Costello syndrome (Lurie, 1994), neurofibromatosis-1 (Takano et al., 1992), chondrodysplasia punctata (Sheffield et al., 1976), fibrodysplasia ossificans progressiva (Connor and Evans, 1982; Rogers and Chase, 1979), and thanatophoric displasia (Martinez-Frias, 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).

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 that age a substantial portion of the subpopulation suffering from lethal genetic disorders has already died. This study is also of practical importance since now in developed countries there is a tendency to postpone childbearing to later ages (Kuliev and Modell, 1990) — a trend that could continue into the future. It is possible that decisions to delay childbearing can have a detrimental influence on the health and longevity of their offspring. The information on potential life-shortening effects of delayed reproduction is important 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.

The first studies on long-term effects of parental age on offspring longevity in humans were made only recently and were based on the statistical analysis of human genealogical data (Gavrilov et al., 1995a; 1995b; 1996a; 1996c; 1997a; 1997c; Gavrilov, Gavrilova, 1997a; 1997b). These studies demonstrated that paternal age at reproduction has a specific threshold life-shortening effect on daughters rather than sons. Since paternal and maternal ages at reproduction are correlated (older mothers tend to have older spouses), it is also important to study the effect of maternal age on the offspring longevity. It was found that for reproductive ages of mothers in the range of 20-39 years there is no effect of maternal age on the longevity of adult children. Since the reproductive life span of females is shorter than 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.

Two observations were made in the above mentioned studies. First, the effect of parental reproductive age on longevity of adult children was observed for fathers only (specific paternal effect). Second, it was shown that paternal age is detrimental for longevity of the daughters only (specific sex-linked effect on daughters). Both observations 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 a 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. 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 at age 13 years is estimated at 36, and thereafter the number increases by 23 divisions per each year (Vogel and Motulsky, 1979). 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 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 one X chromosome only is active in each particular human female cell while 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 to hide critical important genes namely in X chromosome, since it is one of the safest locations in the human genome. The reason for that

is that the level of DNA damage in particular chromosome is determined by its exposure to male environment. For example, the most unfavorable situation is observed for Y chromosome that is male-specific. Since the Y chromosome is always in males while an autosome is in males only half of the time, the level of DNA damage for this chromosome should be especially high. Indeed, it turned out that the primate evolution rates (that are correlated to mutation rates) of the Y linked argininosuccinate synthetase pseudogene is about 2 times higher than that 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 2 copies of it while males have only one copy. Since one-third of the X chromosomes are in males, the X chromosome should have a mutation rate that is two-thirds that of the autosomes. Indeed, it turned out that the X/autosome ratio for silent changes in DNA during primate evolution (that is proportional to mutation rates) is 0.69 (Miyata et al., 1990). Recent studies on rodents also have demonstrated that the rate of substitution of synonymous mutations in X-linked genes to that in autosomal ones is 0.62 ± 0.04, which is consistent with X-linked genes having a reduced mutation rate (McVean, Hurst, 1997). Thus, the X chromosome is 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 critical importance of mutation load on X chromosome is related to a special status of this chromosome in females. As it was already mentioned, in each particular female cell only one X chromosome is active, while 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" by their effects on mortality compared to mutations on other chromosomes.

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

Thus, the current research literature supports the scientific importance of further studies of the postponed parental age effects on human longevity.

2. Results and Discussion

One of important approaches to understand the mechanisms of human longevity is to study an association between parental characteristics (paternal and maternal ages at reproduction and at death) and longevity of their children. In our previous preliminary studies on 8518 persons from European aristocratic families with well-known genealogy we have found a strong inverse relationship between father's age at reproduction and daughter's (not son's) longevity (Gavrilov, Gavrilova, 1997a; Gavrilov et al., 1997a). The results of this preliminary study are summarized in Table 1.

Table 1. Human longevity and sex differential in longevity as a function of father's age at reproduction.

Paternal Age at Reproduction** (years)	Mean Age at Death* ± Standard Error (years)		Sex Differential in Life Span (years)
	Daughters (sample size)	Sons (sample size)	
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

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

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

Note that daughters born by old fathers loose about 4.4 years of their life and these losses are statistically highly significant ($p < 0.01$; Student's test = 3.1), while sons are not significantly affected. This finding is in accord with the mutation theory of aging (Vijg, Gossen, 1993) since paternal age at reproduction is 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, house-keeping genes) sensitive to mutational load might be located in this chromosome (Gavrilov, Gavrilova, 1997a; Gavrilov et al., 1997a).

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

In this next step of our study we have collected, computerized and analyzed the genealogical data on human longevity in more than 700 different European royal and noble families published in the famous edition "Genealogisches Handbuch des Adels" in 1980-1994 (see references in Literature cited) and in other 120 professional genealogical sources, listed elsewhere (Gavrilov et al., 1996a). Offspring life span was analyzed for adults (those who survived by age 30) in order to study the long-term, postponed effects of late reproduction of the parents. The data for offspring born in 20th century was excluded from the analysis in order to have unbiased estimates of longevity for extinct birth cohorts. The data for offspring born before 19th century was 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 multiple linear regression to control for cohort and secular trends and fluctuations in human longevity. Offspring longevity for each particular sex (4566 records for males and 2068 records for females) was considered as a dependent variable in multiple regression model (program 1R in BMDP statistical package) and a function of 5 independent predictors: paternal age at reproduction in the range of 35-55 years (where the life-shortening effect was previously detected) (Gavrilov, Gavrilova, 1997b; Gavrilov, et al., 1997d), 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 detailed description of the sample under study is given in the Table 2.

The results are presented in the Table 3. It is found that the regression slope for daughter's longevity as a function of paternal age at reproduction is negative (-0.16 ± 0.07) and this inverse relationship is statistically significant (Student test is -2.35, P=0.02) even when the effects of other important 4 covariates are taken into account. In the case of sons the association with paternal age at reproduction is much weaker (-0.06 ± 0.05) and statistically insignificant (Student test is -1.20, P=0.23). Thus, this study reconfirms the previous preliminary observations (Gavrilov, Gavrilova, 1997a; Gavrilov, Gavrilova et al., 1995b; 1997a) on the sex-specific life-shortening effect of late paternal reproduction on daughters' longevity and provides strong scientific evidence in favour of these

observations. It is important now to continue these studies further and to check the prediction of the X chromosome hypothesis - the expected specific life-shortening effect of late grandpaternal reproduction from mother's side only.

Table 2. Characteristics of the sample under study.

Variable	Sons	Daughters
Sample size, number of cases	4566	2068
Offspring birth dates, years		
- range	1800-1899	1800-1899
- mean	1860.6	1864.7
- standard deviation	25.2	27.9
Offspring age at death, years		
- range	30-100	30-105
- mean	64.6	73.5
- standard deviation	14.9	15.6
Paternal age at reproduction, yr		
- range	35-55	35-55
- mean	41.4	41.6
- standard deviation	5.1	5.2
Maternal age at reproduction, yr		
- range	16-56	15-51
- mean	30.7	31.0
- standard deviation	5.7	5.8

Paternal age at death, years		
- range	35-99	35-96
- mean	68.2	68.4
- standard deviation	12.0	12.0
Maternal age at death, years		
- range	21-102	19-102
- mean	68.8	69.2
- standard deviation	15.6	15.8
Cohort life expectancy, years		
- range	58.0-72.5	56.1-81.6
- mean	64.7	73.2
- standard deviation	2.3	5.9

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:		
Multiple R	0.2	0.4
F Ratio	37.2	86.3

The results presented above were based on the assumption that the dependence between offspring longevity and paternal age at reproduction could be approximately considered as linear for the paternal ages in the range of 35-55 years. Our next step of the study was to check whether this assumption is valid. For this reason we have re-analyzed the data again 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, $t = 0.16$; $p = 0.87$), while 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 Dr. James Crow on non-linear accelerating increase of mutation rates with paternal age (Crow, 1993; 1995; 1997). One possible explanation for this phenomenon 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, the selection mechanism finally fails and accumulation of mutational load becomes evident (Gavrilov et al., 1996a; 1997a). There may be another explanation of 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 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 and it is therefore important to study the effect of paternal age on a more homogeneous population of longer-lived fathers. The results of our retrospective study of the genealogical records of 8,518 persons from European aristocratic families presented in Table 1 have shown that the life-shortening effect of paternal age is more gradual (as opposed to operating under a threshold) if it is studied on a relatively homogeneous population of long-lived fathers (with life span more than 50 years) (Gavrilov et al., 1996b; 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 significant portion of the offspring are born from middle-aged fathers. It is important to continue these studies further in order to resolve the controversy between threshold and gradual parental age effects observed in different types of data analysis, and this could be done through more detailed multivariate data analysis of the larger sample sizes with control for the possible non-linear effects of other important covariates including paternal longevity.

Another interesting observation is that sex differences in human longevity are the function of paternal age at reproduction. The data presented in Table 1 shows that females live longer than males when fathers are young, while in the case of old fathers sex differences are very small and statistically insignificant (Gavrilova et al., 1995; Gavrilov et al.. 1995b; 1996a; 1996c). This observation may also have an a fundamental explanation in human biology. Since females have two X chromosomes, they are genetically more redundant than males who have only one X chromosome. However when the father is very old and his X chromosome transferred to the daughter is full of 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 1, the column for sex differential in longevity, supporting this hypothesis).

The observed life-shortening effects of late parental reproduction has many other interesting practical and scientific implications. In particular, one should re-examine the problem of heterogeneity in human populations with respect to familial longevity. It is known that the familial component of longevity is small although statistically significant (see Gavrilov, Gavrilova, 1991 for references). What is less known is that longevity data in previous studies were not of sufficient detail to permit controlling for parental age at reproduction which might be an important negative predictor for longevity (Gavrilov et al., 1995b; 1996a; 1997a). Thus, previous estimates of the familial component of human longevity might be biased (underestimated) because of a positive correlation between parental longevity and their age at reproduction (dead parents do not reproduce!). Indeed, much higher estimates for the familial component of human longevity are observed when data are controlled for parental age at reproduction (Gavrilov et al., 1996b). In our study (see Table 4), the longevity of daughters born to long-lived fathers (70 years and above) was 67.2 years while daughters born by short-lived fathers (30-49 years) lived 64.7 years. This difference of 2.5 years is consistent with previous observations (see Gavrilov, Gavrilova, 1991 for references). After controlling for father's reproductive age (reproduction at young age of 20-29 years only) daughters' longevity becomes equal to 69.4 years in the case of long-lived fathers and 63.0 years in the case of short-lived fathers. This difference of 6.4 years is much higher than any other previous estimate made before for adults at age 30 (when data were not controlled for parental age at reproduction). The results mentioned here indicate that familial (and perhaps genetic) components of human longevity are probably underestimated and deserve re-examination in future studies. In particular, it is important to develop a larger genealogical database for humans and to revise the estimates of heritability of human longevity controlling for maternal and paternal ages at reproduction as well as other important covariates such as secular trends and fluctuations in human life expectancy.

Table 4. Daughter's longevity as a function of father's longevity and paternal age at reproduction.

Paternal longevity (years)	Daughter's longevity* ± standard error (years)	
	Total uncontrolled data (sample size)	Data controlled for paternal age (20-29) at reproduction (sample size)
30-49	64.7 ± 0.9 (320)	63.0 ± 1.6 (119)
50-69	65.0 ± 0.4 (1418)	65.3 ± 0.9 (344)
70+	67.2 ± 0.5 (1170)	69.4 ± 1.1 (220)

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

3. Prospects for Future Studies of Parental Age Effects.

The purpose of this section is to discuss the opportunities for further studies of parental age effects on human longevity. One of the interesting directions for such studies might be the use of contour plot analysis.

Contour plots are the maps for the levels of offspring life span (graded from white color for low life span levels to dark black color for high life span levels) as a function of paternal age at childbirth (X-axis) and maternal age at childbirth (Y-axis). The levels of offspring life span are calculated as deviations from the sex-specific cohort mean levels. Areas with equal levels of offspring life span are connected by isolines. The results of this approach are presented at Figure 1 for daughters and Figure 2 for sons.

Contour plot for daughters (Figure 1) demonstrates that the highest levels of life span are observed for those daughters who were born to fathers at ages 35-45 years. After that age there is a decrease in daughters' life span consistent with the previous results described earlier. However, it is interesting to note that the life span of daughters born to young fathers (25-30 years) is also low if maternal age at reproduction was below 35 years. Increased maternal age at reproduction is not associated with decrease of daughters' life span which is consistent with previous results obtained by the method of multiple linear regression.

Contour plot for sons (Figure 2) demonstrates a mysterious diagonal orientation of isolines suggesting the importance of parental age gap (difference between paternal and maternal ages). When father is 10 years older than mother the life span of sons is particularly low. Any change of this parental age gap in any direction results in increase of sons' life span. This mysterious phenomenon does not have satisfactory explanation yet. However it is interesting to note that the parental age gap might be important factor determining the probability of consanguineous marriages (this prediction follows from the models of population genetics).

Another type of data analysis is presented at Figures 3-4 where the levels of offspring longevity are plotted as a function of paternal life span (X-axis) and paternal age at childbirth (Y-axis). Contour plot for daughters (Figure 3) again demonstrates that there is an "ideal" paternal age at reproduction - about 40 years related to the highest daughters' life span. Daughters born to older fathers have shorter life span both in the case of short-lived fathers (60-65 years) and long-lived fathers (80-90 years). However, for younger fathers (below 30 years) daughters' life span is also shorter. One possible explanation of this observation is that short-lived daughters were born to young fathers with high mutation load and short reproductive life span.

The data for sons (Figure 4) again demonstrate the mysterious pattern - they look like the negative image of daughters' pattern (see Figure 3) reflected by mirror. Sons born to fathers at ages 30-40 years have the lowest life span for any level of paternal longevity. Reproduction at younger or older ages results in higher levels of sons' life span (see Figure 4).

The results presented in this section demonstrate that parental age effects are very strong and are not yet understood. So, they should be taken into account in any other studies including studies of heritability of human longevity. Parental age effects also deserve their special investigation in humans and animal models, since such studies could shed the light on the mechanisms determining aging and longevity.

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