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Parental age at conception and offspring longevity

Leonid A Gavrilov and Natalia S Gavrilova

Moscow State University and Russian Academy of Sciences, Moscow, Russia

Introduction

Current knowledge suggests that parental age has many influences on the offspring. This topic has been exhaustively reviewed in Finch's monograph.[1] The major maternal age-related changes in humans are increases in fetal aneuploidy later in reproductive life; Down's syndrome (trisomy 21);[2–8] Klinefelter's syndrome (XXY);[3,9] Edward's syndrome (trisomy 18); and Patau's syndrome (trisomy 13).[2–4] Despite a recent dramatic decrease in fetal death rates, advanced maternal age remains an important independent risk factor for fetal death.[10–12]

The 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.[13–25] In particular, paternal aging is responsible for new dominant autosomic mutations that cause different malformations, including achondroplasia,[13,14,17] Apert or Recklinghausen disease,[13,14] Marfan syndrome[13,14] and osteogenesis imperfecta.[24,25] Increased paternal age at birth was observed among patients with Costello syndrome,[26] neurofibromatosis-1,[27] chondrodysplasia punctata,[28] fibrodysplasia ossificans progressiva,[29,30] and thanatophoric displasia.[31] Advanced paternal age at conception was also associated with increased risk of preauricular cyst, nasal aplasia, cleft palate, hydrocephalus, pulmonic stenosis, urethral stenosis, and hemangioma.[20]

This review is intended to fill one very important gap in our existing knowledge. We need to know whether parental age at conception is really important for the longevity of the main population of so-called 'normal healthy people', who do not suffer from aneuploidy and other obvious genetic abnormalities. To answer this question it is necessary to study the life expectancy of adults (say, at 30 years of age) as a function of parental age at reproduction. By that age most of the subpopulation suffering from genetic abnormalities will have been already eliminated because of higher infant and child mortality, making it possible to study the long-term effects of parental age on human longevity. Research in this area is especially important in view of the tendency in developed countries to postpone childbearing.[32]

Address for correspondence: Leonid A Gavrilov, Centre for Longevity Research, AN Belozersky Institute, Moscow State University, 119899 Moscow, Russia.

Long-term effects of parental age at birth

The first studies on long-term effects of parental age on the longevity of offspring in humans were made only recently and were based on the statistical analysis of human genealogical data.[33–36] These studies showed that paternal age at reproduction has a specific threshold life-shortening effect on daughters rather than sons (see Table 1). Since paternal and maternal ages at reproduction are correlated (older mothers usually have older spouses too), studying also the effect of maternal age on the longevity of the offspring is important. These data are presented in Table 2.

The data show that for mothers between 20 and 39 years no effect of maternal age on the longevity of adult children could be detected. Since the reproductive lifespan of females is shorter than males, the sample size for children of very old mothers (more than 40 years old) was too small to draw any conclusions. Further studies in this direction, on larger sample sizes, are needed in order to make inferences about the independent effects of both paternal and maternal ages at reproduction, on offspring longevities.

Suggested mechanisms of life-shortening in humans born to old parents

Two specific effects were observed in the above-mentioned studies. First, the effect of parental reproductive age on the longevity of adult chil-

Table 1. *Human longevity as a function of father's age at reproduction*

Paternal age at reproduction (years)	Mean age at death[a] ± standard error (years)		Sex differential in longevity (years)
	Daughters (sample size)	Sons (sample size)	
20–29	65.7 ± 0.7 (545)	60.7 ± 0.4 (1312)	5.0 ± 0.8
30–39	65.5 ± 0.5 (985)	60.5 ± 0.3 (2473)	5.0 ± 0.6
40–49	64.6 ± 0.8 (493)	60.2 ± 0.4 (1344)	4.4 ± 0.9
50–59	60.8 ± 1.5 (149)	59.4 ± 0.8 (357)	1.4 ± 1.7

[a]Human longevity was calculated for adults (those who survived to age 30) born in the eighteenth and nineteenth centuries. The data for those born in the twentieth century were excluded from the analysis in order to have unbiased estimates of longevity for extinct birth cohorts.
Source: Gavrilov LA, Gavrilova NS.[36]

Table 2. *Human longevity as a function of mother's age at reproduction*

Maternal age at reproduction (years)	Mean age at death[a] ± standard error (years)		Sex differential in longevity (years)
	Daughters (sample size)	Sons (sample size)	
20–24	65.5 ± 0.8 (453)	60.6 ± 0.6 (723)	4.9 ± 1.0
25–29	66.8 ± 0.8 (463)	61.1 ± 0.6 (765)	5.7 ± 1.0
30–34	65.5 ± 0.9 (331)	60.3 ± 0.7 (522)	5.2 ± 1.1
35–39	65.2 ± 1.3 (176)	60.5 ± 0.9 (273)	4.7 ± 1.6

[a]Human longevity was calculated for adults (those who survived to age 30) born in the eighteenth and nineteenth centuries. The data for those born in the twentieth century were excluded from the analysis in order to have unbiased estimates of longevity for extinct birth cohorts.
Source: Gavrilov LA, Gavrilova NS.[36]

dren was observed for fathers only (specific paternal effect). Secondly, paternal age was detrimental for the longevity of daughters only (specific sex-linked effect on daughters). Both observations may have fundamental explanations in modern biology.

First, it is now well established that the mutation rate in human males is much higher than in females[37] and age of the father is the main factor determining the human spontaneous mutation rate.[37] Thus, we may expect an effect of paternal, rather than maternal, age on offspring longevities, since the mutational load in germ cells is mainly of paternal origin. The reason for specific paternal effect is that the mutation rate is to a great extent determined by the number of cell divisions and DNA replications when mistakes are introduced. Since the number of cell divisions between zygote and sperm (in males) is much larger than between zygote and egg (in females), a much higher accumulation of DNA damage in paternal germ cells should be expected. In the human species the estimated number of cell divisions in females between zygote and egg is 24, largely

independent of age. In males the number of cell divisions between zygote and sperm is much larger. The number of divisions required to produce a sperm at age 13 years is estimated at 36, and after that the number increases by 23 divisions per year.[38,39] Thus, at age 20 the number of cell divisions is about 200 and has increased by age 50 to about 890 cell divisions! Thus, we might predict a specific paternal effect on mutational loads and so, the longevity of the offspring.

The second observation is that high paternal reproductive age is detrimental for daughters only. Since the paternal X-chromosome is specifically inherited by daughters rather than sons, this observation might suggest that critical genes (critical targets for mutational damage) important for longevity, are found in 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 tempting to speculate that the X-chromosome is one of the safest locations in the human genome. The reason for this is that DNA damage in particular chromosomes is determined by exposure to the male environment. For example, the most unfavourable situation is observed for the Y-chromosome, which is male-specific. Since the Y-chromosome is always in males while an autosome is in males only half of the time, DNA damage for this chromosome should be especially high. It turns out that the primate evolution rates (correlated to mutation rates) of the Y-linked argininosuccinate synthetase pseudogene is about twice as high as that of its autosomal counterpart.[40] Thus, the Y-chromosome is the most dangerous place in the human genome and this may be the reason that so few genes are associated with that chromosome. In contrast to the Y-chromosome, the X-chromosome is less exposed to the male environment since females have two copies of it while males have only one. Thus, only one-third of the X-chromosomes are in males, so the X-chromosome should have mutation rates two thirds those of autosomes. It turns out that the X/autosome ratio for silent changes in DNA during primate evolution (that is, proportional to mutation rates) is 0.69.[40]

The nature of threshold effect of paternal age

It is also worth discussing the threshold nature of the effect of paternal age on daughters' longevity. Virtually no effect can be detected before age 50, after which there is a dramatic decrease in longevity (see Table 1). This observation is in accord with previous observations that the relationship between paternal age and mutation rates is nonlinear with great acceleration at old ages.[37] One possible explanation for this phenomenon is competition among sperm cells. Since only one of many sperm cells succeeds in the 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 an accumulation of mutational load become evident.[36]

The threshold nature of the paternal effect can be explained in another way. The population of fathers is heterogeneous and short-lived fathers can participate in reproduction at young ages only. Thus, the detrimental effect of age-related accumulation of a mutational load in paternal germ cells might be compensated by a selection effect (the population of old fathers is also the population of survivors compared with young fathers). In other words, the threshold behaviour might be an artefact caused by the heterogeneity of the population; thus, studying the effect of paternal age on a more homogeneous population of long-lived fathers is important. The results of a long-term follow-up of 8518 persons from European aristocratic families with known genealogy (taken from more than 120 genealogical publications listed elsewhere[36]) are presented in Table 3. It is evident from the data presented in Table 3 that the life-shortening effect of paternal age is a gradual, rather than a threshold effect, if it is studied in a relatively homogeneous population of long-lived fathers (with a lifespan of more than 50 years). This conclusion is very important since the effect of paternal age is not restricted to rare cases of old fathers (50 years and above), but might be consequential for a significant part of the human population born to middle-aged fathers.

Table 3. *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[a] ± standard error (years)		Sex differential in longevity (years)
	Daughters (sample size)	Sons (sample size)	
20–29	66.5 ± 0.7 (592)	61.3 ± 0.4 (1238)	5.2 ± 0.8
30–39	65.9 ± 0.5 (1214)	60.8 ± 0.3 (2580)	5.1 ± 0.6
40–49	64.4 ± 0.7 (694)	60.5 ± 0.4 (1543)	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 or more) in order to eliminate bias caused by correlation between father's and offspring lifespan.
Source: Gavrilov LA, Gavrilova NS.[42]
[b]Human longevity was calculated for adults (those who survived to age 30) born in the eighteenth and nineteenth centuries. The data for those born in the twentieth century were excluded from the analysis in order to have unbiased estimates of longevity for extinct birth cohorts.
Source: Gavrilov LA, Gavrilova NS.[42]

Parental age and sex differentials in longevity

Another interesting observation based on the data presented above is that sex differences in human longevity are a function of paternal age at reproduction. The data presented in Tables 1 and 3 shows that females live longer than males when fathers are young, while for old fathers sex differences are very small and statistically insignificant. This important observation may also have 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 the X-chromosome transferred to the daughter bears a heavy mutational load, and the genetic redundancy is identical in both males and females, since both have only one intact (maternal) X-chromosome. Thus, with an increase of paternal reproductive age, we would expect that sex differences in offspring longevity should decrease.

A revival of longevity genetics

The discovery of life-shortening effects of late parental reproduction has many important practical and scientific implications. In particular, one should re-examine the problem of heterogeneity in human populations with respect to familial longevities. It is well known that the familial component of longevity is very small although it is statistically highly significant (see ref. 42). However, the longevity data in all previous studies were not controlled for parental age at reproduction, a factor that is an important negative predictor for longevity.[34,36] Thus, previous estimates of the familial component of human longevity may be highly biased (underestimated), because of the 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 (see Table 4).

The longevity of daughters born to long-lived fathers (70 years and above) was 67.3 years while daughters born to short-lived fathers (30–49 years) lived for 64.7 years. This difference is 2.6 years only, and is consistent with previous observations (see ref. 42). After controlling for the father's reproductive age (reproduction at the young age of 20–29 years), the daughter's longevity increases to 69.4 years for long-lived fathers, and 63.0 years for short-lived fathers. Thus, the difference is 6.4 years, a much higher estimate than made previously, when data were not controlled for parental age at reproduction.

The results presented here suggest that the

familial, and perhaps genetic, component of human longevity was underestimated and deserves re-examination in future studies. In particular, reconsidering this problem using other animals might be interesting (*Drosophila*, rats, mice, etc.), with a larger genealogical database controlling for the mother's age at reproduction, and other confounding factors.

Future studies of parental age effects on longevity

Besides the proposed fundamental biological explanations of parental age effects, some other cultural and social explanations should be discussed. One promising approach to discriminating between biological and social explanations of aging is to study the effect of the reproductive age of maternal grandfathers on the longevity and morbidity of grandchildren. 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. If this is observed, all other social and cultural explanations of the observed regularities could be excluded. Thus, further studies in this direction are necessary.

Chronic diseases associated with delayed parenting

As well as the overall impact of longevity, it is important to consider what particular diseases could be responsible for life-shortening in adults born to old parents. A preliminary list of such diseases includes:

1) Breast cancer. Several recent studies showed an association of high risk for breast cancer with advanced maternal age at reproduction.[45–47]
2) Testicular cancer. Advanced maternal age at childbirth was observed among first-born men with testicular cancer.[48]
3) Alzheimer's disease. Several studies have investigated parental age as a risk factor for Alzheimer's disease. In most no association was observed between advanced parental age and Alzheimer's disease.[49–53] However, one study showed an association of both maternal and paternal age with Alzheimer's disease.[54]
4) Other mental disorders. In contrast to Alzheimer's disease, for many other mental disorders or abnormalities a strong association with advanced parental age was observed. In particular, it was shown that mental function (measured by psychometric tests) of male offspring is related to the father's, rather than the mother's age. Increase in paternal age was accompanied by decrease in learning capacity among 18-year-old sons.[55] Another study found that mental retardation of unknown aetiology was related to the paternal age, while maternal age and birth order were not significant after readjusting the other factors.[56] In a large group of psychiatric patients (2000) it was shown that the mean age of the father at

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

Paternal longevity (years)	Daughter's longevity[a] ± 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)

[a]Human longevity was calculated for adults (those who survived to age 30) born in the eighteenth and nineteenth centuries. The data for those born in the twentieth century were excluded from the analysis in order to have unbiased estimates of longevity for extinct birth cohorts.
Source: Gavrilov LA, Gavrilova NS, Evdokushkina GN *et al.*[44]

the time of the patient's birth was significantly above the expectation from the general population, and this was highest for schizophrenia.[57] Thus, paternal age at reproduction may be related to the mental performance of the offspring.

Studies on the associations between chronic diseases and parental age at reproduction are now being intensively undertaken and one can expect that the list of studied diseases will be significantly increased in future.

Conclusions

Recent epidemiological studies of human genealogical data have shown strong inverse relationships between the father's age at birth and the daughter's (not the son's) longevity. Since only daughters inherit the paternal X-chromosome, this sex-specific decrease in daughters' longevity may suggest that human longevity genes sensitive to mutational loads might be found in this chromosome. Moreover, much higher estimates of the familial component of longevity for daughters are observed when the data are controlled for paternal age at reproduction. Although a strong inverse relationship between the daughter's longevity and paternal age at reproduction has been shown, this does not prove a cause and effect relationship, and other confounding factors (maternal age in particular) may be involved. Larger epidemiological studies are planned to cast more light on the long-term effects of delayed parenting.

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