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Early-Life Factors Modulating Lifespan

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Introduction

There is a growing interest in the studies of human longevity and in the search of mechanisms, which determine the length of human life. Traditionally these studies have been focused on adult and older ages, usually overlooking or even neglecting the possible role of early-life developmental processes in longevity determination. Recently, however, the situation has dramatically changed, because a new theory of aging and longevity has been suggested, which explicitly predicts the importance of early-life events in lifespan modulation [1]. Moreover, the new facts have been uncovered, which support this idea of early-life programming of human lifespan. The purpose of this chapter is to review new approaches, ideas and findings related to a possible role of early-life factors in longevity determination. This new way of thinking may have important implications both for understanding the mechanisms of human longevity, as well as for further extension of human lifespan.

First we will discuss the fundamental theoretical justification, why early-life events and conditions may be so important in longevity determination. This theoretical justification is provided by the new reliability theory of aging and longevity, which was already described elsewhere with many mathematical details [1]. Therefore, we will skip the mathematics here and will focus more on substantive ideas of this theory, which are particularly interesting to biogerontologists. Then, we will review the recent epidemiological findings, which support the idea of early-life programming of human longevity. The two types of findings will be discussed: (i) the early-life seasonal programming of human longevity (month-of-birth effects on human lifespan), and (ii) the role of paternal age at the time of conception in determining a person's lifespan (presumably through mutation load in paternal sperm cells).

It is important to emphasize that the purpose of this chapter is to provide fresh ideas and findings for further research work, rather then to present them as a completed study. A new fascinating early-life perspective on human longevity is just

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emerging and we have a long way to go through many trials and errors. However, the risks associated with new research paradigm may be compensated by a broader vision of longevity mechanisms.

Theoretical justification for early-life programming of longevity: the reliability theory of aging and longevity

The idea of fetal origins of adult degenerative diseases and early-life programming of late-life health and survival is being actively discussed in the scientific literature [1–11]. It is also suggested that the historical improvement in early-life conditions may be responsible for the observed postponement of many age-related degenerative diseases in recent generations through the process called "technophysio evolution" [12–14]. Theoretical arguments explaining the importance of early-life conditions in later-life health outcomes can be found in the reliability theory of aging and longevity [1, 2]. According to this theory, biological species (including humans) are starting their lives with extremely high initial load of damage, and, therefore, they should be sensitive to early-life conditions affecting the level of initial damage [1, 2]. The main ideas of this theory can be summarized in the following statements:

- Reliability theory is a general theory about systems failure. It allows researchers to predict the age-related failure kinetics for a system of given architecture (reliability structure) and given reliability of its components.
- Reliability theory predicts that even those systems that are entirely composed of non-aging elements (with a constant failure rate) will nevertheless deteriorate (fail more often) with age, if these systems are *redundant* in irreplaceable elements. Aging, therefore, is a direct consequence of systems redundancy. The "actuarial aging rate" (the relative rate of age-related mortality acceleration corresponding to parameter α in the Gompertz law) increases, according to reliability theory, with higher redundancy levels.
- Reliability theory also predicts the late-life mortality deceleration with subsequent leveling-off, as well as the late-life mortality plateaus, as an inevitable consequence of *redundancy exhaustion* at extreme old ages. This is a very general prediction of reliability theory: it holds true for systems built of elements connected in parallel, for hierarchical systems of serial blocks with parallel elements, for highly interconnected networks of elements, and for systems with avalanche-like random failures [2]. The reliability theory also predicts that the late-life mortality plateaus will be observed at any level of initial damage: for initially ideal systems, for highly redundant systems replete with defects, and for partially damaged redundant systems with an arbitrary number of initial defects. Furthermore, reliability theory predicts possible *paradoxical mortality decline in late life* (before eventual leveling-off to mortality plateau) if the system is redundant for *non-identical components* with different failure rates. Thus, in those cases when "apparent rejuvenation" is observed (mortality decline among the oldest-old) there is no need to blame data quality or to postulate initial population heterogeneity, or a "second breath" in

centenarians. The late-life mortality decline is an inevitable consequence of *age-induced population heterogeneity* expected even among initially identical individuals, redundant in non-identical system components [1]. Late-life mortality decline was observed in many studies and stimulated interesting debates because of the lack of reasonable explanation. Reliability theory predicts that the late-life mortality decline is an expected scenario of systems failure [1].

- The reliability theory explains why mortality rates increase *exponentially* with age in many adult species (Gompertz law) by taking into account the *initial flaws (defects)* in newly formed systems. It also explains why organisms "prefer" to die according to the Gompertz law, while technical devices usually fail according to the Weibull (power) law. Moreover, the theory provides a sound strategy for handling those cases when the Gompertzian mortality law is not applicable. In this case, the second best choice would be the Weibull law, which is also fundamentally grounded in reliability theory. Theoretical conditions are specified when organisms die according to the Weibull law: organisms should be relatively free of initial flaws and defects. In those cases when none of these two mortality laws is appropriate, reliability theory offers more general failure law applicable to adult and extreme old ages. The Gompertz and the Weibull laws are just special cases of this unifying more general law [1].
- The theory explains why relative differences in mortality rates of compared populations (within a given species) vanish with age, and mortality convergence is observed (known as the *compensation law of mortality*) due to the exhaustion of initial differences in redundancy levels.
- According to the reliability theory, the exponential growth in mortality rate, as well as other aging phenomena (late-life mortality deceleration and compensation law of mortality), follows naturally from the mechanism of progressive accumulation of random damage in redundant systems and two general features of biosystems [1].

The first fundamental feature of biosystems is that, in contrast to technical (artificial) devices which are constructed out of previously manufactured and tested components, organisms form themselves in ontogenesis through a process of self-assembly out of *de novo* forming and externally untested elements (cells). The second property of organisms is the extraordinary degree of miniaturization of their components (the microscopic dimensions of cells, as well as the molecular dimensions of information carriers like DNA and RNA), permitting the creation of a huge redundancy in the number of elements. Thus, we expect that for living organisms, in distinction to many technical (manufactured) devices, the reliability of the system is achieved not by the high initial quality of all the elements but by their huge numbers (redundancy). It is this feature of organisms, which provides an explanation why the failure rate grows as an exponential rather than a power function of age [1], and it also enables researchers to understand the other mortality phenomena (e.g., compensation law of mortality).

The fundamental difference in the manner in which the system is formed (external assembly in the case of technical devices and self-assembly in the case of biosystems) has two important consequences. First, it leads to the macroscopicity of technical devices in comparison with biosystems, since technical devices are assembled "top-down" with the participation of a macroscopic system (man) and must be suitable for this macroscopic system to use (i.e., commensurate with man). Organisms, on the other hand, are assembled "bottom-up" from molecules and cells, resulting in an exceptionally high degree of miniaturization of the component parts. Second, since technical devices are assembled under the control of man, the opportunities to pretest components (external quality control) are incomparably greater than in the self-assembly of biosystems. The latter inevitably leads to organisms being "littered" with a great number of defective elements. As a result, the reliability of technical devices is assured by the high quality of elements (*fault avoidance*), with a strict limit on their numbers because of size and cost limitations, while the reliability of biosystems is assured by an exceptionally high degree of redundancy (*fault tolerance*) to overcome the poor quality of some elements.

It is interesting to note that the uniqueness of individuals, which delights biologists so much, may be caused by "littering" the organisms with defects and thus forming a unique pattern of individual damage. Our past experience working with dilapidated computer equipment in Russia gave rise to the same thought: the behavior of this equipment could only be described by resorting to such "human" concepts as character, freaks, personality, and change of mood. Interestingly, ideas of this kind proved to be very useful in developing a mathematical theory of aging and longevity for biological systems [1].

The idea that living organisms are starting their lives with a large number of defects has deep historical roots. Biological justification for this idea was discussed by Dobzhansky [15]. He noted that, from the biological perspective, Hamlet's "*thousand natural shocks that flesh is heir to*" was an underestimate and that in reality "the shocks are innumerable" (p. 126) [15]. Also, the system may behave as if it has a large number of initial defects when some of its components are apparently nonfunctional for whatever reason (because of impaired regulation, disrupted communication between components, or "selfish" behavior of DNA, cells, and tissues, etc.). An apparent lack of any function is typical for many structures of living organisms, starting from the molecular level (e.g., nonfunctional, selfish DNA and inactive pseudogenes [16]), up to the level of the human brain [17].

It also follows from reliability theory that even small progress in optimizing the processes of ontogenesis and increasing the numbers of initially functional elements (degree of redundancy) can potentially result in a remarkable increase in lifespan. This optimistic prediction is supported by experimental evidence of increased offspring lifespan in response to protection of parental germ cells against oxidative damage just by feeding the future parents with antioxidants [18]. Increased lifespan is also observed among the progeny of parents with a low respiration rate (proxy for the rate of oxidative damage to DNA of germ cells [2]). The reliability theory also predicts that early-life events may affect survival in later adult life through the level of initial damage. This prediction proved to be correct for such early-life predictor

variables as parental age at a person's conception [19–21] and the month of person's birth [22–23], which are discussed below.

Early-life seasonal programming of human lifespan

In this section we will discuss and test a hypothesis that early-life seasonal environmental exposures in the past (such as seasonal vitamin deficiency) may affect human survival in later life. The rationale for this approach is based on the findings that micronutrient deficiencies play a major role in DNA damaging, human aging and premature deaths from cancer and heart disease [24]. Deficiencies of vitamins B_{12}, folic acid, B_6, niacin, vitamins C and E, appear to mimic radiation in damaging DNA by causing single- and double-strand breaks, oxidative lesions, or both [24]. These health hazards are highly significant because even now in such a developed country as the United States half of the population may be deficient in at least one of these micronutrients [24]. In previous years, when the people who are now elderly were born, vitamin deficiencies were even more acute, particularly in the late-winter season, just before vegetation starts anew (February, in the northern hemisphere).

It is reasonable to hypothesize (and to test this hypothesis) that vitamin deficiencies during critical periods of fetus and infant development may affect the later health and longevity of the deficiency-exposed birth cohorts. For example, preceding vitamin deficiencies in February in the past may produce a subsequent lifespan-shortening effect in February birth cohorts among adults. The same February avitaminosis during the third month of pregnancy may produce another vulnerable birth cohort born in August. The third month of pregnancy is known to be a critical period when the brain is vulnerable, when the nervous system and sense organs develop, when all of the major organs have been established, and when the embryo becomes a fetus [25, 26]. Preliminary studies have confirmed that there are two seasonal minimums in adult life span for those born in February and in August [22]. Adult lifespan minimum in August birth cohorts was also found in the earlier studies [27]. In general, all previous studies found statistically significant seasonality in adult lifespan according to month of birth, but there is controversy over the exact seasonal pattern of lifespan fluctuations [22, 23, 27, 28]. Further studies are required in order to validate the previous findings, address the existing controversies and explore the possible mechanisms of lifespan seasonality.

Early-life seasonal impacts on subsequent adult lifespan may include not only seasonal vitamin deficiency, but also other seasonal impacts, such as infectious diseases. Seasonal peaks of disease occurrence are typical for many conditions [29] including: tularemia and Rocky mountain spotted fever (spring-early summer), the St. Louis encephalitis and other viral encephalitides (late summer-early fall), influenza (mid-winter), measles (rubeola, late winter-early spring), enteric bacterial infections (summer), poliomyelitis (peak in July-August, minimum in March), infectious virus hepatitis (late winter). Some diseases have additional cyclic variation with a periodicity of longer than one year [29], such as, for example, measles (rubeola, 3 year cycle) and meningococcal meningitis (7–9 year cycle). The most drastic effects of infectious agents in pregnancy which probably represent the tip of

the iceberg of the damage to progeny [25], include:

1. for the rubella virus (German measles): cardiac malformation, deafness, cataracts, glaucoma, and tooth defects.

2. for cytomegalovirus: growth retardation, blindness, mental retardation and deafness.

3. for the herpes simplex virus: microcephaly and mental retardation.

4. for varicella (chickenpox): skin scarring, muscle atrophy, and mental retardation.

5. for poliovirus: adult schizophrenia [30]. Poliovirus epidemics peak in July-August and exposure to this virus in the second trimester of gestation seems to produce subsequent adult schizophrenia in February birth cohorts [31]. Adult schizophrenia is also associated with neonatal meningitis caused by another enterovirus, Coxackie B5 [32].

Thus, both infectious agent exposures and vitamin-deficiency exposures should be considered for possible explanation and study of the early seasonal environmental impacts on adult lifespan.

Season of birth and human longevity

We have studied month-of-birth effects on human longevity using particularly reliable data on European aristocratic families. We analyzed data for extinct birth cohorts (born in 1800–1880) with lifespan already known for each particular person. Table 1 presents new striking data that the month of birth is indeed an important predictor for the life expectancy of adult women (30 years and above). In particular, women born in May and December tend to live 2–3 years longer on average compared to those born in February (significant at $p<0.01$). The effects of the months of birth are expressed in Table 1 as a difference from the reference level for those born in February and are point estimates of the differential intercept coefficients adjusted for effects of other variables.

It is important to emphasize that the month of birth continues to be an important predictor for women's lifespan, even after adjustment for the effects of all other explanatory variables including calendar year of birth, maternal lifespan, paternal lifespan and other variables described in the footnotes of Table 1.

Note how regular is the M-shaped dependence of women's lifespan on their month of birth (Table 1). Starting with February "ground zero," the lifespan is increasing monotonically through March and April, reaching its first peak in May–July. Then lifespan decreases forming a local minimum in August. Then lifespan starts to increase again in a regular way through September, October and November, reaching its second peak in December. After that, it drops down through January to February forming the M-shaped pattern (bimodal distribution) with two peaks in May–July

Table 1. Female lifespan as a function of month-of-birth

Month-of-birth	Net effect* in years (point estimate)	Standard error	*p*-Value
February	0.00	Reference level	
March	1.10	0.92	0.2331
April	1.72	0.92	0.0619
May	**2.35**	**0.90**	**0.0090**
June	1.66	0.90	0.0665
July	**1.86**	**0.91**	**0.0404**
August	1.49	0.90	0.0978
September	1.51	0.92	0.0986
October	**1.95**	**0.90**	**0.0308**
November	**2.13**	**0.93**	**0.0229**
December	**3.04**	**0.91**	**0.0009**
January	0.94	0.92	0.3086
February	0.00	Reference level	

*Net effect corresponds to additional years of life gained (or lost) compared to the reference category (lifespan for those born in February).

Results for Table 1 are obtained through multivariate regression analysis of lifespan data (outcome variable) for 6908 women born in 1800–1880 (extinct birth cohorts with lifespan known for each person), who survived by age 30 (focus on analysis of adult lifespan). The following additional predictor variables are also included in the final model because of their predictive value: (1) calendar year of birth, (2) ethnicity (Russian, British and others), (3) loss of father during formative years of childhood (before age 15), (4) loss of mother during formative years of childhood (before age 15), (5) cause of death (violent vs non-violent), (6) early death of at least one sibling (before age 30), (7) high birth order (7+), (8) nobility rank of the father (indicator of social status), (9) large family size (number of siblings 9+), (10) maternal lifespan, (11) paternal lifespan, (12) paternal age at person's birth, (13) late paternal age at first childbirth (50+ years), (14) birth of the first child by mother after age 30, (15) death of mother from violent cause of death. The F-value for regression model is 18.12 ($p < 0.0001$).

Statistically significant effects are highlighted in bold.

and November–December, a local minimum in between (August) and the lowest lifespan for those born in February.

It is interesting to note that the months of February and August are already known in scientific literature as "bad" months to be born. For example, a similar bimodal month-of-birth distribution was found for birth frequencies of cystic fibrosis disease with peak births in February and August [33]. Further studies are required to find out whether this is just a coincidence of findings or a general seasonal pattern.

The fact that such an early circumstance of human life as the month of birth may have a significant effect 30 years later on the chances of human survival is quite remarkable. It indicates that there may be critical periods early in human life particularly sensitive to seasonal variation in living conditions in the past (e.g., vitamin supply, seasonal exposure to infectious diseases, etc.).

As we already mentioned earlier, the 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 [24]. The seasonal lack of these vitamins in late winter/early spring, in coincidence with one of the two critical periods in fetus or child development (the third critical month of pregnancy and the first months after birth), may explain a dramatic life span shortening among those born in August and February. This finding is also consistent with the reliability theory of aging, which emphasizes the importance of the initial level of damage that determines the future length of human life [1–2].

In contrast to females, the male lifespan is less dependent on month of birth, at least in this particular dataset (see Table 2).

The sex specificity of the month-of-birth effects on adult lifespan is a puzzling observation, but it is also a reassuring one from the methodological point of view. Indeed, the data for men and women are taken from the same data sources and are represented by the same set of family variables (because they are brothers and sisters to each other). Therefore, any possible flaws in data collection and analysis (such as omission of important predictor variables, for example) should produce very similar biases both in males and females data. Instead we observe a clear sex-specific seasonal effect, which is reassuring from the methodological perspective.

While discussing the greater response of female lifespan to the season of birth, it is interesting to see whether other traits such as, for example, the female childlessness are also affected by the month of birth. Indeed, studies on Dutch women found that the birth distribution of childless women, as compared with fecunds, was best represented with bimodal curve with zeniths in January and July [34]. It is interesting to note that the two peaks for childlessness (January and July) seems to correspond well with the two observed minimums for female adult lifespan observed in our study (February and August – just only one month shift compared to childlessness findings).

Women may be more sensitive to early-life conditions, because their eggs (oocytes) are formed very early in life. The female human fetus at age 4–5 months possesses 6–7 million eggs. By birth, this number drops to 1–2 million and declines even further. At the start of puberty in normal girls, there are only 0.3–0.5 million eggs. If the number and quality of oocytes is determined early in life, then early-life conditions may have long-lasting effects on hormonal status in later life, fecundity, age at menopause and lifespan.

Our finding that the month of February is "bad" month to be born for female corresponds well with schizophrenia studies. The risk of schizophrenia is higher for persons, whose birth date is close to February, and this seasonal effect is more marked among females [35]. It was also found that pre-natal exposure to influenza epidemic is associated with later development of schizophrenia in females but not in males [36–37].

While discussing studies of month-of-birth effects, it is important to be aware of methodological problems and pitfalls. In some cases a simplistic approach is applied to study the effects of month of birth on human lifespan: mean ages at death are

Table 2. *Male lifespan as a function of month-of-birth*

Month-of-birth	Net effect* in years (point estimate)	Standard error	*p*-Value
February	0.00	Reference level	
March	–0.03	0.87	0.98
April	–1.16	0.87	0.18
May	1.00	0.86	0.24
June	1.37	0.87	0.11
July	–0.94	0.85	0.27
August	–0.80	0.86	0.35
September	–0.01	0.85	0.99
October	–0.59	0.87	0.50
November	–0.81	0.88	0.36
December	–0.36	0.88	0.68
January	0.37	0.87	0.67
February	0.00	Reference level	

*Net effect corresponds to additional years of life gained (or lost) compared to the reference category (lifespan for those born in February).

Results for Table 2 are obtained through multivariate regression analysis of lifespan data (outcome variable) for 7009 men born in 1800–1880 (extinct birth cohorts with lifespan known for each person), who survived by age 30 (focus on analysis of adult lifespan). The following additional predictor variables are also included in the model because of their predictive value: (1) calendar year of birth, (2) ethnicity (Russian, British and others), (3) loss of father during formative years of childhood (before age 15), (4) loss of mother during formative years of childhood (before age 15), (5) cause of death (violent vs non-violent), (6) early death of at least one sibling (before age 30), (7) high birth order (7+), (8) nobility rank of the father (indicator of social status), (9) large family size (number of siblings 9+), (10) maternal lifespan, (11) paternal lifespan, (12) paternal age at person's birth, (13) late paternal age at first childbirth (50+ years), (14) birth of the first child by mother after age 30, (15) death of mother from violent cause of death. The F-value for regression model is 14.90 ($p < 0.0001$).

calculated for people born in different months using cross-sectional data (i.e., death certificates collected during a relatively short period of time [38]). This methodology is flawed and can produce both false positive and false negative findings. For example, if the seasonality of births and infant mortality were more expressed in the past, then the month-of-birth distribution of people would differ in different age groups of the population, thus producing a spurious month-of-birth effect on lifespan (if erroneously estimated through mean age at death). This mistake happens because the mean age at death depends on the age distribution of living people, which may differ depending on month-of-birth. Thus, even if the month of birth does not affect adult lifespan, nevertheless a false positive finding may occur, simply because the

effects of population age structure are not taken into account. On the other hand, month-of-birth effects could be overlooked by this cross-sectional method if the seasonal effects on age-specific mortality rates are proportional. This false negative finding happens because proportional changes in death rates produce a proportional changes in the numbers of deaths in all age groups, and such proportional changes in numbers have no effect on the mean age at death. Thus, a false negative finding may occur, because cross-sectional analysis of death records is blind to proportional changes in age-specific death rates. In our study we avoided this simplistic cross-sectional analysis of death records as a flawed methodology. Instead we applied a cohort approach by following people born in the same calendar years until the last person died (method of extinct generations).

Finally, we would like to comment on the importance to control for socio-economic status while studying the effects of month of birth. This is very important issue because there are significant differences in birth seasonality between different social classes [39, 40]. Therefore, studies of aggregated data for whole countries [38] may simply reflect the well-known differences in procreation habits of different socio-economic groups. In our study we control for socio-economic status both by stratification (only aristocratic families are included into analysis) and by regression (control for nobility rank).

Parental-age effects on human longevity

Practical importance of the studies on parental-age effects

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) to older women) and personal choice [21, 41]. For example, in the United States the number of births to older mothers (35–39 years and 40+ years) more than doubled since 1980 while the number of births to younger mothers (below age 30) did not increase [21].

Birth rates for older fathers (ages 45–49 and 50–54) are also increasing [42] and this trend may even accelerate in the future due to medical progress (Viagra, for example). Moreover, it became possible now to enjoy fatherhood at any old age through an assisted reproduction technique called "intracytoplasmic sperm injection" or ICSI. A few remaining spermatozoa are 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 a clinical death are not an obstacle for fatherhood any longer.

There is, however, one important concern remaining: 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 has 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. Thus there is a need to fill the gap that exists in our knowledge about the possible postponed detrimental effects of late parenting.

Scientific significance of the studies of the 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 the genomic damage is the most critically important force influencing human longevity (mutation theory of aging [43]). One approach to resolving this problem is to study the lifespan of the 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 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 [44–46].

According to existing evidence, parental age has many detrimental influences on the longevity of offspring [47]. The major maternal age-related changes in humans are increases in fetal aneuploidy later in reproductive life such as:

- Down's syndrome (trisomy 21) [48–51],
- Klinefelter's syndrome (XXY) [49–52],
- Edward's syndrome (trisomy 18) and Patau's syndrome (trisomy 13) [48, 49].

Advanced maternal age also remains an important independent risk factor for fetal death [53–55].

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 [56–68]. In particular, paternal age is responsible for new dominant autosomic mutations that cause different malformations, including:

- Achondroplasia [56, 57, 60],
- Apert syndrome [56, 57],
- Marfan syndrome [56, 57],
- Osteogenesis imperfecta [67, 68] and other inherited diseases.

Older paternal age was observed among patients with Costello syndrome [69], chondrodysplasia punctata [70], fibrodysplasia ossificans progressiva [71, 72], and thanatophoric displasia [73]. 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 [63]. Increased paternal age at childbirth is also an important independent risk factor for neonatal and infant mortality [74].

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 (for example, 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" (cited by Robine and Allard [75]). Before our initial studies on this topic [76, 77], other researchers partially addressed the same issue [78, 79]. Jalavisto [78] analyzed 12 786 published family records of the Finnish and Swedish middle class and nobility for those 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 [78] concluded that offspring born to older mothers live significantly shorter while the age of the father was of no importance. This observation deserves to be validated 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 [79]. Multiple discriminant analysis was used in order 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 ten 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 authors 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" (p. 215) [79]. 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 authors 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 [79]. By contrast, increased father's age was uncommon for long-lived offspring [79].

These important and contradictory observations deserve to be validated by using larger sample sizes and controlling for parental longevity. Control for parental longevity is important because among long-lived women the proportion of those able to become mothers after 40 years is 4 times higher compared to "normal" women [80]. 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.

Our initial exploratory studies and findings

Our first studies on long-term effects of parental age at reproduction on offspring longevity in humans were based on the statistical analysis of particularly accurate and reliable genealogical data on European royal and noble families (description of this database is published elsewhere [81–83]). We found that late paternal age at reproduction has a specific life-shortening effect on daughters rather than sons [19, 20, 76, 77, 84]. Attempts to reproduce these results were made later by other authors [75] using archives of 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 the 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 [85]. 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.

Biological ideas related to the studies of the parental-age effects

Two suggestive findings were made in the above mentioned studies [19, 20, 76, 77, 84]. 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 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 [44–46] – with the age of the father demonstrated to be the main factor determining the spontaneous mutation rate of nuclear DNA [44–46]. 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 [86]. 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 [86]. 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 may be 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 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 which are 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 has already been demonstrated 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 [87]. 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 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. 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) [87].

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 [88]. 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 [89]. Mutations of this critical enzyme may result in a decrease in the accuracy of DNA replication and thus a catastrophic increase in mutation rates [90, 91]. 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^{2+} transporting ATPase.

Another possible explanation for the critical importance of mutation load on the X chromosome is related to a special status of this chromosome in females. As already noted, 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 high paternal age on daughters' longevity might be also 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 [92].

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 if their mother was born to an older grandfather [19]. This specific age effect of maternal grandfather was already demonstrated for some X-linked genetic diseases, such as Duchenne muscular dystrophy (caused by mutation in locus on Xp21 [93], hemophilia A and Lesch-Nyhan disease (reviewed elsewhere [86]). However, this hypothesis was never tested before for the duration of human life and we suggest this idea as a hypothesis for future testing.

New revised estimates of paternal-age effects on human longevity

We present here the results of a new validation study on parental-age effects made on a larger dataset with more reliable cross-checked data. This study confirms our earlier findings and provides more definite results on parental-age effects. The dependence of female lifespan on paternal age at reproduction (when daughter was born) is presented in Table 3.

In order to avoid confounding of parental age effects by selective parental survival (short-lived parents are always young parents, because dead parents do not reproduce), the two methods are simultaneously used: (i) stratification, and (ii) regression. Stratification is achieved by considering only those cases, where both parents survived by age 50, which makes a sample more homogeneous with regard to parental lifespan. Note that there is an optimal age to father a daughter. Daughters born to older or younger fathers tend to live shorter lives on average. These are the net effects of paternal age, when all other predictor variables are taken into account, including maternal age effects that surprisingly proved to be less important.

Table 3. *Female lifespan as a function of paternal age at person's birth (5063 cases, both parents lived 50+ years)*

Paternal age	Net effect* in years (point estimate)	Standard error	*p*-Value
15–24	–2.26	1.28	0.078
25–29	–0.36	0.71	0.615
30–34	–0.53	0.62	0.388
35–39	0	Reference level	
40–44	–0.11	0.67	0.868
45–49	–0.95	0.88	0.282
50–54	–1.90	1.16	0.101
55–59	**–5.37**	**1.65**	**0.001**

*Net effect corresponds to additional years of life gained (or lost) compared to the reference category (lifespan of daughters born to fathers of age 35–39). The data are point estimates of the differential intercept coefficients adjusted for other explanatory variables using multivariate regression with nominal variables.

Results for Table 3 are obtained through multivariate regression analysis of lifespan data (outcome variable) for 5063 women born in 1800–1880 (extinct birth cohorts with lifespan known for each person), who survived by age 30 (focus on analysis of adult lifespan). In order to avoid confounding of parental age effects by selective parental survival (short-lived parents are always young parents, because dead parents do not reproduce), the two methods are simultaneously used: (1) stratification, and (2) regression. Stratification is achieved by considering only those cases, where both parents survived by age 50, which makes a sample more homogeneous with regard to parental lifespan. In addition to this, the data on parental lifespan above age 50 are also included in the multivariate regression model as categorized predictor variables (grouped into five-year intervals). The following additional predictor variables are also included in the model because of their predictive value: (1) calendar year of birth, (2) ethnicity (Russian British and others), (3) cause of death (violent vs non-violent), (4) nobility rank of the father (indicator of social status), (5) maternal age at childbirth (in order to discriminate between maternal and paternal age effects), (6) large family size (number of siblings 11+), (7) late paternal age at first childbirth (45–49 years and 50+ years), (8) young maternal age at last childbirth (before 25 years). The F-value for regression model is 10.12 ($p < 0.0001$). Note that there were 103 cases of women born to father at ages 55–59 years and 160 cases of women born to young father (15–24 years).

Statistically significant effects are highlighted in bold.

Shorter lifespan of daughters conceived to older fathers could be explained by age-related accumulation of mutations in DNA of paternal germ cells [21, 46, 83]. Advanced paternal age at person's conception is an important risk factor for such disease of adult age as schizophrenia [94, 95], and such disease of old age as sporadic (non-familial) Alzheimer disease [96].

It is more difficult to explain, why daughters born to particularly young fathers also may live shorter lives. Standard social explanation, that low-income fathers without education start reproducing earlier seems not to be easily applicable to this socially elite group of royal and noble families. To explain this paradox we suggest a

hypothesis that lifespan shortening may be caused by the excessive genomic imprinting of the germ cell DNA in particularly young fathers. Specifically, we hypothesize that the DNA of young fathers is hypermethylated and for this reason it is more prone to mutations. Later in the life, as fathers become more mature, the DNA is partially demethylated, so the risk of mutations may provisionally decline with age (25–30 years). After that the mutation rate may start to increase again because of the copy errors during DNA replication in paternal sperm cells. It is known that the X chromosome is indeed methylated in the male germ line, while both X chromosomes are unmethylated in the female germ line [92]. This may explain why parental age effect on offspring lifespan is sex-specific: only paternal age is important, while maternal age effects are quite small, and also the affected sex are daughters only (that inherit paternal X chromosome). Further studies in this direction are required to test the proposed hypothesis as well as other possible biological and social explanations.

Analysis of the scientific literature suggests that there may be a fundamental biological explanation of the "young father – short daughters' lifespan" paradox. It was found that the risk of congenital heart defects (ventricular septal defects, VSD, and atrial septal defects, ASD) is increased not only among the offspring of the older fathers, but also among the offspring of particularly young fathers – below 20 years [97]. Children born to younger fathers (under 20 years) have increased risk of neural tube defects, hypospadias, cystic kidney, and Down syndrome [61].

In laboratory mouse, offspring born from older mature fathers exhibit better behavioral performances (for spontaneous activity in both sexes, and learning capacity in males) than those born from particularly young post-pubescent fathers [98]. Similar results were obtained for humans in the 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. The curve of such scores produced an inverted U-shape, with poor scores for those conceived to particularly young or old fathers. Maternal age did not appear to play a part in this event. These results pose the problem of identifying genetic and/or biosocial factors associated with young fathers, which might have an impact on the quality of the conceptus [99].

The practical importance of these findings is obvious: the age constrains for the donors of sperm cells in the case of IVF (in vitro fertilization) should be probably revised to exclude not only the old donors, but also those donors who are too young. Of course, more detailed studies are required, before such important practical recommendation could be made.

In contrast to females, the male lifespan does not decrease with late paternal age at person's birth, at least in this particular dataset (Table 4). This observation is the second example (in addition to season-of-birth effects) in our study when the sex differences in response to early-life conditions are observed.

Possible implications from the studies of the parental-age effects

It is important to continue and expand the studies on parental-age effects, because they may have the following significant implications:

Table 4. *Male lifespan as a function of paternal age at person's birth (5313 cases, both parents lived 50+ years)*

Paternal age	Net effect* in years (point estimate)	Standard error	*p*-Value
15–24	**–2.77**	**1.28**	**0.031**
25–29	0.06	0.68	0.935
30–34	–1.05	0.58	0.069
35–39	0	Reference level	
40–44	–0.85	0.64	0.185
45–49	0.01	0.81	0.990
50-54	0.17	1.13	0.878
55-59	–1.69	1.64	0.304

*Net effect corresponds to additional years of life gained (or lost) compared to the reference category (lifespan of sons born to fathers of age 35–39). The data are point estimates of the differential intercept coefficients adjusted for other explanatory variables using multivariate regression with nominal variables.

Results for Table 4 are obtained through multivariate regression analysis of lifespan data (outcome variable) for 5313 men born in 1800–1880 (extinct birth cohorts with lifespan known for each peson), who survived by age 30 (focus on analysis of adult lifespan). In order to avoid confounding of parental age effects by selective parental survival (short-lived parents are always young parents, because dead parents do not reproduce), the two methods are simultaneously used: (1) stratification, and (2) regression. Stratification is achieved by considering only those cases, where both parents survived by age 50, which makes a sample more homogeneous with regard to parental lifespan. In addition to this, the data on parental lifespan above age 50 are also included in the multivariate regression model as categorized predictor variables (grouped into five-year intervals). The following additional predictor variables are also included in the model because of their predictive value: (1) calendar year of birth, (2) ethnicity (Russian British and others), (3) cause of death (violent vs non-violent), (4) nobility rank of the father (indicator of social status), (5) maternal age at childbirth (in order to discriminate between maternal and paternal age effects), (6) large family size (number of siblings 11+), (7) late paternal age at first childbirth (45–49 years and 50+ years), (8) young maternal age at last childbirth (before 25 years). The F-value for regression model is 8.46 ($p < 0.0001$). Note that there were 99 cases of men born to father at ages 55–59 years and 152 cases of men born to young father (15–24 years).

Statistically significant effects are highlighted in bold.

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

2. It is important for epidemiologists and physicians to know whether persons born to older parents represent a risk group that should be screened more carefully for their health problems at older ages. For example, it is recently

found that the older paternal age is a risk factor for schizophrenia [94, 95], prostate cancer [100], and a sporadic form of Alzheimer disease [96], while maternal age has no prognostic importance. If parental-age effects prove to be as important as the effects of smoking, the implications for life insurance practice could become obvious.

3. Older parents (and companies involved in new reproductive technologies at older ages) need to know about potential health risks associated with parenting in later life. In the case of IVF (in vitro fertilization) the age constrains for the donors of sperm and ova cells need to be more carefully considered.

4. On the other hand, if parental-age effects *per se* prove to be insignificant in future studies (i.e., explained through confounding socioeconomic factors), this would be a great relief for older parents and their children. This is a particularly relevant issue today given trends in delaying the childbearing in the industrialized countries. If the parental-age effects prove to be negligible, this finding will become a scientific challenge for biologists who have to explain how human species manage to cope with high mutation load accumulated in aging gamets. This problem has already received increasing attention of the scientific community [46, 101–103].

Finally, we believe that the findings presented in this study should be interpreted with caution and need to be replicated on other datasets. Also, the results of this study indicate the need for separate analysis of data for males and females when late-life consequences of early-life conditions and events are explored. There is a definite need for subsequent full-scale studies of the effects of early-life conditions on sex-specific health outcomes in later life, and our suggestive findings presented here justify the need for expansion of further work in this direction.

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