Multigenerational effects of age at reproduction on longevity. Do grandparental age matter?

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Abstract

The influence of parental age at reproduction on the health and longevity of his offspring is well recognized, but the possibility of the age at reproduction of the grandparents influencing longevity in the subsequent generations is rarely considered. It may however be important to acknowledge the interplay between grandparental and parental influences when exploring the transmission of health and longevity. In this paper, our main interest lies in the multigenerational effects of age at reproduction on the offspring's longevity. Using data from extended ascending genealogies in the 17th and 18th centuries Quebec and event-history modeling methods, we test whether (i) grandparental age at reproduction has consequences for the survival after age 50 of their grandchildren and (ii) whether such effects can be mediated by the parental age at the time of childbirth. We further examine (iii) if these potential influences may be mediated of modified by other early life and in utero characteristics such as parental and grandparental season of birth. In fact, parental and grandparental birth season may well have long-term consequences on their children and grandchildren's mortality outcomes via maternal and paternal epigenetic inheritance. Last, we are also interested (vi) in knowing how the gender composition would affect the results. These findings could have implications for understanding the biological and environmental basis of longevity but also for public health giving the demographic trend toward increasing parental age at conception in many countries.

Keywords: mortality, longevity, multigenerational transmission, parental and grandparental age at reproduction.

1 Introduction

Biological and environmental events occurring in *in-utero* and during early life have been shown to have important effects on health and mortality outcomes throughout the life course (Elo and Preston, 1996; Hayward and Gorman, 2004; Bengtsson and Lindstrom, 2012; Barker, 1998; Gagnon, 2012). The literature also provides increasing empirical support for the idea that life-history experiences of parents can greatly shape their children's future health outcomes. One of the best examples is parental age at conception, which is known to influence the phenotype of subsequent generations via biological, genetic and environmental channels.

Up to now, however, research on parental age effects have rarely considered the possibility of the age at reproduction of the grandparents influencing longevity in the subsequent generations. And yet, one may inquire, for multigenerational research purpose, whether grandfathers and grandmothers age at reproduction also matter for offspring survival. Could variation in life duration between individuals who live to a very old age and those who fall short of the mark rests in the multigenerational transmission of parental and grandparental age at reproduction? Perhaps health and longevity trajectories are not shaped solely by our own experiences, but also by the experiences and histories of our past generations.

Here, we investigate multigenerational effects of age at reproduction in humans using data from extended ascending genealogies in the 17th and 18th centuries Quebec. We test whether (i) grandparental age at reproduction has consequences for the survival of their grandchildren and (ii) whether such effects can be mediated by the parental age at the time of childbirth. We further examine (iii) if these potential influences are altered when controlling for other early-life characteristics such as parental and grandparental season of birth. In fact, parental and grandparental birth season may well have long-term consequences on their children and grandchildren's mortality outcomes via maternal and paternal epigenetic inheritance (Rickard et al. 2012). Last, we were also interested (vi) in knowing how the gender composition would affect the results

Background

Parental age influences on health and mortality

There is a strong relationship between parental age and offspring health and mortality(Bell, 1918; Jalavisto, 1959; Philippe, 1980; Kemkes-Grottenthaler, 2004; Jarry et al., 2013). In the vast majority of studies on this topic, the negative effects of an older parental age at conception have received the most attention. A retrospective analysis of records from the European aristocracy conducted by Gavrilov and colleagues revealed that daughters born to fathers aged 50 years or more were expected to die 4.4 years earlier compared to daughters from younger fathers aged 20-29 when longevity of the father was controlled for (Gavrilov et al., 1997). Smith et al. (2009) used a sample from the Utah Population Database of individuals born between 1850 and 1900 and discovered that for sons, maternal age at birth above 35 was associated with an increase in the sons' adult mortality in comparison with a maternal age between 20 and 29. MyrskylŁ and Fenelon (2012) found that children born to mothers younger than age 25 or older than age 35 have the worse outcomes regarding mortality and other health-related issues. From a biological and physiological point of view, there is a fairly clear consensus that an advanced maternal age

increases the incidence of pregnancy-related medical complications as well as various genetic malformation in the offspring (Liu et al., 2011). One pathway might involve the lower quality of female oocytes in older mothers resulting in an increased risk of birth defects (Pellestor et al., 2005). The mechanisms linking a delayed maternal age at reproduction and long-term morbidity and mortality in the offspring are less clear, but are also likely to involve excess load of maternal defective mitochondria. Oocytes and ovaries of older mothers are more likely to contain damaged mitochondrial DNA which could be transmitted to the next generation and reduce the biological fitness, health and longevity of the offspring (Tarin et al., 1998). Other correlates of advanced maternal age include a decline in the efficiency of the uterus, an increase risk of placental dysfunction, or increased variations in hormonal levels during pregnancy (Johnson et al., 2009; Nelson et al., 2012). Similarly, increasing paternal age has been associated with a range of congenital syndromes, developmental disabilities, neuropsychiatric conditions and neurodevelopmental disorders in the offspring. The most replicated studies in this field have shown a link between an advanced paternal age and increased risk for bipolar disorder, epilepsy, autistic behaviors and schizophrenia (Thacker, 2004; Malaspina et al., 2005; Vestergaard et al., 2005; Frans et al., 2008; Dalman and Allebeck, 2002). Most researchers attribute these associations to the accumulation of chromosomal aberrations and mutations during the maturation of germ cells (Liu et al., 2011; Gavrilov and Gavrilova, 1997). Epigenetic alteration in the sperm from older men has also been proposed as an alternative explanation (Feinberg, 2010).

So far, most of the research studying the link between parental age at reproduction and health and longevity in the offspring have focus almost exclusively on first-generation effects. Much fewer studies have investigated whether the effects of age at reproduction could extend to the third generation. One study has however drew our attention and represents for us a good basis for comparison. Using the Utah Population Database (UPDB), Smith et al. (2013) examine whether very early or very late ages at reproduction among grandparents can affect survival among their grandchildren. Their findings suggest enduring effects of grandparental age independent of those for parental age effects. They found that only young maternal age is associated with significant adverse survival for daughters, whereas young maternal grandmother and young paternal grandfather ages are associated with poorer survival for grandsons.

Multigenerational transmission of health and longevity

Despite the scarcity of studies on grandparental age effects in human populations in the demographic literature, recent medical research provides a biological rationale of why such a multigenerational inheritance of lifetime experiences may occur.

Paternal and grandpaternal influences

Multigenerational and trangenerational effects of the age at reproduction on offspring health and longevity may occur through different pathways. There are opportunities for this down the male line, implying that the grandfather's information is carried by the sperm's chromosome and via telomeres. A telomere is a repeating DNA sequence found at the ends of the body's chromosomes which protects them from mutating (Blackburn and Gall, 1978). Although telomeres are known to shorten with age, thus leading to senescence, those found in sperm-productive stem cells

actually lengthen (Eisenberg et al., 2012). In a recent study, Eisenberg and colleagues(2012) found that children born of older fathers inherit longer telomeres and live longer. Moreover, the authors noticed an additive effect of late reproduction by both fathers and grandfathers on the average length of the telomeres at birth, thus challenging the general argument that an old paternal age at birth may be harmful for the health and longevity of the offspring. Although seemingly paradoxical, this finding makes sense knowing that older fathers pass along longer telomeres and that longer telomeres are associated with a reduced risk of various diseases and a longer survival (Aviv and Susser, 2013).

Maternal and grandmaternal influences

Multigenerational transmission of age at reproduction may also operate down the female line. Evidence from both human and animal studies suggests that the phenotype is influenced by conditions in utero that are themselves settled by factors going back two generations . As Kuzawa pointed out, the maternal phenotype embodies a mothers lifetime of cumulative experiences and exposures which are in turn passed on during fetal life to the offspring, determining its health and longevity (Kuzawa and Quinn, 2009). This mechanism suggest that the offspring phenotype is potentially responsive and sensitive to long-term transgenerational events experienced by the mother in her pre-natal environment (thus experienced by the grandmother during gestation).

With regards to maternal age, it is thought that mitochondria in oocytes from older women harbor increased DNA mutations and deletions (Bentov et al., 2011). This alteration in the female's physiology during aging may result in an adverse intrauterine environment for the offspring, leading to physiological changes in the next generation and so on. A study focusing on maternal transmission in humans found that an advanced grandmaternal age at the time of the birth of the mother was shown to be involved in the etiology of Down syndrome (Malini and Ramachandra, 2006). Another study focusing on fitness in drosophila also found a cumulative age effects across two generations; females from old mothers who also had old grandmothers had the lowest viability (Hercus and Hoffmann, 2000). Furthermore, Wang and von Saal (2000) have demonstrated a transgenerational effect of maternal age in mice, with the birth weight of the offspring depending on their grandmothers' age at pregnancy.

Objectives and expected results

It seems reasonable to think that the longevity phenotype is determine not only by parental characteristics such as parental age at conception, but could be as well predicted by long-term matrilineal and patrilineal experiences.[1] Building from these evidence, we thus propose a multigenerational approach that links grandparental age at reproduction with the grandchild's longevity. We hypothesize that the age at which the grandmother conceived the mother influences the mother's phenotype which in turn influences the grandchild's health and survival. Similarly,

[1]Even though the importance of biological channels is supported by a large and growing literature, other mechanisms may operate. From a social point of view, parents may not provide their children with the same amount of resources over their lifetime. Besides biology and genetics, intergenerational and multigenerational transmission thus refers to the transfer of individual abilities, behaviors, resources, education, wealth across generations. Therefore, we are aware that a completely different stream of literature should deserve our attention before elaborating our final research design and hypotheses.

we hypothesize that a certain grandpaternal age, whether early or delayed, may translate into a particular mortality risk in the grandchild.

Data and Methods

Data source

To investigate whether the effects of a delayed or early age at reproduction could be passed on to subsequent generations, a longitudinal study spanning three generations was needed. The *Registre de la Population du Québec Ancien (RPQA)*, measures up well to the task. The RPQA database contains ascending genealogies of individuals with linked information and demographic biographies, including age at reproduction, birth season, age at first marriage, first birth interval, total parity, and postreproductive survival of the Québec (Canada) Catholic population during the 17th and 18th centuries (Desjardins 1998).

Study population

Data used in this particular study was retrieved from 40043 offspring born between 1636 and 1749 for whom we have information on their dates of birth and death as well as those of their parents and grandparents. Sample sizes and birth year for the entire sample as well as for a restricted sample of probands surviving to age 50 are shown in Table 1. Table 2 illustrates the average age at death among the three generations.

Outcome and control variables

Our outcome measure (Y_{it}) is longevity. In this study, longevity is defined as the age at death of an individuals who lived beyond the age of 50 years. We also test the effect of age at reproduction on overall mortality (Full sample). The main independent variables are the age of both parents at childbirth as well as the age at which the grandparents conceived the parents. We also include in the models individual birth year fixed effects to capture any cohort variations. All models are run separately for both males and females.

Multigenerational transmission of health may be mediated by nongenomic influences, including either indirect mechanisms associated with parental physiology, as we mentioned in the literature, or epigenetic mechanisms. The latter channel refers to environmental stimulus during development, such as nutrition, that can modify gene expression of successive generations through DNA methylation (Curley et al., 2010). Studies involving individuals conceived during conditions of famine have provided evidence of the influence exerted by maternal and grandmaternal nutrition during gestation on the overall health of the adult offspring. For instance, a study of historical records of individuals born in the late nineteenth and early twentieth centuries in northern Sweden reports that offspring longevity is influenced by their paternal grandfathers access to abundant nutrition during his prepubertal slow growth period (Pembrey et al., 2006). Similarly, extending the study to 1890, 1905 and 1920 cohorts, a link was found between the paternal grandmother's food supply and the overall mortality risk of their granddaughters. The authors ascribe these effects to a potential remethylation of epigenetic marks in the sperm and egg during the ancestor's slow growth period (Kaati et al., 2002, 2007). In the light of this

other potential pathway of multigenerational transmission, we therefore include in our models a season of birth variable, which stands as a proxy for intrauterine developmental conditions and for environmental influences occurring in early life. Seasons were defined using the solstices and equinoxes. We also include the season of birth of the parents and grandparents in order to control for the nutritional environment and disease exposures that may have affected the offspring via epigenetic inheritance. Last, in the appropriate models, we test for the inclusion of a variable measuring the age at death of parents and grandparents.

Statistical analysis

To estimate the impact of the age at reproduction on the survival of the third generation, different models were utilized. The first strategy is to apply stratified Cox proportional hazards models with a separate baseline for each set of cousins. Because the dataset includes siblings and cousins, the idea in using stratified models is that we can control for early-life environment and genetic that are shared among them in order to isolate the potential multigenerational effect of grandparental age at reproduction. Hence, variables that are common to cousins, namely grandparents season of birth or grandparents age at death, are not estimated in these analyses. However, giving our various hypothesis, one element of the model specification that still needs consideration is the distinction between maternal and paternal lineages.

Second, we model the hazard of mortality using gender-specific parametric proportional hazard models in which the baseline hazard $\mu(x)$ follow the Gompertz law $\mu(x) = ae^{bx}$. Because siblings and cousins' survival experiences are likely to be clustered, we include a family-specific random effect that accounts for random unmeasured family-level traits shared by cousins. The hazard $\mu(x)$ can be estimated as follows:

$$\mu(t, z_i, X_{ij}) = z_i, \mu_0(t)e^{\beta X_{ij}} \tag{1}$$

where z_i represents the random variable of the shared frailties, X_{ij} observed explanatory variables, and βX_{ij} parameters to be estimated. The frailties, which are assumed to depend on genetic or environmental unobserved characteristics at the extended family scale, are now assumed to be independent and identically distributed. Following the literature on modeling mortality, the frailty z follows a gamma distribution with:

$$z \sim \Gamma(1, \theta) \tag{2}$$

Motivations and implications

There have been a number of population studies showing that children born to older parents have a significantly reduced survival, but few of them assess the possible relationships between the ages of the parents' own parents at the time of their birth and the longevity of the offspring. And yet, we have good reasons to believe that age at reproduction may have long-lasting effect on the longevity of several successive generations. In this research project, we thus take a multigenerational perspective to understand potential pathways leading to longevity. With a rich set of tools, such an historical data and genealogies, we are able to reconstruct maternal and

paternal histories, which can lead us to interesting examples of multigenerational transmission operating through diverse channels.

This study may thus provide evidence that some nongenetic maternal/paternal factors, such as intrauterine environment or epigenetic imprint related to the age at conception, may perpetuate for generations. Giving the demographic trend towards increasing parental age at conception in high-income countries, our findings may have important implications for epidemiology and public health. One could then ask whether this sustained trend could have significant effects on the survival and longevity of future generations.

Tables and figures

Table 1: Sample size and birth window of the three generations

	Full sample (from birth)		Restr. sample (50+)	
Generations	Obs.	Birth year	Obs.	Birth year
Third generation				
Ego	40043	1636-1749	20064	1649-1749
Male	20299	1636-1749	10866	1638-1749
Female	19396	1638-1749	9196	1638-1749
Unknown	348	1670-1749		
Second generation				
Mother	40036	1620-1733	20062	1620-1732
Father	40036	1619-1730	20060	1619-1730
Third generation				
Maternal gm	39950	1602-1715	20013	1602-1715
Maternal gf	39749	1587-1713	19918	1587-1710
Paternal gm	39918	1585-1710	19982	1585-1710
Paternal gf	39597	1575-1704	19853	1575-1704

Table 2: The average age at death for survivors up to at least 50 years of age among probands and from birth among ancestors, and the standard deviation around the average

	Male		**Female**	
Proband and ancestors	Age at death	SD	Age at death	SD
Ego	71.2	10.5	72.1	10.6
Parents	66.4	14.3	63.3	17.6
Maternal grandparents	66.7	14.3	65.1	16.7
Paternal grandparents	66.8	13.9	65.3	16.2

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