Maternal non-Mendelian inheritance of a reduced lifespan? A hypothesis

Martin Wilding · Gianfranco Coppola ·
Francesco De Icco · Laura Arenare ·
Loredana Di Matteo · Brian Dale

Received: 28 November 2013 / Accepted: 14 March 2014 / Published online: 1 April 2014
© Springer Science+Business Media New York 2014

Abstract

Purpose A negative correlation exists between advanced maternal age and reproduction. Current data suggest that this correlation is due to a decline in oocyte quality with respect to female age. Since a new individual is derived from the fusion of a single sperm and egg, we tested whether the quality of this material could influence the long-term physiological health of offspring, by examining whether a link between parental age and lifespan of offspring exists.

Methods We requested a search from the Swedish demographic database POPUM 3 maintained by the University of Umeå, Sweden between years 1700 and 1900. Parameters requested included mothers' and fathers' age at gestation, the lifespan of the children, cause of death of children and the region of birth. **Results** Complete data was obtained for 30,512 children born to 12,725 mothers and fathers. Kaplan-Meier estimators demonstrated a strong relationship between mother's age at gestation and the longevity of offspring. Extrinsic factors such as century of birth also had an effect on the data. The forward stepwise procedure on Cox's model of proportional hazards

suggested that most significant intrinsic factors were mother's lifespan and mother's age at gestation.

Conclusions These data demonstrate that intrinsic and extrinsic factors influence the lifespan of children. Among intrinsic factors, mother's lifespan and age at gestation had a significant influence on the data. The influence of intrinsic factors remained significant despite a strong extrinsic influence. We suggest that the influence of the mother on the lifespan of offspring is due to extra-genomic factors.

Keywords Maternal age · Inheritance · Reproductive physiology

Introduction

The reproductive efficiency of females is known to be negatively correlated with age at gestation in the human. Apart from the decrease in ovarian reserve [19, 38], physiological and clinical evidence has demonstrated that this relationship is caused by defects within the human oocyte [55, 37, 35, 26]. This is perhaps not surprising since the primordial germ cell is formed prior to birth, therefore the age of these cells reflects the age of the mother. However, the biological causes for this relationship are not well defined. Current hypotheses include an increase in the frequency of aneuploidy in the oocyte through errors in meiosis [22] and a decrease in the efficiency of aerobic respiration in the oocyte, leading to a deficit in energy production [43, 44, 52, 53, 50, 14], although the two theories are not mutually exclusive [52].

Advanced parental age at gestation may also have more subtle physiological effects on the health and longevity of offspring, because each individual receives a physiological makeup that is influenced by that of the parents and that this extends beyond the inheritance of the genome. Non-genomic contributions to offspring include the inheritance of the

Capsule A demographic database shows a correlation between parental age and longevity of children in humans.

M. Wilding (✉)
Centre for Reproduction and Advanced Technology, St. Georges
House, 3-5 Pepys Road, London SW20 8NJ, UK
e-mail: martinwilding@hotmail.com

G. Coppola · L. Di Matteo · B. Dale
Centro Fecondazione Assistita, Clinica Villa del Sole, Via Manzoni
15, 80122 Naples, Italy

F. De Icco · L. Arenare
IMM, CNR, Via Pietro Castellino, 80100 Naples, Italy

L. Di Matteo
Facoltà di Medicina e Chirurgia, II Università degli Studi di Napoli,
Via Costantinopoli, 16, 80100 Naples, Italy

mitochondria through mitochondrial DNA (mtDNA) of the mother and the centrosome of the father [42, 7]. Therefore, the inheritance of sub-optimal organelles could influence the long-term health of offspring. Epigenetic alterations of the genome can also be inherited [34], suggesting that post-genetic influences on the genome can be carried forward into subsequent generations. Correlations between the lifespan of parents and siblings has been suggested through many animal models and is termed ‘the Lansing effect’ [29, 30, 40]. In *Drosophila melanogaster* a non-nuclear factor influences lifespan [54]. Advanced paternal and maternal age in mice also appears to decrease the postnatal development, reproductive efficiency and lifespan of offspring [45–47, 15, 16]. In humans, both paternal age [18, 17] and maternal age [6, 27, 41] have been suggested to influence the lifespan of daughters.

Many hypotheses, both intrinsic to the biology of reproduction, and extrinsic (socio-economic etc.), have been proposed to explain the effect of advanced age on the health of offspring. One intrinsic theory suggests that DNA mutations accumulate in the parental genome, leading to an increased risk of producing offspring with genetic disease [10, 11]. The theory further suggests a correlation would exist between fathers of advanced age and their offspring because DNA repair is reduced during spermatogenesis, remaining efficient in the primordial oocyte, although recent evidence suggests that DNA repair also declines in ovaries [1, 2, 48]. Extrinsic theories include the efficiency of materno-fetal nutrition which declines with respect to age, causing gestational complications, premature delivery and low birth weight and in consequence programming offspring of mothers of advanced age to a shorter lifespan [5, 24, 23, 3], although this hypothesis has not been universally accepted [8, 31, 36]. A socio-economic theory however suggests that advanced maternal age has a positive effect on the lifespan of offspring due to increased experienced and socio-economic advantages associated with age [36].

Here, we investigate whether parental age may have a longer term influence on human offspring than simply on pregnancy and childbirth alone. We used an extraction from a demographic database over a 200 year period in order to neutralize the influence of confounding factors. Our data suggests that both extrinsic and intrinsic elements influence lifespan, but intrinsic maternal factors remain highly influential.

Materials and methods

We requested a database search from the Swedish demographic database POPUM 3 Demografiska Databasen, Umeå Universitet, S-901 87 Umeå, Sweden. This database is particularly useful because it provides a full demographic record of Swedish citizens from the year 1700 onwards. Parameters requested were mothers date of birth, the date of birth of each

child of individual mothers, date of birth of the father of each child (where known), sex, and date of death of the offspring. Where known, a cause of death was also included in the data. The four regions of Sweden included in the search were North Inland, Sundsvall, Skellefteå, and Linköping. Extracts from the years 1700–1900 were requested from the regions, in order to ensure the complete records (i.e. date of death) of all offspring.

Data was selected where the date of birth and death for the subject, birth and death of both mother and father was known. Moreover number of children in the family and place of birth was also recorded. Data was deselected where one of the above parameters was not recorded; where the sex of the individual was unknown or hermaphrodite, or where the cause of death was obviously non-natural (i.e. ‘hanged’, ‘murdered’ or ‘lost in the forest’).

Data was processed and statistically analysed using SPSS software (IBM, USA). The Kaplan-Meier estimator was used to plot the survival function from lifetime data [25]. The Log rank and Wilcoxon test were applied to test for homogeneity of the KM survival curves. Cox’s model of proportional hazards [9] with the forward stepwise procedure was used to test the relative influence of variables within the database on the outcome. Accumulated risk of death was calculated as the negative log of the survival function. The power of the test was determined as >0.80 for all analyses. Students’ *t*-test was used to determine the significance of populations and the *z*-test was used to test the significance of proportions.

Results

Complete data was obtained from a total 30,512 children (born to 12,725 mothers and fathers), according to the records in the database. The Kaplan-Meier (KM) estimator for survival of children records a median of 6 years ($n=30,512$, Table 1) and a mean of 22.9 ± 0.16 years (mean $\pm$ sd, $n=30,512$, Fig. 1a and b). Century of birth affected significantly the survival data. In the 18th century, the median longevity of offspring was 3 years ($n=5,191$) whereas this increased to 58 years in the 19th century ($n=25,320$, Fig. 2a and b). The Log Rank test and Wilcoxon test were performed to measure the homogeneity of the curves, and both tests demonstrated that these curves differed in a highly statistically significant

Table 1 Percentile of ages of death, all children

Percentile	Lifespan (years)	95 % Confidence interval
25	0	0
50	6	6–7
75	44	43–45

The data is taken from all 30,512 children recorded in the database

Fig. 1 **a** Kaplan-Meier estimate of general survival function for all offspring born between 1700 and 1900 according to the database. The x-axis represents lifespan of children (years), and the y-axis is the proportion of individuals deceased at the relative age. The data represents a total of 30,512 individuals for which complete data is available. **b** Accumulated risk curve for lifespan of offspring born between 1700 and 1900. The graph is plotted as the negative log of the KM survival function (y-axis) against lifespan of individuals (years)

manner ($p < 0.0001$). Analysis of the data demonstrates that this difference was due to a large proportion of deaths among newborns in the 18th century (Table 2 and Fig. 2).

According to the database, the median age at which women gave birth over the two centuries was 31 years. We used this value to plot a KM survival curve and therefore test whether the age of the mother influenced the lifespan of offspring. The KM survival curve showed a highly significant decrease in the survival function for offspring born to mothers of age greater than 31 years (Fig. 3a and b). The median lifespan of offspring born to mothers younger than 31 years was 10 years whereas children born to mothers of age greater than 31 years lived a median of 4 years. Again, the Log Rank test and Wilcoxon test demonstrated that the differences between curves were highly statistically significant ($p < 0.0001$), indicating that the lifespan of children born to mothers below 31 years of age is significantly longer than that of mothers over this age. The differences remained highly significant in both the 18th and 19th centuries, even considering the increase in deaths among newborns in the 18th century (Fig. 4a and b and Table 3).

Fig. 2 **a** Comparison of Kaplan-Meier estimate of general survival function for offspring born between 1700 and 1799 and those born between 1800 and 1899 according to the database. The x-axis represents lifespan of children (years), and the y-axis is the proportion of individuals deceased at the relative age. The red curve is the data of offspring born between 1700 and 1799 ($n = 5,191$) whereas black represents survival data of children born between 1800 and 1899 ($n = 25,320$). **b** Accumulated risk curve comparing the lifespan of offspring born between 1700–1799 and 1800–1899. The graph is plotted as accumulated risk of death (y-axis) against lifespan of individuals (years). The red curve is the data of offspring born between 1700 and 1799 ($n = 5,191$) whereas black represents survival data of children born between 1800 and 1899 ($n = 25,320$). The graph is plotted as the negative log of the KM survival function (y-axis) against lifespan of individuals (years)

Lifespan of offspring decreases in relation to mother's age at gestation even in individual families (Fig. 5). These data suggest that mother's age at birth (cutoff 31 years) has a negative influence on the lifespan of offspring.

The above data shows that the lifespan of offspring is influenced by intrinsic factors such as mother's age at birth, and extrinsic factors such as century of birth. Interestingly, mother's age at birth remained a significant influence on lifespan through both centuries suggesting that intrinsic factors are fundamental to the dataset. Intrinsic factors include parents' age at birth and lifespan, whereas extrinsic factors could include maternal experience and socio-economic influences such as access to healthcare and education in diverse regions of the country. Although it is not possible to account for all intrinsic and extrinsic factors in the present work, measurable variables that could be extracted from the present database include the longevity of both mother and father, age of father at birth, gender of the child and total number of

Table 2 Percentages of deaths among newborns

	All mothers' ages	Mothers age <31 years	Mothers age >31 years	Significance (<i>p</i> -value)
18th century	37.39 % (1,941/5,191 births)	37.98 % (986/2,596 births)	40.00 % (1,038/2,595 births)	0.14
19th century	11.99 % (3,038/25,320 births)	12.00 % (1,520/12,660 births)	12.04 % (1,525/12,660 births)	0.92

The number of deaths among newborns are recorded as death in the first year of life. Significance is calculated through the *z*-test. Data are not significantly different ($p>0.05$)

children born to a particular mother. We tested the relative influence of each of these variables on the lifespan of children by using the forward stepwise procedure with Wilcoxon's chi-squared test on Cox's model of proportional hazards ([9], Table 4). Although extrinsic factors such as number of children per mother influenced the data, intrinsic factors such as mothers' lifespan and age at birth also had significant effects (Table 4). The data suggest that the most significant intrinsic factors that influenced the longevity of offspring in the present

work are mother's age at the child's birth and the longevity of the mother (Table 4).

Discussion

Reproduction involves the inheritance of the male and female genome, but also the inheritance of extra-genomic factors such as the mitochondria (through the mitochondrial DNA) [12] from the mother and the centrosome (through the

Fig. 3 **a** Comparison of Kaplan-Meier estimate of general survival function for offspring born to mothers in relation to median age. The red curve is the data of offspring born to mothers of age over 31 years ($n=15,255$) whereas black represents survival data of children born to mothers of less than or equal to 31 years ($n=15,256$). **b** Accumulated risk curve comparing the lifespan of offspring born to mothers in relation to median age. The graph is plotted as accumulated risk of death (y-axis) against lifespan of individuals (years). The red curve is the data of offspring born to mothers of age over 31 years ($n=15,255$) whereas black represents survival data of children born to mothers of less than or equal to 31 years ($n=15,256$). The graph is plotted as the negative log of the KM survival function (y-axis) against lifespan of individuals (years)

Fig. 4 **a** Comparison of Kaplan-Meier estimate of general survival function for offspring born to mothers in relation to median age (cutoff 31 years) and century of birth. The red ($n=2,596$) and black ($n=2,595$) curves represent the 18th century whereas green ($n=12,660$) and blue ($n=12,660$) curves are data from the 19th century. Blue and red—mothers greater than 31 years of age. Green and black—mothers less or equal to 31 years of age. **b** Accumulated risk curve comparing the lifespan of offspring born to mothers in relation to median age and century of birth. The graph is plotted as accumulated risk (negative log of the KM survival function) of death (y-axis) against lifespan of individuals (years). The red ($n=2,596$) and black ($n=2,595$) curves represent the 18th century whereas green ($n=12,660$) and blue ($n=12,660$) curves are data from the 19th century. Blue and red—mothers greater than 31 years of age. Green and black—mothers less or equal to 31 years of age

Table 3 Significance of survival curves differentiated for mother's age at birth

Test	Chi-square	p
Log rank	3,442.7	<0.0001
Wilcoxon	3,011.3	<0.0001

spermatozoon) from the father. These data alone suggest that the physiological makeup of new individuals is dependent on more than simply the genes of their parents. It is well established that the reproductive efficiency of parents is influenced by age, particularly in the case of the female. In the present work, we further speculate that the inheritance of the physiological makeup of the gametes from ageing parents can influence the health (measured in the present work as lifespan), of their offspring.

We used a demographic database to test whether maternal age at gestation influences the lifespan of offspring. From the database of 47,734 children, 17,222 children were excluded due to incomplete datasets, leaving 30,512 children analysed. We used the Kaplan-Meier estimator of survival function to estimate the longevity of children born in this period. The median age of death of all offspring analysed was 6 years (Table 1). Differentiation of survival data for century of birth shows a significant difference in the results. In fact, in the 18th century, the median lifespan of children was 3 years whereas in the 19th century, the median rose to 58 years of age. Although these data appear to demonstrate a dramatic improvement in survival of children in the 19th century, analysis of the deaths at birth shows a significantly higher proportion of neonatal deaths in the 18th century (Table 2). The median age of the mother at birth in the present data was 31 years. We tested whether the age of the mother at birth influenced the longevity of offspring by comparing the KM survival curves in relation to this age. Whether data was differentiated for century of birth, or plotted together, children born to mothers younger than 31 years of age lived a significantly longer

Table 4 Significance of variables in order of rank

Variable	Rank	Chi ² value	Relative risk
Century	1	1,600.8	1.758
Mothers lifespan (years)	2	421.9	0.990
Mothers age at birth (years)	3	171.9	1.014
Fathers' lifespan (years)	4	66.4	0.996
Fathers age at birth (years)	5	23.6	1.006
Childs' gender	6	9.1	1.040
Number of children born to each mother	7	5.4	1.005

The Forward Stepwise procedure was used to determine the relative rank of influence of each of the above variables on longevity of offspring. Relative risk was calculated through the method of 'Maximum Likelihood Estimation'

lifespan than those born to older mothers (Figs. 3 and 4 and Table 3). These data strongly suggest that the age of the mother at birth is a significant influence on the lifespan of offspring.

The lifespan of children may be influenced by many factors, both intrinsic and extrinsic. It has been suggested that both mothers' and fathers' age at birth strongly influence the lifespan of offspring, both in humans and animal models [29, 30, 40, 45–47, 15, 16, 18, 17, 6, 27, 41]. In the 18th and 19th centuries in Sweden, lifespan of offspring could also be influenced by many extrinsic factors such as living conditions. We tested the relative influence of all factors measurable in the present database. Our data suggest that, although many extrinsic factors including century and region of birth could significantly influence the longevity of offspring, intrinsic factors such as mother's lifespan and mothers' age at birth had fundamental effects.

Which intrinsic biological factors are inheritable principally through the female germ line, in a pattern related to age? Gross oocyte defects such as chromosome abnormalities may be inherited in relation to the age of the mother (Downs' syndrome for example), but cause immediate, drastic effects on the health and therefore lifespan of offspring, and transmission to offspring is unlikely due to the low probability of reproduction in these individuals. Nuclear genetic abnormalities, for example mutations that cause genetic disease such as Muscular Dystrophy are usually transmitted in a Mendelian fashion and can be sex-linked, but are not known to be transmitted in relationship to the age of the mother. Therefore the present data suggests that nuclear genetic factors are not primarily involved.

If the genome does not significantly contribute to the effect shown, is it possible that extragenomic factors are involved? Extragenomic factors contributed by the female germ line to offspring include the mitochondria (in the form of mitochondrial DNA or mtDNA [7]). We and others have previously suggested that the mitochondrial activity of oocytes loses

Fig. 5 Mean lifespan of children born to the same mother. The data is an analysis of 22 mothers producing 10 children in their lifetime. Means of the lifespan of each sibling are recorded. Data shows mean ages with standard deviation represented as error bars. Grey line is the correlation between child number and lifespan ($r=-0.19$)

efficiency in relation to the age of the mother [33, 50–53]. Therefore it is possible that sub-pathological losses of mitochondrial activity can affect the physiology of individuals that inherit these organelles, and this may have long-term physiological consequences such as reduced lifespan. Another possibility is that gene expression profiles change in ageing individuals as they have been shown to occur in the mouse [21]. This may again lead to sub-pathological damage to gametes and health consequences for offspring born to these individuals.

Extrinsic factors that may influence the lifespan of offspring could include socio-economic factors such as experience of the mother, and physiological factors such as the environment to which the unborn foetus was exposed. Experience of the mother suggests that children to older mothers should live longer. Since this was not the case in the present analysis, experience appears not to have any significant effect on the lifespan of offspring. Physiological factors could include the environment which the developing foetus is exposed to in females of advanced age, and this could be further influenced by the external environment. There is some evidence that pregnancies are higher risk in mothers of advanced age, with a consequential increase in the incidence of low birth weight neonates (<2,500 g) and a reduction in the number of gestational weeks in relation to age. In the present data, we could not directly exclude these two factors, because gestational weeks and birth weight were not registered until later time periods (1950's). However, we suggest that the survivability of low birth weight neonates and after premature delivery is limited in the historical period of this work (1700–1900). Furthermore, although there is a published decrease in gestational weeks in relation to maternal age [32, 4, 28], in reality this is minimal (<7 days according to [13]) and other risk factors for advanced maternal age do not increase significantly (1–5 % according to [32, 28]). Therefore, we suggest that gestational factors contribute little to the relationship described in this work. The gestational environment however could be further influenced by the external environment. The 1944 famine in Holland for example has been characterized by an epigenetic imprint on individuals born in this time period [20, 49], and this appears further to be somewhat inheritable [39]. Although socio-economic factors (expressed as century of birth in the present work), are also strongly related to lifespan of offspring, these do not appear to influence the intrinsic relationships (Fig. 4), suggesting that intrinsic factors significantly influence the lifespan of offspring in the presence of variable extrinsic factors.

In summary, we have demonstrated a correlation between mothers' age at gestation, and the lifespan of children. The relationship is non Mendelian, and principally inherited through the mother. We speculate that the relationship is caused through the contribution of mtDNA, although other factors could be responsible. We have previously suggested

that the degeneration of mitochondria with respect to maternal age affects the reproductive potential of these individuals. We now suggest that the same mechanism causes longer term effects on the individual than previously anticipated.

Acknowledgements This work was self-funded. We thank Erik Törlund and staff of the Demografiska Databasen, Umeå Universitet, S-901 87 Umeå, Sweden for their excellent database. We also thank Vincenzo Monfrecola for his help in the preparation of the work.

Conflicts of interest We declare that no conflicts of interest are present.

References

1. Aitken RJ, Clarkson JS, Fishel S. Generation of reactive oxygen species, lipid peroxidation, and human sperm function. *Biol Reprod*. 1989;41:183–97.
2. Alvarez G, Touchstone JC, Blasco L, Storey BT. Spontaneous lipid peroxidation and production of hydrogen peroxide and superoxide in human spermatozoa. Superoxide dismutase as major enzyme protectant against oxygen toxicity. *J Androl*. 1987;8:338–48.
3. Andersen AN, Osler M. Birth dimensions, parental mortality, and mortality in early adult age: a cohort study of Danish men born in 1953. *Int J Epidemiol*. 2004;33:92–9.
4. Astolfi P, Zonta LA. Risks of preterm delivery and association with maternal age, birth order and fetal gender. *Hum Reprod*. 1999;14:2891–4.
5. Barker DJP, Eriksson JG, Forsen T, Osmond C. fetal origins of adult disease: strength of effects and biological basis. *Int J Epidemiol*. 2002;31:1235–9.
6. Bell AG. The duration of life and conditions associated with longevity. A study of the Hyde Genology. Washington D.C.: Genealogical Record Office; 1918.
7. Birky Jr CW. Uniparental inheritance of mitochondrial and chloroplast genes: mechanisms and evolution. *Proc Natl Acad Sci U S A*. 1995;92:11331–8.
8. Cogswell ME, Yip R. The influence of fetal and maternal factors on the distribution of birthweight. *Semin Perinatol*. 1995;19:222–40.
9. Cox DR. Regression models and life-tables. *J R Stat Soc Ser B*. 1972;34:187–220.
10. Crow JF. How much do we know about spontaneous human mutation rates? *J Environ Mol Mutagen*. 1993;21:122–9.
11. Crow JF. The high spontaneous mutation rate: is it a health risk? *Proc Natl Acad Sci U S A*. 1997;94:8380–6.
12. Cummins JM. Mitochondria: potential roles in embryogenesis and nucleocytoplasmic transfer. *Hum Reprod Update*. 2001;7:217–28.
13. Delpisheh A, Brabin L, Attia E, Brabin BJ. Pregnancy late in life: a hospital-based study of birth outcomes. *J Women's Health*. 2008;17:965–70.
14. Eichenlaub-Ritter U, Wieczorek M, Lüke S, Seidel T. Age related changes in mitochondrial function and new approaches to study redox regulation in mammalian oocytes in response to age or maturation conditions. *Mitochondrion*. 2011;11:783–96.
15. García-Palomares S, Navarro S, Pertusa JF, Hermenegildo C, García-Pérez MA, Rausell F, et al. Delayed fatherhood in mice decreases reproductive fitness and longevity of offspring. *Biol Reprod*. 2009;80:343–9.
16. García-Palomares S, Pertusa JF, Miñarro J, García-Pérez MA, Hermenegildo C, Rausell F, et al. Long-term effects of delayed fatherhood in mice on postnatal development and behavioral traits of offspring. *Biol Reprod*. 2009;80:337–42.

17. Gavrilov LA, Gavrilova NNS. Parental age at conception and offspring longevity. *Rev Clin Gerontol*. 1997;7:5–12.
18. Gavrilov LA, Gavrilova NS, Semenova VG, Evdokushkina GN, Krut'ko VN, Gavrilova AL, et al. Maternal age and lifespan of offspring. *Dokl Biol Sci*. 1997;354:287–9.
19. Gougeon AN. The biological aspects of risks of infertility due to age: the female side. *Rev Epidemiol Sante Publique*. 2005;53(Spec No 2): 2S37–45.
20. Hajkova P. Epigenetic reprogramming—taking a lesson from the embryo. *Curr Opin Cell Biol*. 2010;22:342–50.
21. Hamatani T, Falco G, Carter MG, Akutsu H, Stagg CA, Sharov AA, et al. Age-associated alteration of gene expression patterns in mouse oocytes. *Hum Mol Genet*. 2004;13:2263–78.
22. Hassold T, Jacobs P. Trisomy in man. *Annu Rev Genet*. 1984;18:69–97.
23. Jacobsson B, Ladfors L, Milsom I. Advanced maternal age and adverse perinatal outcome. *Obstet Gynecol*. 2004;104:727–33.
24. Jolly M, Sehore N, Harris J, Robinson S, Regan I. The risks associated with pregnancy in women aged 35 years or over. *Hum Reprod*. 2000;15:2433–7.
25. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457–81.
26. Keefe DL. Ageing and infertility in women. *Med Health RI*. 1997;80: 403–5.
27. Kemkes-Grottenthaler A. Parental effects on offspring longevity—evidence from 17th to 19th century reproductive histories. *Ann Hum Biol*. 2004;31:139–58.
28. Khoshnood B, Wall S, Lee KS. Risk of low birth weight associated with advanced maternal age among four ethnic groups in the United States. *Matern Child Health J*. 2005;9:3–9.
29. Lansing AI. A transmissible, cumulative and reversible factor in aging. *J Gerontol*. 1947;2:228–39.
30. Lansing AI. Evidence for aging as a consequence of growth cessation. *Proc Natl Acad Sci*. 1948;34:304–10.
31. Lawlor DA, Mortensen L, Andersen AN. Mechanisms underlying the associations of maternal age with adverse perinatal outcomes: a sibling study of 264 695 Danish women and their firstborn offspring. *Int J Epidemiol*. 2011;40:1205–14.
32. Lee KS, Ferguson RM, Corpuz M, Gartner LM. Maternal age and incidence of low birth weight at term: a population study. *Am J Obstet Gynecol*. 1988;158:84–9.
33. Linnane AW, Marzuki S, Ozawa T, Tanaka M. Mitochondrial DNA mutations as an important contributor to ageing and degenerative diseases. *Lancet*. 1989;1:642–5.
34. Margueron R, Reinberg D. Chromatin structure and the inheritance of epigenetic information. *Nat Rev Genet*. 2010;11:285–96.
35. Munné S, Cohen J, Grifo J, Sultan K, Alikani M, Tomkin G, et al. Implantation failure of morphologically normal human embryos is due largely to aneuploidy. *Fertil Steril*. 1995;64:382–91.
36. Myrskylä M, Fenelon A. Maternal age and offspring adult health: evidence from the health and retirement study. *Demography*. 2012;49:1231–57.
37. Navot D, Drews MR, Bergh PA, Guzman I, Karstaedt A, Scott RT, et al. Age-related decline in female fertility is not due to diminished capacity of the uterus to sustain embryo implantation. *Fertil Steril*. 1994;61:97–101.
38. Nelson SM, Telfer EE, Anderson RA. The ageing ovary and uterus: new biological insights. *Hum Reprod Update*. 2013;19:67–83.
39. Pembrey ME, Bygren LO, Kaati G, Edvinsson S, Northstone K, Sjöström M, et al. Sex-specific, male-line transgenerational responses in humans. *Eur J Hum Genet*. 2006;14:159–66.
40. Priest NK, Mackowiak B, Promislow DEL. The role of parental age effects on the evolution of aging. *Evolution*. 2002;56:927–35.
41. Smith KR, Mineau G, Garibotti G, Kerber R. Effects of childhood and middle-adulthood family conditions on later-life mortality: evidence from the Utah population database, 1850–2002. *Soc Sci Med*. 2009;68:1649–58.
42. Sutovsky P, Schatten G. Paternal contributions to the mammalian zygote: fertilization after sperm-egg fusion. *Int Rev Cytol*. 2000;195: 1–65.
43. Tarin JJ. Aetiology of age-associated aneuploidy: a mechanism based on the 'free radical theory of ageing'. *Hum Reprod*. 1995;10:1563–5.
44. Tarin JJ. Potential effects of age-associated oxidative stress on mammalian oocytes/embryos. *Mol Hum Reprod*. 1996;2:717–24.
45. Tarin JJ, Brines J, Cano A. Long-term effects of delayed parenthood. *Hum Reprod*. 1998;13:2371–6.
46. Tarin JJ, Gómez-Piquer V, Manzanedo C, Miñarro J, Hermenegildo C, Cano A. Long-term effects of delayed motherhood in mice on postnatal development and behavioural traits of offspring. *Hum Reprod*. 2003;18:1580–7.
47. Tarin JJ, Gómez-Piquer V, Rausell F, Navarro S, Hermenegildo C, Cano A. Delayed motherhood decreases life expectancy of mouse offspring. *Biol Reprod*. 2005;72:1336–43.
48. Titus S, Li F, Stobezki R, Akula K, Unsal E, Jeong K, et al. Impairment of BRCA1-related DNA double-strand break repair leads to ovarian aging in mice and humans. *Sci Transl Med*. 2013;5: 172ra21.
49. Tobi EW, Lumey LH, Talens RP, Kremer D, Putter H, Stein AD, et al. DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. *Hum Mol Genet*. 2009;18: 4046–53.
50. Van Blerkom J. Mitochondria in human oogenesis and preimplantation embryogenesis: engines of metabolism, ionic regulation and developmental competence. *Reproduction*. 2004;128:269–80.
51. Wilding M, Dale B, Marino M, di Matteo L, Alviggi C, Pisaturo ML, et al. Mitochondrial aggregation patterns and activity in human oocytes and preimplantation embryos. *Hum Reprod*. 2001;16:909–17.
52. Wilding M, De Placido G, De Matteo L, Marino M, Alviggi C, Dale B. Chaotic mosaicism in human preimplantation embryos is correlated with a low mitochondrial membrane potential. *Fertil Steril*. 2003;79:340–6.
53. Wilding M, Di Matteo L, Dale B. The maternal age effect: a hypothesis based on oxidative phosphorylation. *Zygote*. 2005;13:317–23.
54. Yonemura I, Motoyama T, Hasekura H, Boettcher B. Cytoplasmic influence on the expression of nuclear genes affecting life span in *Drosophila melanogaster*. *Heredity (Edinb)*. 1991;66:259–64.
55. Zheng CJ, Byers B. Oocyte selection: a new model for the maternal-age dependence of Down syndrome. *Hum Genet*. 1992;90:1–6.