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Senescence of Reproduction may Explain Adaptive Menopause in Humans: A Test of the "Mother" Hypothesis

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ABSTRACT The "mother" hypothesis is one of the main adaptive explanations of human menopause. It postulates that reproductive cessation constitutes a strategy that has been selected for during human evolution because mothers at older ages might maximize their fitness by investing resources in the survival and reproduction of their living children rather than by continuing to reproduce. This study provides a test of this hypothesis. Fertility functions that maximize fitness are built into a model incorporating the fact that the survival of females during the rearing period is a major determinant of their children's survival. Results are given according to different scenarios of increase with mothers' age of maternal mortality risk and risk of stillbirth and birth defects (on the assumption that these females do not experience menopause). Different estimates of the effect of a mother's death on her child's survival were also incorporated. Finally, a population genetics framework allows us to estimate selection on these optimal fertility functions. To determine whether or not these fertility functions show a menopause, three criteria are discussed: the rapidity of fertility decline, if any; the magnitude of selection on menopause compared with a nonmenopausal strategy; and the selection on survival during post-reproductive life. Our results show that menopause and subsequent post-reproductive life are significantly advantageous when two conditions are satisfied: a marked increase in stillbirth and risk of birth defects as well as in maternal mortality with mother's age. Am J Phys Anthropol 000:000–000, 2008.

Peccei (2001a) defines menopause as "a nonfacultative cessation of fertility that occurs in all female conspecifics well before the senescence of other somatic systems and the end of the average adult life span." Two specific features therefore characterize menopause: a rapid cessation of fertility and a period of post-reproductive life. From an evolutionary perspective, menopause is puzzling because evolution favors life-history strategies that maximize the individuals' number of descendents. Cessation of reproduction should lower this number. Evolutionary biologists have discussed two main explanations of menopause (Peccei, 2001a): menopause is an adaptation (i.e., a genetically programmed physiological phenomenon that has been positively selected for during human evolution) or menopause is an epiphenomenon of another evolutionary process (i.e., menopause has never been directly selected for). The epiphenomena hypotheses considers menopause a product of antagonistic pleiotropy favoring early-fertility at the expense of late fertility (Gosden and Faddy, 1998; Leidy, 1999) or the by-product of an increase in lifespan or life expectancy (Weiss, 1981; Gosden and Telfer, 1987). Conversely, adaptive theories assume that human females experience menopause because, during human evolution, females that had ceased reproducing before the end of their life gained a fitness advantage over their still-fertile female conspecifics.

The two main adaptive theories are the "mother" and the "grandmother" hypotheses. The "mother" hypothesis was first developed by Williams (1957). It states that, when offspring fitness depends on maternal care and when the risk of death linked to reproduction rises with age (i.e., maternal mortality), then it is more advantageous to stop reproduction to maximize the investment in already-born offspring than to continue to reproduce with a high risk of death. This hypothesis is supported by the extreme child altriciality (child dependency on adult care) and the high maternal mortality observed in humans. Many studies show that maternal care is a major determinant of child survival, and, as a corollary, that a mother's death soon after birth, but also during late childhood, compromises considerably her child's survival (reviewed by Sear and Mace, 2008). It is also well known that maternal mortality increases rapidly beyond the age of 35, both in populations having direct access to modern medicine (e.g., Czeizel, 1988; Donoso and Villarroel, 2003; Temmerman et al., 2004) and for those with-

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out (e.g., Mostafa et al., 1991; Mbizvo et al., 1993; Midhet et al., 1998). For example, in the contemporary United Kingdom population, females older than 40 have a risk of death during childbirth, which is seven times higher than females of age 35, and 30 times higher than females of age 30 (Temmerman et al., 2004). Both high child altriciality and high maternal mortality might result in humans from the effect of a decrease of the size of the pelvis channel due to the acquisition of bipedalism combined with an increasing brain size, which led to the risky birth of premature children in our species (Leutenegger, 1987). The "mother" hypothesis was extended to the "grandmother hypothesis," in which grandmothers increase their fitness by investing in their daughters' fertility and their grandchildren's survival (Hawkes et al., 1998; Sear et al., 2000). New views on the grandmother hypothesis also suggest that, given the existence of menopause, this gain in fitness of non reproductive grandmothers even at old ages may explain the long postreproductive period observed in humans (Jamison et al., 2002; Voland and Beise, 2002; Hawkes, 2003; but see also Peccei, 2001b).

With regards to the "mother" hypothesis, reproductive cessation allows mothers to increase their fitness by investing at two levels: in the survival of immature children (level 1) and in the fertility of their mature children (level 2). In this study, we propose a new method to test whether or not the first level of the "mother" hypothesis explains menopause, and we test this hypothesis using estimates of how maternal care is needed for a child to survive until maturity. More precisely, the first level of the "mother" hypothesis refers to the fact that, because maternal care is needed by children to survive during the rearing period and because a mother has to stay alive to care for her children, the mother's survival is therefore a major determinant of her children's survival (or conversely the death of a mother compromises her child's survival). If females experience maternal mortality (defined as the female risk of death during childbirth), then a negative relationship links a female's future reproduction with the survival of her previous children. Consequently, the first level of the "mother" hypothesis states that it may be more advantageous for a female to stop her reproduction because this reduces her risk of death during the childhood of her living children and increases their later chances of surviving until maturity.

Adaptive hypotheses of menopause have been extensively discussed and reviewed (Patridge, 1993; Packer et al., 1998; Sherman, 1998; Peccei, 2001a,b; Perls and Fretts, 2001; Lahdenperä et al., 2004). Comparatively, few studies have tested the "mother" hypothesis and even fewer using real estimates (Rogers, 1993; Peccei, 1995; Moss de Oliveira et al., 1999; Shanley and Kirkwood, 2001; Shanley et al., 2007). Moreover, results are diverse and contradictory. Computer simulations show that the combined effect of the negative consequence of mother's death on offspring survival and the risk of death linked to reproduction lead to a self-organised cessation of reproduction (Moss de Oliveira et al., 1999). Peccei (1995) shows that the "mother" hypothesis is bound to make menopause selectively advantageous when the mother's survival increases her daughter's year-to-year survivorship to reproductive age. Further, Shanley and Kirkwood (2001) provide evidence that the "mother" hypothesis is not sufficient to explain menopause but a composite model considering the effects of both mothers and grandmothers does. Closely similar results were found by Shanley et al. (2007) using data on survival, fecundity and maternal and grand maternal investment from rural Gambia. More drastically, Rogers (1993) concludes that, as far as the first level of the "mother" hypothesis is concerned, this hypothesis is incapable of accounting for the evolution of menopause. However, one can argue that these contradictory results come from several difficulties linked to these analyses.

First, to assess that menopause is adaptive, one should provide evidence that reproductive cessation is more advantageous than continuing reproduction. As menopause is ubiquitous in humans, the first difficulty is therefore to set up demographic parameters in the case of the absence of menopause (i.e., the null hypothesis). Shall we assume a slow decrease of fertility (i.e., a senescence of reproduction) or constant fertility rates? How do we expect maternal mortality to change in cases where females would be able to reproduce after menopause? For example, Rogers (1993) tested the "mother" hypothesis using an increase of the risk of dying in childbirth of up to 10% after menopause. Why not more? It is not unreasonable to assume that the reproductive system senesces linearly as do other physiological systems (Sehla and Yatesa, 2001), or exponentially as do mortality hazards (Gompertz, 1825), until childbirth leads to certain death either of the mother or the child.

Second, except for Shanley et al. (2007), all other studies suffer from the lack of data on how maternal care is needed for children to survive in humans. This includes the survival of a motherless child at birth and to what extent a child becomes independent of maternal care with age.

Third, it is important to distinguish between two types of demographic traits, which can be considered to explain adaptive menopause at the first level of the mother's theory: those that impact but are not sufficient to explain menopause (insufficient) and those that are necessary to explain it (necessary, see Table 1). Menopause may have appeared if, at a given age, to continue reproducing would decrease women's fitness. In the case of the first level of the mother hypothesis, this may have arisen because of the combination between the effect of a mother's death on her child's survival, and mortality in child-birth. Together, these lead to women's further reproduction compromising their living progeny's chances of survival. Maternal mortality and the relationship between maternal survival and children's survival are therefore the two "necessary" demographic traits for menopause to appear. Any demographic trait that decreases the contribution of late reproduction to fitness lowers the advantage of continuing reproduction as females' age increases. Such traits may facilitate the apparition of menopause by decreasing the benefit of continuing to reproduce but they are nevertheless "insufficient" to explain adaptive menopause: even if the contribution to fitness of late reproduction is weak or null, these demographic traits lead to low or no advantage of reproducing, but not to a negative effect of late reproduction on fitness. For example, mortality at old ages decreases the number of females reaching a given age, and thus reduces the mean number of children produced by females at this age-class and diminishes the contribution of late fertility to fitness (Medawar, 1952). Another insufficient demographic trait is the dramatic increase in stillbirth and birth defects probabilities with mothers' age observed in humans. For example, Reddy et al.

TABLE 1. Variations in demographic parameters involved in the first level of the "mother" hypothesis and their demographic and evolutionary outcomes

Variations in demographic parameters	Demographic outcomes	Evolutionary outcomes
Increase in females' mortality with age	Decreases the probability of having children at old ages	Decreases the contribution of late reproduction to fitness (not sufficient)
Increase in stillbirth and the risks of birth defects with age	Makes reproduction less efficient with age	Decreases contribution of late reproduction to fitness (not sufficient)
Increase in maternal mortality with age	(1) Decreases the probability of having children at old ages	(1) Decreases contribution of late reproduction to fitness (not sufficient)
	(2) When linked with maternal care, decreases the survival of already born children because child survival until maturity is conditional on her mother's survival during the rearing time	(2) Increases the fitness benefit of a cessation of the reproduction strategy (necessary)

(2006), using a data set including 5,458,735 singleton gestations in the contemporary population of USA show that women aged older than 40 have a risk of stillbirth, which is 1.88 times higher than in women younger than 35. This risk is associated with a dramatic increase in birth defects due to both chromosomal and non chromosomal anomalies in women older than 35 (Czeizel, 1988; Fretts and Usher, 1997; Al Hosani et al., 2005; Cleary-Goldman et al., 2005; Tan et al., 2005; Reddy et al., 2006). Thus, the older the mother is at childbirth, the lower is the child's ability to reach adulthood whilst the mother is alive and the lower is the contribution of late fertility to fitness.

To our knowledge, the rise in stillbirth and birth defects with mother's age has not yet been integrated in studies testing the "mother" hypothesis. In this study, we propose a modelling framework incorporating all demographic traits discussed above that allows us to test for the first level of the "mother" theory by constructing the optimal age trajectory of fertility integrating the fact that a child's survival depends on her mother's survival during the rearing period. Optimal fertility schedules were defined as the age-trajectories that maximize the females' Net Reproductive Rate, R_0 (i.e., the expected number of children who survive until sexual maturity born to a given adult female). We then incorporate this optimal fertility function into a population genetic framework to analyze the role played by natural selection and genetic drift in the emergence of menopause and to examine if the resulting minimum effective population sizes allowing the emergence of menopause are realistic for past human populations. More precisely, each age-specific fertility function was optimized for a set of initial parameters: 1) a general mortality function, 2) an initial fertility constant over all ages, 3) a function of age-specific maternal mortality, 4) an age-specific stillbirth and birth defect probabilities function, and 5) a function modelling the effect of a mother's death on her child's survival. Different functions for maternal mortality rates and stillbirth and birth defects probabilities were modelled on the assumption that human females do not experience menopause. Moreover, analyses were performed using two functions of the effect of a mother's death on her child's survival: 1) one estimated from the population of ancient Quebec data from previous studies (Pavard et al., 2005, 2007b) and 2) one that models a population with a lower level of allocare (defined as all possible care behaviors of the community members, which compensate maternal care and lessen the impact of mother's death on child's survival; Pavard et al., 2007b). We aim to determine whether the corresponding optimal age-specific fertility shows a sudden cessation of reproduction, and if so, we discuss the intensity of selection on such strategy.

METHODS

In what follows, 1) we describe a new model allowing calculation of the mean child survival until maturity as a function of the mothers' survival during the whole childhood and as a function of the importance of maternal care for children's survival, 2) we define the different parameters used in this study, 3) we detail the calculation of the females' net reproductive success (R_0) for our model, 4) we describe the algorithm used to determine the optimal fertility function maximizing the females' R_0 under a given set of parameters, and 5) we integrate this optimal fertility function into a population genetic framework to assess if this function exhibits a menopause or not, and to estimate forces of selection on emergence of a menopause and a post-reproductive life.

Child's survival as a function of mother's age at childbirth, u_x

In a previous study, we proposed a model where child's survival until age at maturity is a function of mother's survival during the rearing period (Pavard et al., 2007b). Suppose a cohort of children. Their mothers will die after their birth at different ages $x + y$, where x is the mother's age at child's birth and where y is the number of years between the mother's age at the birth of the child and her age at death (with y defined between 0 and ∞). The variable y is also the age that children would be when their mother died if they survived until then. For simplicity, we denoted y the child's age at mother's death. Let us also assume that all children are similarly cared for while their mother is alive (more precisely, the care that a child receives from her mother is independent of her mother's age x). Children's survival is compromised if their mother dies before they reach the age at maturity (hereafter called M) because of the subsequent lack of maternal care. If mothers die after M, children have reached maturity ($y \geq M$) and mother's death no longer impacts on children's survival. We can then express children's survival until maturity as a discrete function of the child's age at her mother's death y, denoted w_y. The function w_y increases therefore steadily with y between 0 and M (the older the child at the death of her mother, the lower the impact of this death on her

survival) and reaching asymptotically a constant value at age M and after ($w_y = w_M$ for $y \geq M$). This function describes how a mother's death affects her child's survival until maturity and captures therefore the strength of the relationship between maternal care and a child's survival. We are now interested in calculating the mean survival until maturity of children produced by women at any given age x, with $x \geq M$. Let us denote this probability u_x. Suppose that a woman gives birth to a child at age x. This women can die at any age $x + y$ (so, when her child has reached the age y) with a probability $(s_{x+y}/s_x)q_{x+y}$, where s_x and s_{x+y} are the women's survival probability at age x and $x + y$, respectively, and q_{x+y} is the probability of death between age $x + y$ and $x + y + 1$ of women surviving at age $x + y$. The probability u_x is therefore equal to the sum over all the child's ages y of the product between 1) the child's probability of surviving until maturity according to her age at mother's death w_y and 2) the probability of the mother of dying when the child reaches this age y (which corresponds to age $x + y$ of the mother). It can be calculated as follows (see Pavard et al., 2007b, for more details):

$$u_x = \sum_{y=0}^{\infty} w_y \left(\frac{s_{x+y}}{s_x}\right) q_{x+y}. \quad (1)$$

We will now calculate the net reproductive rate R_0 for any i) age-trajectory of mothers' survival s_x, ii) age-trajectory of fertility m_x, and iii) any function of the effect of mother's death on child's survival w_y.

Different parameters used in this study

The effect of a mother's death on her child's survival until sexual maturity, $\mathbf{w_y}$**.** Pavard et al. (2005) used a large database on the pre-industrial population of early Quebec to study the children relative risk of dying specifically due to the loss of maternal care following the death of their mother. More precisely, the effect of a mother's death on her child survival was estimated from the population file maintained by the Programme de recherche en démographie historique (PRDH) at the Université de Montréal (see www.genealogy.umontreal.ca). On the basis of these results, the authors provide an estimate of the 0–15 survival probability as a function of their age at mother's death y (Pavard et al., 2007b, see Fig. 1). This function, denoted w_y, continually climbs with the child's age at its mother's death: the older the child is when her mother dies, the lower is the effect of the former's death on the latter's chances of survival. Since fathers, relatives and even the community as a whole can also be care-providers and since nonmaternal breast-feeding and adoption are frequent in human populations, the probability of reaching age $M = 15$ years for children whose mothers died soon after their birth is not null ($w_0 \neq 0$). This phenomenon is mainly the product of human socialization, which emphasizes the role of secondary caretakers (other than the mother) and has been showed in many populations (see Sear and Mace, 2008 for a review). We call this effect allocare. Because it is likely that the level of allocare is especially high in the case of the population of early Quebec and because it is reasonable to assume that this level was much lower in pre-historical population, a second function is modelled for a population with a lower level of allocare (Pavard et al., 2007b). More precisely, the second function corresponds to a population for which the probability of surviving until maturity of a motherless child at birth is null ($w_0 = 0$). Both functions are modelled by logarithmic functions $w_y = aLn(y + 1) + b$ (with $a = 0.0763$, $b = 0.5043$; and $a = 0.2626$, $b = 0$, respectively).

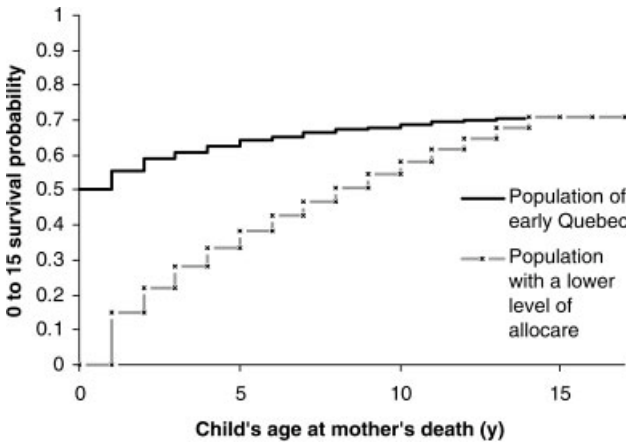

Fig. 1. Effect of a mother's death on her child survival: 0–15 child's probability of survival as a function of its age y at a mother's death, w_y (from Pavard et al., 2007b) in the case of the population of ancient Quebec and for a population with a lower level of allocare, respectively.

Maternal mortality, $\mathbf{mm_x}$**.** We call maternal mortality the mother's risk of death during childbirth as a function of the mother's age, mm_x. In populations devoid of access to modern medicine, the risk of death in childbirth outside hospital is less than 1% per birth. It is a J-shaped function of age: the risk declines after the first birth and rises for high-parity females (Mace, 2000; see also Introduction). Concerning the population of early Quebec, maternal mortality rates are around 1% for females younger than 35 (Desjardins, personal communication) and rise slowly until 1.5% at age 45. After age 45, there is obviously no maternal mortality observed in humans because of menopause. Let us assume that, if reproduction were to continue, maternal mortality would increase until a given age X for which $mm_x = 1$ for $x \geq X$. In other words, we assume that a female is certain to die during childbirth after age X. Various functions were used to model maternal mortality after 45 with X equal to 65, 70, 75, 80, 85, and 90, respectively. Here maternal mortality is linearly shaped before age 45 (it equals 1% at age 15 and 1.5% at age 45) and gamma shaped after 45. As the cumulated gamma function reaches 1 only asymptotically, we choose to define age X as the age at which a cumulated gamma function reaches 0.99 such that:

$$mm_x = \int_0^x \frac{1}{b^a \Gamma(a)} x^{(a-1)e^{\frac{-x}{b}}} + 0.01, \quad (2)$$

where $a = 182.9627$ and $b = 0.3$ for $mm_{x\geq 65} = 1$; $a = 127.1783$ and $b = 0.45$ for $mm_{x\geq 70} = 1$; $a = 96.6111$ and $b = 0.63$ for $mm_{x\geq 75} = 1$; $a = 76.9759$ and $b = 0.8$ for $mm_{x\geq 80} = 1$; $a = 61.1163$ and $b = 0.8$ for $mm_{x\geq 85} = 1$ and $a = 51.8213$ and $b = 1.28$ for $mm_{x\geq 90} = 1$. Results presented in this study are computed using these cumu-

lative gamma functions of maternal mortality after age 45. However, very similar results have been obtained using linear and exponential Weibull functions.

Stillbirth and birth defect probabilities as a function of a female's age, $\mathbf{d_x}$**.** In human populations, older mothers have a high risk of stillbirth and birth defects (see Introduction). Let us denote d_x the stillbirth and birth defects probability as a function of mothers' age x. As there is an obvious correlation between stillbirth and birth defects on the one hand, and maternal mortality on the other, and to simplify our model, we consider that the probabilities of stillbirth and birth defects follow the same age-specific functions as those used for maternal mortality (see above). We therefore used a range of d_x functions similar to the mm_x functions described above. We consider here that the overall age-specific fertility m_x takes into account all births, including stillbirth and birth defects. We define therefore a new function of the age-specific fertility m_x^* that does not take into account childbirth and birth defects. This new age-specific fertility function corresponds to the age-specific fertility rates m_x decreased by the proportion of stillbirth and birth defects d_x such as $m_x^* = m_x(1 - d_x)$.

Probability of survival of an adult female experiencing maternal mortality, $\mathbf{s_x^*}$**.** Let us denote s_x^{nomm} the probability of surviving to age x of adult females (i.e., females surviving at age $M = 15$ such that $s_M^{\text{nomm}} = 1$) who are not experiencing maternal mortality. The survival probabilities s_x^{nomm} and the age-specific fertility m_x are estimated in the case of the population of early Quebec. More precisely, the survival probabilities s_x^{nomm} do not include the death of females occurring during the month following the childbirth. This survival function without maternal mortality s_x^{nomm} is fitted using a two parameter Gompertz function $s_x^{\text{nomm}} = e^{\frac{a}{b}(1-e^{bx})}$, with $a = 0.004$ and $b = 0.047$. Now, the probability for a female surviving at age x to die during childbirth between x and $x + 1$, denoted q_x^{mm}, is the product of age-specific fertility m_x and age-specific maternal mortality mm_x, (i.e., $q_x^{\text{mm}} = m_x mm_x$). Thus, the overall mortality rate q_x^* (which includes the risk of dying due to childbirth and due to any other causes) is the sum of the mortality rate without maternal mortality q_x^{nomm} and the age-specific maternal mortality rate q_x^{mm} minus their product as follows:

$$q_x^* = q_x^{\text{nomm}} + q_x^{mm} - (q_x^{\text{nomm}} q_x^{mm}). \tag{3}$$

Therefore, we calculated the overall age-specific survival probability $s_x^* = \prod_{t=M}^{x}(1 - q_x^*)$ for any i) age-specific survival probability without maternal mortality s_x^{nomm}, ii) age-specific fertility m_x, and iii) age-specific maternal mortality mm_x.

Net reproductive rate, R_0

The net reproductive rate R_0 is defined here as the mean number of children surviving at sexual maturity produced by a female surviving at maturity during her remaining life-time. It is therefore the sum over all females' ages x (for $x \geq$ M) of the product between 1) the adult females' survival s_x^*, 2) the females fertility m_x^*, and 3) the children's survival probability until maturity u_x. Finally, the expression for R_0 taking into account both maternal mortality and stillbirth and birth defects is given by:

$$R_0 = \sum_{x=M}^{\infty} s_x^* m_x^* \left(\sum_{y=0}^{\infty} w_y \frac{s_{x+y}^*}{s_x^*} q_{x+y}^* \right). \tag{4}$$

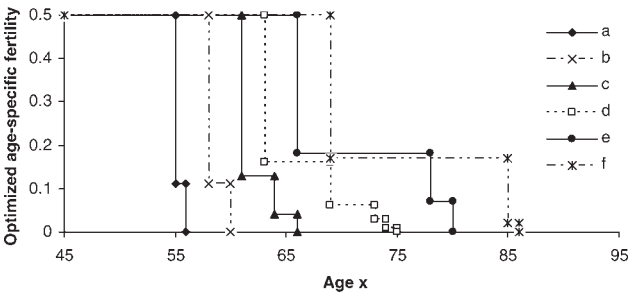

Fig. 2. Examples of optimized age-specific fertilities according to different modelled maternal mortality risk mm_x and stillbirth and birth defects probabilities d_x; $mm_x = d_x$; **a**) $mm_{x\geq 65} = 1$, **b**) $mm_{x\geq 70} = 1$, **c**) $mm_{x\geq 75} = 1$, **d**) $mm_{x\geq 80} = 1$, **e**) $mm_{x\geq 85} = 1$, and **f**) $mm_{x\geq 90} = 1$; initial fertility M_i is equalled to 0.5, the effect of a mother's death on her child's survival w_y is estimated for the early Quebec population.

Optimal fertility

Our method is based on a two-step algorithm. The first step A consists of finding the minimal age at which it is more advantageous to stop reproduction than to continue. Since it may be that a decrease in fertility at this minimal age is more beneficial than a total cessation of reproduction, the second step B consists in finding a new fertility value, for this minimal age and above, that maximize fitness more so than does a total cessation of reproduction. Let us assume that we begin the first step with an initial age-specific fertility independent of age such as $m_x = M_i$. Therefore, following Eq. (4), an initial $(R_0)_{A1}$ can be calculated using the constant initial age-specific fertility rate, M_i. Then, an age B1 at which reproduction stops ($m_x = 0$ for $x \geq$ B1) is searched so that the net reproductive rate corresponding to this strategy $(R_0)_{B1}$ is higher than the initial $(R_0)_{A1}$ [i.e., it is more advantageous to stop reproduction than to continue with it, $(R_0)_{B1} > (R_0)_{A1}$]. In a second step, we look for a new constant age-specific fertility $M_1 \geq 0$ for ages x after B1 (an age-specific fertility equal to M_i before B1 and M_1 after B1) so that the corresponding net reproductive rate $(R_0)_{A2}$ is maximal $[(R_0)_{A2} - (R_0)_{B1}]_{\max}$. If the two steps are repeated z times, our method finds z ages at which it is more advantageous to stop reproduction than to continue and z new age-specific fertility values for which it is more beneficial to keep reproducing at a lower rate than to stop. Thus, step by step, the method designs a new fertility function that maximizes the R_0 (for an example, see Fig. 2). The optimal fertility construction stops at the zth step 1 if no age Bz exists or at the zth step 2 if no new age-specific fertility M_z such as $(R_0)_{Az+1} > (R_0)_{Bz}$ can be found. Optimal fertility functions are then built from a set of initial parameters: 1) survival with age, 2) initial fertility independent of age, 3) maternal mortality in child-birth with age, 4) stillbirth and birth defects with age, and 5) how maternal care is needed for children to survive up to maturity. Initial pa-

rameters regarding fertility allows us to decompose fertility into a component that is independent of senescence (initial fertility M_i) that capture the magnitude of early fertility, and a component that varies with age and captures senescence of reproduction (stillbirth and birth defect probabilities d_x, see discussion).

Definition of menopause

Three points have to be examined to determine whether menopause is an adaptive phenomenon. First, optimal age-trajectories of fertility must show a cessation of reproduction. Our approach shows empirically that an age B1 can always be found at which age-specific fertility decreases if there exists X with $mm_{x\geq X}$ and $d_{x\geq X}$ equals 1 (for an example, see Fig. 2). However, according to the modelled mm_x and d_x, optimized age-specific fertility can drastically decline to zero (cases a–c in Fig. 2) or suddenly drop off and then show a long period of constant age-specific fertility before reaching zero (cases d–f in Fig. 2). Thus, we need a specific criterion to decide whether such a decrease corresponds to menopause. For this purpose, the ratios of the initial fertility M_i at age B1 and fertility at age B1 plus 5 years were estimated. This value allows us to estimate the speed of decline in fertility.

Secondly, the difference in fitness between the two strategies (constant age-specific fertility M_i vs. the optimized age-specific fertility function) must to be not negligible. Let us call $(R_0)_i$ and $(R_0)_f$ the net reproductive rate, respectively, corresponding to these both strategies. By definition, $(R_0)_f > (R_0)_i$ if any age B1 can be found. Let us assume that each strategy is heritable and coded by an allele. The coefficient of selection σ corresponding to the beneficial allele coding for the cessation reproduction will be $\sigma = 1 - (R_0)_f/(R_0)_i$ with $\sigma < 0$. It is considered that this allele will be significantly positively selected if $|\sigma| > 1/2(\mathrm{Ne})$, where Ne is the effective size of the population (Whitlock and Bürger, 2004). If $|\sigma| < 1/2(\mathrm{Ne})$, the allele is said to be nearly neutral, its probability of fixation becomes independent of selection and is driven only by genetic drift. Let us call Ne_1, the smallest effective size required for the effect of selection to be higher than the effect of genetic drift such that $\mathrm{Ne}_1 = 1/(2|\sigma|)$. It is then considered that an allele coding for the strategy of reproduction cessation will fix with a reasonable probability as soon as the effective size of the population is higher than Ne_1. This definition of effective size Ne_1 is obviously a simple measure of the intensity of selection pressures without any assumptions about the number of genes or alleles involved in menopause.

Thirdly, if menopause is the result of an adaptive process, the survival of females after cessation of reproduction must significantly increase their fitness. Thus, it is important to determine if the death of a female after age B1 will affect her fitness. Let us consider a population where reproduction follows our optimized age-specific fertility. Let us also consider an allele **A** lethal to its bearer between ages z and $z + 1$ and a healthy allele **a**. The mean number of effective children of a female **a** is the net reproductive rate $(R_0)_z^a$ and corresponds to the above $(R_0)_f$ (i.e., the average number of children surviving until maturity of an adult female whose fertility corresponds to the optimal age-specific fertility). The net reproductive rate $(R_0)_z^A$ of a female **A** who is certain to die before age $z + 1$ and can be computed by setting the mortality rates such as $q_z^* = 1$. Then the selection coefficient corresponding to a deleterious allele **A** leading to the certain death of the carrier at age z will be $\sigma_z^A = 1 - (R_0)_z^A/(R_0)_f$ with $0 < \sigma_z^A < 1$. It is considered that the negative selection against the allele **A** is strong enough to override the effect of the genetic drift if $\sigma_z^A \gg 1/(2\mathrm{Ne})$ (Whitlock and Bürger, 2004). The probability of fixation of the deleterious allele is then considered to be negligible. In this study, the minimum effective sizes Ne required for negative selection to overcome genetic drift is calculated for alleles leading to the death of the carrier at two ages z equal to B1 + 5 and B1 + 10. Let us denote these values Ne_2 and Ne_3. The intensity of negative selection operating on these alleles allows us therefore to estimate the advantage for a female of surviving 5 years after B1 with Ne_2 and 10 years after B1 with Ne_3.

Applications

Optimized fertility functions are constructed for four initial constant fertilities (0.2, 0.3, 0.4, and 0.5), six maternal mortality, and stillbirth-birth defects functions and two functions modelling the effect of a mother's death on her child's survival w_y as described above. To each optimized age-specific fertility corresponds an age B1, the ratio of initial age-specific fertility M_i at age B1 + 5, and three effective sizes Ne_1, Ne_2, Ne_3.

RESULTS

The results are shown in Tables 2 and 3 for the two functions of the effect of a mother's death on her child's survival w_y (i.e., Quebec and population with a lower level of allocare). An age B1 at which a decrease in age-specific fertility is more advantageous than to reproduce with a constant fertility rate is found for each set of parameters. The age X is the age at which $mm_x = 1$ and $d_x = 1$ for $x \geq X$. The higher the value of X or the smaller the value M_i, the later is the decrease in age-specific fertility (age B1). A linear relationship is observed between age B1 and age X. Both the slope and the intercept of the linear regression increase as M_i decreases. More generally, the initial value of age-specific fertility M_i has less of an effect on age B1 than age X. Both slope and intercept are smaller in the model with a lower level of allocare than for the population of early Quebec. Thus, an increase in the relationship between the survival of mothers and those of their children leads to an earlier decrease in fertility.

The minimum value B1 equals 50. For the population of early Quebec, the minimum and the maximum differences between X and the corresponding age B1 equals 7 years (for $M_i = 0.2$ and $X = 65$) and 21 years (for $M_i = 0.5$ and $X = 90$), respectively. Corresponding values equal 12 years (for $M_i = 0.2$ and $X = 65$) and 32 years (for $M_i = 0.5$ and $X = 90$) for the population with a lower level of allocare. Thus, according to the parameters set, there can be a delay of from 7 to 32 years between age B1 (at which fertility starts to diminish) and X (at which reproduction can no longer increase reproductive success).

The percentage of fertility M_i remaining at age B1 + 5 is equal to 0% in all cases where X is less or equal to 75 (for the population of early Quebec) and where X is less or equal to 70 (for the population with a lower level of allocare). More precisely, the decrease in age-specific fertility is all the more sudden as X is smaller. The percentage of M_i at age B1 + 5 increases with X until it reaches

TABLE 2. Results using the estimate of the effect of a mother's death on her child's survival w_y *for the population of Quebec*

Initial fertility M_i		Age X at which $mm_{x\geq X} = 1$ and $d_{x\geq X} = 1$					
		65	70	75	80	85	90
0.5	B1	55	58	61	63	66	69
	% of Mi at age B1 + 5	0	0	0	18	36	34
	Ne_1	776	1345	2832	4925	11113	27659
	Ne_2	692	1717	4878	10402	26017	73164
	Ne_3	7335	18282	48995	114160	450086	1512048
0.4	B1	56	59	62	65	69	72
	% of Mi at age B1 + 5	0	0	0	13	35	38
	Ne_1	998	2065	4425	10031	34612	93345
	Ne_2	874	2033	5559	18037	86128	248923
	Ne_3	10306	23355	56633	183073	1851747	∞
0.3	B1	57	60	64	68	73	77
	% of Mi at age B1 + 5	0	0	0	0	10	37
	Ne_1	1574	3947	10027	31421	190805	962171
	Ne_2	1045	2296	8716	42208	357760	2886513
	Ne_3	13468	26754	103620	565592	2862083	∞
0.2	B1	58	63	67	72	78	83
	% of Mi at age B1 + 5	0	0	0	0	0	0
	Ne_1	3005	7573	36305	149712	1970923	1988379
	Ne_2	1170	5601	18681	139018	1970924	1988379
	Ne_3	14977	94664	274883	∞	∞	∞

Rows: minimum age B1 at which the optimized age-specific fertility decreases, ratio of initial age-specific fertility at age B1 + 5, effective size Ne_1 for which selection favors a cessation reproduction strategy, effective size Ne_2 and Ne_3 for which selection favors a female's survival at age B1 + 5 and B1 + 10 respectively. Columns: modelled maternal mortality mm_x and stillbirth and birth defects probabilities d_x ($mm_x = d_x$); $mm_{x\geq 65} = 1$, $mm_{x\geq 70\ =\ 1}$, $mm_{x\geq 75} = 1$, $mm_{x\geq 80} = 1$, $mm_{x\geq 85} = 1$, $mm_{x\geq 90} = 1$.

TABLE 3. Results using the effect of a mother's death on her child's survival w_y *modelled for a population with a lower level of allocare*

Initial fertility M_i		Age X at which $mm_x \geq X = 1$ and $d_x \geq X = 1$					
		65	70	75	80	85	90
0.5	B1	50	51	53	55	56	58
	% of Mi at age B1 + 5	0	0	10	8	12	26
	Ne_1	63	102	98	97	145	163
	Ne_2	41	41	54	75	74	105
	Ne_3	308	280	338	472	407	592
0.4	B1	51	52	54	56	58	59
	% of Mi at age B1 + 5	0	0	10	10	25	33
	Ne_1	60	104	115	121	163	227
	Ne_2	48	47	61	84	109	114
	Ne_3	428	338	392	533	662	641
0.3	B1	51	53	55	57	59	61
	% of Mi at age B1 + 5	0	0	13	13	17	37
	Ne_1	110	139	173	192	274	346
	Ne_2	42	53	66	90	114	157
	Ne_3	311	380	426	561	673	940
0.2	B1	53	55	58	60	62	65
	% of Mi at age B1 + 5	0	0	5	15	15	30
	Ne_1	123	190	229	318	544	740
	Ne_2	60	74	123	165	202	386
	Ne_3	564	614	1069	1261	1358	2711

Rows and columns are the same as in Table 2.

around 30 to 40% when X equals 90. With regard to M_i, the decrease in fertility is more abrupt when M_i is small. More generally, the effect of M_i on the decrease in fertility is lower than the effect of age X.

In the population of early Quebec, Ne_1 is always higher than 100 and increases quickly as X increases. Ne_1 is however always lower than 10,000 if $X \leq 75$ and $M_i \geq 0.3$. Concerning the model with a lower level of allocare, Ne_1 is lower than or around 100 in most cases and always lower than 1000. With the population of early Quebec, Ne_2 is always higher than 100 and Ne_3 is always higher than 1000. Ne_2 is however lower than 10,000 if $M_i \geq 0.3$ and $X \leq 75$. Under these conditions, the model with a lower level of allocare shows Ne_2 always to be lower than 100 and Ne_3 always to be lower than 1000. More generally the minimum effective sizes required for selection (positive or negative) to operate are much smaller in the case of the lower level of allocare, especially for high X.

DISCUSSION

Our results provide evidence that there is always an age at which it is more advantageous to decrease reproduction if maternal mortality and the stillbirth and birth defect probabilities rise up to 1 after age 45. With the

population of early Quebec and the model with a lower level of allocare, an age B1 is always found that yields a decrease of more than 90% of the initial fertility in less than 5 years for X inferior to 80. Because we can consider that such a brutal decrease of fertility in less than 5 years is a sudden cessation of reproduction, we focus on these cases hereafter.

The effective size of the whole human species during Pleistocene is estimated to be around 10,000 breeding individuals (Harpending et al., 1998). Thus, if selection on an allele is strong enough to override the genetic drift of an effective size inferior to 10,000, then it is likely that such an allele has been selected during human evolution. More generally, as it is likely that the effective size of the whole human species has continuously increased in the past, the smaller the minimal effective size such that selection overrides the genetic drift, the more selection may have been efficient in human populations living in a distant past. In the model with a lower level of allocare, Ne_1 is always lower than 1000. With the population of early Quebec, Ne_1 was always smaller than 10,000 for X inferior to 75 and $M_i \geq 0.3$. Thus, cessation of reproduction could have been a strategy positively selected in the past if we assume that maternal mortality and stillbirth and birth defect probabilities would increase markedly with age in absence of menopause.

Is this assumption unreasonable? Physiologists define reproductive senescence as a decline in offspring production with age due to a decrease in the efficiency of cells or organs involved in reproduction, while demographers are exclusively interested in the decline in fertility at older ages. According to both definitions, it is obvious that the increase in stillbirth and birth defect probabilities with mother's age corresponds to reproductive senescence. The lack of historical demographic data makes the estimation of the increase of stillbirth and birth defect probabilities with mother's age difficult for past populations. However, evidence shows that stillbirth rates increase with mother's age from 2% at the beginning of the reproductive life up to 8% for mothers with ages over 45 (Hart, 1998; see also Introduction). It therefore seems likely, that the overall stillbirth and birth defect probabilities would continue this steep raise in cases where females would be able to reproduce after menopause. The increase in maternal mortality with age can be seen as a part of general senescence as long as reproduction continues and as a part of reproductive senescence in the sense that it compromises the children's chances of survival (i.e., decreases children "quality" with mother's age at childbirth). Since Gompertz (1825) demography has provided considerable evidence for an exponential increase in mortality rates at old ages. As childbirth is especially risky in humans and involves many physiological systems, it is likely that, in the absence of menopause, maternal mortality rates would increase even faster with age than general mortality. Intuitively, if a woman at old age (from age 65 to 90 in our example) has a reasonable chance of surviving up to the next age, can we imagine that, in the absence of modern medicine, this woman would be able to survive the energetic cost of a gestation and a delivery? In this context, our results provide evidence that a sudden cessation of the reproduction strategy may be an adaptation in response to an increase in maternal mortality and stillbirth and birth defect probabilities with age, and therefore in response to the senescence of reproduction.

An increase in initial fertility M_i has an effect on both the precocity of menopause and the duration of post-reproductive life that is positively selected for. It is well-documented that fertility is higher in humans than in great apes (Mace, 2000). Human's short birth intervals may therefore have had a strong impact on the emergence of menopause in humans. Overall, appearance of menopause is favored by large fertility at the peak of reproductive life, and by an accentuated senescence of reproduction at the end of reproductive life. Both may be very characteristic of human fertility and evidence has been found that both could emerge from the increased altriciality of human babies resulting from the acquisition of bipedalism (Pavard et al., 2007a).

In the results presented here, the age at which cessation of reproduction occurs is always above 51. Nevertheless, we modelled only one effect of the first level of "mother" hypothesis. It is likely that a composite model (such as e.g., Shanley and Kirkwood, 2001; Shanley et al., 2007) taking into account 1) an increase in the fertility of mature children by a surviving mother (the second level of the "mother" hypothesis) and 2) an increase in the survival of grandchildren (the "grandmother" hypothesis), would lead to an earlier cessation of reproduction. Moreover, researchers believe that adaptive menopause appeared in early homo between 1 and 2 millions years ago (Peccei, 2001a). The adult and child mortality observed in the population of early Quebec is likely to be lower than in these ancestral populations. The same is true for the effect of mother's death on child survival considered in this study. Consequently, the overall impact on mother's fitness of the combined effect of the effect on mother's death on child survival and the mother's survival probability during the rearing time is expected to be higher in pre-historical populations.

If we consider that Ne_3 inferior to 10,000 is a reliable measure of positive selection in ancestral human populations, the survival of females up to 10 years after age B1 is always positively selected in the model with a lower level of allocare and never positively selected in the population of early Quebec. Thus, it is reasonable to assume that the intensity of allocare has a fundamental effect on the long post-reproductive life observed in humans. Allocare could have been weak or absent in ancestral human populations, as is observed in great apes today, in the sense that adoption and nursing of motherless juveniles is rarely observed in primates (see Maestripieri (2000) for a review of cases described).

Note that in our model this low level of allocare does not exclude a positive effect of a grandmother on children's survival after the death of the mother. Only the mothers' mortality at old ages (at the end of their reproductive life and after) is relevant in studying the emergence of menopause in the context of the mother hypothesis. At these ages, the probability that a grandmother will still be alive after the death of the mother is extremely low. The allocare modelled here is therefore not provided by grandmothers but by other caregivers. The main effect attributed to grandmothers in research into the "grandmother hypothesis" (i.e., the enhancement of their first daughters' fertility and of their first grandchildren's survival) may still exist but is not explicitly modelled here. However, to have a significant impact on the emergence of menopause and on the post-reproductive life in a population exhibiting such a low level of allocare, grandmothers would have to be the main care-

giver replacing the mother, far ahead of the father, the older siblings or other relatives.

Overall, our model is more relevant to the explanation of the emergence of menopause than the extended post-reproductive life. Even when it does suggest longer post-reproductive life (e.g., for lower levels of allocare), as pointed out by Shanley et al. (2007), maternal care alone cannot explain extended post-reproductive life beyond the age at which children's survival becomes independent of maternal care. However, conditional on the demonstrated emergence of menopause, recent alternative models may then be combined with our model to explain extended post-reproductive life; for example models considering the genetic inter-dependence of males and females despite their demographic differences (Tuljapurkar et al., 2007) or variance in onset of late-onset diseases (Pavard and Metcalf, 2007).

For the first time, we provide theoretical evidence that the first level of the "mother" hypothesis alone is a phenomenon sufficient to explain the menopause observed in the human species and at least part of the subsequent post-reproductive life when two conditions are satisfied: 1) a marked increase in stillbirth-birth defects with age (this phenomenon is "not sufficient") and 2) a dramatic increase in maternal mortality at older ages (this phenomenon is "necessary"). Since both phenomena occur in senescence of reproduction, the question of adaptation of the human menopause consists mainly of knowing why human females seem to experience an important senescence of reproduction. Although the existence of menopause in nonhuman primates is a controversial topic (e.g., Fedigan and Pavelka, 2001 but see also Wich et al., 2004), there is new evidence for a similar rate of follicular depletion with age in chimpanzees and humans (Jones et al., 2007) and for an increasing risk of unsuccessful pregnancy with age in chimpanzees (Roof et al., 2005). If these results are confirmed and if data on maternal mortality and stillbirth-birth defects probabilities become available for non human primates, further studies could use our modelling approach to test the emergence of menopause in these species.

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