



Emergence and maintenance of menopause in humans: A game theory model



Valentin Thouzeau^{a,b,*}, Michel Raymond^a

^aInstitute of Evolutionary Sciences, CNRS, IRD, EPHE CC 065, University of Montpellier, Place Eugène Bataillon, 34095 Montpellier cédex 05, France

^bEco-Anthropology and Ethnobiology Lab, UMR 7206, 57 rue Cuvier, Museum National d'Histoire Naturelle, 75005 Paris, France

ARTICLE INFO

Article history:

Received 10 May 2016

Revised 14 July 2017

Accepted 19 July 2017

Available online 22 July 2017

Keywords:

ESS

Maternity cost

Grandmothering

Conflict over resources

Kin selection

Pleiotropy

ABSTRACT

Menopause, the permanent cessation of ovulation, occurs in women well before the end of their expected life span. Several adaptive hypotheses have been proposed to solve this evolutionary puzzle, each based on a possible fitness benefit derived from an early reproductive senescence, but no consensus has emerged. The construction of a game theory model allowed us to jointly study the main adaptive hypotheses in emergence and maintenance of menopause. Four classical hypotheses on the benefits of menopause were considered (decreased maternal mortality, increased grandmothering, decreased conflict over reproductive resources between older and younger females, and changes in their relatedness) plus a fifth one derived from a possible pleiotropic trade-off. Interestingly, the conditions for the emergence of menopause are more restrictive than those for its maintenance due to the social and familial changes induced by the occurrence of non-reproductive older women.

© 2017 Elsevier Ltd. All rights reserved.

1. Introduction

Menopause, the permanent cessation of ovulation, occurs in women well before the end of their expected life span. This trait has been a longstanding evolutionary puzzle (Williams, 1957; Hamilton, 1966), and the various hypotheses proposed could be classified in two main categories (for a review, see Croft et al., 2015). The non-adaptive hypotheses assume that the age of reproductive senescence (i.e. menopause) is constrained, and study the conditions of expansion of life expectancy beyond the last reproduction (see Table 1). The adaptive hypotheses assume that the age of somatic senescence is constrained, and study the selective conditions which could accelerate reproductive senescence (see Table 2).

In humans, age at menopause is variable, heritable (van Asselt et al., 2004) and evolutionary costly for females because it implies stopping reproduction (Hamilton, 1966). If menopause is an adaptation per se, rather than a byproduct (i.e., the consequence of a constraint), it is necessary that any fitness advantage offsets the obvious disadvantage of curtailed childbearing. These benefits proposed in the context of adaptive hypotheses are put forward to explain the evolution of menopause. In this study, we proposed to

evaluate the relative importance of these hypotheses in the emergence and the maintenance of human menopause.

The first possible benefit of menopause could concern a higher number of mature offspring. When maternal mortality during child delivery is increasing with age, stopping reproduction increases the survival of earlier born offspring who are still under the dependence of the mother (mortality cost hypothesis, Hypothesis 1, Table 2). This means that older females stop reproducing to raise previous offspring without taking the risk of dying with a new childbirth. Higher fertility could also result from a trade-off between an efficient early reproduction and an earlier reproductive senescence. Such an effect, akin to the antagonistic and pleiotropic theory of somatic senescence (Hamilton, 1966), has not been empirically described. Benefits of menopause could extend to kin, with the expectation that these benefits, weighted by the kinship coefficient, are at least higher than the cost of menopause (Hamilton, 1964). This includes the grandmother hypothesis, which assumes that menopause increases the survival and fecundity of the grandchildren (Hypothesis 2, Table 2).

More recently, it has been proposed that menopause could emerge from the asymmetrical relatedness between older and younger females in patrilocal groups, with a context of costly competition within the family unit (Cant and Johnstone, 2008). Because relatedness asymmetry generates more selection with more interactions between individuals, this hypothesis corresponds to two distinct effects: a conflict over resources and an asymmetrical relatedness. Co-breeding within a family unit can be costly

* Corresponding author.

E-mail addresses: vthouzeau@mnhn.fr (V. Thouzeau), michel.raymond@umontpellier.fr (M. Raymond).

Table 1
Non-adaptive hypotheses of the evolution of human menopause.

Hypothesis	Verbal expression of the hypothesis	References
1. Lifespan artifact	Recent expansion of life expectancy due to niche construction and medicine could allow older women to live well beyond the depletion of the ancestral stock of oocytes.	Peccei (2001)
2. Patriarch	Longevity in males is supposedly highly selected. Higher somatic life expectancy in women could be a by-product of the selection for older males.	Marlowe (2000)
3. Mate choice	Male preference for younger females could allow an accumulation of deleterious mutations with an effect on older females. This accumulation could ultimately lead to menopause.	Morton et al. (2013)
4. Grandmothering	Grandmothering increases the survival of grandchildren. Higher somatic life expectancy could be an adaptation that favors helping kin.	Kim et al. (2014)
5. Insurance against uncertainty	Higher somatic life expectancy could decrease the risk of dying by chance before the end of the reproductive life.	Tully and Lambert (2011)

Table 2
Adaptive hypotheses of the evolution of human menopause.

Hypothesis	Verbal expression of the hypothesis	References
1. Maternal mortality cost	Young children are highly dependent on maternal care. Moreover, maternal mortality increases with age. Therefore, menopause could ensure maternal care by avoiding maternal mortality.	Peccei (2001) Pavard et al. (2007)
2. Grandmothering	Grandmothering increases the survival of grandchildren and daughter fecundity. Menopause could be an adaptation that favors helping kin.	Hill and Hurtado (1991) Hawkes et al. (1998) Hawkes (2004) Volland and Beise (2002) Gibson and Mace (2005)
3. Conflict over resources	Co-breeding is costly in the same family unit as resources are limited. Menopause could be the result of a limitation in the competition between younger and older women of the same family.	Reeve et al. (1998) Cant and Johnstone (2008) Mace and Alvergne (2012)
4. Asymmetrical relatedness	A patrilocal social structure implies an asymmetrical relatedness between younger and older females of a family unit: The daughter in-law is not related to the children of her mother in-law, but the mother in-law is related to the children of her daughter in-law. This asymmetry is predicted to give younger females a decisive advantage in reproductive conflicts with older females.	Marlowe (2004) Cant and Johnstone (2008) Johnstone and Cant (2010) Lahdenperä et al. (2012) Úbeda et al. (2014)
5. Trade-off between menopause and migration	Most human societies have a female-biased migration structure and display resource heterogeneity between groups. A trade-off gene between menopause and higher chances of marrying up (e.g., due to greater attractiveness) could be selected for in such a context.	Original hypothesis (see Bovet et al., 2017 , for a possible trade-off between age of menopause and attractiveness)

because competition for resources may lead to a significant loss of those resources; thus, ending competition (menopause) could be advantageous in some conditions (Hypothesis 3, [Table 2](#)). A patrilocal social structure implies an asymmetrical relatedness between younger and older females of a family unit: The daughter in-law is unrelated with the children of her mother in-law, but the mother in-law is related with the children of her daughter in-law (which is not the case in the matrilocal social structure), and this asymmetry could lead to a decisive advantage for younger females and favor menopause (Hypothesis 4, [Table 2](#)). This hypothesis depends on the pattern of dispersal of human populations, different in other species such as ape or killer whales ([Johnstone and Cant, 2010](#)).

The recent description of a correlation in women between attractiveness at a younger age and reproductive senescence ([Bovet et al., 2017](#)) suggests that some indirect social benefits could be associated with menopause in some social contexts. For example, attractiveness increases the probability of females of accessing better quality males and holding more resources, thus increasing reproduction and survival. When these fitness benefits outweigh the cost of menopause, menopause is indirectly selected as long as the trade-off between attractiveness when young and menopause is maintained (Hypothesis 5, [Table 2](#)).

These various hypotheses are not mutually exclusive, and some of them were previously explored to explain the emergence of menopause. Hypotheses 1 and 2, for example, seem insufficient

alone to explain menopause; their combination, however, generates sufficient interaction ([Shanley and Kirkwood, 2001](#); [Shanley et al., 2007](#)). Similarly, hypotheses 3 and 4 in combination seem theoretically sufficient to explain menopause ([Cant and Johnstone, 2008](#)), particularly in association with hypothesis 2 ([Lahdenperä et al., 2012](#)). However, it is unclear if they help to understand the emergence or rather the maintenance of menopause or both. This is because social and familial environments depend on whether menopause does or does not exist; thus, the conditions for its emergence do not necessarily explain its stability as well. In the study of the emergence of menopause ([Chan et al., 2016](#); [Aimé et al., 2017](#)), the evolutionary problem is: “Should an older female stop reproducing in a population with reproductive older females?” In the study of the maintenance of menopause, the evolutionary problem is “Should an older female reproduce in a population with non-reproductive older females?” It is this latter question which is usually addressed when empirical data from current populations are considered, as the benefits of reproducing versus not reproducing are estimated in a context of non-reproducing older females (menopause is already present and fixed). When considering theoretical studies (e.g., [Rogers, 1993](#); [Cant and Johnstone, 2008](#)), the distinction between these two questions is not apparent, and a close look indicates that a relatedness structure in which older females do not reproduce is a priori assumed (details in Supplementary Information); thus, it is unclear if their results could be applied to understand the origin of menopause.

Additionally, previous models assumed that menopause does not modify the structure of relatedness in a family unit. Models only consider the case in which an older woman competes each time with a daughter (or a daughter-in-law). This is the case if menopause already emerged: a younger woman is the daughter (or daughter-in-law) of an older woman in a family unit. But if menopause did not emerge, a younger woman may be the daughter of a woman who reproduced in the previous time step when she was old. That type of younger woman cannot compete with her mother because she was already older when she gave birth to her, but she may compete with an older sister for example. If we assume that the demography is stable—only one individual can reach a reproductive status at each time step—and if we assumed in the meantime that only a daughter (or a daughter-in-law) of the younger woman may reach the reproductive status, we nullify the evolutionary impact of the children produced by an older woman. In other words, to assume that relatedness does not change with reproductive strategies is equivalent to assume that menopause already emerged, and we solve only one side of the issue (Supplementary Information, Fig. 2). This is the case if the relatedness in a family unit is locked (Cant and Johnstone, 2008) or if real data in which menopause obviously already emerged are used to parameterize the model (Hill and Hurtado, 1991). Then, it is clear that the ecological context—reproductive strategies and relatedness—shaped the evolution of human menopause.

Here, the aim was to build a theoretical framework to: 1) study the emergence of human menopause and the conditions for its maintenance, 2) assess the relative importance of each proposed hypothesis, and 3) study the possible interactions between them. To this end, a game theory model was built to explore all the adaptive hypotheses with a mathematical model. We choose to use adaptive dynamics tools to take into account the mutual retro-action between ecology and evolution. We studied the evolution of a trait (menopause) and its impact on the ecological context, and how in return this ecological context modified the forces that shaped the evolution of this trait. Using an adaptive dynamics framework, Úbeda et al. (2014) showed that the chaotic hormonal phase during the cessation of ovulation in humans may be explained by an intragenomic conflict between paternally and maternally inherited genes. We propose here to use adaptive dynamics to evaluate the relative importance of the five main adaptive hypotheses in emergence and maintenance of menopause. We focused on individual fitness, rather than population growth (Shanley and Kirkwood, 2001; Shanley et al., 2007; Kim et al., 2014), to take into account the inclusive fitness benefits of increased survival of offspring versus grand-offspring.

2. Materials and methods

Our aim was to model jointly the five hypotheses described in Table 2 and the interactions between them. To achieve this, we determined the conditions under which the evolutionary trajectory of the female's reproductive strategies leads to a population of non-reproductive older females from a population of reproductive older females (in case of the study of emergence) or a population of non-reproductive older females (in case of the study of maintenance), and if this state is stable. It generalizes the model of Cant and Johnstone (2008), itself based on the “tug-of-war” of Reeve et al., (1998), whereby each party exerts partial control over the outcome, and takes into account the modification of structure of relatedness due to the emergence of menopause. Note that we didn't generalize the model of Johnstone and Cant (2010).

2.1. Model building

It is considered that an older and a younger female are competing for the same reproductive resources. Each female can invest in competitive effort to increase her personal share of this communal resource and thus increase her reproduction (but decrease the reproduction of her competitor). Let o and y be the competitive efforts of the older and the younger female, respectively, with $o \in [0, 1]$ and $y \in [0, 1]$. These variables measure the proportion of selfish behavior in the appropriation of resources. It is assumed that the older woman can be advantaged in the competition for resources due to her status. The proportion of resources available to the older female is equal to $o/(o + by)$, whereas the proportion of resources available to the younger female is equal to $by/(o + by)$. The parameter b , a positive constant, reflects the relative competitive ability of the younger female. If $b = 1$, the younger woman is not disadvantaged in the competition for resources. On the other hand, if $b < 1$, the younger woman is disadvantaged and obtains less resources than the older women for the same competitive effort.

It is assumed that the number of mature offspring produced by a woman is directly proportional to the amount of resources available. Consider a family with an older female i and a younger female j . The competitive effort of the older women is o_i , whereas the competitive effort of the younger female is y_j . Let N_o^{ij} be the normalized number of mature offspring produced by the older female i in competition with the female j and N_y^{ij} be the normalized number of mature offspring produced by the younger female j in competition with the female i . In the standard case in which no

Table 3

List of symbols and their links with hypotheses (as defined in Table 2) explaining menopause.

Symbol	Name	Hyp.	Note
b	Younger female disadvantage	None	The older female can have a dominant status. This parameter measures the relative disadvantage in the competition over resources of younger females. This parameter is expected to be lower than 1 and is not linked with any specific hypothesis.
μ_i	Mortality	1	Death probability in each age-class from risks linked with reproduction. The parameter μ_o can be higher than μ_y
P	Cost of mortality	1	Loss of fitness from lack of child care in case of mother death.
G	Grandmother effect	2	Gain of grand-offspring from grandparental care. It can be higher than 1.
D	Resource depletion rate	3	Measures the potential of resource depletion if an individual maximizes his competitive effort.
m	Matrilocal rate	4 and 5	Proportion of female migration. If $m = 0$, the structure is strictly patrilocal, and it is strictly matrilocally if $m = 1$. If $m = 0.5$, there is no migration bias.
C	Trade-off between menopause and attractiveness	5	This is a synthetic parameter that measures the gain in resources of a younger woman signaling a higher immediate fertility at the expense of a low competitive effort in older age. It includes the choosiness of males and the heterogeneity of resources between groups.

other hypothesis is taken into account,

$$N_o^{ij} = \frac{o_i}{o_i + by_j}$$

$$N_y^{ij} = \frac{by_j}{o_i + by_j}$$

During its entire reproductive life, an individual j produces N_{tot}^j mature offspring. Consider a female j exhibiting the competitive efforts y_j (when she is young) and o_j (when she is old). When j is young, she competes with the older female i . When j is old, she competes with the younger female k . We have:

$$N_{tot}^j = N_y^{ij} + N_o^{jk}$$

The inclusive fitness I_o^j of a trait o_j is equal to the total number of offspring produced by a female j that exhibit this trait plus the total number of offspring of her young competitor k weighted by their relatedness. We define:

$$I_o^j = \frac{1}{2} N_{tot}^j + A_o N_{tot}^k$$

In addition, symmetrically, we define I_y^j as:

$$I_y^k = \frac{1}{2} N_{tot}^k + A_y N_{tot}^j$$

2.2. Adaptive dynamics

The mean traits o_{res} and y_{res} in a population modify I_o and I_y , so it is important to link the evolution of o and y with the modification of the ecological context. To this end, the canonical equation of the adaptive dynamics helps to take into account the feedback between ecology and evolution (Dieckmann and Law, 1996):

In the particular case of a homogeneous population, all the individuals exhibit the traits o_{res} and y_{res} . We define:

$$I_o^{res} \text{ and } I_y^{res}, \text{ with } o = o_{res} \text{ and}$$

$$y = y_{res} \text{ for all individuals in the population.}$$

In such a population, a mutant trait o_{mut} or y_{mut} may appear that is slightly different from the resident trait. We define:

$$I_o^{mut} = I_o^j, \text{ with } o = o_{res}, o_j = o_{mut} \text{ and } y = y_{res}$$

and

$$I_y^{mut} = I_y^k, \text{ with } o = o_{res}, y = y_{res} \text{ and } y_k = y_{mut}$$

If a mutation is beneficial, which means, $I_y^{mut} > I_y^k$ or $I_o^{mut} > I_o^k$, the mutant trait can invade and replace the population of the resident trait, and the mutant trait becomes the resident trait. To study the evolution of the traits o_{res} and y_{res} , we calculate their evolutionary path using the canonical equation of adaptive dynamics (named Eq. (1), Dieckmann and Law, 1996):

$$\frac{do_{res}}{dt} = k \cdot \frac{\partial}{\partial o_{mut}} I_o^{mut} o_{res}$$

$$\frac{dy_{res}}{dt} = k \cdot \frac{\partial}{\partial y_{mut}} I_y^{mut} y_{res}$$

This approach supposes that the system reaches an ecological equilibrium before the occurrence of any mutation (i.e., a single deviant with a trait (o_{mut} or y_{mut}) slightly different from the resident trait). If $I_o^{mut} > I_o^{res}$ or $I_y^{mut} > I_y^{res}$, the mutant trait invades the population, until the equilibrium is reached. Then, another mutation is performed, and the system evolves iteratively. For a given set of parameters, the evolutionary path of o and y can result in an evolutionary equilibrium (o^* , y^*). It is considered that menopause emerges when $o^* = 0$ and $y^* > 0$.

Table 4

Minimum value of each parameter for the emergence or maintenance of menopause, when only one factor is considered. For an explanation of each parameter, see Table 3. The set of default parameters is: $b = 0.9$, $P = 0$, $\mu = 0$, $G = 0$, $D = 0$, $m = 0.5$ (or $m = 1$ when C is tested) and $C = 0$. Initial conditions are $o_i = y_i = 1$ for the emergence and $o_i = 0$ and $y_i = 1$ for the maintenance.

Parameter	Emergence	Maintenance
P	0.7	0.5
G	1.75	0.5
D	None	none
m	None	none
C	0.63	0.35

Then, it is possible to draw the evolutionary trajectory of a couple (o , y) from any initial condition (o_i , y_i). So, it is possible to study the emergence of menopause ($o_i = y_i$) from any ecological context as well as its maintenance ($o_i = 0$ and $y_i > 0$). In this way, we looked for the ecological cases in which o converges to a negligible value compared to y , which means the older female's reproduction stops and stays negligible, i.e., menopause is maintained. Solving the canonical equation leads to a very complex analytical solution, so numerical resolution was used with the language C++ and the IDE software CodeBlocks 13.12 (code available in Supplementary Information).

2.3. Modeling the five hypothesis

Each hypothesis modifies the inclusive fitness I_o and/or I_y (details in SI). The maternal mortality cost (hypothesis 1) decreases by a proportion P the number of children produced by a woman who die at the change of time step. Conversely, the grandmothing (hypothesis 2) increase by a proportion G the number of children produced by a younger woman if the older woman stops to reproduce. The ratio of grandmothing decreases linearly with an increase of the reproductive effort of the older woman. The conflict over resources (hypothesis 3) decreases by a proportion D the total amount of resources when the competitive effort of the two women is maximum. The ratio of resources depletion decreases linearly with a decrease of the competitive efforts of the two women. The asymmetrical relatedness (hypothesis 4) depends on the migration bias m , which allows all structures between pure matrilocality and pure patrilocality. Finally, the trade-off between marrying up (the consequence of a higher attractiveness) and menopause (hypothesis 5) increase the number of children produced by a younger woman who marries up by a proportion C , relatively to the difference between her reproductive effort when she will be older and the mean reproductive effort of the older women.

3. Results

This approach leads to the evolutionary trajectory of the couple (o , y) from an initial condition (o_i , y_i) under a given set of parameters (example in Fig. 1). This trajectory ends in an equilibrium (o^* , y^*), and the menopause corresponds to o^* being negligible compared to y^* . The repetition of this analysis makes it possible to vary the set of parameters and study the new equilibrium (example in Fig. 2).

Alone, hypotheses 1, 2 and 5 can lead to the emergence and the maintenance of menopause, while hypotheses 3 and 4 are not sufficient by themselves (see Table 4). The parameter values required for hypotheses 1, 2 and 5 are relatively high (see discussion); however, there is the possibility that a combination of these hypotheses could favor the emergence of menopause. With this model, it is possible to study the equilibrium of the system for a large number

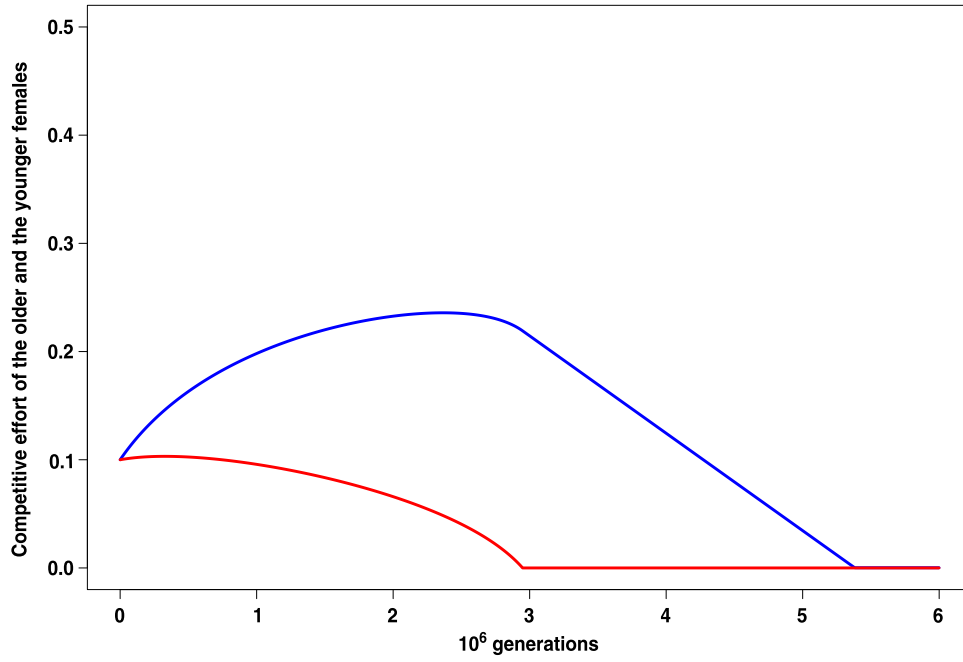


Fig. 1. Evolution of the competitive efforts o (blue line) and y (orange line) as a function of time for the given set of parameters: $b=0.9$, $P=0$, $\mu=0$, $G=0.8$, $D=0.5$, $m=0.5$ and $C=0$. Initial conditions are $o_i=y_i=0.1$. For this set of parameters, at equilibrium, $o^*=0$ and $y^*>0$.

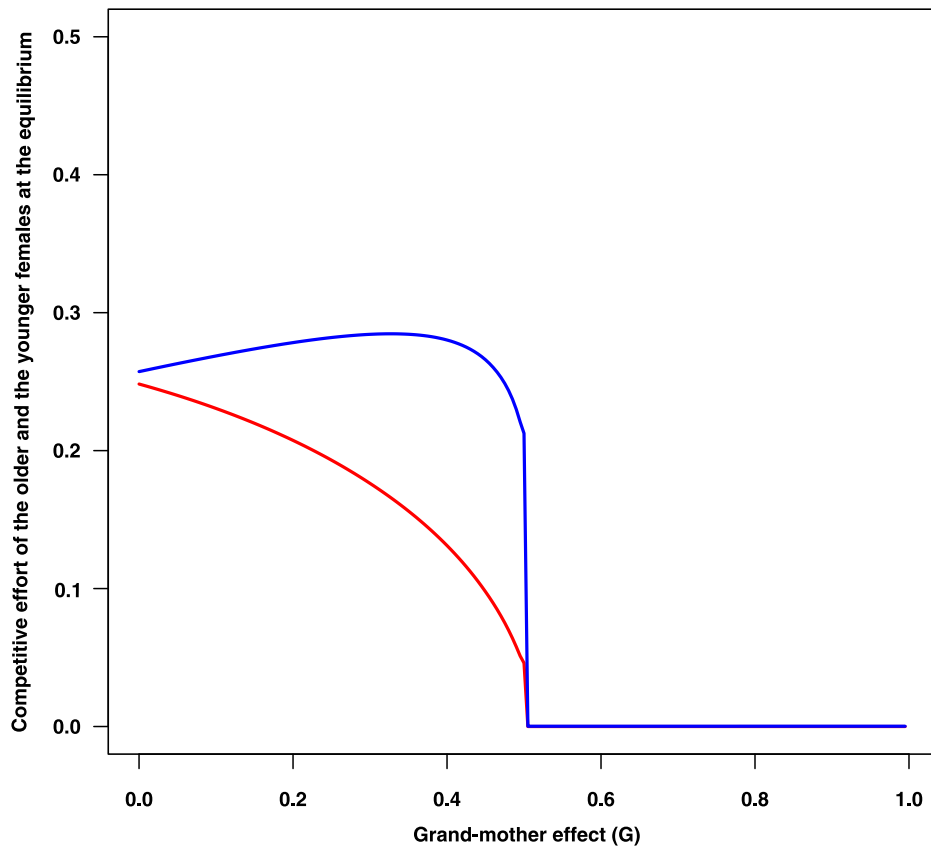


Fig. 2. Competitive efforts o^* (blue line) and y^* (orange line) at equilibrium as a function of the parameter G for the given set of other parameters: $b=0.9$, $P=0$, $\mu=0$, $D=0.5$, $m=0.5$ and $C=0$. Initial conditions are $o_i=y_i=0.1$. See Fig. 1 for details regarding computation for $G=0.8$.

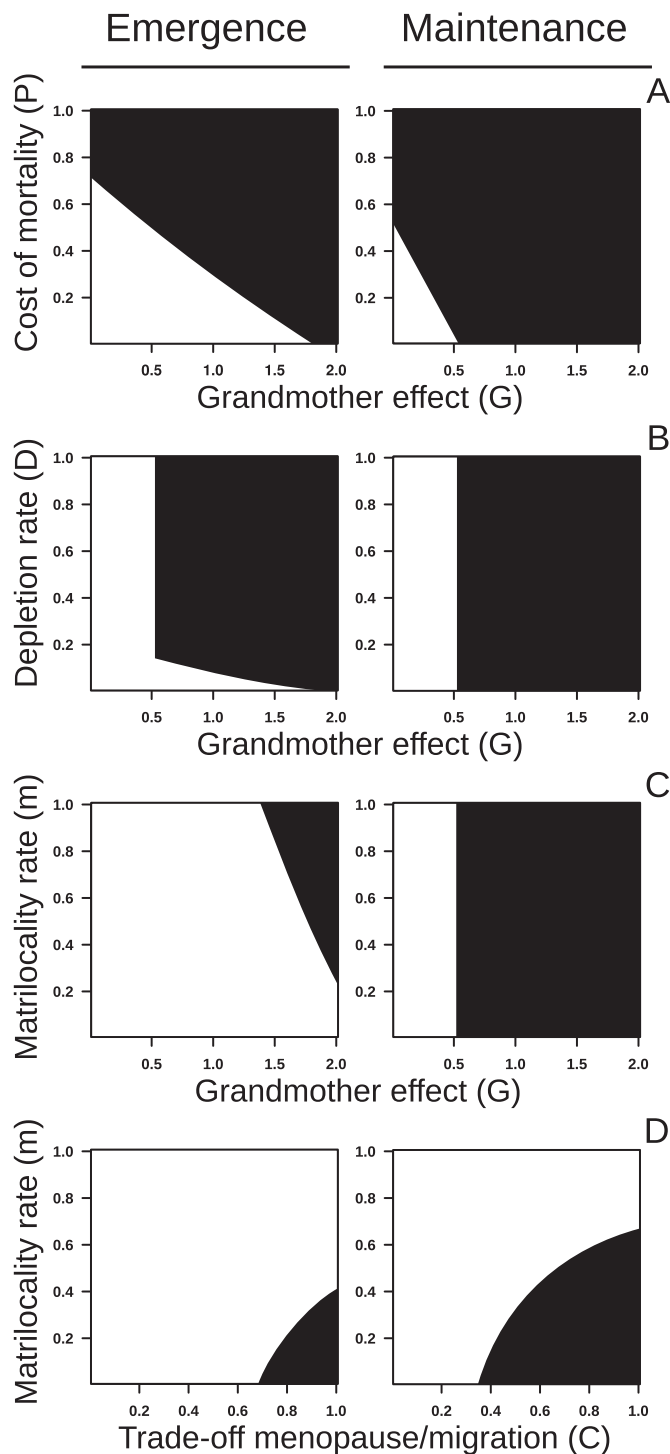


Fig. 3. Evolution of menopause as a function of initial conditions and combination of parameters. Black areas correspond to menopause, whereas white areas correspond to co-breeding between younger and older women. Initial conditions are: Emergence column: $o_i = y_i = 1$; Maintenance column: $o_i = 0$ and $y_i = 1$. Default parameters are $b = 0.9$, $P = 0$, $\mu = 0$, $G = 0$, $D = 0$, $m = 0.5$, $C = 0$.

of combinations of parameters. For instance, an increase in parameter P (associated with hypothesis 1 of the maternal mortality cost) combined with an increase in parameter G (associated with the “grandmother hypothesis”, hypothesis 2) leads to the facilitation of the emergence and to the maintenance of menopause. This combination is additive, that is, the effect of the sum of these hypotheses is equivalent to the sum of the effects of each one (Fig. 3A). However, some combinations are not purely additive. For instance,

the combination of hypotheses 2 and 3 are more than additive. In this case, the value of parameter G necessary to the evolution of menopause is the same (approximately 0.5) when the proportion of resources potentially depleted (as a consequence of reproductive competition) is at least above a threshold of 15% and increases sharply below this threshold (Fig. 3B).

The study of the equilibrium (o^*, y^*) according to the initial condition (o_i, y_i) allows a comparison of the conditions of emergence with the conditions of maintenance of menopause. For a given set of parameters, our model shows that menopause evolution is sensitive to the initial conditions. In a context in which older females do not reproduce (i.e., the initial conditions of the maintenance of menopause; thus, $o_i = 0$), menopause is favored, whereas in a context in which older women do reproduce (i.e., initial condition of the emergence of menopause; thus, $o_i = y_i$), menopause is disadvantaged (Fig. 3A–D). Thus, the conditions for the emergence of menopause are more stringent than the conditions for its maintenance, which means that a decrease in the reproduction of the older females modifies the ecological context, and this modification itself precisely favors the maintenance of menopause.

An example of the differences between maintenance and emergence is apparent in the study of the migration system (patrilocality or matrilocality). In a situation in which the older women breed (i.e., $o_i = 1$), menopause is disadvantaged in a patrilocal context and favored in a matrilocal context. However, if older women do not breed (i.e., $o_i = 0$), menopause is not influenced by the migration system.

4. Discussion

The present work suggests that the conditions favoring the maintenance of menopause are not equivalent to the conditions favoring its emergence and that both situations should thus be studied separately. Indeed, female reproductive strategies in a population alter the social environment and determine the benefits of a trait. This change affects competition for reproductive resources and the average relatedness between interacting individuals. Thus, the evolution of menopause should not be studied outside its ecological context or without considering the feedback between the evolution of this trait and the resulting ecology. In a context in which older females reproduce in the same proportion as younger females, their mean relatedness with the offspring of a younger female is reduced (e.g., $< 1/4$); thus, the inclusive fitness benefits of ceasing reproduction are reduced (details are in Supplementary Information). In contrast, in a context in which older females stop reproducing, their relatedness with offspring of a younger female is higher (e.g., $= 1/4$), which increases the benefits of not reproducing. As a consequence, menopause creates favorable conditions for its maintenance by positive feedback.

4.1. Maintenance of menopause

Is there only one factor alone that is able to maintain menopause? The cost of maternal mortality (hypothesis 1) is connected to the parameters P and μ_i . For menopause to be maintained, the minimum loss of fitness linked to a mother's death is $P = 0.5$, i.e., half of the offspring. This is a high cost, although empirical data suggest that the loss of a mother significantly increases the risk of death of a fair part of her children, and a 50% loss is not an unrealistic figure (Sear and Mace, 2008). A higher maternal mortality (parameter μ_o) of older females actually promotes the evolution of menopause, but an increase up to the maximum realistic values of this parameter (ca. 0.03; see Lahdenperä et al., 2012) has a negligible impact. The grandmother effect (hypothesis 2) is described with parameter G . Menopause is maintained when

G is at least close to 0.5 (see Fig. 2), although current estimates are close to 0.2 (Gibson and Mace, 2005). The conflict of resources (hypothesis 3) is described with parameter D . For the maximum value of D (i.e., $D=1$, all reproductive resources could be depleted during a conflict), menopause is not maintained when none of the other hypotheses are considered. The asymmetric relatedness (hypothesis 4) is described with parameter m , which varies between matrilocality ($m=1$) and patrilocality ($m=0$). Without an association with another factor, there are no values of m able to maintain menopause, as relatedness asymmetry does influence selection but does not generate selection in itself. This is consistent with studies that do not detect a decreased age at menopause in a patrilocality system compared to a matrilocality one (Snopkowski et al., 2014). The trade-off between menopause and marrying up (hypothesis 5) is described with parameters m and C . This effect is favored with a female-biased migration and is the maximum when all females migrate (in a patrilocality society). For such a case, values of C above 0.35 allow the maintenance of menopause. However, there are no direct estimates of such a synthetic parameter C . Nevertheless, as menopause is also maintained in matrilocality societies, this factor alone is probably insufficient. Thus, it seems that none of the hypotheses alone could explain the maintenance of menopause.

When several hypotheses are considered together (e.g., hypotheses 1 and 2 or 1 and 5, or 2 and 5), menopause is more easily maintained (Fig. 3). In contrast, adding hypothesis 3 to any other one does not facilitate the maintenance of menopause, suggesting that the conflict over reproductive resources does not play a decisive role in this case. Female-biased migration facilitates the effect of a trade-off effect (hypotheses 4 and 5), as expected. However, the migration system (patrilocality/matrilocality) does not interact substantially with the other hypotheses.

4.2. Emergence of menopause

The minimum conditions for the emergence of menopause are equal or more restricted than for its maintenance, when all hypotheses are considered alone (Table 4). Thus, it is unlikely that the emergence of menopause could be explained by only one of the hypotheses considered in this model. The only exception could be the trade-off hypothesis (hypothesis 5). Menopause certainly evolved during the palaeolithic (Caspari and Sang-Hee, 2004), possibly in societies organized in groups with female-biased transfer, such as the modern hunter-gatherers. A trade-off effect could be at play in such context and promote menopause, as groups among which women transfer are certainly not equal, some being better off and more powerful than others, thus favoring females signaling higher immediate fertility. Nevertheless, the relevance of this hypothesis is difficult to evaluate without estimates of the synthetic C parameter (which capture the increase in immediate fertility at the expense of a low competitive effort in older age, the choosiness of males and the heterogeneity of resources between groups) in hunter gatherer populations.

Interestingly, a combination of hypotheses (Fig. 3) greatly facilitates the emergence of menopause. The assumption that there is competition for reproduction in groups (hypothesis 3) is sound, as there is empirical evidence for such reproductive competition in humans (Lahdenperä et al., 2012; Mace and Alvergne 2012) and other animals (e.g., Young and Clutton-Brock, 2006). Interestingly, when competition depletes at least a minimum percentage of the reproductive resources, this greatly favors the emergence of menopause. For instance, the value of G required for the emergence of menopause is 1.75, without any additional hypotheses. If 15% or more of resources are subject to depletion (i.e., $D \geq 0.15$), this value changes to 0.5. Nevertheless, to our knowledge, no study provides a clear estimation of the D parameter. This is due to the difficulty of measuring the impact of an inter-generational compe-

tion because menopause precisely enables limiting the reproductive overlap.

An increase in maternal mortality has a negligible impact on the emergence of menopause. Maternal mortality is minimal in non-human primates (Dixson, 1998), suggesting that a low maternal mortality was prevalent during the emergence of menopause, and this is consistent with a negligible effect of the intrinsic mortality in this model. Thus, it is possible that the relatively high maternal mortality in humans is only a derived condition, occurring during or after the emergence of menopause, rather than a determinant of menopause.

The migration system influences hypotheses 2 and 5 in opposite directions. A matrilocality system increases the influence of grandparental care, leading to the emergence of menopause, probably because the relatedness between old and young women competing for reproduction is high, thus enhancing kin selection effects. In a patrilocality structure, this relatedness is diluted, thus reducing the impact of inclusive fitness effects. However, a patrilocality system increases the influence of the trade-off between menopause and marrying up (see Maintenance).

Overall, it is difficult to evaluate if the parameter values required for the emergence of menopause are realistic. This is because there are no estimates of such values in extant human populations, as all of them already display menopause. In addition, human life-history traits probably co-evolved with menopause (see below).

Our model has three main limitations. First, it does not take into account extra pair paternity (EPP), a factor that tends to disadvantage menopause (see SI of Cant and Johnstone, 2008). Indeed, the average relatedness between a female and the descendants of another female of the same family decreases with an increase in EPP, which causes a reduction in the impact of inclusive fitness assumptions. However, EPP reduces relatedness between older females and descendants of younger females but only in a patrilocality context. This decrease in relatedness reduces the kin-selection benefits of menopause; it is therefore simply expected that the EPP destabilizes menopause in a patrilocality social structure. In addition, the human EPP rates have been estimated at around 1% across several human societies over the past several hundred years (Larmuseau et al., 2016), suggesting that its quantitative impact is limited. Thus, it is expected that the qualitative results remain unchanged. Second, the structure of the model is only composed of three age classes, inherited from the model of Reeve et al., (1998). This structure involves fixing the parameters describing a long period of time of an individual, and a multiple age class model (Johnstone and Cant, 2010) with more detailed parameterization of the life-history traits would be more realistic but might expose the model to highly complex and unusable results.

Additionally, in this model, the parameters are fixed, and only the competitive efforts can change. Moreover, it is reasonable to assume that the life-history traits co-evolved with the decreasing reproduction of older females. In particular, a high maternal mortality of older females may be a consequence rather than a cause of the emergence of menopause. In addition, the strong dependency of children in infancy may have been permitted by the increase in the efficiency of grandparental care. Additionally, the decrease in the reproductive potential of older females during the emergence of menopause probably led to a preference for younger females (older females are preferred in chimpanzees; see Muller et al., 2006). This evolved preference for younger females may have contributed further to the development of menopause. It was stressed that the issue of menopause is both a problem of adaptation and constraints (Peccei, 2001), but taking into account the co-evolution between adaptation and constraints is rarely considered. Most biological and ecological factors considered here have a stabilizing effect on menopause after its emergence, but this may

not be the case for other changes. In conclusion, our work shows that the emergence and maintenance of menopause are two intrinsically related but not equivalent issues.

Acknowledgments

We thank Loïc Etienne for helpful suggestions, Jean-Baptiste André, Charlotte Faurie, and Samuel Pavard for helpful comments on the manuscript. This is contribution 2017.151 of the Institut des Sciences de l'Évolution de Montpellier (UMR CNRS 5554). This study was supported by the Agence Nationale pour la Recherche 'HUMANWAY' project (ANR-12-BSV7-0008-01).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jtbi.2017.07.019.

References

- Aimé, C., André, J.-B., Raymond, M., 2017. Grandmothering and cognitive resources are required for the emergence of menopause and extensive post-reproductive lifespan. *PLoS Comput. Biol.* 13, e1005631.
- Bovet, J., et al. 2017. Women's attractiveness is linked to expected age at menopause. (submitted for publication).
- Cant, M.A., Johnstone, R.A., 2008. Reproductive conflict and the separation of reproductive generations in humans. *Proc. Natl. Acad. Sci.* 105, 5332–5336.
- Caspari, R., Sang-Hee, L., 2004. Older age becomes common late in human evolution. *Proc. Natl. Acad. Sci. USA* 101, 10895–10900.
- Chan, M.H., Hawkes, K., Kim, P.S., 2016. Evolution of longevity, age at last birth and sexual conflict with grandmothering. *J. Theor. Biol.* 393, 145–157.
- Croft, D.P., et al., 2015. The evolution of prolonged life after reproduction. *Trends Ecol. Evol.* 30, 407–416.
- Dieckmann, U., Law, R., 1996. The dynamical theory of coevolution: a derivation from stochastic ecological processes. *J. Math. Biol.* 34, 579–612.
- Dixon, A.F., 1998. *Primate Sexuality: Comparative Studies of the Prosimians, Monkeys, Apes, and Humans*. Oxford University Press.
- Gibson, M.A., Mace, R., 2005. Helpful grandmothers in rural Ethiopia: a study of the effect of kin on child survival and growth. *Evol. Human Behav.* 26, 469–482.
- Hamilton, W.D., 1964. The genetical evolution of social behaviour. I. *J. Theor. Biol.* 7, 1–16.
- Hamilton, W.D., 1966. The moulding of senescence by natural selection. *J. Theor. Biol.* 12, 12–45.
- Hawkes, K., O'Connell, J.F., Jones, N.G.B., Alvarez, H., Charnov, E.L., 1998. Grandmothering, menopause, and the evolution of human life histories. *Proc. Natl. Acad. Sci.* 95, 1336–1339.
- Hawkes, K., 2004. Human longevity: the grandmother effect. *Nature* 428, 128–129.
- Hill, K., Hurtado, A.M., 1991. The evolution of premature reproductive senescence and menopause in human females. *Human Nat.* 2, 313–350.
- Johnstone, R.A., Cant, M.A., 2010. The evolution of menopause in cetaceans and humans: the role of demography. *Proc. R. Soc. B* 277, 3765–3771.
- Kim, P.S., McQueen, J.S., Coxworth, J.E., Hawkes, K., 2014. Grandmothering drives the evolution of longevity in a probabilistic model. *J. Theor. Biol.* 353, 84–94.
- Lahdenperä, M., Gillespie, D.O.S., Lummaa, V., Russell, A.F., 2012. Severe intergenerational reproductive conflict and the evolution of menopause. *Ecol. Lett.* 15, 1283–1290.
- Larmuseau, M.H.D., Matthijs, K., Wenseleers, T., 2016. Cuckolded fathers rare in human populations. *Trends Ecol. Evol.* 31, 327–329.
- Mace, R., Alvergne, A., 2012. Female reproductive competition within families in rural Gambia. *Proc. R. Soc. B* 279, 2219–2227.
- Marlowe, F., 2000. The patriarch hypothesis. *Human Nat.* 11, 27.
- Marlowe, F., 2004. Marital residence among foragers. *Curr. Anthropol.* 45, 277–284.
- Morton, R.A., Stone, J.R., Singh, R.S., 2013. Mate choice and the origin of menopause. *PLoS Comput. Biol.* 9 (6), e1003092.
- Muller, M.N., Thompson, M.E., Wrangham, R.W., 2006. Male chimpanzees prefer mating with old females. *Curr. Biol.* 16, 2234–2238.
- Pavard, S., Sibert, A., Heyer, E., 2007. The effect of maternal care on child survival: a demographic, genetic, and evolutionary perspective. *Evolution* 61, 1153–1161.
- Peccei, J.S., 2001. Menopause: adaptation or epiphenomenon? *Evol. Anthropol.* 10, 43–57.
- Reeve, H.K., Emlen, S.T., Keller, L., 1998. Reproductive sharing in animal societies: reproductive incentives or incomplete control by dominant breeders? *Behav. Ecol.* 9, 267–278.
- Rogers, A.R., 1993. Why menopause? *Evol. Ecol.* 7, 406–420.
- Sear, R., Mace, R., 2008. Who keeps children alive? A review of the effects of kin on child survival. *Evol. Human Behav.* 29, 1–18.
- Shanley, D.P., Kirkwood, T.B., 2001. Evolution of the human menopause. *Bioessays* 23, 282–287.
- Shanley, D.P., Sear, R., Mace, R., Kirkwood, T.B., 2007. Testing evolutionary theories of menopause. *Proc. R. Soc. B* 274, 2943–2949.
- Snopkowski, K., Moya, C., Sear, R., 2014. A test of the intergenerational conflict model in Indonesia shows no evidence of earlier menopause in female-dispersing groups. *Proc. R. Soc. B* 281, 20140580–20140580.
- Tully, T., Lambert, A., 2011. The evolution of postreproductive life span as an insurance against indeterminacy. *Evolution* 65, 3013–3020.
- Úbeda, F., Ohtsuki, H., Gardner, A., 2014. Ecology drives intragenomic conflict over menopause. *Ecol. Lett.* 17, 165–174.
- Van Asselt, K.M., et al., 2004. Heritability of menopausal age in mothers and daughters. *Fertil. Steril.* 82, 1348–1351.
- Voland, E., Beise, J., 2002. Opposite effects of maternal and paternal grandmothers on infant survival in historical Krummhörn. *Behav. Ecol. Sociobiol.* 52 (6), 435–443.
- Williams, G.C., 1957. Pleiotropy, natural selection, and the evolution of senescence. *Evolution* 11, 398–411.
- Young, A.J., Clutton-Brock, T., 2006. Infanticide by subordinates influences reproductive sharing in cooperatively breeding meerkats. *Biol. Lett.* 2, 385–387.