# Understanding the occurrence of menopause and post-reproductive lifespans

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**Foreword**
This research has been conducted for my bachelor's thesis in Ecology and Evolution at Rijksuniversiteit Groningen. I would like to thank my supervisor, Prof. Hannah Dugdale, for aiding me through the entire process.

**Summary**
The cause for several independent evolution events of menopause and extended PRLS in humans and certain species of apes and toothed whales is not yet confirmed. Several hypotheses exist, some of which have been tested more thoroughly than others. This study combines important pieces of existing evidence in favor of and against these hypotheses and compares them to try and find an answer to the research question: "Which theories offer the most probable explanation for the occurrence of menopause and extended post-reproductive lifespans?", investigating empirical evidence and theoretical models. None of the hypothesis has been rejected in this study mainly due to a limited number of studies, however, evidence shows that the stopping-early and grandmother hypotheses, as well as the embodied capital model, seem unlikely to answer the research question for apes. In humans, the most probable hypotheses seem to be the three live-long hypotheses. Finally, in toothed whales, foundations for the daughter-in-law, anti-cancer and self-domestication hypotheses are present making these hypotheses the most likely. The cause for the evolution of menopause and extended PRLS could be different for each species, while it is also likely that multiple hypotheses are partially true for certain species due to interactions between traits, contributing to the complexity of the problem.

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**Introduction**

This paper will try to answer the question "Which theories offer the most probable explanation for the occurrence of menopause and extended post-reproductive lifespans? by investigating, discussing and comparing several hypotheses based on evidence from studies on humans and several other species of mammals

Throughout literature and history, menopause has been defined as "the cessation of spontaneous menses for 12 months" (Takahashi & Johnson, 2015). In the modern world, menopause most often tends to start in women aged 49 to 52 (Morabia et al., 1998). Menopause occurs in the form of a transition spanning multiple years that consists of the reproductive, menopausal transition and postmenopausal phase, in contrast to an individual timepoint, which it is often seen as. Females experience ovulation and atresia, a process through which the follicle fails to develop resulting in the absence of ovulation and egg release. As a result of these two processes, the oocytes which they carry as a baby are gradually lost, posing different effects on their physiology. In the early phase of the menopausal transition, lowered secretion of inhibin B leads to an increase of FSH, more follicular recruitment and accelerated follicular loss while estradiol levels remain relatively constant. However, this follicle loss will lead to more variation in the ovarian response to FSH over time, causing more fluctuation in estrogen levels and eventually the normal reproductive cycle is lost. Finally, estrogen levels decline when the entire set of ovarian follicles is used and/or lost, since the ovary can't respond to high FSH levels, for which lowered estradiol elevated FSH levels are indications of the postmenopausal period (Takahashi & Johnson, 2015).

Consensus is lacking regarding the extent to which postreproductive lifespans occur among species, with opinions varying from PRLS occurring only in humans and a few toothed whale species. to all mammals (Ellis, Franks, Nattrass, Cant, et al., 2018). Captive population data (Croft et al., 2015) and varying definitions of PRLS (Levitis et al., 2013) underly this problem. Species with PRLS enter a postreproductive stage in which they cease to reproduce and experience menopause while reproductive and somatic rates senescence have diverged, resulting in females living for an extended period while being unable to reproduce. This diversion of somatic and reproductive senescence is in contrast to aging theory, which expects these physiological systems to senesce at similar rates (Levitis et al., 2013). A species is assumed to have a postreproductive lifespan in females if postreproductive females contribute more than 5% to the total years lived by adult females in a population, expressed in postreproductive representation, PrR (Ellis, Franks, Nattrass, Cant, et al., 2018).

A study which attempted to investigate whether post-reproductive lifespans occur in 52 species of wild mammals found three species for which significant proportions of adult female years were lived by postreproductive individuals in the population, as calculated from the years lived after divided by the years before cessation of reproduction (PrR): humans hunter gatherers (PrR= 0.34), killer whales (PrR= 0.34) and short finned pilot whales (PrR= 0.26). Those species all showed similar probabilities of surviving until cessation of reproduction (p=0.59, 0.73, 0.61 resp.), as well as substantial post-reproductive lifespans (26, 29, 13 years resp.) (Ellis, Franks, Nattrass, Cant, et al., 2018). Another study found similar results, with humans, killer whales and short finned pilot whales being the only species to exhibit extended PRLS (Foote, 2008). Killer whale PRLS might even be the longest apart from humans, ceasing reproduction from age 30-40 with a life expectancy reaching over 90 years old (Olesiuk et al., 2005). Ellis published another study five months later in which he attempted to use physiological data to measure the relative rate of reproductive senescence in toothed whales. Results showed that beluga whales (PrR= 0.27) and narwhals (PrR= 0.24) also had a significant PRLS, with rate of reproductive senescence divided by rate of somatic senescence being 1.69 and 1.14 respectively. Additionally, results indicated several independent evolution events for female PRLS in toothed whales (Ellis, Franks, Nattrass, Currie, et al., 2018). Croft (2015) suggested that reproductive

senescence might occur at higher rates than somatic senescence in more species of toothed whale, and that a lack of sufficient data would likely result in false negatives (Croft et al., 2015).
Menopause and PRLS are found in one of the two closest relatives among extant primates as well, chimpanzees. One study found that in wild chimpanzee populations, females regularly lived past their reproductive phase (PrR= 0.195), with a decrease in fertility after age 30 and no observed births after age 50. This means that the length of PRLS in chimpanzees is around half that of traditional humans on average, however, an increase in FSH an LH levels and a decrease in progestins and estrogens indicated large similarities to the reproductive transition of humans (Wood et al., 2023).
Evidence for extended PRLS in other animals is on the rise, with recent discoveries on physiology of honeybees as an example. Physiologically older workers show a decline in probability of reproduction as their ovaries become less activated. It is suggested that this happens because a period of at least two weeks is necessary for the activation of ovaries. Therefore, physiologically older workers could die before they produce eggs. Investing energy into reproduction could thus be less beneficial to workers' fitness than investing in care for relatives' offspring (Kuszewska et al., 2024).

In general, it is accepted that mutation-selection balance and inter-temporal tradeoffs in reproductive effort provide the answers to why we age. First, mutation-selection balance is achieved when the mutation rate is greater than the force of selection. This revolves around the fact that selection has a smaller effect on the group of older individuals since most of them die due to accumulated risks over time, leading to a smaller number of individuals in this group for selection to act upon, resulting in accumulation of deleterious characteristics among elders and ultimately senescence.
Senescence is caused by inter-temporal tradeoffs as well, with antagonistic pleiotropy at the foundation. Antagonistic pleiotropy, when the same genes can influence fitness differently throughout an organism's life history, causes some genes to increase fitness earlier in life but decrease fitness later. Since selection acts more strongly on genes that increase fitness early in life as younger individuals outnumber older ones, even when they decrease fitness when they're older, this can have senescence as a result (Williams, 1957).

**Research question:**
Which theories offer the most probable explanation for the occurrence of menopause and extended post-reproductive lifespans?

## Adaptive hypotheses

**Stopping early hypothesis**
Already in 1957, Williams came up with the "stopping early hypothesis" as an adaptive explanation for menopause. He acknowledged that in a post-reproductive lifespan, apart from producing viable gametes, caring for offspring is necessary too for the survival of parental genes. After the youngest child has become self-sufficient, fathers gradually, and females abruptly enter the post-reproductive lifespan. Therefore, he suggested that there would be substantial advantages of not producing and investing more energy into care for extant offspring since pregnancy-associated risks increase in woman aged forty-five or fifty. This reproductive adaptation would also diminish the negative effects of childbirth mortality on raising extant children. Furthermore, menopause would be an adaptation to a long period of dependence of offspring on their parents (Williams, 1957).

Evidence in favor of the stopping early hypothesis could be induced from Penn & Smith's (2007) study on a preindustrial North American population which found significant declines in the probability of survivorship for parents of both sexes with higher childbirth rates after the final birth, especially in women over 50. Although stronger in women, shorter birth intervals had a negative effect on parental survivorship and the survival probability of offspring decreased to larger extent when mothers died. (Penn & Smith, 2007). Similarly, studies on killer whales found that the probability of death after

maternal death increased 31 times for males under 30 and 8.3 times for males over 30 years, with similar or even more extreme results for death of post-reproductive females (Foster et al., 2012). This relation complies with the kinship dynamics of killer whales, as a daughter's offspring are raised within the group increasing the competition therein, resulting in an inclusive fitness advantage for mothers to invest more in sons' survival (Johnstone & Cant, 2010) through aiding in foraging or risky encounters (Mann, 2000).

Hawkes et al. (1998) opposed the stopping-early hypothesis, stating that other primates' fertility does not end early even though mothers among these species provide extended care, an example of which are chimpanzees with low survival rates for late-borns (Goodall, J. 1986; Goodall, J. 1989). Low adult mortalities and human longevity are thought to be the main factors involved in the distinct human life histories, not early termination of fertility (Hawkes et al., 1998). Similarities between humans and chimpanzees in the speed at which the follicle reserve becomes depleted confirm this, since reproductive senescence is likely to have stayed the same as in our common ancestor (Hawkes & Coxworth, 2013).

Other evidence against the stopping early hypothesis was found according to demographics of premodern Finns and Canadians, where the risk for a woman to die from giving birth increased from middle age but remained relatively low at 1-2% at age 50 and is predicted to reach 2-8% at age 70. Additionally, children only experienced a decreased survival probability, ultimate fitness and lifespan when losing their mother in their first two years, since after 2 years other family members could compensate for the loss of maternal care (Lahdenperä et al., 2011).

To conclude, Williams (1957) showed advantages of ceasing reproduction and investing in care for the living offspring because of increased pregnancy-associated risks, to which Penn & Smith added evidence as well. It could be argued that the preindustrial population North America does not represent the situation of our ancestors accurately enough. Foster et al. (2012) indicated a strong effect of (postreproductive) maternal death on offspring survival.
The opposition consists of the studies conducted by Hawkes et al. (1998), Hawkes & Coxworth (2013) and Lahdenperä et al. (2011). Coxworth and Hawkes and suggested that reproductive senescence has remained equal from our ancestor, which might prove to be crucial for the rejection of the stopping-early hypothesis as it is in sharp conflict with the assumption of advanced menopause. Lahdenperä et al. (2011) showed that the influence of maternal death on their offspring's fitness is small. More research on the maternal effects on offspring as an explanation for menopause and extended PRLS is needed since consensus has not been reached. However, there is a substantial amount of evidence against the stopping-early hypothesis compared to evidence in favor of the hypothesis, thus, this hypothesis has not been able to explain the evolution of menopause and extended PRLS in humans. Studies supporting the live-long hypotheses which will be discussed next will add to the opposing evidence for the stopping-early hypothesis.

## Live-long hypotheses

Postmenopausal longevity could be the main factor involved in the formation of distinct human life histories instead of early cessation of fertility (Hawkes et al., 1998). Three sub hypotheses with selection on three different types of intergenerational care as the cause for the evolution of extended PRLS will be discussed, namely the Grandmother Hypothesis, the Embodied Capital Model and the Daughter-in-Law Hypothesis.

All three hypotheses assume that intergenerational care by older, non-reproductive females increase reproductive success of reproductive females to an extent that the costs of slowed ageing for reproductive capacity of reproducing females earlier in life are compensated for. Reproduction by older females would be selected against since it would limit their potential in grandmothering, the

provision of care for younger reproducing females. The result would be slowed aging including somatic senescence but excluding reproductive senescence. (Hawkes et al., 1998).

**Grandmother Hypothesis**

Hawkes et al. (1998) proposed that (post-reproductive) mothers forage well enough to gather enough food not only for themselves, but also for one or more of their own children, or even their daughter and niece's children. When a mother has just given birth, she is less able to forage since she must spend more energy on care for the baby, thus help of relatives becomes more important. Care from grandmothers would increase selection on deleterious mutations later in life since these would reduce her potential to provide care. This selection would enhance the contribution of a grandmother's genes to the next generations, increasing her inclusive fitness (Hamilton, 1964). Care from grandmothers, also called "grandmothering", could slow ageing since slower senescence, although commonly related to reduced fertility earlier in life, could be favored. According to the grandmother hypothesis, the amount of care an elder female can provide for the younger generations is dependent on strength in relation to body size (Hawkes et al., 1998).

Charnov's model, which characterizes important tradeoffs involved in the formation of mammalian life histories, was used by Hawkes et al. (1998) to test the grandmother hypothesis. It assumes that growth can be divided into the phases from conception to independence and independence to maturity, with independence composing the weaning stage. Body mass (W) and a production coefficient (A) determine growth rate to large extent. The size at adult maturity and the production one can spend on offspring vary directly with the production coefficient, which is low in primates relative to other mammals and is lowest in humans.

The model assumes that the period of growth from independence to maturity is related to tradeoffs in reproducing earlier and growing for a longer period. (Charnov, 1991). Results showed that humans become mature at a later age than other primates of relatively similar size, indicating benefits from a longer growth period for the capacity of maternal care and grandmothering, as was expected when the hypothesis was true.

If the grandmother hypothesis would be correct, the care by grandmothers would increase fecundity and infant growth rates by providing food to nursing women and children. For fecundity, this was found to be true since human intervals between births were the shortest. If humans would wean their babies early, the ratio of size at independence to adult size would be expected to be low, however, ratios were similar to that of the other great apes. The specific combination of a short human birth interval and late age at maturity was more than double as extreme as that of the other great apes. (Hawkes et al., 1998).

Penn & Smith (2007) also tested the effects of grandmothering on the numbers of grandchildren. Even though less grandchildren were produced by prematurely dying mothers aged below 30, the number of grandchildren was not significantly affected by maternal mortality after adjusting for parity ($P = 0.57$). The decrease in the number of adult offspring was therefore suggested to result in a lower number of grandchildren, not the amount of grandparental care (Penn & Smith, 2007).

In summary, the grandmother hypothesis poses that strength-dependent post-reproductive female care for grandchildren would increase selection on deleterious mutations later in life and slow ageing. Charnov's model provided evidence in favor of the hypothesis for humans but against the hypothesis for other great apes, indicating benefits from longer growth for grandmothering (Hawkes et al., 1998). According to Penn & Smith (2007) their study, the number of grandchildren was not significantly affected by grandparental care. The observed differences between humans and other great apes are quite remarkable and could aid in finding a definite answer to why human PRLS is substantially longer than in other great apes, however, it remains uncertain what the grandmother hypothesis could explain regarding the evolution of menopause and extended PRLS in toothed whales. Studies on the

grandmother hypothesis are limited, especially in other animals, thus according to the studies presented here, the grandmother hypothesis could not yet be rejected nor confirmed.

**Embodied Capital Hypothesis**

While the Grandmother Hypothesis expressed care as a function of strength, the Embodied Capital Model uses a combination of skill intensiveness of the human foraging niche and neural capital development instead. As investments at a younger age result in energetic returns later in life which increase their own fitness and/or that of their children and grandchildren. Like with the grandmother hypothesis, if the benefits of reproducing become smaller than the costs with age, dedicating resources to altering the fitness of children and grandchildren would become favorable. Another difference is that the Embodied Capital Model considers it advantageous for older females and males to stop reproducing as well because, in traditional hunter-gatherer populations, they divided the investments in reproduction, production and parental care. (Aimé et al., 2017).

According to a study from Kaplan et al. (2000), humans differ from other primates in four traits regarding life history: Long lifespans, extended offspring dependence, postreproductive elders providing care for reproducing individuals and care by males (Kaplan et al., 2000). Humans begin to produce more resources than they consume at age 18-20 and produce more than chimpanzees, whose net productivity becomes positive at age 5 as they require less training to obtain their nutritional needs as their diet exists for 94% of collected foods compared to the 91% extracted or hunted food diet of humans (Lancaster & Kaplan, 2010; Milton & Demment, 1988).
As is known now, in some chimpanzee populations individuals regularly live long lives reaching ages of more than 50 years old and menopause and extended PRLS occur in chimpanzees as well, although PRLS duration is only around half that of human hunter-gatherers (Wood et al., 2023).

The embodied capital hypothesis was tested more recently by using Artificial Neural Networks to simulate humans' life histories. Interactions between foraging niche, rate of skill learning, difficulty of the environment and depletion rate of somatic and cognitive capital together influenced PRLS duration. Low skill intensiveness of the foraging niche was related to a shorter PRLS, but high skill intensiveness did not always result in a long PRLS. Menopause and extended PRLS evolved at least once, with substantially similar patterns of reproductive and somatic senescence to the ones derived from traditional hunter gatherers in certain views. The stopping early hypothesis was not a determinant of menopause, while grandmothering as well as early investments in brain performance were found to be necessary for the evolution of menopause and extended PRLS. Cognitive performance declined minimally with age relative to the decline in physical condition in the simulation, as confirmed in other studies (Gurven et al., 2017; Schwarz et al., 2016). This study by Aimé et al. indicates that cognitive abilities and a skill-intensive role of humans in the environment are therefore likely to have led to the emergence of extended PRLS (Aimé et al., 2017).

In summary, the embodied capital model holds that selection favored the cessation of reproduction due to an age-dependent tradeoff between the costs and benefits. Investing more energy into grandparental care increases indirect fitness and the amount of care one can provide depends on the skill intensiveness of the foraging niche and the neural capital development (Aimé et al., 2017). Skill-related differences in resource production and the age at which net positive productivity is reached in humans and chimpanzees could be evidence against the embodied capital model in apes (Lancaster & Kaplan, 2010). The Artificial Neural Networks simulation found effects of foraging niche, neural capital and grandparental care on PRLS evolution and duration (Aimé et al., 2017). Although Wood et al. (2023) stated that chimpanzees may live past the age of 50 and show long PRLS as well, their PRLS is only half of that of humans, thus this does not reject the possibility for the embodied capital model to explain the exceptionally long PRLS in humans. The studies presented here provide strong evidence against the stopping-early hypothesis while indicating a substantial role of grandparental care in the

evolution of menopause and extended PRLS in humans. The question remains whether grandparental care should be measured in strength or in a combination of skill intensiveness of the foraging niche and neural capital development, but since no studies have showed direct opposing evidence to the embodied capital model so far, the model might have a slight advantage over the grandmother hypothesis.
The number of studies on the Embodied Capital Model as a cause for the evolution of menopause and extended PRLS is limited throughout literature, especially on other animals than humans, thus future science should elaborate further on this topic.

**Daughter-in-law hypothesis**
Intergenerational competition between co-breeding in-laws might be a possible explanation as well for menopause and extended post-reproductive lifespans. In in-laws, relatedness between mother-in-law and her daughter will be 50% while that between mother-in-law and the offspring of her daughter-in-law will be 25%. Daughters-in-law relatedness to her own offspring is 0.5, while she is unrelated to the offspring of her mother-in-law's offspring. If mother-in-law and daughter-in-law were to have an overlap in their reproductive period, selection would act more strongly on daughters-in-law to outcompete their mother-in-law. Therefore, reproduction after menopausal age would be selected against in the elder generation (Cant & Johnstone, 2008). Dispersal patterns can also affect competition, since if elder females were to continue reproducing, with patrilocality, young females join other groups which potentially leads to more competition with their mothers-in-law, while with matrilocality, daughters experience more competition from their own mothers. In other great apes, dispersal is mostly done by females, possibly suggesting that human ancestors did the same, however, this remains largely uncertain. (Johnstone & Cant, 2019).

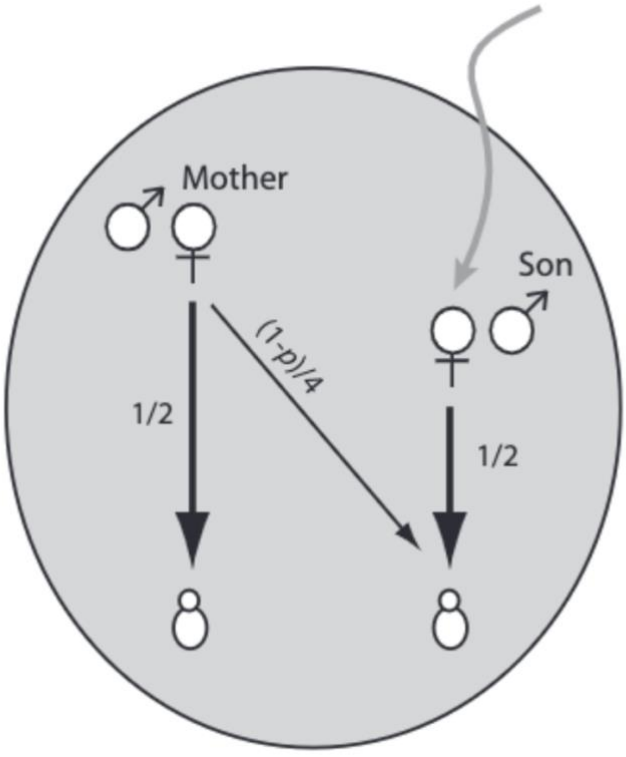


Figure 1. Asymmetries in relatedness in families under patrilocality.
Parents are indicated by gender symbols. The younger female is unrelated to the mother's offspring, while the mother is related by (1-p)/4 to the children of an immigrating female, where the probability of extra-pair paternity is represented by p (Cant & Johnstone, 2008).

Using a dataset on pre-industrial Finns, Lahdenperä (2012) found that only 6.6% of mothers gave birth no longer than 2 years after receiving their first grandchild, indicating that intergenerational

reproductive overlap was uncommon. When children of mothers-in-law were born simultaneously with children of daughters-in-law, survival rates decreased significantly by 50% and 66% for the two generations of children respectively, while no significant effect was observed between mothers and daughters.

Their model showed that selection for cessation of reproduction after 51 years could be caused by the maternal death risks regarding childbirth and benefits from grandmothering, confirming the results form Cant & Johnstone (2008) their study. Grandmothering loss and reproductive conflict among in-laws reduced inclusive fitness with 43 and 51% respectively when delaying reproduction from 41 years (the mean age at last reproduction) to 46 under patrilocality. Maternal mortality with childbirth explained only 2% of the observed variation, thus the stopping early hypothesis did not gain support from the model (Lahdenperä et al., 2012).

Another study on killer whales found results which indicate the relevance of relatedness based on similar relatedness-patterns to what the daughter-in-law theory predicts, high costs from coreproduction between generations for older females and high benefits from leadership by older females for group survival. (Croft et al., 2017).

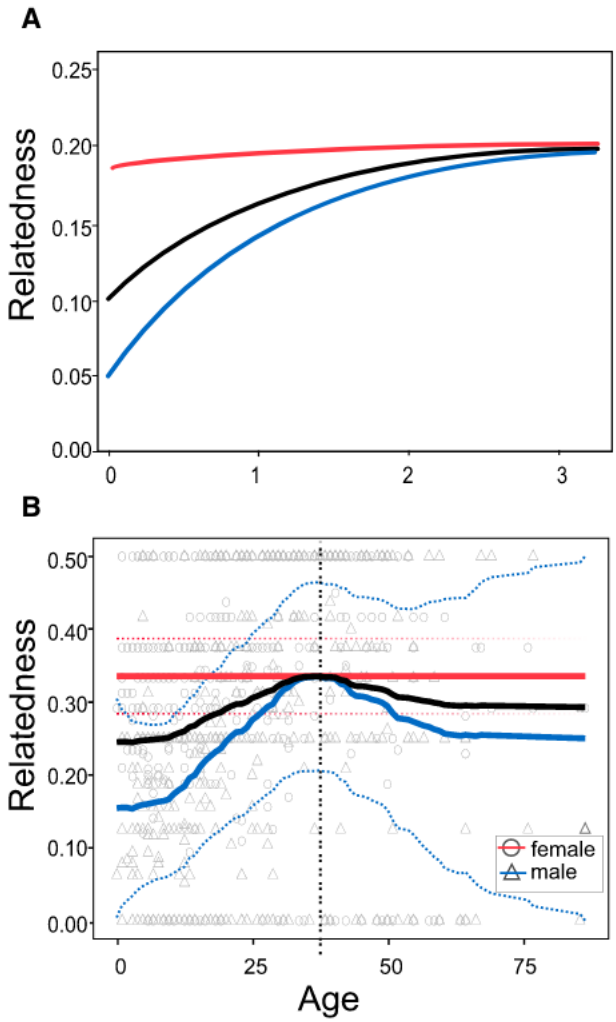


Figure 2. Local relatedness changes with age in killer whales.
(A) Relation between female age (adjusted to mean generation time) and mean relatedness to others from a matriline from Johnstone & Cant (2010), assuming no post-reproductive period in females. Red lines indicate females, blue lines indicate males and black lines indicate the mean relatedness across both sexes. (B) Relation between maternal relatedness and female age for in total 200 Northern and

Southern resident killer whales consisting of 846 whale-years. Data was used from 1980, 1990 and 2000. A local linear trend model has been used to plot the lines, which indicate relatedness patterns similar to (A), with dotted lines indicating the SEs. Raw empirical data has been plotted as well. The age at which female lifetime fecundity has been realized for 95% is shown by the vertical dotted line (Croft et al., 2017)

In summary, the daughter-in-law hypothesis poses that strong competition from daughters-in-law against mothers-in-law as a result of assymmetries in relatedness leads to the evolution of menopause and extended PRLS (Cant & Johnstone, 2008). Studies in humans and killer whales found supporting evidence in fitness costs of coreproduction between mothers-in-law and daughters-in-law (Croft et al., 2017; Lahdenperä et al., 2012). The likelihood of care by elders for younger females and cessation of reproduction to avoid reproductive conflict playing a role in the evolution of menopause and extended PRLS gaines additional support from the studies on the daughter-in-law hypothesis. For great apes, the foundation for the hypothesis is there since patrilocality is expected to increase in-law competition (Johnstone & Cant, 2019). This also holds for killer whales according to patterns in relatedness, costs of co-reproduction between generations and benefits of care by older females (Croft et al., 2017). The question remains whether reproductive conflict between mother and daughter or mother-in-law and daughter-in-law was a cause for the evolution of menopause and extensive PRLS. Studies which critically assess the daughter-in-law hypothesis or which provide opposing evidence are limited throughout literature, so future research should focus on testing the hypothesis further to diminish uncertainty.

**Anti-cancer defense hypothesis**

Where previously discussed hypotheses are all related to changes in an individual's fitness through care, the anti-cancer hypothesis looks at fitness changes caused by cancer as a possible explanation for the evolution of menopause and extended PRLS.

Pregnancy initially increases cancer risk by promoting the spread of cancer cells from one organ or tissue to another and/or stimulating oncogene-activated cells to develop into tumors. However, full-term pregnancies decrease the risk of developing breast cancer when occurring early in life, since the lifetime exposure to estrogen becomes lower when the number of menstrual cycles is reduced. Given mentioned initial risks of pregnancy, supporting a regular reproductive physiology while preventing the fatal invasion of cancers would not be possible for reproducing older females. Insufficient cancer defenses are supposedly a constraint in evolutionary context, since cancer-associated traits were unable to evolve while other mechanisms evolved to compensate for insufficient cancer defenses (Boutry et al., 2020).

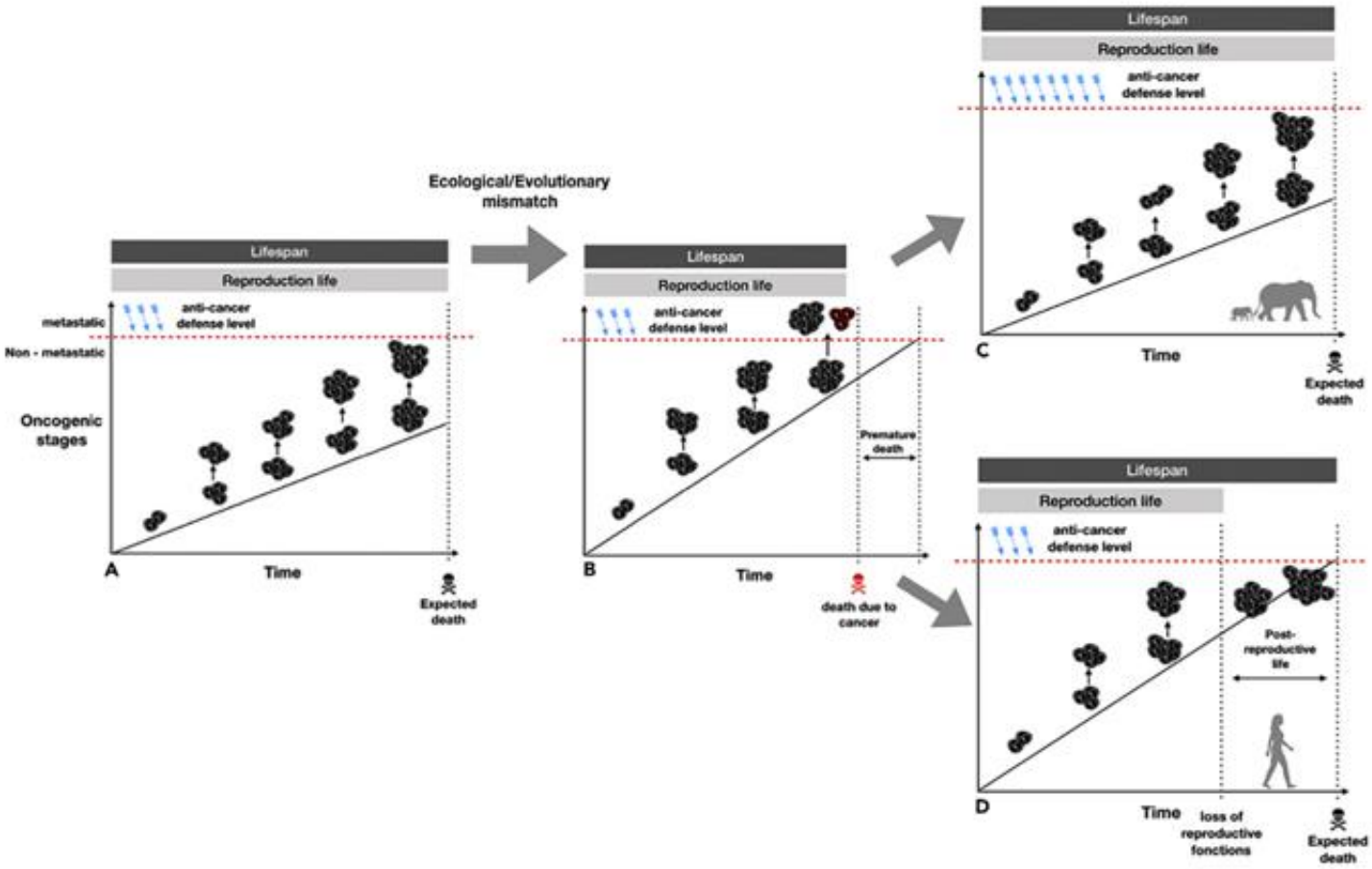


Figure 3. Defense against cancer, risk of cancer and a conceivable pattern of menopausal evolution. (A) In species with defenses against cancer coinciding with the risk of cancer, reproduction increases the risk of developing tumors, however, it does not result in metastatic cancer since the tumors spread slowly over time. This assumes maximum fitness and reproduction over the entire lifespan. (B–D) (B) Reproduction increases metastatic cancer risks with increasing age in females through relatively weak cancer defenses, leading to reduced fitness and lifespans. Natural selection either result in situation (C) through selecting for stronger cancer defenses, leading to a similar situation as in (A), or result in (D) through selecting for earlier cessation of reproduction in females to maintain a higher fitness than in (B) through maintenance of health in combination with grandparenting. The scenario of (D) can be reversed to situation (A) and (C) if investment in cancer defense is selected for. Figure modified from (Thomas et al., 2019) (Boutry et al., 2020).

Other studies have also found that females which experience menopause later have a higher chance of developing breast (Monninkhof et al., 1999), endometrial and ovarian (De Graaff & Stolte, 1978; Ossewaarde et al., 2005) cancer in relation to the amount of exposure to estrogen. Examples of positive health effects of delayed menopause include decreased overall mortality (Jacobsen, 2003), increased overall survival and life expectancy (Ossewaarde et al., 2005), lower probability of cardiovascular diseases (De Kleijn, 2002; Ossewaarde et al., 2005) and a lower probability of bone complications (Gold, 2011; Kritz-Silverstein & Barrett-Connor, 1993; Parazzini et al., 1996; Van Der Voort et al., 2003)

A review on marine mammal neoplasia suggested the influence of pollution through estrogen-imitating chemicals called xenoestrogens, possibly resulting in tumor development in seals (Bäcklin et al., 2003) and belugas, while in the latter, long pregnancy and periods of lactation were suggested to add to the cancer risk (Martineau et al., 2002; McDonald, 2002; Newman & Smith, 2006).

In summary, the anti-cancer hypothesis poses that initially increased age-dependent pregnancy-associated risks for tumor development due to increased estrogen exposure levels caused the evolution of menopause and extended PRLS to compensate for weak anticancer defenses (Boutry et al., 2020). Several studies confirm the positive relation between increased estrogen exposure and cancer risk in marine mammals, providing a foundation for the hypothesis. Delayed menopause has many positive effects on fitness too however. Due to the contrast between the fitness risks and benefits of estrogen exposure, the hypothesis remains uncertain. It might seem logical that selection favoring the benefits early in life would be greater than selection against the risks later on, especially considering that expected life spans were much shorter in hunter-gatherers so the chance of reaching an age at which the costs outweigh the risks was small. The anti-cancer hypothesis can not be confirmed nor rejected, but future research might reveal the answer and find more species in which selection acts on trade-offs between mentioned risks and benefits including animals exhibiting menopause and extended PRLS.

## Non-adaptive hypotheses

**By-product hypothesis**

Through the perspective of direct fitness benefits, the problem with the live long hypotheses is that selection on older females is low since their contribution to the gene pool of the next generation is smaller than that of younger females, thus there is little pressure to shape menopause (Stearns & Ebert, 2001). Gosden et al. (1998) suggested a nonadaptive explanation with menopause as a byproduct of atresia. Total oocyte loss is found in humans and two other primates, bonobos and rhesus macaques (Finch and Sapolsky 1999). Oocytic atresia, which is found in most mammals, is the process in which a follicle does not fully develop and is removed, preventing egg release and ovulation. Atresia is suggested to be selective by cessation of nourishment for oocytes with mitochondria containing deleterious mutations based on condition-related signals which the mitochondria emit through their biochemical profile. (Jansen & Boer, 1998; Krakauer & Mira, 1999; Stearns & Ebert, 2001). Without atresia, deleterious mutations would accumulate through population bottlenecks since mitochondria reproduce asexually (Muller, 1964). Variations in the number of developed oocytes would lead to variation in the age of onset of menopause, with menopause occurring when the oocyte reserve is fully depleted (Gosden et al., 1998).

There are three predictions to this hypothesis:
(1) The percentage of defective mitochondria decreases from 3-month-old embryos until they are born. (2) The number of mitochondria that are introduced into an oocyte ought to be low, optimally consisting of just one. The exact number was not known; however, it was suggested to be below 10 (Jansen, de Boer, 1998). Too many mitochondrial genomes would result in removal of too many oocytes. (3) The signals that lead to the cessation of development of an oocyte should be related in function to the performance of mitochondria. (Stearns & Ebert, 2001). These three hypotheses have not been confirmed to this day.

Although no direct evidence exists for atresia as the cause of the evolution of menopause, there is indirect evidence based on changes in follicle numbers. Antral follicles go through different phases, from small to medium and ultimately large. On average, selection for dominant follicles through atresia occurs most frequently in small and medium antral follicles (Conti & Chang, 2016). Relations between the age-dependent decline in the size of the small antral follicle reserve and a decrease in primordial follicle numbers have been found (Monniaux et al., 2014). Also, when certain chemotherapy agents predominantly destroy primordial follicles, dormant primordial follicle activation increases leading to earlier menopause through an advanced depletion of the follicle reserve (Kalich-Philosoph et al., 2013; Wang et al., 2019).

Evidence from studies on follicular atresia in the theca interna shows that in cells which express receptors for luteinizing hormone (LH) to produce an important precursor of estrogen for regulation of the menstrual cycle, genes associated with 'cell cycle and DNA replication' were downregulated (Hatzirodos, Hummitzsch, et al., 2014). In total, 12 of the down-regulated genes in case of atresia in the theca interna (Hatzirodos, Irving-Rodgers, et al., 2014) are related to or the same as 8 of the 37 DNA-repair genes in early menopause-associated loci (Laven et al., 2016; Rodgers & Laven, 2020).

Furthermore, an increase in mitochondrial DNA copies led to a reduced size of initial follicle reserve in a study on the effects of obesogenic maternal diets on embryonic development. A higher number of mtDNA copies often compensates for inefficient ATP production due to deleterious mitochondria and atresia, however, it increases the exposure to reactive oxygen species, highly reactive unstable molecules containing oxygen, possibly resulting in primordial follicular damage (Aiken et al., 2016).

There is however also opposing evidence indicating that mutations do not accumulate in mitochondrial DNA in the oocytes (Boucret et al., 2017). The cause for this is suggested to be oxidative shielding of the mitochondrial DNA by localized antioxidant- (Hammond et al., 2016.; Zhang et al., 2015) and melatonin (Tamura et al., 2017) production near the oocyte, protecting the oocyte from highly reactive unstable molecules containing oxygen named damaging reactive oxygen species (Fraser et al., 2020). However, another study did find evidence that mitochondrial DNA continues to accumulate deletions and mutations despite oxidative shielding of the mtDNA (Sreerangaraja Urs et al., 2020; Tesarik & Mendoza-Tesarik, 2023).

In summary, the non-adaptive by-product hypothesis poses that menopause and extended PRLS are byproducts of atresia, which selectively removes oocytes containing deleterious mitochondria, leading to advanced depletion of the follicle reserve (Gosden et al., 1998). The three hypotheses by Stearns & Ebert (2001) were not confirmed. Multiple studies possibly provided indirect evidence for the by-product hypothesis in humans through relations in follicle depletion and advanced menopause, in specific genes and in mtDNA and reactive oxygen species.
Boucret et al. (2017) provided evidence against the by-product hypothesis regarding oxidative shielding, however, Sreerangaraja et al. (2020) found opposing results. It remains uncertain to what extend oxidative shielding prevents accumulation of mutations in the mtDNA, which is important to clarify since this accumulation is one of the main assumptions of the hypothesis. The by-product hypothesis could be explanatory for the evolution of menopause and extended PRLS in apes, since the foundation of total oocyte loss has been observed in several species. To conclude, the by-product hypothesis could not be confirmed nor rejected as there is no consensus among the studies providing indirect evidence and direct evidence is lacking, thus, future research should focus on this topic to find direct evidence and confirm the three assumptions by Stearns & Ebert (2001) for humans as well as for other animals.

**Self-domestication hypothesis**
It is speculated that there might be other socioecological components than grandparental care to the evolution of menopause and extended PRLS like domesticity and captivity. Domesticity increases age-specific fertility rates in a large group of animals that are bred to reproduce more frequently while decreasing age-specific mortality rates. Higher fecundity results in earlier follicular exhaustion, while the probability of living past the moment of primordial follicle depletion increases with lower mortality. The self-domestication hypothesis assumes that follicular exhaustion and increased expected lifespan, resulting from domestication-like conditions, led to the evolution of extended PRLS before the evolution of grandparental care (Ellison & Ottinger, 2014)

The systems of social interactions of humans and toothed whales have been suggested to exhibit similarities which could potentially be seen as a common context for the occurrence of post-reproductive lifespans in females. There are also features of human social systems that toothed whales, and potentially all other animals exhibit as well, like complementary age- and sex-class-specific labor division, "pooled energy budgets" and the division of food, which enhance physiology of the individual. An example of this are female orcas which guide younger individuals to foraging sites to help their kin raise offspring (Nattrass et al., 2019). This socioecology, like domesticity and captivity, results in lower age-specific mortality and higher age-specific fecundity. "Self-domestication" could have provided a foundation for the evolution of post-reproductive lifespans in humans (Ellison and Ottinger, 2014) and killer whales (Nattrass et al., 2019), but possibly in other animals as well. Alloparenting, care by individuals other than the biological parents, is likely to have significantly affected emotional control, pro-sociality and altriciality in humans and other great apes like chimpanzees (Burkart et al., 2014; Hrdy, 2011; Isler & Van Schaik, 2012; Johnstone & Cant, 2010).

The evolution of human social systems might be defined more accurately as selection for self-restraint and pro-social behaviour than by self-domestication as social structures in humans have developed throughout time to become more complex, whereas brain size increased throughout the largest part of human evolution. Social structures of domesticates however have become less complex through domestication, while their brain size has decreased as well (Shilton et al., 2020).

In summary, the self-domestication hypothesis poses that self-induced domesticity and captivity-like effects increased the age-specific fertility rate and decreased age-specific mortality rates. This has resulted in earlier follicular exhaustion and an increased probability of living past the moment of follicular depletion (Ellison & Ottinger, 2014), with grandparental care evolving afterwards. Indirect evidence in favor of the self-domestication hypothesis consists of similarities in the effects of social interactions on fertility and mortality between killer whales and humans (Ellison & Ottinger, 2014). The degree to which self-domestication is an accurate representation for the evolution of human social systems could be argued, since selection for self-restraint and pro-social behaviour might fit the observations more precisely (Shilton et al., 2020). The self-domestication hypthesis can not be confirmed nor rejected since the amount of relevant studies and evidence is quite low. The similarities between humans, killer whales and other great apes social systems might prove to be of importance in finding a universal cause for the evolution of menopause and extende PRLS in the animal kingdom as a whole. Studies which critically assess the self-domestication hypothesis and present opposing evidence are lacking throughout literature, thus further research could elaborate further on this topic, especially by trying to create theoretical models and simulations to predict the effects of self-domestication on the evolution of menopause and extended PRLS.

**Conclusion**

The research question, "Which theories offer the most probable explanation for the occurrence of menopause and extended post-reproductive lifespans?", remains to be answered using the evidence from discussed studies.

The stopping early hypothesis does not seem likely to offer a sufficient explanation for the human case, since the amount of opposing evidence is relatively large compared to the supporting evidence. Studies regarding apes and killer whales are lacking, however, extended care by elders combined with low survival rates in late-born chimpanzees add to the unlikeliness of this hypothesis in apes.

The grandmother hypothesis has not yet been able to sufficiently answer the research question for apes and toothed whales, with small sizes at maturity contributing to the unlikeliness in apes. Regarding humans, the question remains unanswered, but Charnov's model offered some interesting results and could be elaborated on further.

The embodied capital model is unlikely to answer the question for apes due to the low skill-intensive foraging niche and young age at net positive productivity, while no studies tested the hypothesis for

toothed whales. It remains uncertain whether the hypothesis is true for humans but according to the hopeful results from Aimé et al. (2017) their study, it seems possible that future research will find more supporting evidence.
Foundations for the daughter-in-law hypothesis are present in apes regarding dispersal patterns and in multiple ways in toothed whales, especially killer whales. Although the relatedness theory is interesting, no direct evidence for the hypothesis was found in apes, humans, and toothed whales and the number of studies is limited.
A foundation for the anti-cancer hypothesis is present according to relations between estrogen exposure and increased cancer risks in certain marine mammals which thus far have not been shown to experience menopause and extended PRLS, which is yet to be confirmed in the species of toothed whales which have been confirmed experience menopause and extended PRLS. No studies tested the hypothesis on apes however, and whether the hypothesis is true for humans and essentially all species remains uncertain since estrogen exposure offers fitness costs but also several benefits.
The by-product hypothesis remains uncertain since the possibility of accumulation of deleterious mutations in mitochondria in the oocytes is debated due to the largely unknown effects of oxidative shielding. A foundation is present for humans and apes however, in which total oocyte loss has been confirmed, although studies on toothed whales are limited in this regard.
Lastly, the self-domestication hypothesis has foundations in humans, toothed whales and apes since positive effects of social interactions on individuals' fitness have been observed. The hypothesis should be tested further, but it might provide an answer to the research question in all studied species at once.
It is possible that there is not one hypothesis which explains the evolution of menopause and extended PRLS, with multiple hypotheses interacting and contributing resulting in a mixed answer to the research question. Future research should elaborate further on this topic, focusing also on other species than humans since most studies have been conducted on human data. Artificial intelligence and theoretical models could aid in this as well, providing a solid base for research in this field to build on.

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