# The Evolutionary Ecology of Menopause: Implications for Public Health

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# Abstract

Evolutionary perspectives on menopause have focused on explaining why female early reproductive cessation emerged and why it is rare throughout the animal kingdom. However, less attention has been given to explaining patterns of diversity in menopausal traits (e.g. age at menopause, duration of the peri-menopausal period, symptomatology). To address this, we propose a multi-level, inter-disciplinary framework combining proximate, physiological understandings of ovarian ageing with ultimate, evolutionary perspectives on ageing. We first review known patterns of diversity, and how menopause is currently defined and measured. We examine current evolutionary theories for the emergence of early reproductive cessation and evaluate their adequacy in explaining the age of menopause. We show that ovarian ageing is highly constrained by ageing of the follicle - the structure containing the oocyte - suggesting that ovarian ageing can be explained by processes involved in somatic ageing. Given this, we explore whether the genetic, ecological and life-history determinants of somatic senescence also underpin the onset of menopause. We conclude by discussing how an evolutionary ecology of menopause could inform public health research and discourse. We argue that a greater commitment to studying menopausal variation within such a framework can validate currently identified patterns of diversity and its determinants.

# 1. Introduction

Menopause, as per the World Health Organisation definition [1], corresponds to the permanent cessation of menstruation in human females. While menopause is a ubiquitous phenomenon of the human female ageing experience, there is considerable variation in the age at menopause, and how menopause is experienced both within, and between populations [2-5]. Yet, there have been only limited attempts to provide a holistic framework for understanding patterns of diversity, with research focusing either on the emergence of menopause as a Darwinian puzzle or on the proximate determinants of ovarian ageing. To address this deficit, this paper proposes an interdisciplinary and multi-level framework, combining proximate, biomedical understandings of menopause variation with an ultimate, evolutionary ecology perspective.

## *What is menopause?*

When conducting interdisciplinary research, one must acknowledge that disciplines use different definitions for the same term. In the biomedical and population health sciences, menopause is defined as an event reached when a woman has not had a menstrual cycle for the past 12 months [6]. Following this final menstrual period (FMP), a woman is considered to have experienced menopause. Menopause, which indicates the cessation of reproductive function, naturally occurs in the fourth or fifth decade of a woman’s life – although some women may experience menopause due to a pathology of the reproductive system before the expected age of cessation of reproductive function [6]. In the biomedical sciences, the transition towards menopause is generally understood in terms of the physiological processes of ovarian ageing and follicular atresia - the apoptosis (or programmed cell death) of oocytes (egg cells) (Box 1) [7]. These lead to fluctuations in hormone levels, decreasing genetic quality of oocytes, decreased chances of successful pregnancy, and ultimately, the cessation of reproductive function [8-10]. Menopause is thus preceded by peri-menopause, a period characterized by the irregularity of menstrual cycle length and frequency as well as the experience of vasomotor symptoms (e.g. hot flushes/night sweats [6]), urogenital discomfort, anxiety, depression, and joint aches [6]. While menopause itself is the complete cessation of periods, it is best understood as a process rather than an event [3]. Indeed, individuals will be peri-menopausal for some years prior to their final menstrual period (FMP).

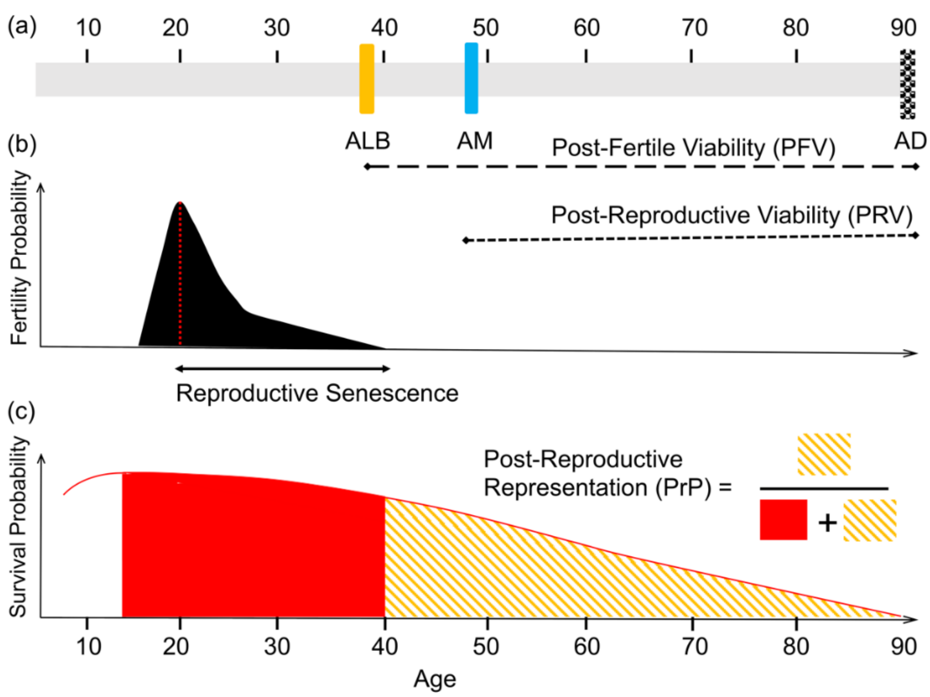


**Figure 1: Measuring post-reproductive lifespan: the differences between post-fertile viability (PFV), post-reproductive viability (PRV), reproductive senescence and a post-fertile lifestage (PFLS).** ALB: Age at last birth; AM: Age at menopause; AD: Age at death. ***(a) A woman's hypothetical lifespan***. Post-fertile viability is defined as the length of time between age at last birth, which typically occurs between 39 and 41 years (reviewed in Towner) and age at death. By contrast, post-reproductive viability is defined as the length of time between age at menopause and age at death. ***(b) Reproductive senescence***. Reproductive senescence corresponds to fertility decline over age, which culminates in the cessation of fertility (ALB). ***(c) Post-reproductive representation.*** The extent to which a species displays a post-reproductive lifestage is informed by the ratio of post-fertile adult years lived relative to the total adult years lived (PrP). For the sake of simplicity, the age at the onset of actuarial senescence was set at the age at first reproduction ([7]).

From an evolutionary standpoint, however, menopause is often conflated to the cessation of fertility rather than the cessation of reproduction function *per se.* Thus, menopause is approached as a demographic rather than a physiological phenomenon, whereby emphasis is placed upon the proportion of a population who are post-fertile (e.g. [11]). To establish whether a post-fertile life stage has evolved in any given species, the proportion of individuals who outlive their last reproductive event is calculated. In this way, "menopause" is estimated through the age at last birth, especially in non-menstruating species, and thus it does not indicate the cessation of menstruation as it does in humans. However, menopause and age at last birth do not always coincide: if an individual becomes post-fertile following their last birth, they might not necessarily be post-reproductive (Figure 1, [12]) if they are still cycling. Further, according to demographic data from historical and contemporary human populations, age at last birth frequently precedes the cessation of reproductive cycles, on average up to 10 years before [13]. Additionally, procedures such as hysterectomy and tubal ligation may also bring an end to the possibility of reproduction, but not necessarily to the menstrual cycle [6]. Thus, menopause in the biomedical sense is not to be conflated with the evolution of a post-reproductive life stage [12].

### *Human variation in age at menopause*

Self-reported age at menopause is variable, with population mean age throughout the 20$^{th}$ Century being anywhere between 44.6 and 54.5 years of age across different geographic regions [2], and between 46 and 51.7 years of age in studies conducted between 1990-2010 (Figure 2). Temporal changes in age at FMP occur across

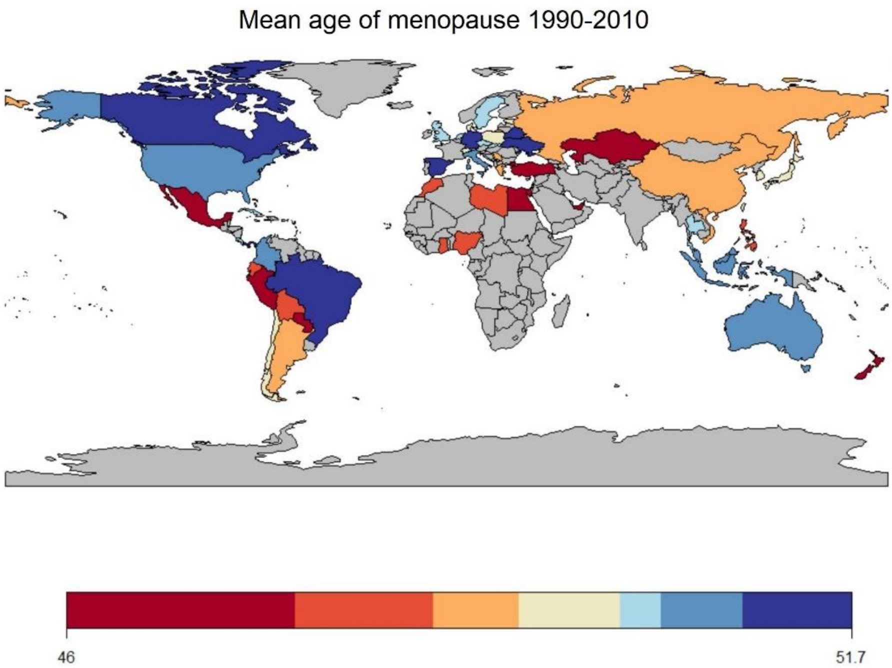


**Figure 2: Variation in final menstrual periods (FMP)**. (a) Variation in self-reported mean age at FMP measured between 1990-2010 across countries. Broadly, mean age of menopause is higher in the Global North than in the Global South, but due to the lack of measurement of age at menopause across populations, there is a sizeable uncertainty associated with this pattern. Additionally, the measurement of age at menopause in the studies included here may also be subject to the limitations discussed in Section 1. See supplementary information for references, sample sizes and years during which the data were collected.

different birth cohorts, with a cohort study in Sweden identifying a 1 month increase of menopausal age with each year of birth [14].

Previous epidemiological research has identified several factors affecting menopausal age, which can be categorised into reproductive life history, socio-economic status (SES) and lifestyle factors. Regarding reproductive life history, early age at menopause is associated with early menarche [15, 16] and nulliparity [15, 17] while increasing parity (number of pregnancies) is associated with later age at menopause [15, 17-19]. Various markers of lower SES or indicators of stress in early life (household crowding; father's social class; parental divorce, poor cognitive ability, maternal smoking; perception of being thin) [16, 19, 20] and later in life (educational status, regional purchasing power [17, 21]) are associated with an earlier age at menopause. The relationship between socio-economic status and age at menopause is potentially mediated by lifestyle factors such as smoking and BMI - smoking has a strong association with earlier age at menopause [2, 16, 18, 21-23] while there is a weak association between lower BMI and earlier age at menopause [24]. The extent to which those different associations can be understood as an evolved physiological response to the experience of ecological factors experienced at various developmental stages has been little discussed to date (but see Sievert [3]).

A major issue for understanding current patterns of diversity in the age at menopause is the methodology employed to produce data on the timing of the final menstrual period. There are a number of limitations to both measuring menopause within populations and interpreting the results:

(i) The measurement of FMP may only be confirmed retrospectively. This increases the difficulty of recruiting women who are newly post-menopausal for cross-sectional studies.

(ii) The irregularity of menstrual cycles may result in periods longer than 12 months where a woman appears to be anovulatory, especially towards the later peri-menopause where menstrual cycles tend to be longer [25]. It is possible that a woman does not experience a period in 12 months, then experiences bleeding. This bleeding may be considered a period, or it may not be a menstrual cycle but the result of reproductive malignancies which can occur in the post-menopausal body [6].

(iii) One must distinguish between menstrual bleeding and other forms of withdrawal bleeding. If a woman is taking combined oral contraceptives or hormone replacement therapy, bleeds are not menstrual cycles but rather withdrawal bleeds under the control of medication [26]. Prescription guidelines advise a change away from combined oral contraceptives to a progesterone based contraceptive over the age of 50 (or 35 for smokers or people with other risk factors [6]), given the high risk of thromboembolism [26]. After this, bleeding may stop, and the individual may be considered post-menopausal. However, any bleeding experienced while on oral contraception is a withdrawal bleed, and a woman's reproductive capacity may have ceased prior to stopping oral contraceptive usage. A woman's true age at menopause therefore becomes masked by oral contraceptive usage [6, 26]. Similarly, the use of combined HRT during the peri-menopausal stage can also produce withdrawal bleeds [6]. These examples highlight the importance of defining menopause as the cessation of menstrual cycles, rather than all forms of bleeding, as bleeding can also originate from the use of hormonal contraceptives and HRT.

(iv) If a woman is using progesterone-only contraceptive methods, age at menopause may also be masked by amenorrhoea produced by contraceptive usage. The chance of amenorrheoa by 12 months using the Mirena/levonorgestrel releasing intra-uterine system (the hormonal coil) is 20-80% - this form of contraception has the highest continuation rates in women aged 39-48 [27].

(v) There is no clinical diagnostic tool able to discern menopausal status through measuring hormone levels. While the testing of FSH levels may be diagnostic for cases of early menopause (<45), FSH levels are unreliable for assessing menopausal status due to fluctuations in levels throughout peri-menopause [1, 26]. Additionally, levels of the anti-mullerian hormone (AMH), even in multiple assessments, are unreliable for assessing ovarian reserve, due to the wide variation in levels of AMH within populations, as well as lack of a uniform AMH decline [28].

(vi) There are methodological limitations to the epidemiological studies into age at menopause when interpreting results. These include the use of discrete categories or "binning" (eg. <45, 46-50, 51-55, 56+), which may obscure any smaller trends in age at menopause. Additionally, in cases where data is collected from ageing cohorts which did not ask for age at menopause but rather for whether the participant had reached menopause, the midpoint between the 2 cohort waves where menstruation is present and then absent are taken as the final menstrual period.

## *Human variation in other dimensions of the menopause experience*

When investigating patterns of diversity in menopause, one must establish variation not only in age at final menstrual period, but also in the length of the peri-menopausal period as well as the type and severity of menopausal symptoms. The peri-menopausal period is a multifaceted experience – it is not only characterised by the timing of FMP but also by the experience of menopausal symptoms, irregularity of menstrual cycles, and duration of the peri-menopausal period. To date, there has been little research documenting and explaining diversity of the peri-menopausal experience (see [29, 30] for examples). Research into patterns of bleeding within North American populations has identified a general pattern of increasing cycle lengths, and heaviness of bleeding as FMP approaches [25]. However, 12%-25% of women across various studies reported minimal to no changes in bleeding patterns before amenorrhoea indicative of the FMP [25], suggesting that there is significant unexplained variation in the experience of the peri-menopausal period within populations.

Further methodological considerations must be made when studying diversity in menopausal symptoms. The emergence and duration of symptoms can be used in conjunction with menstrual cycle irregularity to identify if a woman is peri-menopausal. When investigating menopausal symptoms, it is key not to assume uniformity of symptomatology across populations [3]. The prevalence and severity of symptoms across populations vary, e.g. symptoms such as hot flushes are widely reported in Western countries but are seldom reported in other populations, for instance throughout East Asia [3]. Several epidemiological studies note that vasomotor symptoms (VMS) such as hot flushes and night sweats are more likely and more frequent amongst women of European and Latin American descent, African American and Hispanic women in the USA, women living in South East Asia, women with anxiety, hypertension as well as HIV and women who are obese [4]. Studies have similarly found that women from India and the Middle East, as well as Chinese and Japanese American women experienced fewer VMS [4]. Variation also occurs in symptom manifestations, such as the locations where VMS are felt in the body. For example American women may flush on their face and upper chest, Mexican women may flush on the back of the neck, while women who wear headscarves may flush on the top of their heads, under their scarves [31] In addition, women who have undergone a bilateral oophorectomy (surgical removal of both ovaries) also report experiencing more severe VMS from the onset, rather than the gradual increase in severity found amongst most other women [32]. Other symptoms may be more important to the menopausal experience in some populations, such as joint aches and pains amongst Asian populations [31]. Thus, in order to study the population-level experience of menopause as comprehensively as possible – especially cross-culturally – assumptions surrounding symptom experience cannot simply be transposed from one population to another.

To conclude, there seems to be significant variation worldwide in age at menopause and other menopausal traits, although the data underpinning this picture are somewhat problematic due to methodological considerations. It is also notable that most data pertain to Western and Northern Countries (with the exception of Brazil), limiting our ability to apprehend temporal and spatial patterns of diversity in women's final menstrual period. Those limitations in mind, in the next section we evaluate and contrast the relevance of current evolutionary theories on the evolution of early reproductive cessation for understanding patterns of diversity in menopause, i.e. the age at final menstrual period.

# 2. Integrating ultimate and proximate explanations

In order to produce an interdisciplinary evolutionary framework for accounting for menopause diversity in humans, one must evaluate the extent to which proximate and ultimate explanations are aligned. Here we show that ultimate adaptationists perspectives on the evolution of menopause are incompatible with current proximate physiological understandings of ovarian ageing. Adaptationist perspectives conflate menopause with the phenomenon of age at last birth; they do not consider the multifactorial determinants of age at last birth; and they do not have the capacity to explore variation in menopausal age in a way that complements proximate explanations of ovarian ageing. Rather, we show that by-product hypotheses for the emergence of menopause are compatible with the biomedical literature on ovarian ageing, offering new avenues for investigating the determinants of variation in the experience of menopause.

## *Adaptive Hypotheses*

Adaptationist interpretations of menopause consider the paradoxical occurrence of fertility cessation to hold an adaptive benefit given females do not directly increase their fitness consistently throughout their adult life. These hypotheses often centre on the trade-off between increasing a female's reproductive fitness and the increased mortality and reduced capacity for longevity that later life pregnancy and parturition entail. Such theories are predicated on the gains to inclusive fitness incurred by being able to look after offspring and grandoffspring as a post-menopausal female, as well as the benefits of ceasing reproduction in order to avoid competition for resources with other, younger females in the society [11, 33-42]. Despite being popular theories for the emergence of reproductive cessation, adaptationist hypotheses are subject to the same limitations due to their assumption that reproductive cessation is interchangeable with menopause, and that the only determinant of fertility cessation towards later life is the decline in physiological reproductive capacity. As stated previously, contemporary explorations into the age at last birth in historical and traditional human populations show that menopause often occurs 10 years before reported menopause [43]. Whether menopause and age at last birth have ever coincided over evolutionary times is unknown, but the possibility that the two phenomena can be decoupled suggests that it is erroneous to assume the cessation of fertility is dependent solely on physiological reproductive decline. Rather, birth spacing and parity in humans are subject to proximate determinants of fertility driven by sociocultural and biological factors other than reproductive senescence [44]. These have been categorised by demographer John Bongaarts as exposure factors (whether partners are available for reproduction), deliberate marital fertility control factors (contraception/natural family planning techniques, induced abortion), and natural marital fertility factors (lactational infecundability, frequency of intercourse, pathological sterility, spontaneous intrauterine mortality) [13].

Adaptationist perspectives on their own do not offer much scope for studying variation of the age at and experience of menopause as they more often approach menopause as an event of reproductive cessation. Some exploration has been made into how variation in menopausal age occurs based on factors such as matrilocal and patrilocal dispersal patterns, and the presence of maternal kin in the household [38, 45]. If contemporary patterns of menopausal variation were due to factors implicated in adaptationist hypotheses, then menopausal age and experience would be expected to correspond to daughter's reproductive success, and dispersal patterns. Studies have found little support for modification of menopausal age based on either mediating factor, nor have they been able to give suggestions for proximate mechanisms which might explain how age at menopause could be affected by factors like dispersal and daughter's reproductive success. Thus, adaptationist perspectives – taken in isolation - are insufficient for providing ultimate explanations for understanding diversity in menopausal traits that can complement proximate understandings of ovarian ageing. This does not negate their relevance in understanding age at last birth, or the applicability of such hypotheses in other species which exhibit menopause, for instance the killer whale (*Orcinus orca)* [42, 46].

### *By-Product Hypotheses*

By-product theories view menopause as an epiphenomenon, co-produced by the finite nature of a female's oocyte supply and the causes of lifespan longevity which allow females to outlive this supply [35, 36]. In other words, menopause has emerged in human females because actual (somatic) longevity has increased, while reproductive longevity has not. While males generate gametes throughout their life, females possess a finite supply of gametes, produced while the female is *in utero*. As the female menstrual cycle involves hormonal production both from the pituitary gland and the oocytes, the depletion of oocytes impedes the function of the reproductive system. Menopause therefore becomes the phenotypic expression of follicle depletion in females. The emergence of menopause as a life history stage in human females involves the decoupling of selection pressure on actual lifespan and on reproductive lifespan, which implicates both an increased selection for lifespan longevity and a lack of selective pressure on elongated female reproduction throughout hominin evolution [47]. Levitis, Burger & Bingaman Lackey state that "*even a more favourable environment could not produce post-fertile survival in such a species because anything that would extend longevity would also extend reproduction*" [12], suggesting that a decoupling of reproductive and actual lifespan would need to occur prior to the evolution of extended lifespan in hominins. Thus, a post-reproductive lifespan can only evolve if individuals already have the ability to outlive their own reproductive period [12]. Phenomena such as younger mate preference by human males may contribute to this decoupling - a female reproductive skew originates from mating preferences in humans [48], where early age at last birth in human females reduces the selective pressure on extended reproductive lifespan [35].

When menopause is conceptualized as the outcome of ageing of the reproductive system, by-product hypotheses for the evolution of menopause are compatible with current physiological understandings of cellular senescence, an important evolutionary determinant of longevity. Indeed, rates of reproductive cell senescence, as measured by ovarian ageing, are not independent from rates of somatic senescence, in particular that of the follicle containing the germ cell (oocyte). In this way, ageing of the human female reproductive capacity is constrained by somatic ageing of the follicles, as measured by the rate of follicular atresia. This is because the somatic cells supporting reproduction are not as well protected from oxidative damage as the oocyte and ovary are and thus age faster (Box 1). Why this is the case is puzzling and might suggest that there has been little selection for extending female reproductive capacity commensurate to lifespan, at least in humans.

### *Menopause as the by-product of ageing of the reproductive system*

Menopause is co-produced by ovarian ageing and follicular depletion together; yet ovarian ageing is constrained by somatic ageing of the follicle (Box 1). Ovarian ageing is the process whereby the ovaries decline in their ability to recruit and develop successful oocytes [49], similarly to the decreased function found in senescent cells. Ovarian ageing adversely affects female fertility, reducing the probability of successful pregnancy due to increasingly poor quality of follicles. The follicle is the cellular structure containing both the oocyte and surrounding granulosa cells and is recruited

**Box 1: Ovarian ageing is constrained by somatic processes**

Perhaps one central issue to integrating ovarian ageing with somatic processes of ageing is that the oocyte itself is a germ cell. While the oocyte may possess multiple defence mechanisms against ageing, the somatic granulosa cells which surround the oocyte in the follicle *are* subject to somatic ageing. As the somatic granulosa cells decrease in quality, the quality of the overall follicle (including the oocyte itself) decreases, and is at risk of undergoing apoptosis.

Ovarian ageing is often associated with the dysregulation of respiration in ovarian ageing, and thus centred on the role of mitochondria. Mitochondria are responsible for the energy production and regulation of various cellular signaling pathways within the oocyte, and thus they are also responsible for producing reactive oxygen species (ROS) and reactive carbonyl species (RCS) through respiration. Primordial follicles are produced in utero and can be kept in a state of arrested prophase for upwards of 50 years and so there is potential during this arrest for damage to accumulate in the oocyte while it is quiescent [95]. However, the oocyte itself is well protected against oxidative damage, and it has been suggested that localised antioxidant production around the oocyte offers adaptive protection against DNA damage caused by ROS and during its suspended lifespan [95, 96]. Localised production of melatonin in the ovary, which has antioxidant properties, also supports the presence of protective measures in the ovary against the impact of long-term exposure to ROS [97]. As such, mitochondrial DNA in the oocyte is not shown to accumulate mutations during ovarian ageing in the way predicted if there were no methods of oxidative shielding [98].

The granulosa cell becomes the determinant of follicular atresia, as well as the increasing genomic instability of ageing oocytes [8, 50, 96, 98]. Follicular atresia is initiated through the granulosa cells, which accompany the oocyte from oogenesis to the creation of the antral follicle. The quality of the granulosa cells and thus of the ovarian microenvironment is a tangible site of interest for studying determinants of ovarian ageing [10, 50].

during the follicular phase of the menstrual cycle. If the follicle is of low quality, it will undergo atresia – programmed cell death - hypothesised to be under the control of the supporting granulosa cells [10, 50] . As the ovary ages, both the quantity and the quality of follicles, and thus oocytes, in the ovary decreases [51], a process referred to as follicular depletion. As only one oocyte is released during ovulation, the main source of follicle loss during the lifetime is atresia.

Follicular depletion becomes implicated in determining the age at menopause when depletion causes the number of follicles to be below that required to support menstruation [52]. At this point, menstrual cycles become dysregulated and ultimately cease. Conventional understandings of follicular atresia rates have considered the rate to be biphasic – with accelerated rates of atresia occurring beyond the age of 35 [52]. This, however, has been shown to be the result of misinterpreting plots of follicular atresia rates [52] . Rather, accelerated rates of follicular atresia tend to occur much later, and are more likely within several years of the onset of menopause [52]. This suggests that processes underpinning the process of follicular atresia are key to the transition towards menopause.

The rate of follicular atresia is potentially influenced by the inflammatory profile of the menstrual cycle: ovulation is characterized by inflammation of the ovaries, while menstruation has been deemed a “massive inflammatory event” [53]. Inflammation is major determinant of the ageing process because it releases reactive oxidative species (ROS), which are free radicals implicated in the aetiology of many non-communicable diseases through the promotion of cell senescence [54]. It remains to be investigated how repeated cycles of ovulation and menstruation influence ageing of the granulosa cells and thus follicular atresia. Diversity in cyclical life-history due to either anovulatory cycles, pregnancies or hormonal contraceptives is likely to be important for explaining patterns of reproductive senescence and the onset of menopause.

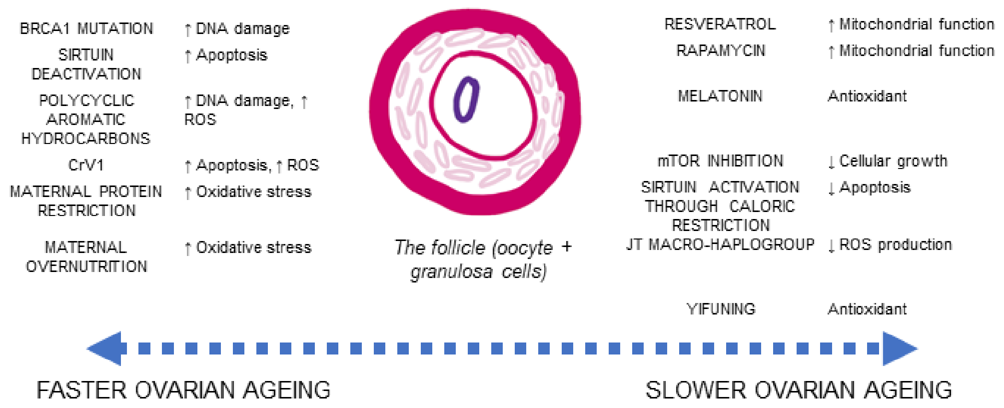


**Figure 3: Agents which influence ovarian ageing.** Agents are written in bold, with their respective effect on rates of ovarian ageing to the right. ROS (reactive oxidative species) produces oxidative stress, which contributes to cellular senescence and cell apoptosis. Conversely, agents which contain antioxidants improve overall mitochondrial function, slowing down the rate of cellular senescence.

Exploring whether ovarian ageing is underpinned by similar processes as those of cellular senescence reveals that rates of ovarian ageing, follicular depletion and the onset of menopause may be shaped by evolutionary ecological factors that are also known to influence somatic ageing variation (Figure 3). Overall patterns of ageing and senescence are understood evolutionarily through the Disposable Soma hypothesis, [55] where the body’s capacity to accumulate deleterious senescent cells is attributed to declining selective pressure on maintenance mechanisms as age increases, due to increasing extrinsic mortality risk [55]. In this way, age-related health decline results from accumulated damage and sub-optimal functioning of bodily systems on the molecular, cellular and organ level [55]. Rates of cellular senescence can vary depending on the interaction between an organism and ecological factors (e.g. food availability, stress, pathogen load), producing patterns of ageing rates which vary within and between populations.

# 3. Understanding Patterns of Diversity in Menopause

In this section, we review the evidence for the role of genetic, environmental and reproductive factors in explaining diversity in somatic senescence rates, with a view to investigate how those might be applied to understanding diversity in reproductive ageing. We show that there are common genetic factors between extreme longevity and age at menopause with regards to genes mediating metabolic profiles, metabolism and oxidative shielding. Following research showing that the early life environment influences the pace of reproductive development and life-history "strategy", we hypothesize that poor early life environment may result in lower embodied capital, and thus earlier age at menopause. Finally, we propose that women who experience a higher number of cumulative ovulatory menstrual cycles may experience earlier age at menopause through the cumulative exposure of localised inflammation in the female reproductive organs during ovulation. We show that the phenotype of age at menopause is the result of an interaction between genetic, ecological factors and the cycling life-history.

## *Genetic factors*

Genetic factors between ovarian ageing and overall somatic ageing show similarities in the biochemical pathways in which they are implicated. Human longevity is a complex biosocial trait, with genetics being highly context-dependent and rates of senescence resulting from a dynamic process [56]. There are no genes which "code for" longevity in humans [56], and associations between alleles and longevity occur where such alleles produce a phenotype conducive for long life, especially amongst centenarians (individuals who have lived to age 100). Such phenotypes include metabolic profiles characterised by preserved glucose tolerance and insulin sensitivity; compressed morbidity and disability in later life, and general avoidance or postponement of age-related diseases; and decreased DNA methylation compared to others of the same chronological age [56]. Such phenotypes are conducive of reduced levels of accumulated damage contributing to the functioning of bodily systems on the molecular, cellular and organ levels. These phenotypes may therefore promote both somatic longevity and reproductive longevity, thus postponing age at menopause.

Genetic factors which have been identified as contributing to the phenotype of somatic longevity, reproductive longevity or both include the following:

**APOE:** the APOE gene codes for apolipoprotein E, which helps maintain structural integrity and function of cholesterol rich lipoproteins. The protein structure of APOE varies and is found to exist in 3 different isoforms which alter its function. Isoforms APOEe2, APOEe3 and APOEe4 are positively associated, not associated or negatively associated with longevity, respectively [56]. Regarding menopause, association between isoforms and reproductive longevity have been inconclusive. Heterozygous APOEe3/4 carriers show a delayed age at menopause compared to APOEe3/3 carriers in a Chinese population [57]. Both APOEe4 and APOEe2 isoforms have been associated with predicted an earlier age at menopause amongst Iranian females and women of European descent, respectively [58, 59].

**Sirtuins:** Sirtuins are proteins which modulate metabolism, cell proliferation and genome stability. Regulation of several sirtuin genes – SIRT5 and SIRT7- have been found to have a positive association with longevity, while a minor SIRT6 homologous allele, affecting its function, has been associated with decreased lifespan [56]. Variation in sirtuin regulation has been linked to reproductive longevity, with downregulation of SIRT1, SIRT3 and SIRT6 being linked to an increased rate of ovarian ageing [51].

**Mitochondrial Haplotype J:** Mitochondrial DNA Haplotype J is hypothesised to reduce the output of both ATP (the product of respiration) and ROS. The mtDNA J haplotype has been positively associated with somatic longevity in European populations [56], and was underrepresented amongst French women with depleted ovarian reserves undergoing fertility treatment [60], suggesting it plays a role in reproductive longevity.

**FOXO3:** FOXO3 is a gene which downregulates activity on the IGF1 pathway, helping to maintain a metabolomic profile conducive to longevity [56]. Associations between expression of FOXO3 and reproductive longevity are unknown.

**IL6:** Modulation of interleukin 6, a multifunctional cytokine associated with inflammatory responses by a minor allele has also been associated with longevity and the aetiology of age related disease [56]. Associations between IL6 modulation and reproductive longevity are unknown.

Additional single nucleotide polymorphisms (SNPs) associated with age at menopause have been linked to genes involved in hormonal regulation, immune function and DNA repair pathways [61]. A candidate gene located on the Human Leukocyte Antigen (HLA-B) transcript has been associated with age at menopause as well as Type-1 diabetes and rheumatoid arthritis [61]. Such a gene implicates a pro-inflammatory component to physiological pathways mediating rates of ovarian ageing [61]. BRCA1 mutations also confer an increased rate of ovarian ageing, hypothesised to be due to increased rates of double strand DNA breaks in follicles, causing subsequent increase in the rate of follicular atresia (Box 1, [62]).

Determinants of longevity and somatic senescence are hugely complex, with genetic factors only explaining a small proportion of variation in longevity [56]. GWAS-identified loci and their related function only explain 2.5-4.1% of population variation in the age at menopause [61]. The genetic contribution to age at menopause, and overall senescence rates may be overpowered by ecological and environmental factors and so must be considered in relation to other exogenous factors. Despite the low contribution genetic variation makes, these studies indicate that processes of non-communicable diseases and ovarian ageing are underpinned by similar metabolic and inflammatory processes.

## *Ecological factors*

Rates of age-related health decline are in part mediated by an individual's ability to accrue somatic capital – a factor dependent on environmental constraints on energy available for their growth and development. Somatic capital can be understood as the energetic investments made by the body in growth and maintenance of tissue beds and organs [63] which will depreciate over time through wear and tear. As the body's ability to maintain cellular and tissue function decreases over time, mechanisms in the ageing body must rely on their existing somatic capital to ensure optimal function is maintained. Somatic capital accrual can be influenced by the life history strategy of the individual. Life history theory [64, 65] broadly describes patterns of growth, reproduction and mortality in an individual's life and in a given environment. One particularly influential concept in life-history evolution is that of the "fast-slow continuum", which accounts for the fact that many life-history traits co-vary across and within species [66]. Age at menopause may therefore be understood as an outcome of a life-history strategy, itself contingent on the somatic capital of the female reproductive system, determined by ecological factors (e.g. food availability, stress, pathogen load). Using a life history theory approach allows investigating whether variation in age at menopause reflects overall rates of ageing in the body or is specific to reproductive senescence.

*Extrinsic mortality*

Life history theory posits that in environments with high extrinsic mortality (i.e. mortality independent of an individual's phenotype), metabolic investment in reproduction is prioritized at the expense of other fitness components (somatic maintenance, growth) [66]. This leads to the acceleration of an organism's life-history (hence a "fast life-history" strategy) [67-69] and is hypothesised to affect rates of ageing and development of age-related diseases. In humans, age at first birth in England is younger in deprived areas compared to more affluent areas, suggested to be a response to the ecological context of poverty [69], with girls from moderately stressful environments of nutritional inadequacy experiencing accelerated pubertal timing [70]. In turn, low embodied capital of the reproductive system may cause sub-optimal tissue defence [71] against the oxidative stress of menstruation and reproduction, increasing rates of follicular atresia. This may ultimately accelerate reproductive ageing towards menopause. In comparison, those living in energy rich, low mortality environments may accrue higher somatic capital due to a slower life history strategy [70]. Higher socio-economic living conditions may therefore be associated with later age at menopause given the prolonged ability for tissue maintenance in those with higher somatic capital.

This predictive framework is in line with trends in epidemiological studies where earlier age at menopause is found amongst low/middle-income populations, as well as amongst those who were exposed to poor environmental conditions earlier in life [16, 17, 19-21]. Furthermore, in Western populations earlier age at menopause has been associated with increased risk of cardio-vascular diseases (CVD), atherosclerosis, stroke and osteoporosis [21, 72] while later menopause being associated with a reduced risk of CVD and all-cause mortality, but increased risk of breast and ovarian cancer, and osteoporosis [21, 24, 72, 73]. Finally, studies into oestrogen-receptor negative breast cancer rates suggest that a fast life history strategy may result in higher incidence of breast cancer amongst women from lower socioeconomic status [68].

*Infectious diseases*

Additional metabolic trade-offs between growth, maintenance and reproduction can occur in the presence of infectious disease where energy is allocated to the immune system at the expense of other bodily functions [64]. Sievert has previously explored the relationship between age at menopause and exposure to infectious diseases over the life course amongst Bangladeshi women living in London. They were found to have a significantly earlier age at menopause than other women living in London, with earlier age being strongly associated with a history of infectious disease exposure on multiple occasions [47]. As immune defences against pathogens is energetically costly, pathogen load may also contribute towards reducing bodily investment in the growth and maintenance of the body. Studies researching the effect of prolonged infection on age at menopause show a younger age at menopause amongst women with HIV compared to women without HIV [74] in the Bronx, although this result is not entirely consistent [75]. There is potential for expanding research into the influence of infectious diseases on age at menopause by studying the impact of infections earlier versus later in life; population level patterns where malaria is endemic; and immunocompromised populations.

*Cyclical Life History*

Further ecological influence over age at menopause may occur through factors mediating the number of menstrual cycles a female will experience throughout her lifetime. Reproduction in human females is characterised by cyclical fertility, with menstrual cycles completed approximately between 24 and 38 days [53], with the end of non-conceptive cycles characterized by menstruation. As mentioned, ovulation and menstruation are also significant inflammatory events, occurring monthly in the female reproductive organs. Localised inflammation in the ovaries occurs during the inflammation-mediated repair of the corpus luteum immediately after ovulation [53]. Furthermore, the ovaries are the site of oestrogen production – hormones which can act as pro-inflammatory, depending on dose. As this cyclical inflammation is beneficial to reproduction during the menstrual cycle, conferring fitness benefits earlier in life, more frequent cyclical ovulation within humans might directly influence the onset of menopause through the antagonistic pleiotropic effects of cyclical inflammation.

This cyclical, systematic inflammation may contribute towards damage of the granulosa cells and ovarian microenvironment, resulting primarily in the accelerated senescence of the female reproductive function relative to other organs of the body. We therefore suggest that variation in rates of ovarian ageing may result from the exposure of the female reproductive system to this cyclical inflammation. The number of menstrual cycles a woman experiences – and thus her cumulative exposure to cyclical inflammation – is mediated by many factors. Proximate determinants influencing the number of menstrual cycles in contemporary females include age at menarche, parity, breastfeeding and use of hormonal contraception. The evolutionary medicine literature already considers high cumulative levels of oestrogen exposure as a risk factor for the development of oestrogen receptor positive breast, ovarian and endometrial cancers [5, 76, 77]. Given tumorigenesis also operates through cellular damage and mutations, it is not implausible to consider the effect of concentrated cumulative oestrogen exposure on cellular senescence of the reproductive organs.

To consider the impact of cumulative exposure to ovulation and oestrogen as mediated by the menstrual cycle expands the possibility that ovarian ageing rates may vary according to total number of menstrual cycles experienced in a female's reproductive lifespan. Preliminary epidemiological data supports this claim, with nulliparity (as a discrete entity), being significantly associated with earlier ages of menopause [15, 17]. Normally cycling nulliparous women who are not taking any form of hormonal contraception do not experience the gaps in ovulation that occur during the gestation period and breastfeeding. To expand this research, we suggest that the female reproductive life history should be considered in its entirety – e.g. as total number of menstrual cycles experienced - rather than as a composite of discrete entities (e.g. age at menarche, parity, breastfeeding and use of hormonal contraception) as it is often approached within epidemiological studies. Extending theories of the impact of cumulative menstrual cycles to understanding diversity in the onset of menopause, and viewing the female reproductive system in its totality through cumulative number of menstrual cycles, may prove to be a promising avenue of research into variation into menopausal age. It is worth noting that evolutionary theories often investigate the trade-off between somatic longevity and reproductive success (see [78]). However, this trade-off becomes nuanced when considering the impact of reproductive life history on reproductive longevity. As mentioned previously, the processes of reproductive and somatic ageing are physiologically similar. Thus, reproductive life history becomes implicated in both reproductive and somatic longevity.

In this section, we have only explored possible evolutionary ecological determinants of variation in relation to age at menopause, and there is little to no mention of other facets of the menopause experience. This is mostly due to the limitation of research into other facets of menopause in both public health and evolutionary anthropology. However, there is potential for application of evolutionary ecological theory (and not exclusively those involved with ageing) into these other facets, including duration of the peri-menopausal period, patterns of menstrual cycling during the peri-menopausal period, incidence of menopausal symptoms and variation of symptoms experienced during menopause.

# 4. Implications for Public Health

As ageing populations are perceived to present challenges to the maintenance of population health, healthcare provision, demographic structure and society, there is increasing importance placed on research aiming to understand and predict patterns of ageing [79]. However, current public health approaches towards understanding diversity in the experience of menopause (age and symptoms) and its impact on health and overall wellbeing are scarce. Here we show that an ecological approach to variation in menopause might help with (1) nuancing assumptions about the 'normal' menopause, (2) understanding the relationship between menopause and health decline, (3) interrogating whether earlier menopause and diseases of old age originate from the same ecological determinants of health and (4) how understanding variation in menopause experience can benefit wider studies into successful ageing.

*Stimulating public health research into the diversity of menopausal experience*

Despite a substantial focus within public health on ageing [80], menopause as a facet of the female ageing experience is often excluded from research questions into ageing and subsequent public health interventions (e.g. breast cancer screening). For instance, out of the 15 ageing cohort studies found on the Gateway to Global Ageing Data [79], a harmonised dataset aiming at providing resources to support cross-national research on ageing, only 5 studies collected any form of data on menopause from their female participants. The questions and cohort studies which did include menopause-related variables are found in Table 1. The observation that menopause is excluded from ageing cohort studies, which premise themselves on collecting data on the multifactorial nature of the ageing experience, reveals the absence of menopause from public health discourses of ageing, which suggests that its impact on the ageing experience is neglected. Any relationships existing between menopause and health are unable to be identified, allowing prevalent biomedical assumptions to prevail. Ignorance of menopause as a facet of female ageing creates a measurement trap, in which lack of information is both the cause and the effect of continuing exclusion [81].

| Cohort | Region | Years | Variables |
|---|---|---|---|
| **TILDA** | Ireland | Pilot | • gone through menopause;<br>• age menopause started;<br>taken prescription hormones;<br>• number of years taking hormones;<br>• number of years took prescription hormones |
| | | 2010 | |
| | | 2012 | |
| **NICOLA** | Northern Ireland | 2015 | • gone through menopause;<br>• age menopause started;<br>• used prescription hormones;<br>• number of years taking hormones;<br>• number of years took hormones |
| | | 2017 | • used hormones since menopause;<br>• still using/stopped using hormones;<br>• number of years taking hormones;<br>• number of years took hormones |
| **HRS** | USA | 2008 | • current stage of menopause;<br>• how old when finished menopause (>40, >45, >55) |
| | | 2010 | |
| | | 2012 | |
| | | 2014 | |
| | | 2016 | • current stage of menopause;<br>• how old when finished menopause;<br>• year finished menopause |
| **CHARLS** | China | 2011 | • Age at menarche;<br>• has menopause started |
| | | 2013 | |
| | | 2015 | • age at menarche;<br>• has menopause started;<br>• age at menopause |
| **CRELES** | Costa Rica | 2005 | • age at menarche;<br>• age at last menstruation;<br>• ever used HRT to treat menopause for 3+ years |
| | | 2010 | |

**Table 1. Menopause-related variables in the Gateway to Global Aging Data, produced by the USC Program on Global Aging**, Health & Policy, with funding from the National Institute on Aging.

Since the 90s, several longitudinal studies have been started, many with the specific aim of understanding the impact of HRT usage on later life health among post-menopausal women such as The Women's Health Initiative (WHI, [82, 83]) and Million Women Study (MWS,[84]). Study of Women's Health Across the Nation (SWAN) and the International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events (InterLACE) are currently collecting and synthetizing health data on peri- and post-menopausal women. Inclusion of questions around the menopausal experience in ageing cohort studies, and expansion of menopause-related research questions beyond HRT and later-life health outcomes will help to corroborate the data collected by SWAN and InterLACE, and improve the robustness of research into menopause.

*Reframing the menopausal transition as normal*

Understanding menopausal variation can help alleviate the assumptions still present within the biomedical approaches of menopause. Biomedical perspectives of menopause were for most of the 20th century predicated on the assumption that menopause and the oestrogen-deficient body were inherently "risky" [30, 85], with this risk to be countered through the prescription of hormone replacement therapy during the post-menopausal life stage [85]. While the WHI and MWS revealed the health risks associated with indiscriminate long-term prescription of HRT (to the extent that the experimental studies had to be prematurely ended [83]), assumptions surrounding the causality of post-menopausal health issues as well as a lack of recognition of menopause experience variation may arguably still persist within Western biomedicine and public health.

Further, public health research into menopause variation can primarily help nuance the designation of the menopausal transition as 'normal' or 'pathological'. Current UK guidelines state that any woman entering menopause at age <40 are experiencing premature ovarian insufficiency while those entering menopause at age <45 are experiencing early menopause [1] . As there is little consensus on hormonal diagnosis of ovarian ageing, and given that variation in age at menopause exists within and between populations, normal 'earlier' menopause in some women may be accidentally pathologised, while abnormal but 'later' menopause may remain undiagnosed in others. Current biomedical understandings of 'normal' menopause are predicated on normative views of how a 'normal' body should behave [86]. Gathering data to explore the true variation of menopausal age within and between populations will allow this assumption to be challenged.

*Rethinking menopause as the by-product rather than the catalyst of biological ageing*

Age at menopause is associated with varying health outcomes, with earlier age at menopause being generally associated with increasing risk of all-cause mortality [21, 72]. Thus, age at menopause is often used to identify at-risk groups of older women, who could then be targeted with preventative screening programmes and treatment against associated diseases such as cancers, CVD and osteoporosis prior to any manifestation of disease. However, risk factors for health and disease that accelerate biological ageing may also contribute to earlier age at menopause rather than menopause itself being the catalyst for biological ageing [87]. For instance, menopause has been associated with epigenetic processes linked to cellular senescence and ageing when epigenetic biomarkers of methylation are compared to chronological age [87] (USA & European populations, n=3110). The epigenetic age at blood was found to have a negative correlation with age at menopause, which supports observational studies that found that for every one year increase in age at menopause, the age-adjusted mortality rate decreases by 2% [87]. In this study, there is a suggestion of directionality, with post-menopausal women who had late onset of menopause found to be epigenetically younger than women with early onset menopause. Thus, risk factors for health and disease that accelerate biological ageing may also contribute to earlier age at menopause rather than menopause itself being the catalyst for biological ageing [87]. Such research nuances prevailing assumptions around menopause being the cause or catalyst of poor health and disease in later life.

Contrasting with contemporary biomedical perspectives, an ecological approach to understanding diversity in the onset of menopause may show that correlations between earlier menopause and diseases of old age originate from the same life history determinants of health, encompassing somatic capital and life history strategies and the wider socio-cultural determinants of health. Such studies would fall into the emergent discipline of evolutionary public health [88], where both proximate and ultimate explanations into patterns of population health and disease are considered within the theoretical framework [88]. An understanding of how ecological and evolutionary contexts throughout life can help explain patterns of health in older age within and between socioeconomic strata due to developmentally and environmentally determined patterns of energy allocation [88]. Evolutionary public health allows the integration of menopause within overarching understandings of ageing and senescence in life history as well as its inclusion in public health data collection and approaches to ageing. This is not to say that menopause has no adverse impact on the health of ageing females, but its insertion into large-scale health data collection would allow any risk factors emerging from menopause to be identified and nuanced, combating the pathologisation of menopause as a whole.

Aside from evolutionary ecological approaches towards menopause, there is also scope for integrating menopause into the wider evolutionary medicine paradigm. Reconceptualising health, from an evolutionary perspective, as a means to an end of reproductive success [88] requires the recognition that reproductive function is intrinsically intertwined with ‘non-reproductive’ health. The peri- and post-menopausal body can be reconceptualised as the female body with minimal interaction between the reproductive system and other bodily systems. In doing so, there is incentive to study how the dysregulation and cessation of the menstrual cycle may impacts the immune system (for review see [53]), or the aetiologies of non-communicable diseases.

*Diversity in menopausal experience and the capacity for successful ageing*

While the study of variation may be useful in understanding disease risk, it may be equally important to consider how and why variation in age and experience affects an individual’s capacity for “successful” ageing [89]. There is an increasing awareness of “successful ageing” in Public Health and gerontology, which encompasses the social, cultural and psychological impact of growing older beyond the increasing health risks. In this view, the ageing experience is expanded beyond the disease risk and frailty to include facets of the ageing experience that are more important to the individual [89]. Therefore, approaches to menopause as a component of female ageing should also be expanded beyond focusing on health risks.

Facets of the menopausal experience and wider female ageing are already being studied and could benefit from taking the existence of variation into account. This includes areas such as menopause in the workplace [90]; grandmothering, its impact on familial health and how menopause may affect the ability to alloparent [91]; female personhood during the life course [92]; menopause and sexuality; and more critical medical anthropological perspectives on menopause, biopower and pharmaceutical intervention [85, 93]. Expanding focus onto how diversity in the experience of menopause impacts the wider social and cultural experience of growing older will improve the robustness of public health perspectives on women's ageing, closer to actual lived experience.

# Conclusion

The goal of this paper is to stimulate an interdisciplinary, multi-level framework for understanding the role of evolutionary and ecological factors in shaping patterns of menopausal experience diversity. By engaging with the definitions of menopause across disciplines, we can ensure that proximate and ultimate approaches to menopause are addressing the same phenomenon, i.e. the cessation of menstrual cycles, rather than broader features of the post-fertile lifespan. We have shown the compatibility of biomedical, physiological understandings of ovarian ageing with evolutionary theories viewing the emergence of menopause as a by-product of recent increases in longevity (e.g. the reproductive-somatic mismatch hypothesis [94]). This suggests that evolutionary hypotheses usually applied to somatic senescence (e.g. the Disposable Soma hypothesis, the antagonistic pleiotropy hypothesis, the embodied-capital theory) may also become fruitful for understanding patterns of diversity in menopausal traits.

A consistent theme throughout this paper has been to highlight potential areas where menopause research is lacking, and which can be expanded both in the medical sciences and in human ecological studies. We also suggest potential implications for approaches towards ageing women's health in public health and the wider medical sciences. Within public health, we suggest that menopause is currently excluded from public health approaches to ageing and that its continued exclusion cannot be justified. Not only should menopause be measured in ageing cohort studies, but its measurement should be done with the methodological considerations outlined earlier in mind. We also posit that recognition of variation in menopause may help nuance assumptions surrounding normalcy and the menopause, and the clinical cut-offs made between 'normal' and 'abnormal' menopause. We further recognise that through the application of evolutionary theories of ageing towards menopause variation there is an opportunity to reconceptualise menopause as a process of ageing, rather than its cause. This might stimulate novel research questions into which processes underlay both reproductive and overall senescence. This also stands in contrast to the social construction of menopause as a pathology within western biomedicine, and reaffirms the menopausal transition as normal, rather than inherently pathological.

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## Author Contributions

AF wrote article, with editing, feedback and guidance from AA, EW and CJ

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## Conflict of interest.

None.

## Data availability.

Data used to produce Figure 2 is available in Supplementary Information.

# References


1. NCC-WCH, *Menopause: Full Guideline*. 2015, NICE.
2. Laisk, T., et al., *Demographic and evolutionary trends in ovarian function and aging.* Human reproduction update, 2018.
3. Sievert, L.L., *Menopause: A Biocultural Perspective*. 2006: Rutgers University Press.
4. Monteleone, P., et al., *Symptoms of menopause - global prevalence, physiology and implications.* Nat Rev Endocrinol, 2018. **14**(4): p. 199-215.
5. Jasienska, G., et al., *Human reproduction and health: an evolutionary perspective.* The Lancet, 2017. **390**(10093): p. 510.
6. Hillard, T., et al., *Management of the Menopause (6th edition)*. Post Reproductive Health. Vol. 23. 2017. 180.
7. Narkwichean, A., et al., *Efficacy of Dehydroepiandrosterone (DHEA) to overcome the effect of ovarian ageing (DITTO): A proof of principle double blinded randomized placebo controlled trial.* European Journal of Obstetrics & Gynecology and Reproductive Biology, 2017. **218**: p. 39-48.
8. May-Panloup, P., et al., *Ovarian ageing: the role of mitochondria in oocytes and follicles.* Human Reproduction Update, 2016. **22**(6): p. 725-743.
9. Luderer, U., *Oxidative Stress Is a Driver of Normal and Pathological Ovarian Aging*, in *Inflammation, Aging, and Oxidative Stress*, S.C. Bondy and A. Campbell, Editors. 2016. p. 213-237.
10. Tatone, C. and F. Amicarelli, *The aging ovary-the poor granulosa cells.* Fertility and Sterility, 2013. **99**(1): p. 12-17.
11. Cant, M.A., R.A. Johnstone, and A.F. Russell, *Reproductive conflict and the evolution of menopause*, in *Reproductive Skew in Vertebrates: Proximate and Ultimate Causes*. 2009. p. 24-50.
12. Levitis, D.A., O. Burger, and L.B. Lackey, *The human post-fertile lifespan in comparative evolutionary context.* Evolutionary Anthropology, 2013. **22**(2): p. 66-79.
13. Mattison, S., et al., *Evolutionary demography of age at last birth: integrating approaches from human behavioural ecology and cultural evolution.* Philosophical Transactions of the Royal Society B-Biological Sciences, 2018. **373**(1743).
14. Rodstrom, K., et al., *Evidence for a secular trend in menopausal age: a population study of women in Gothenburg.* Menopause, 2003. **10**(6): p. 538-43.
15. Mishra, G.D., et al., *Early menarche, nulliparity and the risk for premature and early natural menopause.* Human Reproduction, 2017. **32**(3): p. 679-686.
16. Ruth, K.S., et al., *Events in Early Life are Associated with Female Reproductive Ageing: A UK Biobank Study.* Scientific reports, 2016. **6**(1): p. 24710.
17. Duarte, E., et al., *Structured additive regression modeling of age of menarche and menopause in a breast cancer screening program.* Biometrical Journal, 2014. **56**(3): p. 416-27.
18. Gold, E.B., et al., *Factors associated with age at natural menopause in a multiethnic sample of midlife women.* American Journal of Epidemiology, 2001. **153**(9): p. 865-874.
19. Mishra, G., R. Hardy, and D. Kuh, *Are the effects of risk factors for timing of menopause modified by age? Results from a British birth cohort study.* Menopause, 2007. **14**(4): p. 717-724.
20. Hardy, R. and D. Kuh, *Social and environmental conditions across the life course and age at menopause in a British birth cohort study.* Bjog-an International Journal of Obstetrics and Gynaecology, 2005. **112**(3): p. 346-354.
21. Schoenaker, D., et al., *Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and meta-analyses of studies across six continents.* International Journal of Epidemiology, 2014. **43**(5): p. 1542-1562.
22. Hardy, R. and D. Kuh, *Does early growth influence timing of the menopause? Evidence from a British birth cohort.* Human Reproduction, 2002. **17**(9): p. 2474-2479.
23. Gold, E.B., et al., *Factors Related to Age at Natural Menopause: Longitudinal Analyses From SWAN.* American Journal of Epidemiology, 2013. **178**(1): p. 70-83.
24. Henderson, K.D., et al., *Predictors of the timing of natural menopause in the multiethnic cohort study.* American Journal of Epidemiology, 2008. **167**(11): p. 1287-1294.
25. Harlow, S.D. and P. Paramsothy, *Menstruation and the Menopausal Transition.* Obstetrics and Gynecology Clinics of North America, 2011. **38**(3): p. 595-607.
26. FSRH, *FSRH Clinical Guideline: Contraception for Women Aged over 40 years*, in *Current Clinical Guidance*. 2017, Faculty of Sexual and Reproductive Healthcare.

27. Currie, H., *The perimenopause: presentation and management*, in *Women's Health Concern Annual Symposium 2019*. 2019: Marylebone, London.
28. de Kat, A.C., et al., *Unraveling the associations of age and menopause with cardiovascular risk factors in a large population-based study.[Erratum appears in BMC Med. 2017 Mar 29;15(1):74; PMID: 28356103].* BMC Medicine, 2017. **15**(1): p. 2.
29. Lock, M. and P. Kaufert, *Menopause, local biologies, and cultures of aging.* American Journal of Human Biology, 2001. **13**(4): p. 494-504.
30. Lock, M.M., *Encounters with aging : mythologies of menopause in Japan and North America*. 1993, Berkeley ; London: University of California Press.
31. Sievert, L.L., *Menopause across cultures: clinical considerations.* Menopause-the Journal of the North American Menopause Society, 2014. **21**(4): p. 421-423.
32. Sturdee, D.W., et al., *The menopausal hot flush: a review.* Climacteric, 2017. **20**(4): p. 296-305.
33. Williams, G.C., *Pleiotropy, Natural Selection, and the Evolution of Senescence.* Evolution, 1957. **11**(4): p. 398.
34. Hawkes, K., et al., *Grandmothering, menopause, and the evolution of human life histories.* Proceedings of the National Academy of Sciences of the United States of America, 1998. **95**(3): p. 1336-1339.
35. Peccei, J.S., *Menopause: Adaptation or epiphenomenon?* Evolutionary Anthropology: Issues, News, and Reviews, 2001. **10**(2): p. 43-57.
36. Ellison, P.T., *Reproductive ecology and human evolution*. 2001, New York: Aldine Transaction.
37. Packer, C., *The ecology of menopause.* Sex and Longevity: Sexuality, Gender, Reproduction, Parenthood, 2001: p. 91-101.
38. Cant, M.A. and R.A. Johnstone, *Reproductive conflict and the separation of reproductive generations in humans.* Proceedings of the National Academy of Sciences, 2008. **105**(14): p. 5332.
39. Kirkwood, T.B. and D.P. Shanley, *The connections between general and reproductive senescence and the evolutionary basis of menopause.* Annals of the New York Academy of Sciences, 2010. **1204**: p. 21-9.
40. Hawkes, K. and J.E. Coxworth, *Grandmothers and the evolution of human longevity: a review of findings and future directions.* Evolutionary anthropology, 2013. **22**(6): p. 294-302.
41. Galbarczyk, A. and G. Jasienska, *Timing of natural menopause covaries with timing of birth of a first daughter: Evidence for a mother-daughter evolutionary contract?* Homo-Journal of Comparative Human Biology, 2013. **64**(3): p. 228-232.
42. Croft, D.P., et al., *Reproductive Conflict and the Evolution of Menopause in Killer Whales.* Curr Biol, 2017. **27**(2): p. 298-304.
43. Towner, M.C., I. Nenko, and S.E. Walton, *Why do women stop reproducing before menopause? A life-history approach to age at last birth.* Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences, 2016. **371**(1692): p. 20150147.
44. Bongaarts, J., *A Framework for Analyzing the Proximate Determinants of Fertility.* Population and Development Review, 1978. **4**(1): p. 105-132.
45. Skjaervo, G.R. and E. Roskaft, *Menopause: No support for an evolutionary explanation among historical Norwegians.* Experimental Gerontology, 2013. **48**(4): p. 408-413.
46. Cant, M.A. and D.P. Croft, Current Biology, 2019. **29**(6): p. R215-R218.
47. Sievert, L.L., *Anthropology and the study of menopause: evolutionary, developmental, and comparative perspectives.* Menopause-the Journal of the North American Menopause Society, 2014. **21**(10): p. 1151-1159.
48. Takahashi, M., R.S. Singh, and J. Stone, *A Theory for the Origin of Human Menopause.* Frontiers in Genetics, 2017. **7**.
49. Wang, T.R., et al., *Mitochondrial dysfunction and ovarian aging.* American Journal of Reproductive Immunology, 2017. **77**(5).
50. Banerjee, S., et al., *Female Reproductive Aging Is Master-Planned at the Level of Ovary.* Plos One, 2014. **9**(5).
51. Zhang, J.J., et al., *Are sirtuins markers of ovarian aging?* Gene, 2016. **575**(2): p. 680-686.
52. Leidy, L.E., L.R. Godfrey, and M.R. Sutherland, *Is follicular atresia biphasic?* Fertility and Sterility, 1998. **70**(5): p. 851-859.
53. Alvergne, A. and V. Högqvist Tabor, *Is Female Health Cyclical? Evolutionary Perspectives on Menstruation.* Trends in Ecology & Evolution, 2018. **33**(6): p. 399.
54. Franceschi, C. and J. Campisi, *Chronic Inflammation ( Inflammaging) and Its Potential Contribution to Age-Associated Diseases.* Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 2014. **69**: p. S4.

55. Kirkwood, T.B.L., *Time of our lives : the science of human ageing*. 1999, London: Weidenfeld & Nicolson.
56. Giuliani, C., P. Garagnani, and C. Franceschi, *Genetics of Human Longevity Within an Eco-Evolutionary Nature-Nurture Framework.* Circulation Research, 2018. **123**(7): p. 745-772.
57. Meng, F.T., et al., *ApoE genotypes are associated with age at natural menopause in Chinese females.* Age, 2012. **34**(4): p. 1023-1032.
58. Koochmeshgi, J., et al., *Apolipoprotein E genotype and age at menopause.* Ann N Y Acad Sci, 2004. **1019**: p. 564-7.
59. Tempfer, C.B., et al., *Polymorphisms associated with thrombophilia and vascular homeostasis and the timing of menarche and menopause in 728 white women.* Menopause, 2005. **12**(3): p. 325-30.
60. May-Panloup, P., et al., *Mitochondrial macro-haplogroup JT may play a protective role in ovarian ageing.* Mitochondrion, 2014. **18**: p. 1-6.
61. Stolk, L., et al., *Meta-analyses identify 13 loci associated with age at menopause and highlight DNA repair and immune pathways.* Nature Genetics, 2012. **44**(3): p. 260-U55.
62. Lin, W.N., et al., *Ovarian Aging in Women With BRCA Germline Mutations.* Journal of Clinical Endocrinology & Metabolism, 2017. **102**(10): p. 3839-3847.
63. Kaplan, H., J. Lancaster, and A. Robson, *Embodied capital and the evolutionary economics of the human life span.* Population And Development Review, 2003. **29**: p. 152.
64. Ellison, P.T., *Energetics and reproductive effort.* American Journal of Human Biology, 2003. **15**(3): p. 342.
65. Gluckman, P.D., A. Beedle, and M.A. Hanson, *Principles of evolutionary medicine*. 2009, Oxford: Oxford University Press.
66. Stearns, S.C., *The evolution of life histories*. 1992, Oxford ; New York: Oxford University Press. xii, 249 p.
67. Stearns, S.C., et al., *Experimental evolution of aging, growth, and reproduction in fruitflies.* Proceedings of the National Academy of Sciences of the United States of America, 2000. **97**(7): p. 3309.
68. Hidaka, B.H. and A.M. Boddy, *Is estrogen receptor negative breast cancer risk associated with a fast life history strategy?* Evolution, medicine, and public health, 2016. **2016**(1): p. 17.
69. Nettle, D., *Dying young and living fast: Variation in life history across English neighborhoods.* Behavioral Ecology, 2010. **21**(2): p. 387.
70. Ellis, B.J., *Timing of pubertal maturation in girls: An integrated life history approach.* Psychological Bulletin, 2004. **130**(6): p. 920-958.
71. Noguera, J., *Interacting effects of early dietary conditions and reproductive effort on the oxidative costs of reproduction.* PeerJ, 2017. **5**(3).
72. Forman, M.R., et al., *Life-course origins of the ages at menarche and menopause.* Adolescent health, medicine and therapeutics, 2013. **4**: p. 1-21.
73. Ossewaarde, M.E., et al., *Age at menopause, cause-specific mortality and total life expectancy.* Epidemiology, 2005. **16**(4): p. 556-562.
74. Schoenbaum, E.E., et al., *HIV infection, drug use, and onset of natural menopause.* Clinical Infectious Diseases, 2005. **41**(10): p. 1517-1524.
75. Conde, D.M., A.M. Pinto-Neto, and L. Costa-Paiva, *Age at menopause of HIV-infected women: A review.* Gynecological Endocrinology, 2008. **24**(2): p. 84-86.
76. Aktipis, C.A., et al., *Modern reproductive patterns associated with estrogen receptor positive but not negative breast cancer susceptibility.* Evolution, Medicine, and Public Health, 2014. **2015**(1): p. 52.
77. Jasienska, G., et al., *The Arc of Life Evolution and Health Across the Life Course*. 2017. p. VIII, 200 p. 32 illus., 9 illus. in color.
78. Kirkwood, T.B.L. and R.G.J. Westendorp, *Human longevity at the cost of reproductive success: Trade-offs in the life history.* Sex and Longevity: Sexuality, Gender, Reproduction, Parenthood, 2001: p. 1-6.
79. USC programme on Global Ageing, H. and Policy. *Gateway to Global Aging Data, Produced by the USC Program on Global Aging, Health & Policy, with funding from the National Institute on Aging*. 2018 [cited 2018 June]; Available from: https://g2aging.org/?
80. Beard, J.R. and D.E. Bloom, *Towards a comprehensive public health response to population ageing.* The Lancet, 2015. **385**(9968): p. 658.
81. Graham, W.J., *Outcomes and effectiveness in reproductive health.* Social science & medicine, 1998. **47**(12): p. 1925.

82. Rossouw, J.E., G. Anderson, and A. Oberman, *The Women's Health Initiative baseline summary—foreword*. Vol. 13. 2003. S1-S4.
83. Nabel, E.G., *The Women's Health Initiative—A Victory for Women and Their Health.* Jama, 2013. **310**(13): p. 1349.
84. The Million Women Study Collaborative, G., *The Million Women Study: design and characteristics of the study population.* Breast Cancer Research, 1999. **1**(1): p. 73-80.
85. Harding, J., *Bodies at risk: Sex, surveillance and hormone replacement therapy*, in *Foucault, health and medicine*, A.R. Petersen and R. Bunton, Editors. 1997, Routledge: London.
86. Wiley, A.S. and J.M. Cullin, *Biological normalcy.* Evolution, medicine, and public health, 2020. **2020**(1): p. 1-1.
87. Levine, M.E., et al., *Menopause accelerates biological aging.* Proceedings of the National Academy of Sciences of the United States of America, 2016. **113**(33): p. 9327-9332.
88. Wells, J.C.K., et al., *Evolutionary public health: introducing the concept.* The Lancet, 2017. **390**(10093): p. 500.
89. Rowe, J.W. and R.L. Kahn, *Successful Aging 2.0: Conceptual Expansions for the 21st Century.* J Gerontol B Psychol Sci Soc Sci, 2015. **70**(4): p. 593-6.
90. Hardy, C., *Menopause in the workplace: what to consider*, B.M.S. Bms, Editor. 2019.
91. Sear, R., *Beyond the nuclear family: an evolutionary perspective on parenting.* Current Opinion in Psychology, 2016. **7**: p. 98-103.
92. Pickard, S., *From the third age to the third sex: A feminist framework for the life course.* J Aging Stud, 2019. **49**: p. 56-65.
93. Padamsee, T.J., *The pharmaceutical corporation and the 'good work' of managing women's bodies.* Social Science & Medicine, 2011. **72**(8): p. 1342-1350.
94. Cohen, A.A., *Female post-reproductive lifespan: a general mammalian trait.* Biological Reviews, 2004. **79**(4): p. 733-750.
95. Hammond, E.R., et al., *Oocyte mitochondrial deletions and heteroplasmy in a bovine model of ageing and ovarian stimulation.* Molecular Human Reproduction, 2016. **22**(4): p. 261-271.
96. Zhang, D.D., et al., *Increased DNA damage and repair deficiency in granulosa cells are associated with ovarian aging in rhesus monkey.* Journal of Assisted Reproduction and Genetics, 2015. **32**(7): p. 1069-1078.
97. Tamura, H., et al., *Long-term melatonin treatment delays ovarian aging.* Journal of Pineal Research, 2017. **62**(2).
98. Boucret, L., et al., *Deep sequencing shows that oocytes are not prone to accumulate mtDNA heteroplasmic mutations during ovarian ageing.* Human Reproduction, 2017. **32**(10): p. 2101-2109.