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EMAS position statement: Predictors of premature and early natural menopause



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ABSTRACT

Introduction: While the associations of genetic, reproductive and environmental factors with the timing of natural menopause have been extensively investigated, few epidemiological studies have specifically examined their association with premature (< 40 years) or early natural menopause (40–45 years).

Aim: The aim of this position statement is to provide evidence on the predictors of premature and early natural menopause, as well as recommendations for the management of premature and early menopause and future research.

Materials and methods: Literature review and consensus of expert opinion.

Results and conclusions: Strong genetic predictors of premature and early menopause include a family history of premature or early menopause, being a child of a multiple pregnancy and some specific genetic variants. Women with early menarche and nulliparity or low parity are also at a higher risk of experiencing premature or early menopause. Cigarette smoking (with a strong dose–response effect) and being underweight have been consistently associated with premature and early menopause. Current guidelines for the management of premature and early menopause mainly focus on early initiation of hormone therapy (HT) and continued treatment until the woman reaches the average age at menopause (50–52 years). We suggest that clinicians and health professionals consider the age at menopause of the relevant region or ethnic group as part of the assessment for the timing of HT cessation. In addition, there should be early monitoring of women with a family history of early menopause, who are a child of a multiple pregnancy, or who have had early menarche (especially those who have had no children). As part of preventive health strategies, women should be encouraged to quit smoking (preferably before the age of 30 years) and maintain optimal weight in order to reduce their risk of premature or early menopause.

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1. Introduction

Timing of menopause is an indicator of ovarian function and has important health implications. Natural menopause is commonly defined as the time when a woman has experienced 12 consecutive months of amenorrhoea without obvious cause [1], such as removal of both ovaries (bilateral oophorectomy), chemotherapy or radiotherapy for cancer. The International collaboration on the Life course Approach to reproductive health and Chronic disease Events (InterLACE) [2] recently reported that the average age at natural menopause across 21 studies from 10 countries ranged from 47 to 53 years, varying across ethnic groups from 48 years for women of South Asian background to 50 years for Caucasian women living in Australia and Europe, and 52 years for Japanese women [3]. These results are primarily obtained from women living in high-income countries, hence the average age at menopause for women in low- and middle-income countries may lie outside this range.

Menopause before the age of 40 is commonly referred to as *premature menopause*, although *primary ovarian insufficiency (POI)* is currently considered the most apposite term to denote the loss of ovarian function as it does not specify definitive failure [4]. Menopause that occurs between 40 and 45 years is termed *early menopause*. Data from the InterLACE consortium indicate that in the general female population of high-income countries, the prevalence of premature menopause is 2% (range 1–3%) and of early menopause is 7.6% (range 5–10%), suggesting that almost one in 10 women have premature or early menopause [5]. Recent reviews have concluded that premature or early menopause is associated with an increased risk of all-cause mortality, cardiovascular disease, type 2 diabetes, depression, osteoporosis and fracture [6–11]. There is some evidence that premature menopause is associated with greater than average cognitive decline in later life [12], but current studies do not support a consistent association between early menopause and dementia risk [13].

Premature menopause is often idiopathic, but there are some genetic and autoimmune links, with X chromosome defects being the most common genetic contributors [14]. Few epidemiological studies have specifically examined the associations of non-genetic factors with premature and early menopause [5,15,16]. This position statement highlights the genetic, reproductive, lifestyle, and early-life and social/environmental factors associated with premature and early natural menopause. As findings in relation to premature menopause are limited, we focus on early menopause but include evidence specific to premature menopause where it is available.

2. Risk factors for premature and early natural menopause

2.1. Genetic factors

2.1.1. Heritability

Heritability estimates of age at menopause in mothers, daughters and sisters provide evidence for the contribution of genetic factors to the timing of menopause. The Framingham Heart Study reported that the heritability estimate for the adjusted age at natural menopause for the pooled sample of original and offspring cohorts was 0.52 [17]. This suggests that genetic effects explain at least half of the inter-individual variation in age at natural menopause. Cross-national heritability estimates for age at menopause of twin sisters range from 0.31–0.53 in an Australian sample [18], 0.63 in a UK sample [19], to 0.71–0.72 in a Dutch sample [20]. Mother–daughter pair data from the Netherlands give a heritability estimate of 0.44 [21].

2.1.2. Family history

Since genetic factors explain a substantial proportion of the variability in age at natural menopause, family history may be an important predictor of age at menopause. Early menopause (≤ 45 years) in a mother, sister, aunt or grandmother was associated with six-fold

increased odds (OR 6.1, 95% CI 4.0–9.3) of early menopause after adjustment for smoking, education, parity and body mass index [22]. The risk of early menopause was strongest among women with a sister or multiple relatives with early menopause (9- to 12-fold increased odds) and those who had premature menopause (i.e. ≤ 40 years) (8-fold increased odds).

2.1.3. Multiple pregnancy

Twin registries in the UK and Australia indicate that twins have a significantly higher prevalence of POI than the general population, with a 3-fold and a 5-fold greater prevalence at the 40-year and 45-year thresholds [23]. Although the prevalence of POI in monozygotic (identical) and dizygotic (non-identical) twins was similar, ages at menopause were more concordant among monozygotic than among dizygotic twins. If one twin experienced menopause before age 40, her identical sister was almost seven times as likely to do so at the same age, confirming that the risk of POI has a strong heritable component. Findings from the UK Biobank have also shown that being a child of a multiple pregnancy was associated with a 50% increased likelihood of early menopause, after adjusting for early-life risk factors, including maternal smoking, birthweight, age at menarche, having breastfed as a baby and body composition at the age of 10 years [24].

It has been hypothesised that poor intrauterine growth, manifested as low birthweight, may lead to a decreased peak number of primordial follicles, which in turn may be associated with earlier menopause in adult life [25]. Foetal growth restriction, however, has not been found to restrict ovary growth and development [26]. Studies of twins have shown no significant association between difference in birthweight and difference in age at menopause in either monozygotic or dizygotic twin pairs [23,25]. Instead, there was some indication that twins with POI were heavier at birth than twins with normal or later age at menopause [25]. Further research is needed to explore the mechanisms underlying the higher risk of POI among twins.

2.1.4. Genetic variants

A recent meta-analysis of 22 genome-wide association studies (GWAS) with nearly 40,000 women of European ancestry confirmed the four previously established loci related to age at natural menopause, on chromosomes 5, 6, 19 and 20 [27,28], and identified 13 new loci [29]. Candidate genes located at or near identified loci include genes implicated in DNA repair (*EXO1*, *HELQ*, *UIMC1*, *FAM175A*, *FANCI*, *TLK1*, *POLG* and *PRIM1*), immune function (*IL11*, *NLRP11* and *PRRC2A*) and hormone regulation (*FSHB*, *STAR* and *BCAR4*) [29]. In addition, several genes (*WNT4*, *RSPO1*, *FOXL2* and *BRCA2*) critical for ovarian development and function have been identified [30,31], though further research is required to better understand their role in maintaining ovarian identity. However, previous GWAS excluded women with menopause before the age of 40 years [27,28]. The Breakthrough Generations Study (BGS) selected four common single-nucleotide polymorphisms (SNPs) at the four established loci and tested the associated risk of early menopause (≤ 45 years) [32]. All four SNPs were associated with an increased risk of early menopause (either including or excluding menopause before age 40), but the study was not sufficiently powered to detect the association with POI itself. The results suggest that genetic variants associated with the timing of menopause are also significant risk factors for early menopause [32]. Recent genetic studies have identified several genetic variants associated with POI, but results are conflicting [33,34] and many of these studies have methodological flaws and are underpowered [34].

2.2. Reproductive factors

2.2.1. Age at menarche

The timing of puberty has been linked to age at natural menopause. Findings from InterLACE with pooled data from over 50,000 post-menopausal women from nine studies in the UK, Scandinavia, Australia

and Japan have shown that women with early menarche (≤ 11 years) were at higher risk of premature menopause [relative risk (RR) 1.80, 95% confidence interval (CI) 1.53–2.12] and early menopause (RR 1.31, 95% CI 1.19–1.44), compared with those who had menarche at 13 years [5]. Data from the Nurses' Health Study II (NHS II) ($n = 108,811$) [35] and the China Kadoorie Biobank ($n = 17,076$) [36] also showed that early menarche was associated with premature and early menopause in American and Chinese women respectively, though the definition of early menarche was different (≤ 9 years versus 12 years in the NHS II, and ≤ 12 years versus 15 years in the China Biobank study). Furthermore, a case-control analysis of 11,781 cases of early menopause (< 45 years) and 173,641 controls (who had menopause or were still premenopausal at 45 years or over) in the UK Biobank identified an association between earlier age at menarche and early menopause [24].

2.2.2. Parity

Nulliparity has also been associated with earlier onset of natural menopause [37,38], while higher parity has been reported to be related to later age at menopause [39]. The InterLACE consortium used individual-level pooled data to show that nulliparity was associated with an increased risk of premature menopause (RR 2.26, 95% CI 1.84–2.77) and early menopause (RR 1.32, 95% CI 1.09–1.59) [5]. Furthermore, nulliparity strengthened the association between early menarche and the risk of premature and early menopause, with women who had early menarche and nulliparity having a 5-fold increased risk of premature menopause and a 2-fold risk of early menopause. Findings from the China Kadoorie Biobank also suggested that lower parity and older age at first birth were associated with early menopause [36].

On the other hand, premature or early menopause is an important indicator of ovarian hormone deficiency and infertility in young women [40,41]. Women with POI do not respond to traditional fertility treatments. Thus, their options for having children may be limited to adoption, donor embryo or egg donation with the use of *in vitro* fertilisation (IVF) [41]. However, up to 25% of women with POI may spontaneously ovulate, and they still have a 5–10% chance to conceive following diagnosis, and approximately 80% of the reported pregnancies have resulted in a healthy birth [42,43]. There is no secular trend of a decrease in age at menopause in recent decades, even though the average parity in developed countries has progressively dropped over this period [3]. Therefore, the potential confounding role of infertility or subfertility in the association between parity and age at menopause should be considered.

2.2.3. Characteristics of the menstrual cycle

Some evidence from a large prospective study has shown that length and regularity of early-life menstrual cycles may be early indicators of age at menopause. The NHS II study ($n = 108,811$) found that short menstrual cycles (< 25 days versus 26–31 days) and very regular cycles (± 3 days versus always irregular/no periods) at ages 18–22 years were strongly associated with a higher risk of early menopause (< 45 years) [35]. It also found that women with shorter and more regular cycles had lower levels of premenopausal anti-Müllerian hormone (AMH), a biomarker of ovarian reserve. The possible role of polycystic ovarian syndrome (PCOS) and the use of oral contraceptives (OC) might have confounded the findings. Assessment for PCOS and of OC use related to menstrual cycle irregularities should be considered for future studies [35].

2.3. Lifestyle factors

2.3.1. Cigarette smoking

Among the lifestyle factors studied, cigarette smoking has been the most consistently linked to earlier age at natural menopause [44–48]. A meta-analysis of 15 studies showed that smoking was associated with an almost one year earlier age at natural menopause [45]. Smoking is thought to have an anti-oestrogenic effect, in part due to the increased

production of adrenal androgens, which resists or blunts the functions of oestrogens [49,50]. Furthermore, cigarette smoking results in decreased oestrogenic efficacy, due to the fast hepatic clearance of oral oestrogens among smokers [51]. In other words, smoking can jeopardise the success of oral hormone therapy.

A pooled analysis of 17 studies from InterLACE ($n = 207,231$) found that current smokers were at twice the risk of premature menopause (< 40 years) and had an 80% increased risk of early menopause (40–44 years) compared with never smokers [15]. Even former smokers were at a higher risk of premature and early menopause, but to a much lesser extent, with risk increased by around 10–15%. This study found significant dose–response associations in both current and former smokers, in that higher intensity, longer duration, higher cumulative dose, earlier age of initiation and shorter time since quitting smoking were all associated with higher risks of premature and early menopause. Among these factors, the duration of smoking was the strongest predictor. Smokers who had quit for more than 10 years had a similar risk as never smokers, highlighting the clear benefits of early smoking cessation (preferably before the age of 30 years) for decreasing the risk of premature or early menopause [15].

2.3.2. Body mass index

Body size and fat distribution have been considered in relation to the timing of menopause. Higher peripheral production of oestrone in the adipose tissue of obese women is hypothesised to contribute to a later onset of menopause [52]. In addition, adipose tissue functions as a specialised endocrine and paracrine organ that produces an array of adipokines, including leptin. It is known that leptin can act centrally at the hypothalamus and pituitary and peripherally at the ovary and reproductive tract, and thereby contribute to maintaining normal reproductive function [53,54]. In contrast, being underweight may trigger early menopause as a result of malnutrition, over-exercising, weight-loss diet and having concurrent or a history of chronic illness (e.g. chronic obstructive pulmonary disease) [55–57]. In addition, less adipose tissue leads to lower leptin levels, which have been associated with early menopause (< 45 years) [58].

A meta-analysis of nine observational studies with a total of 313,482 women found that being underweight was associated with earlier age at menopause, whereas being overweight or obese was associated with later age at menopause [52]. Recently, two large prospective studies showed a J-shaped relationship between body mass index (BMI) and the risk of early menopause (< 45 years) [16,59]. A pooled analysis of 11 prospective studies from the InterLACE consortium ($n = 24,196$) found that underweight women had over twice the risk of early menopause, and the risk remained after adjusting for smoking status [16]. To minimise the influence of weight change during the menopausal transition, a sensitivity analysis was performed, examining the association for women who experienced onset of menopause at least five years after the collection of baseline BMI data. The associations of underweight and overweight/obesity with the risk of early menopause remained or even strengthened, suggesting that the effect of BMI may have been partly attenuated by baseline BMI recorded in the perimenopausal period [16]. The NHS II ($n = 78,759$) reported similar results, though the effect of being underweight on risk of early menopause was slightly attenuated and was not significant among non-smokers [59]. Furthermore, weight change between early and middle adulthood seemed to be associated with early menopause. Women who lost 20 or more pounds from age 18 to 35 had a higher risk of early menopause than women who gained 5.1–15 pounds, though after adjustment for reproductive factors the risk was attenuated and no longer significant [59].

2.4. Early-life and social/environmental factors

Table 1 gives an overview of the genetic, reproductive, lifestyle, and early-life and social/environmental risk factors for premature and early menopause. While evidence has shown that early-life circumstances

Table 1
Overview of the risk factors for premature and early menopause.

| Risk factors | Premature Menopause (POI) (< 40 years) | Early Menopause (40–45 years) |
|---|--|-------------------------------|
| Genetic factors | | |
| Family history of premature or early menopause | ↑ | ↑ |
| Being a child of a multiple pregnancy | ↑ | ↑ |
| Specific genetic variants | ↑ | ↑ |
| Reproductive factors | | |
| Early menarche | ↑ | ↑ |
| Nulliparity, low parity | ↑ | ↑ |
| Short and very regular menstrual cycle | . | ↑ |
| Lifestyle factors | | |
| Cigarette smoking | ↑ | ↑ |
| Underweight | ↑ | ↑ |
| Obesity | ↔ | ↔ |
| Early-life and social/environmental factors | | |
| High birthweight ^a | . | . |
| Poor childhood growth and early-life nutrition ^a | . | . |
| Low childhood socioeconomic status ^a | . | . |
| Poor childhood cognitive function ^a | . | . |
| Childhood abuse ^a | . | . |
| Parental divorce ^a | . | . |
| Low educational and occupational level ^a | . | . |
| Intimate-partner violence | . | ↔ |

↑: increased risk; ↔: no effect on risk; .: no evidence available; POI, primary ovarian insufficiency.

^a These factors have been identified as associated with earlier age at menopause, but specific evidence is not available with respect to premature or early menopause.

and social/environmental factors are associated with the timing of natural menopause, almost no findings have been reported in relation to premature or early menopause. Nevertheless, it is still worthwhile to review the body of evidence that points to a cumulative effect on age at menopause of adverse exposures in early life and childhood, and of social/environmental conditions in early adulthood.

2.4.1. Birthweight, childhood growth and early-life nutrition

In a recent systematic review of 11 studies [60], nine reported no association between low birthweight and age at natural menopause, while three studies reported an association of higher birthweight and of higher ponderal index [birthweight/height³ (kg/m³)] with earlier age at menopause [61,62]. It is thought that women of lower socioeconomic status are exposed to dietary deprivation, particularly during childhood [63]. There was evidence of an association between earlier age at natural menopause and prenatal and childhood famine (particularly for severe famine experienced between the ages of 2 and 6 years) [64,65], low bodyweight (at age 1 or 2 years) [61,66,67] and not having been breastfed [66,67]. Overall, the findings suggest that poor early-life nutrition and poor childhood growth may influence the timing of menopause.

2.4.2. Childhood socioeconomic status

There is accumulating evidence that early-life socioeconomic circumstances influence reproductive health across the life course [24,68,69]. Adverse socioeconomic circumstances in childhood have been found to have a greater impact on age at natural menopause than the experience of such circumstances in adulthood [67,69,70]. The cumulative effect of childhood socioeconomic deprivation on age at menopause may be partly mediated by childhood nutrition, which influences both linear growth and age at menopause [70]. Cognitive function and early emotional stress may also be mediating factors related to this social gradient [69].

2.4.3. Childhood cognitive function

Cognitive function across the life course is associated with the timing of natural menopause, with the strongest effect found for childhood cognitive ability [71]. This suggests that ovarian steroids across the life course influence both neurodevelopment and the timing of menopause [71]. Evidence from two birth cohort studies in the UK

showed that lower cognitive scores in childhood were associated with earlier age at menopause [72]. Furthermore, childhood intelligence was correlated with age at natural menopause, which may be attributed to both central neural mechanisms and the effects of childhood intelligence on general health in adulthood [73].

2.4.4. Childhood abuse

Early-life experience of violence may affect ovarian function and reproductive ageing via dysregulation of stress responses [74,75]. Women who experienced abuse during childhood or adolescence had more extreme levels of ovarian hormones during the menopausal transition, suggesting that early experience of abuse may lead to neuroendocrine disruption, which in turn affects ovarian function [75]. The Avon Longitudinal Study of Parents and Children found that childhood sexual abuse was associated with earlier age at menarche and menopause, but the finding for earlier age at menopause needs to be confirmed in studies with larger samples [76].

2.4.5. Parental divorce

A few studies have addressed the role of family structure and relationships in the timing of menopause. Women who experienced parental divorce before the age of five years tend to have earlier menopause than those whose parents did not divorce, highlighting the possibility that early emotional stress may be a contributing factor [68,69]. The effect of parental divorce was not weakened by adult socioeconomic status, smoking, parity, marital status or BMI, or by adult psychological events. This suggests that negative life events in childhood may have effects additional to those of disadvantage and poor health behaviours in adulthood [69]. Paternal absence, specifically first occurring between 6 and 11 years of age, was also associated with earlier age at menopause and a shorter reproductive lifespan [76]. This limited evidence is consistent with the psychosocial acceleration theory, which proposes that adverse life events in childhood accelerate sexual maturity via stress hormones that activate the hypothalamic-pituitary-adrenal axis prematurely [77]. Psychological stress increases the release of stress hormones that affect the physiology of the ovaries [78].

2.4.6. Education, occupation and income

A systematic review has suggested that there is some evidence that a

lower level of education is associated with earlier menopause, with 22 out of 29 studies finding a weak association (but for 10 studies it was significant) [63]. A meta-analysis of 11 studies also showed that women with a lower level of education experienced menopause 0.6 years earlier than those with a high level and 0.3 years earlier than those with a middle level of education [45]. A similar result was found for low occupational level, while there was no effect of income on age at menopause. No evidence is available, however, regarding an association between educational or occupational level and the risk of early menopause. Mechanisms by which adverse socioeconomic conditions across women's lifespan relate to an early decline in ovarian function may involve exposures that influence the rate of oocyte depletion over the life course [79].

2.4.7. Intimate-partner violence

A population-based cohort of 6000 midlife women in Australia found that those who experienced intimate-partner violence were at increased risk of early menopause (< 45 years) [80]. This association remained after accounting for stress but was attenuated and no longer significant after adjusting for smoking. The mediation analyses showed that cigarette smoking explained 36.7% of the overall relationship between intimate-partner violence and early menopause after adjustment for educational level, income difficulties and age at menarche. While psychological stress may play a role in the timing of menopause, there is not sufficient evidence to show that stress poses an additional risk of early menopause.

3. Recommendations

Women with POI or early menopause experience an extended period of time with loss of ovarian hormone activity, and have increased risks of persistent vasomotor menopausal symptoms, cognitive or affective disorders, heart disease, stroke, bone loss and overall mortality [81]. The most recent recommendations are set out in the 2017 hormone therapy position statement of the North American Menopause Society (NAMS) [81]. This identifies women with POI or early natural or induced menopause or who have had surgical menopause before the age of 45 years, and particularly before the age of 40 years, as being appropriate candidates for hormone therapy (HT). For these women, the statement recommends early initiation of HT and its continued use at least until the median age of menopause (50–52 years), unless contraindicated (for example, in women with hormone-sensitive cancer). This is based on observational evidence on the prevention of risks related to early oestrogen loss and adverse health outcomes. Longer duration of HT may be considered for symptomatic women. Younger women may require higher doses of HT for symptom relief or protection against bone loss. The European Menopause and Andropause Society (EMAS) position statement [82] and the NICE guideline [83] also support this recommendation regarding HT use for women with POI.

The evidence presented here has highlighted differences in age at menopause across regional and ethnic groups (for some of these groups it is less than 50 years). In addition, the current recommendations on the use of HT by younger women are based on limited scientific evidence [81,83]. Better-quality data are urgently needed to optimise the management of young women with POI and early menopause and thereby improve their short-term quality of life and long-term morbidity and mortality [83]. Appropriate doses of HT, calcium and vitamin D, adequate exercise, and screening to detect medical issues may be effective in the management of women with POI or early menopause [81]. It is also important to consider referring women with POI or early menopause to specialists [83].

Since tests to predict age at menopause are lacking, family history on age at menopause and reproductive and environmental risk factors are important indicators to identify those women who are at increased risk of premature or early menopause. Studies of gene–environment

interactions are warranted to unravel the complex interplay of genetic, social and environmental factors associated with the risk of premature and early menopause.

We make the following recommendations:

- clinicians and other health professionals should consider population-specific age at menopause (including variations by ethnicity) as part of the assessment for the timing of HT cessation;
- monitoring for early menopause should be offered to women with a family history of early menopause, who are a child of a multiple pregnancy or who experienced early menarche (particularly nulliparous women), as they are at substantially increased risk of premature and early menopause;
- preventive health strategies should be implemented to encourage women to quit smoking (preferably before age 30) and maintain optimal body weight, to lower their excess risk of premature and early menopause.

4. Summary

- Premature menopause (also known as primary ovarian insufficiency or POI) is defined as menopause before the age of 40, while early menopause is defined as menopause between the ages of 40 and 45.
- Genetic factors contribute to around 50% of the variation in age at natural menopause. A family history of premature or early menopause, being a child of a multiple pregnancy and some specific genetic variants have been identified as risk factors for premature and early menopause.
- Early menarche, nulliparity or low parity, cigarette smoking and being underweight are strong reproductive and lifestyle risk factors associated with premature and early menopause.
- Current clinical guidelines for the management of premature and early menopause focus on early initiation of HT and its continued use until the average age of menopause (50–52 years for white Western women).
- We suggest that the timing of HT cessation should account for the age at menopause of the relevant ethnic or regional group rather than assuming it is 50–52 years. In addition, we suggest there should be early monitoring for women who have a family history of premature or early menopause, who are a multiple-birth child or who had early menarche (especially nulliparous women) to prevent adverse health outcomes associated with premature and early menopause.
- More broadly, women should be encouraged to quit smoking (preferably before the age of 30 years) and maintain optimal weight to reduce their risk of premature and early menopause.
- Further research is needed in the form of studies that have sufficient statistical power to investigate premature and early menopause, including, for example, the mechanisms behind the higher risk of POI among twins, and the social and environmental factors that are already known to increase the risk of earlier menopause.

Contributors

Gita D. Mishra and Hsin-Fang Chung prepared the initial draft, which was circulated to all other named authors (EMAS board members) for comments and approval; production was coordinated by Irene Lambrinouadaki and Margaret Rees.

Conflict of interest

Gita D. Mishra, none declared.
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