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The Timing of the Age at Which Natural Menopause Occurs

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The age at the final menstrual period holds intrinsic clinical and public health interest because the age at which natural menopause occurs may be a marker of aging and health.[1–3] Later age at natural menopause has been associated with:

- longer overall survival and greater life expectancy[4] and reduced all-cause mortality[5];
- reduced risk of cardiovascular disease[4,6–11] and mortality from cardiovascular[12] and ischemic heart disease,[13] stroke,[14] angina after myocardial infarction,[15] and atherosclerosis[16];
- less loss of bone density,[17] and a reduced risk of osteoporosis[18] and fracture[19];
- but an increased risk of breast,[20,21] endometrial, and ovarian[4,22–25] cancers.

In addition, women who have undergone bilateral oophorectomy under the age of 45 years have been observed to be at increased risk of mortality from cardiovascular disease, particularly if they were not treated with estrogen.[26] However, women who underwent natural menopause before age 45 years had an increased risk of ischemic heart disease that was not attenuated by use of hormone therapy.[27] Further, early menopause has been associated with earlier decline in cognitive function.[28–30] Because 40 million women in the United States alone and several hundred million worldwide[31] experienced the menopausal transition between 1990 and 2010 due to the aging of the baby boomer generation,[32] millions of women are undergoing or have recently undergone the menopause transition, and the timing of their final natural menstrual periods could have important clinical and health implications, because one third of women's lives is spent postmenopause.

Although menopause is a universal phenomenon among women, the timing of the onset and the duration of the menopausal transition and the timing of the final menstrual period are not.[33] Most of our knowledge and perceptions of menopause have been based largely on studies of white women, and many have been studies of clinic-based, rather than population-based, samples of women. Thus, until recently, much of the knowledge about the timing of the natural final menstrual period has been affected by the nature of the samples of women studied and a number of other methodologic differences in the studies of this phenomenon, which must be considered in comparing and summarizing their results.

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METHODOLOGIC CONCERNS

Most studies of the menopausal transition have been cross-sectional, rather than longitudinal, in design, providing an opportunity for distortion of the true picture of the timing of the final natural menstrual period, particularly for understanding factors that precede and may affect the timing of menopause. Further, definitions of menopause or the final menstrual period have varied from study to study in terms of the number of months of amenorrhea considered to represent in retrospect the final menstrual period. Studies have also varied with regard to which factors have been included in multivariable analyses that control simultaneously for the effects of multiple variables, which also makes the studies not directly comparable.

The analysis of age at natural menopause in a number of studies has been calculated as a simple mean, rather than using the less-biased survival or multivariable time-to-event analytic approaches. These last two approaches include more information and observations for every woman studied, because all women are included but withdrawn or censored when they experience surgical menopause, start using menopausal hormone therapy or oral contraceptives (OC; which generally masks the natural cessation of menses), or are still premenopausal.[34] Also, the accuracy of reporting of age at menopause can vary by whether menopause was natural and by duration from the time of the final menstrual period to the time of the interview about menopause, the latter being directly affected by the age group of the study sample.[35] Further, in some studies that have reported age at menopause, it is unclear if the age at the final menstrual period is being reported, the more frequent approach, or if the age at cessation of menses plus 1 year of amenorrhea, the World Health Organization's definition of menopause.[31] is what is reported, a more rare occurrence.[36] Most studies do not use a hormonally based definition of menopause.

Recently, more information has been published regarding differences in the timing of menopause experienced by samples of women of different socioeconomic, racial/ethnic, and lifestyle backgrounds, and standardization of instruments and definitions has increased, resulting in a fuller, clearer, and more insightful picture regarding the underlying physiology.

SUMMARY OF UNDERLYING PHYSIOLOGY

Menopause is defined as the cessation of menstruation which reflects cessation of ovulation owing to a loss of ovarian follicles, which in turn results in reduced ovarian production of estradiol, the most biologically active form of estrogen,[37,38] as well as increased circulating concentrations of follicle-stimulating hormone (FSH) and decreased concentrations of inhibin, which inhibits the release of FSH.[37] Age at menopause may be more sensitive to varying rates of atresia of ovarian follicles[39] than to the absolute number of oocytes depleted,[40] but menopause is reached when depletion of follicles reaches approximately 1000 (from a peak of 5 million follicles at mid-gestation and 2 million at birth).[41,42] The age at which sufficient depletion of follicles occurs is affected by the number of follicles achieving migration to the gonadal ridge during gestation, their mitotic abilities until mid-gestation, and the rate of follicular atresia.[42,43]

As circulating estrogen concentrations decline during the menopausal transition, variations in the regularity, timing, and nature of menstrual bleeding may occur.[44] As menstrual cycles become increasingly irregular, bleeding may occur after an inadequate luteal phase or without ovulation,[44] usually indicated by a short luteal phase, characteristic of women over the age of 40 years.[45,46] Such cycles may be associated with insufficient FSH (or insufficient FSH responsiveness of the follicle) in the follicular phase, in turn resulting in lower luteal phase estrogen and progesterone secretion. Lack of a corpus luteum, resulting in

estrogen secretion (even hyperestrogenicity[45,47]) unopposed by progesterone, may lead to profuse bleeding.

The nature and timing of bleeding may vary both within and between women. What is known about the host, environmental, or lifestyle factors that may affect such variation is summarized herein. Although some factors have been identified that are associated with early age at natural menopause, the relation of many has not been examined, and most have not been examined in relation to duration of the perimenopause.

Factors Related to Timing of Menopause

Results from cross-sectional studies have indicated that endocrine changes characteristic of the onset of the perimenopause begin at around age 45.[48] The median age at menopause among white women from industrialized countries ranges between 50 and 52 years and at onset of the perimenopause is 47.5 years,[49–53] with slight evidence of increasing age at menopause over time.[53–57] These onsets seem to vary by race and ethnicity[58–60] and are affected by demographic and lifestyle factors.[50,51,55,57–69] Although some studies have reported no familial relationship, 1 study has reported that age at menopause was positively associated with maternal age at menopause,[61] and 1 recent study has shown genetic control of age at menopause in a study of twins.[70] However, a number of potentially modifiable factors which may affect estrogen metabolism, including body mass index (BMI), diet (particularly calories and alcohol intake), and passive smoke exposure have not been examined, nor has the time-varying effect of these and of the other factors that have been previously identified been examined in longitudinal analyses of sufficiently large and diverse study populations.

Sociodemographic Differences

International and geographic differences—Several studies have indicated that women living in developing countries (including Latin America, Indonesia, Singapore, Pakistan, Chile, and Peru) experience natural menopause several years earlier than those in developed countries.[71–76] Some work has also indicated that women living in urban areas have a later natural menopause than women in rural areas.[62] Women living at high altitude in the Himalayas or in the Andes of Peru undergo natural menopause 1 to 1.5 years earlier than those living at lower altitudes or in less rural areas.[72,77–79] It is unclear whether these geographic and international differences in the age at natural menopause reflect genetic, socioeconomic, environmental, racial/ethnic, or lifestyle differences and whether and how these affect physiology.

Racial/ethnic differences—Some studies have reported that African American[59] and Latina[58,60] women have natural menopause about 2 years earlier than white women. However, 1 small study in Nigeria reported the average age at menopause to be 52.8 years,[80] over 1 year later than that generally reported for white women in industrialized nations. Mayan women, despite their high parity (see Reproductive History), have been reported to experience natural menopause fairly early, at about age 45.[81] In contrast, Asian women tend to have similar age at menopause to Caucasian women,[58,82] although Thai women have been reported to have a lower median age at menopause, at age 49.5 years, despite their high parity,[83] and Filipino Malay women have been reported to have an earlier average age at natural menopause at 47 to 48 years.[84]

Differences by socioeconomic status

A number of studies have observed that lower social class, as measured by the woman's educational attainment or by her own or her husband's occupation, is associated with an earlier age at natural menopause.[51–54,57,58,61,71,85,86] However, results from a British birth

cohort indicated that early life socioeconomic status (SES) was more strongly associated than adult status with age at natural menopause,[87] although even the relation of early life SES was greatly attenuated when adjusted for childhood cognitive ability and having been breastfed.[88] One study found that education was more strongly associated with age at natural menopause than occupation.[52] Most studies that have examined the relation of marital status have found that single women undergo an earlier natural menopause, and this association cannot be explained by nulliparity.[52,89,90]

Health-Related Influences

Menstrual and reproductive history—The age at which the final natural menstrual period occurs may be a marker for hormonal status or changes earlier in life.[91] In the landmark Treloar longitudinal study of largely white, well-educated women, those whose median menstrual cycle length between the ages of 20 and 35 years was fewer than 26 days underwent natural menopause 1.4 years earlier than women with cycle lengths between 26 and 32 days, whereas a later natural menopause (mean = 0.8 year later) was observed in women with cycle lengths of 33 days or longer.[92] In addition, 9 or more days of variability in cycle length has been associated with a later age at natural menopause in this and other studies,[52,59] although 1 study reported an earlier natural menopause in women with irregular menses.[53]

Increasing parity, particularly among women of higher SES, has also been associated with later age at natural menopause,[50–52,55,57,58,61,90,91,93–96] consistent with the theory that natural menopause occurs after oocytes have been sufficiently depleted.[93] Although some studies have reported no familial relationship, 1 study reported that women's age at natural menopause was positively associated with their mother's age at natural menopause,[61] and 1 study of twins showed genetic control of age at natural menopause.[70] Age at menarche has been fairly consistently observed not to be associated with age at menopause, after adjusting for parity and cycle length,[52,53,55,83,89,97,98] as have prior spontaneous abortion, age at first birth, and history of breastfeeding.[52,97,98]

A number of studies have reported that women who have used OCs have a later age at natural menopause.[52,58,61,63,72,98] an observation that is also consistent with the theory that OCs delay depletion of oocytes. However, the finding has not been wholly consistent across studies, because 1 study reported that this delay became nonsignificant after a time-dependent adjustment for when OCs were used,[52] and another study reported that OC users had a significantly earlier natural menopause than nonusers, although this association was not consistent across 5-year age groups.[50]

Body mass and composition—Several studies have examined the relation of body mass to age at menopause, with inconsistent findings. Some studies have reported that both increased BMI (indicated by weight over height squared) and upper body fat distribution (indicated by waist-to-hip ratio) were associated with later age at natural menopause[50,57,96,99,100] and increased sex hormone concentrations.[100] However, at least as many other studies have reported no significant association of BMI with age at natural menopause.[51,52,54,59,101,102] Some studies have found a relationship between lower weight[69] or increased upper body fat distribution[101] and earlier age at natural menopause, particularly among smokers. One study reported earlier natural menopause in women on weight reduction programs or who had gained more than 26 pounds between the ages of 20 and 45 years.[59]

Some of these apparently inconsistent findings may be explained by differences in study design (cross-sectional or retrospective vs prospective) or analysis (eg, inadequate or varying control of confounding variables or survival analysis vs. comparison of crude

means). In general, the better designed and analyzed studies have shown no relation of body mass or body fat distribution to age at the final natural menstrual period. Although body mass and composition may be related to age at natural menopause, they are also related inversely to physical activity, alcohol consumption, and education, and positively related to infertility and parity.[103] Further research is needed in which all of these potentially confounding variables are simultaneously controlled in the statistical analyses of data from large study samples to be able to assess adequately the independent contribution or interactive effect of body mass and composition and these other factors on the age at the natural final menstrual period and duration of menopause transition, using appropriate longitudinal study design and data analysis techniques.

Familial, genetic, and early childhood factors—In recent years, studies of factors related to age at natural menopause have begun to focus on genetic factors that may be related. Results of family and twin studies suggest that familial and genetic factors may play an important role, with estimates of heritability ranging from 30% to 85%.[70,104,105] In 1 relatively large cross-sectional study and 1 large longitudinal British birth cohort study, a strong association was found between mothers' and daughters' ages at natural menopause,[88,106] which have also been found in a few other smaller studies,[107–109] but few longitudinal studies have investigated this relationship. One European genome-wide association study of nearly 3000 women identified 6 single nucleotide polymorphisms in 3 loci on chromosomes 13, 19, and 20 associated with age at natural menopause.[110] A Dutch study showed that polymorphisms of an estrogen receptor gene were associated with earlier natural and surgical menopause.[111] Results of genome-wide association studies, using samples from thousands of women in the Nurses' Health Study and the Women's Genome Health Study, identified 13 single nucleotide polymorphisms on 4 chromosomes that were associated with age at menopause.[112] Analyses of candidate genes from 9 biologically plausible pathways, using the same samples from the same women in these 2 studies, indicated that the steroid hormone metabolism and biosynthesis pathways were associated with age at natural menopause and that genes involved in premature ovarian failure were also significantly associated with age at menopause.[113] Two single nucleotide polymorphisms of the tumor necrosis factor receptor family have also been shown to be significantly associated with age at natural menopause.[114]

A number of analyses have been conducted on prospective data collected across the lifespan from a nationally representative birth cohort of nearly 1600 British women born in 1946 and followed to age 53 years, the Medical Research Council National Survey of Health and Development. These analyses have revealed that women who had a low weight at 2 years of age had an earlier natural menopause,[115] whereas those who were heaviest at 2 years of age had a later natural menopause.[89] Those who were breastfed had a later natural menopause.[115] Another cohort study in England also found that low weight at 1 year of age was associated with earlier natural menopause.[116] However, an Australian twin study and the English cohort study found no association of birth weight with age at natural menopause.[116,117] The British birth cohort and other cohort studies have shown that poorer cognitive ability in childhood was associated with earlier natural menopause,[118–120] suggesting that perhaps markers in early life may determine not only age at natural menopause, but may also predict the adverse health outcomes that are associated with early age at menopause. Further, additional findings from the British birth cohort indicate that women whose parents divorced early in their lives had an earlier natural menopause than other women, suggesting that early life stressors may also be related to early menopause.[87,88]

Environmental Influences

Active and passive smoke exposure—Perhaps the single most consistently shown environmental effect on age at menopause is that women who smoke stop menstruating 1 to 2 years earlier than comparable nonsmokers.[50,51,55,57–59,61,63–68,86,96,121] and have a shorter perimenopause.[122] Some studies have shown a dose–response effect on atrophy of ovarian follicles, in that heavy smokers have an earlier natural menopause than light smokers.[61,67,69,123,124] Former smokers have only a slightly earlier age at natural menopause than those who never smoked, and increased time since quitting diminishes the difference.[123,125] The latter observation of only a slightly earlier natural menopause in former smokers is inconsistent with the presumed toxic effect of smoking on ovarian follicles, resulting in their atrophy and thus earlier menopause, because such an effect should be nonreversible so that former smokers would also experience the earlier natural menopause observed in current smokers. If the dose–response effect is a true effect, the apparent paradox might partly be explained by fewer years of smoking and thus toxic exposure to the ovaries in former smokers than in current smokers of similar age.

The polycyclic aromatic hydrocarbons in cigarette smoke are known to be toxic to ovarian follicles[126,127] and thus could result in premature loss of ovarian follicles and early natural menopause among smokers. Because drug metabolism is enhanced in smokers,[128] estrogen also may be more rapidly metabolized in the livers of smokers, which could lead to an earlier reduction of estrogen levels.[99] Further, smoking has also been observed to have antiestrogenic effects.[129] Greater prevalence of hysterectomy among premenopausal smokers than nonsmokers[100,123] apparently does not account for smokers having an earlier natural menopause.[130] Only 1 study has shown that nonsmoking women whose spouses smoked had an age at natural menopause resembling that of smokers[131]; thus, very little is known about the effect of passive or secondhand smoke exposure on the age at which the final natural menstrual period is experienced.

Occupational/environmental factors—Although almost nothing is known about the relations of occupational or other environmental factors to age at the final natural menstrual period and duration of the menopausal transition, occupational exposures and stressors (such as shift work, hours worked, hours spent standing, and heavy lifting) have been related to increased risk of adverse pregnancy outcomes[132–135] and changes in menstrual cycle length and variability as well as fecundability.[136–139] In addition, such environmental exposures as dichlorodiphenyltrichloroethane and polychlorinated biphenyls have been shown to have estrogenic activity and to be associated with an increased risk of breast cancer,[140,141] although this association has not been consistently observed.[142,143] Thus, the presumed endocrine effects of such exposures make it reasonable to expect that occupational and environmental exposures may be related to endocrine disruption that is reflected in altered age at natural menopause. One study showed a modest effect on age at natural menopause in women in Seveso, Italy, who were exposed to 2,3,7,8-tetrachlorobenzo-p-dioxin, a halogenated compound that may affect ovarian function, during a chemical plant explosion in 1976.[144] Another study showed that exposure to 1,1-dichloro-2,2-bis(p-chlorophenyl) ethylene was also associated with earlier natural menopause.[145]

Physical activity: Physical activity is associated with a number of changes in hormonal parameters [estradiol, progesterone, prolactin, luteinizing hormone (LH), and FSH), both during and after intense physical activity.[146–148] The concentrations of these hormones tend to be lower at rest among women who are physically active.[146,147,149,150] Also, athletes tend to have a later age at menarche and increased occurrences of anovulation[151] and amenorrhea[152] and, among those who menstruate, a shortened luteal phase and reduced mean and peak progesterone levels.[104,149] Although physical activity is associated with

decreased concentrations of reproductive hormones and frequency of ovulation, few studies have examined the effect of exercise on age at natural menopause, although 1 modestly sized study reported no relationship,[59] and 1 large study of Chinese women showed a later age at natural menopause associated with leisure time physical activity during adolescence and adulthood.[94]

Diet: One early study from Papua, New Guinea, suggested that malnourished women ceased menstruation about 4 years earlier than well-nourished women,[153] consistent with other studies showing that women with greater weight[62,69] and height[89] may have a later age at natural menopause. Findings regarding the relationship of specific dietary patterns to age at menopause have been inconsistent. For example, vegetarians were observed to have an earlier age at natural menopause in 1 study,[154] whereas another study in Japan reported that higher green and yellow vegetable intake was significantly associated with later age at natural menopause.[155] Further, a large cross-sectional study of Japanese women found that higher intakes of fat, cholesterol, and coffee were significantly associated with earlier natural menopause after controlling for age, total energy, parity, menarche age, and relative weight.[156] A longitudinal study of nearly 5000 German women observed that high carbohydrate consumption and high intake of vegetable, fiber, and cereal products were related to an earlier age at natural menopause, whereas higher intake of total fat, protein, and meat were associated with a later natural menopause.[157] The large, prospective Shanghai Women's Health Study found that higher total intake of calories, fruits, and protein was significantly associated with later age at natural menopause, whereas vegetable, fat, soy, and fiber intakes were not significantly related to age at menopause.[94] Inclusion of meat in the diet of vegetarians has been observed to increase the episodic releases of LH and FSH and the length of the menstrual cycle.[158] Thus, meat may modify the interaction of hormones along the hypothalamic-pituitary-ovarian axis. A couple of studies have reported that increased meat or alcohol consumption is significantly associated with later age at menopause, after adjusting for age and smoking.[61,121] Dietary fiber (whose intake tends to be inversely related to meat intake) may interrupt enterohepatic circulation of sex hormones, leading to the lower circulating estrogen concentrations among vegetarian women.[159] Nonetheless, a low-fat, high-carbohydrate intervention diet to prevent breast cancer in over 2600 women with extensive mammographic density followed for an average 7 years did not influence the timing of natural menopause, except a significantly earlier natural menopause was observed in those with low BMI who were on the intervention diet.[160]

Premenopausal women administered soy have shown increased plasma estradiol concentrations and follicular phase length, delayed menstruation, and suppressed midcycle surges of LH and FSH.[161] Among postmenopausal women fed soy, FSH and LH did not decrease significantly, nor did sex hormone-binding globulin increase, and little change occurred in endogenous estradiol or body weight, although a small estrogenic effect on vaginal cytology was observed.[162] However, the role of dietary fiber, phytoestrogens, fat, protein, and other nutrients in affecting age at menopause and duration of the perimenopause remains to be systematically studied, but has potentially important implications for prevention of chronic disease in midlife and older women.

CONCLUSION

Despite important methodologic differences, the limitations in the study designs used and the populations studied in the accumulating literature regarding factors that affect the age at which the natural final menstrual period is experienced, an interesting and complex picture is emerging. A number of demographic (eg, education, employment, race/ethnicity), menstrual and reproductive (eg, parity and OC use), familial and genetic, and lifestyle (eg, smoking, weight, physical activity and diet) factors seem to be important determinants of the

age at which natural menopause occurs. Smoking, lower parity, and lower SES have been found fairly consistently to be associated with earlier menopause, an indicator of reduced longevity. However, the relationships with African American and Latina race/ethnicity, vegetarian diet, and undernutrition, body mass and composition, and physical activity have been inconsistent, possibly owing to varying methodologic approaches and limitations (Table 1).

Other relationships remain largely unexplored (eg, passive smoke exposure and occupational and other environmental exposures). Therefore, much remains to be learned about how these factors affect follicular atresia and hormone levels and thus determine the onset and potentially the duration of the perimenopause and the timing of the final menstrual period. Furthermore, increased understanding of the underlying physiologic mechanisms of these influences needs to include potential genetic, metabolic, and racial/ethnic differences in physiologic responses to lifestyle factors and other environmental exposures and the interaction of genetic factors with these lifestyle and environmental factors. Increasing knowledge about these relationships ultimately offers women and their health care providers enhanced understanding and choices, based on greater knowledge, to deal with the individual presentations of menopause.

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Table 1

Factors related to earlier and later age at natural menopause

Factors Consistently Related to Earlier Age at Natural Menopause (References)	Factors Inconsistently Related to Age at Natural Menopause (References)
Low socioeconomic status[51–54,57,58,61,71,85–88]	Race/ethnicity[58–60,80–84]
Low/parity[50–52,55,57,58,61,90,91,93,96]	Body mass index or body com position[50–52,54,57,59,62,69,98–101]
Not using oral contraceptives[50,52,58,61,63,72,98]	Physical activity[59,94]
Active smoking[50,51,55,57–59,61,63–69,86,96,121,124–126]	Dietary (vegetable, meat, fat, fiber) intake[61,121,153–157,160]