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AHA SCIENTIFIC STATEMENT

Menopause Transition and Cardiovascular Disease Risk: Implications for Timing of Early Prevention

A Scientific Statement From the American Heart Association

ABSTRACT: Cardiovascular disease (CVD) is the leading cause of death in women, who have a notable increase in the risk for this disease after menopause and typically develop coronary heart disease several years later than men. This observation led to the hypothesis that the menopause transition (MT) contributes to the increase in coronary heart disease risk. Over the past 20 years, longitudinal studies of women traversing menopause have contributed significantly to our understanding of the relationship between the MT and CVD risk. By following women over this period, researchers have been able to disentangle chronological and ovarian aging with respect to CVD risk. These studies have documented distinct patterns of sex hormone changes, as well as adverse alterations in body composition, lipids and lipoproteins, and measures of vascular health over the MT, which can increase a woman's risk of developing CVD postmenopausally. The reported findings underline the significance of the MT as a time of accelerating CVD risk, thereby emphasizing the importance of monitoring women's health during midlife, a critical window for implementing early intervention strategies to reduce CVD risk. Notably, the 2011 American Heart Association guidelines for CVD prevention in women (the latest sex-specific guidelines to date) did not include information now available about the contribution of the MT to increased CVD in women. Therefore, there is a crucial need to discuss the contemporary literature on menopause and CVD risk with the intent of increasing awareness of the significant adverse cardiometabolic health–related changes accompanying midlife and the MT. This scientific statement provides an up-to-date synthesis of the existing data on the MT and how it relates to CVD.

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Cardiovascular disease (CVD) is the leading cause of death in women.[1] According to the 2012 American Heart Association (AHA) survey of female awareness, knowledge, and perceptions related to CVD[2] and more recent data from 1011 US women (25–60 years of age) from the Women's Heart Alliance survey published in 2017, only 56% of women are aware of this fact.[3]

CVD AND MENOPAUSE

Women develop coronary heart disease (CHD) several years later than men, with a notable increase in CHD risk during midlife,[4] a period coincident with the menopause transition (MT). This observation led to the hypothesis that the MT contributes to the increase in this risk.[4]

Over the past 20 years, longitudinal studies of women transitioning through menopause have contributed substantially to our understanding of the relationship between the MT and CVD risk. These studies have documented distinct patterns of alterations in endogenous sex hormones and adverse changes in body fat distribution, lipids, and lipoproteins, as well as structural and functional measures of vascular health over the MT.[5] The reported findings underline the significance of the MT as a time of accelerating CVD risk, which emphasizes the importance of monitoring and potentially intervening during midlife.

GOAL OF THIS SCIENTIFIC STATEMENT

The latest 2011 AHA guidelines of CVD prevention in women[6] did not incorporate the MT as a CVD risk factor. Therefore, there is a compelling need to discuss the implications of the accumulating body of literature on the MT and CVD risk. Therefore, the purpose of this scientific statement is to raise awareness of the significant adverse cardiometabolic health–related changes accompanying midlife and the MT. This statement highlights the complexity of the MT as a multidimensional transition during midlife and summarizes critical literature on the link between CVD risk and multiple menopause-related characteristics, beyond the dynamic hormonal alterations accompanying the MT. Moreover, the statement identifies critical cardiometabolic health changes relevant to the MT that are independent of chronological aging and reviews the current cardiovascular health status of midlife women using the AHA Life's Simple 7 components. Available evidence on effects of lifestyle interventions, as well as menopausal hormone therapy (MHT) use and lipid-lowering therapeutic options, on CVD risk is also discussed, with a particular focus on the timing of these interventions relevant to the MT. Finally, the implications of the evolving literature for menopause-related changes in cardiometabolic health on current guidelines specific to preventing CVD in women are presented.

THE MENOPAUSE TRANSITION

Epidemiology of Menopause

Menopause signifies the permanent cessation of ovarian function and women's transition from a reproductive to a nonreproductive phase of life. It marks a critical stage characterized by remarkable changes in hormonal and menstruation patterns, as well as both physiological and psychosocial symptoms.

The experience of 12 consecutive months of amenorrhea not the result of other causes defines natural menopause.[7] A 2018 published pooled analysis of 234 811 postmenopausal women from 17 cross-sectional and observational studies across 7 countries reported the median age at natural menopause to be 50.0 years (interquartile range, 48.0–53.0 years).[8] Natural menopause is considered premature if it occurs before 40 years of age and early if it occurs between 40 and 45 years of age.[9] Approximately 10% of women experience menopause before 45 years of age (1.9% before 40 years of age and 7.3% at 40–45 years of age).[8] With the mean life expectancy at birth of 81 years for a US woman, many US women will spend up to 40% of their lives as postmenopausal.[9,10]

Stages of Reproductive Aging

Reproductive aging includes 7 stages: 5 before and 2 after the final menstrual period (FMP; Figure 1).[11–12c] Not all women will experience each of these 7 stages. Moreover, the duration of each of these stages varies between women, and each stage is characterized by variable changes in the menstruation pattern, hormonal levels, and menopause-related symptomatology, underscoring the complexity of studying the MT and its potential for health-related sequelae. The Stages of Reproductive Aging Workshop + 10[12] defined the MT as the time when a menstrual cycle becomes variable or other menopause-related symptoms begin until the time of the FMP (Figure 1).[11–12c]

Depending on the menstrual cycle variability level, women could be classified as being in the early (a persistent difference in consecutive menstrual cycle length of at least 7 days) or the late (at least 60 days of amenorrhea experienced at least 1 time) transition stage. The perimenopause, which encompasses the most highly symptomatic years, begins with the onset of intermenstrual cycle irregularities (±7 days) or other menopause-related symptoms and extends 12 months after menopause, thus persisting 1 year longer than the MT[12] (Figure 1).

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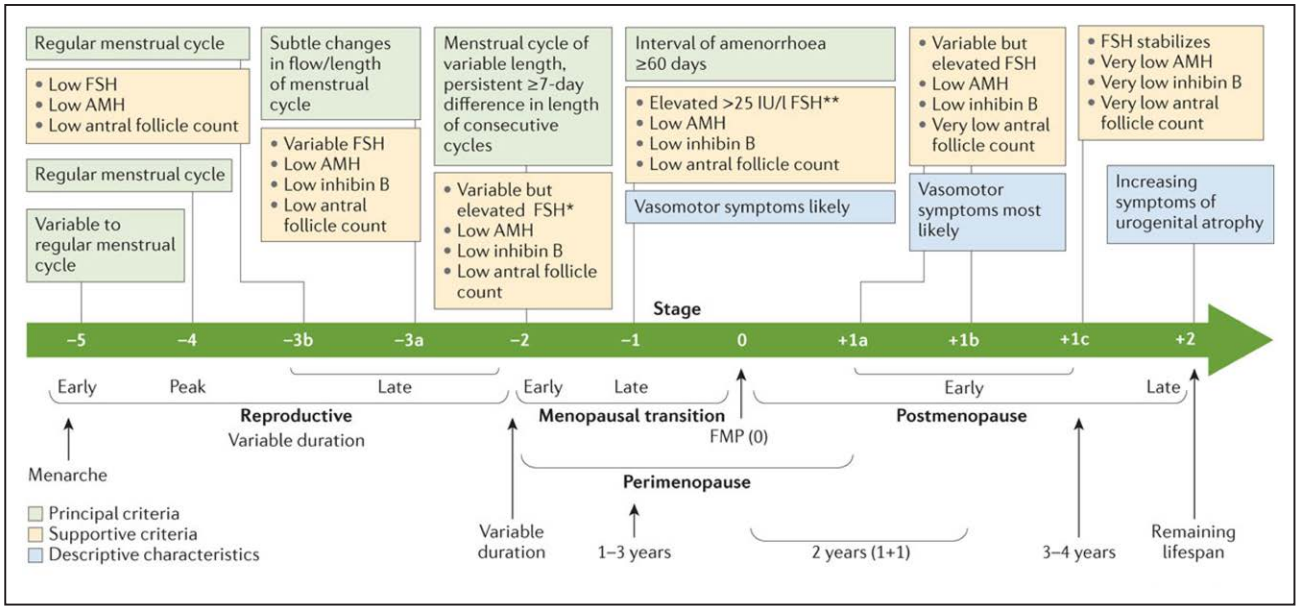

Figure 1. The Stages of Reproductive Aging Workshop (STRAW) +10 staging system for reproductive aging in women.
STRAW defined 7 stages ranging from the onset of menstrual cycles at menarche and the reproductive age to the perimenopausal and postmenopausal phases. Principal (menstrual cycle), supportive (biochemical and imaging), and descriptive (symptoms) criteria are used to characterize the phases. AMH indicates anti-Müllerian hormone; FMP, final menstrual period; and FSH, follicle-stimulating hormone. *Blood drawn on cycle days 2 to 5. **Approximate expected level based on assays using current international pituitary standard. Reprinted from Davis et al[11] with permission from Springer Nature. Copyright © 2015, Macmillan Publishers Limited. Adapted from Harlow et al[12] with permission from The Endocrine Society, copyright © 2012, The Endocrine Society; from Harlow et al[12a] with permission from Taylor & Francis Ltd, copyright © 2012, Taylor & Francis Ltd; from Harlow et al[12b] with permission from the American Society for Reproductive Medicine, copyright © 2012, American Society for Reproductive Medicine, published by Elsevier Inc; and from Harlow et al[12c] with permission, copyright © 2012, The North American Menopause Society.

As a standardized staging system for reproductive aging, the Stages of Reproductive Aging Workshop provides consistent classification of menopause stages across studies of midlife women, facilitating research to disentangle the health effects of ovarian and chronological aging. Moreover, this gold-standard staging system serves as a clinical tool for women and their healthcare providers, guiding fertility assessment, contraceptive needs, and decision making.[12]

Cardinal Hormonal Changes of the MT

The MT is characterized by dynamic changes in estradiol and follicle-stimulating hormone levels. Prospective studies of the MT, including SWAN (Study of Women's Health Across the Nation) and the Melbourne Women's Midlife Health Project, reported a decline in estradiol as early as 2 years before the FMP and a rise in follicle-stimulating hormone 6 years before this time point.[13] However, not all women experience a uniform pattern of estradiol decline or follicle-stimulating hormone rise over the MT (Figure 2A and 2B).[13,13a] That is, estradiol increases significantly 5.5 years before the FMP in 44.5% of midlife women, with a steep early decline almost 1 year before the FMP (estradiol rise–early decline) or a late estradiol decline after the FMP (estradiol rise–late decline). Two other common patterns of estradiol decline that are experienced by 55.5% of midlife women: a slow-decline or a flat pattern (Figure 2A).[13] Follicle-stimulating hormone rises in various degrees among midlife women (Figure 2B).[13]

Menopause-Related Symptomatology

As women traverse the MT, they may experience multiple symptoms such as hot flashes and night sweats (ie, vasomotor symptoms), mood changes (eg, depression and anxiety), and sleep and cognitive disturbances, as well as genitourinary and sexual function changes.[14–19] Links between many of these symptoms and CVD risk have been found (see the Menopause Characteristics Relevant to CVD Risk section).

Vasomotor Symptoms

Vasomotor symptoms are the most common menopause-related symptoms (≈80% of midlife women) that affect a woman's quality of life and may require medical treatment. Vasomotor symptoms can last for 10 years, with a longer duration among women whose symptoms begin early in the MT. The timing and frequency of vasomotor symptoms vary over the MT, with 4 patterns having been identified: (1) early onset of vasomotor symptoms 11 years before FMP with a later decline, (2) onset near the FMP with a later decline, (3) persistently high frequency, and (4) persistently low frequency.[14,15]

The cause of vasomotor symptoms seems to be multifactorial, with reproductive hormones playing an

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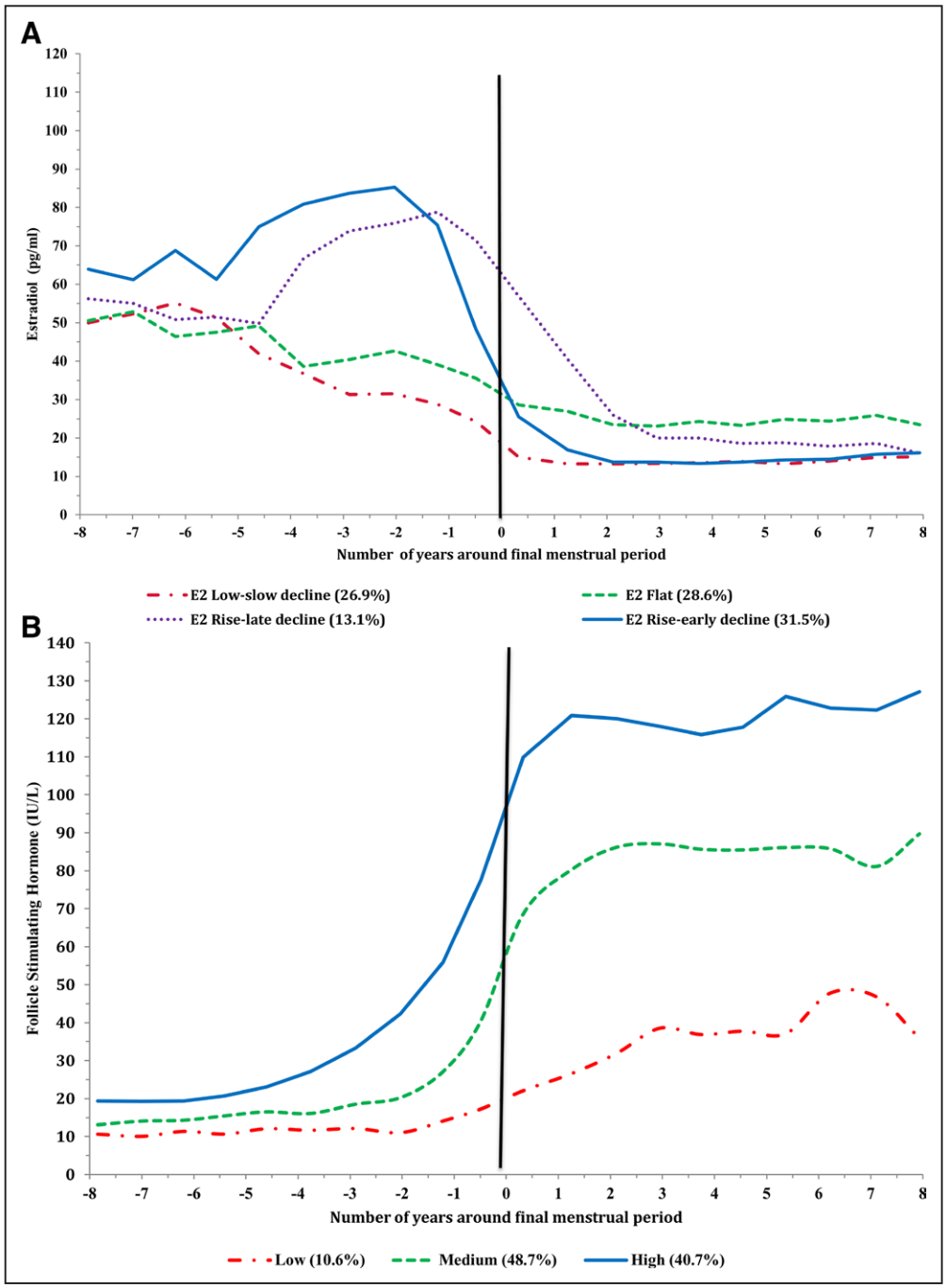

Figure 2. Trajectories of estradiol (E2; A) and follicle-stimulating hormone (B) over the menopausal transition. Reprinted from El Khoudary and Thurston[13] with permission from Elsevier. Copyright © 2018, Elsevier Inc. Adapted from Tepper et al,[13a] by permission of Oxford University Press on behalf of the Endocrine Society.

integral role. Other factors found to be related to a higher occurrence and severity of vasomotor symptoms include obesity before menopause, cigarette smoking, higher levels of anxiety and depression, lower level of education, and premenopausal symptoms. Data on physical activity, diet, and alcohol consumption and their associations with vasomotor symptoms occurrence are not consistent.[14]

Sleep Disturbance

Sleep disturbance is a common complaint during the MT. Women report poorer sleep during the perimenopause stage than the late reproductive age, with the severity of sleep-disordered breathing increasing as women transition from premenopause to postmenopause, independently of chronological aging or changes in body habitus.[16,17] Recent analyses of longitudinal data from SWAN (n=1258 midlife women) showed that only 15% of midlife women report increasing sleep complaints (waking up frequently) during perimenopause, and the remainder experience a stable increase in sleep complaints consistent with an aging-related increase in sleep problems not specific to menopause.[18] Vasomotor symptoms, hormonal changes, comorbid conditions,

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obesity, and psychosocial factors have been linked to increased sleep disturbances during the MT.[15,16]

Depression and Anxiety

Well-designed longitudinal studies of clinical depression reported 2- to 5-fold higher risk for major depressive episodes during perimenopause compared with late premenopause.[15,19] Moreover, midlife women are more likely to experience anxiety symptoms over the MT, which peak during late perimenopause. Both depression and anxiety symptoms tend to decline after menopause.[15,19]

Factors Influencing Natural Menopause Timing

Age at natural menopause is viewed as a marker of not only reproductive aging but also somatic aging and general health. Later age at natural menopause has been linked to a longer life expectancy, higher bone mineral density and lower risk of fracture, and reduced all-cause mortality, CVD, and cardiovascular death, yet greater breast (among obese) and ovarian cancer risk.[20–26]

Race/Ethnicity

Results from studies testing whether the timing of natural menopause differs by race/ethnicity are inconsistent.[27–31] Compared with non-Hispanic White women, Japanese American women may experience menopause at a later age,[28,29] whereas Hispanic,[28,29] Native Hawaiian,[28] and Black[30] women may experience menopause at a relatively younger age. These differences may be driven by variations in socioeconomic, lifestyle, and health factors.[31]

Reproductive History Factors

A number of factors have been implicated in the timing of natural menopause. Women with an average cycle length of <26 days, consistent with faster follicle depletion, may reach menopause 1.4 years earlier than women with longer cycles.[32] On the other hand, studies associating menstrual cycle irregularity with age at natural menopause provide inconclusive results,[30,33,34] whereas higher parity has consistently been linked to a later age at natural menopause.[27,30,33–36] Several studies did not show an association between age at menarche and age at menopause after adjustment for parity and cycle length.[27] However, a recent pooled analysis across 9 cohorts associated early age at menarche (≤11 years) with 80% increased risk of premature and 32% increased risk of early menopause, and the risk doubled in nulliparous women.[35] Data on oral contraceptive use are not conclusive.[27,29,33,37]

Weight and Body Mass

Several studies reported a positive association between premenopausal weight, higher body mass index (BMI) and waist-to-hip ratio, and later age at natural menopause.[31,33,34] Conversely, other studies showed that women who are underweight in early or midadulthood or have low BMI have elevated risk for early menopause.[28,36,38] However, other studies failed to show a similar association.[29,30,37,39] Most recently, cross-trait linkage disequilibrium score regression analyses showed significant negative genetic correlations between age at natural menopause and BMI, weight, and waist and hip circumference, suggesting a genetic pleiotropy (eg, genetic variants associated with both earlier age at menopause and traditional CVD risk factors).[40,41]

Premenopausal Cardiovascular Health

Although menopause timing is hypothesized to contribute to CVD risk, the associations may be bidirectional. That is, data from the Framingham Heart Study showed that higher total cholesterol, systolic blood pressure (SBP) and diastolic blood pressure (DBP), and other cardiovascular risk factors before menopause were associated with earlier menopause, independently of smoking status.[42] In addition, in a pooled analysis of 177 131 women from 9 studies, a first CVD event before 35 years of age was associated with a doubling of the risk of an early menopause, whereas a first event occurring after 35 years of age was associated with menopause at 51 years of age.[43] It is thus possible that worse premenopausal cardiovascular health could influence the onset of natural menopause.[42]

Physical Activity, Diet, and Alcohol Consumption

Physical activity is associated with lower concentrations of reproductive hormones and frequency of ovulation and therefore could potentially be associated with a later age at natural menopause.[27] However, results are not consistent.[30,31,33,36,37,44]

Most dietary patterns and individual dietary components have not been consistently linked to earlier or later age at menopause.[33,36,37,45–47] A 2016 systematic review and meta-analysis of 22 articles from 20 unique studies on the association between alcohol intake and onset of menopause showed that low and moderate alcohol consumption might be associated with later onset of menopause, although the magnitude of the reported association was low.[48]

Cigarette Smoking

A 2008 published systematic review of 109 studies confirmed a link between cigarette smoking and earlier age at natural menopause.[49] Women who smoke are likely to undergo natural menopause ≈1 year earlier than nonsmokers.[27] A recent pooled analyses of >220 000 postmenopausal women from 17 studies across 7 countries revealed that higher intensity, longer duration, higher cumulative dose, earlier age at starting smoking, and shorter time since quitting smoking

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are associated with greater risk of premature and early menopause among both current and former smokers.[8]

Genetics

Evidence suggests that the age at menopause is a complex genetic trait with a wide estimate of heritability that ranges from 31% to 87%.[50] Genome-wide association studies have implicated common genetic loci affecting several potential gene candidates across multiple molecular pathways, including DNA repair, immune function, and neuroendocrine pathways of ovarian function.[40,41,51–54] Moreover, epigenetic studies suggest that early age at menopause is associated with blood DNA methylation patterns linked to accelerated aging (the epigenetic clock), supporting some coheritability between age at natural menopause and epigenetic age acceleration.[55] These findings suggest shared molecular pathways between ovarian and somatic aging that may explain how menopause timing could affect aging of different body systems, including the cardiovascular system.

MENOPAUSE CHARACTERISTICS RELEVANT TO CVD RISK

Several MT characteristics have been evaluated in relation to CVD risk. These include age at menopause, type of menopause, menopause stages, endogenous estradiol, and menopause-related symptoms.

Age at Natural Menopause

A 2016 pooled meta-analysis of 32 observational studies of 310 329 nonoverlapping women reported that, compared with women with menopause at ≥45 years of age, women with early-onset menopause (<45 years of age) had a significantly higher risk of overall (relative risk [RR], 1.50 [95% CI, 1.28–1.76]) and fatal (RR, 1.11 [95% CI, 1.03–1.20]) CHD, even after adjustment for established CVD risk factors. In addition, women experiencing menopause at 50 to 54 years of age had a lower RR of fatal CHD than those with menopause before 50 years of age (RR, 0.87 [95% CI, 0.80–0.96]).[23] Other studies have reported similar findings.[56]

In a meta-analysis pooling data from 3 prospective studies that included 3568 heart failure events, compared with women with later onset of menopause, women who experienced early menopause (at <45 years of age) had a significantly greater risk of heart failure (hazard ratio [HR], 1.33 [95% CI, 1.15–1.53]).[57]

Some evidence suggests a reverse association between age at natural menopause and total CVD risk.[58,59] Among 1684 women ≥65 years of age at baseline from the Iowa EPESE (Iowa Established Populations for the Epidemiological Study of the Elderly), later age at natural menopause (≥55 years) was related to increased all-cause and cardiovascular mortality.[59] However, these results are contrary to those from the EPIC-CVD case-cohort study (European Prospective Investigation Into Cancer and Nutrition–CVD) of 15 402 European women 35 to 70 years of age at baseline, which reported an inverse dose-response relationship (continuous and approximately linear across the menopausal age range) between age at menopause and CHD risk (adjusted HR, 1.02 [95% CI, 1.01–1.03] per 1-year decrease).[60]

Type of Menopause

Previous studies suggest that CHD risk varies by type of menopause, with risk being higher for menopause caused by bilateral oophorectomy (BSO) with no estrogen therapy use than for natural menopause.[61] A 2007 review underscored the importance of assessing this risk in the setting of age at surgery relative to the timing of natural menopause.[62] In this report, hysterectomy without BSO was not associated with increased CVD risk, whereas there was little to no association between BSO and CVD risk when BSO occurred around the time of natural menopause. However, CHD risk was substantially higher when BSO occurred at a younger age (<40–45 years).[62] Other studies have found similar results.[60,63] According to a large cohort study of 144 260 postmenopausal women in the United Kingdom, the risk for composite CVD among women with BSO before 40 years of age did not differ from that in women with premature natural menopause (<40 years).[64]

In an effort to understand mechanistic pathways by which surgical menopause might increase CHD risk compared with natural menopause, researchers assessed changes in CVD risk factors from before to after surgery and changes from before to after natural menopause.[65,66] In a longitudinal analysis from the SWAN study of nearly 2000 women observed over 9 years across the FMP or age at surgery, hysterectomy with or without ovarian conservation was not a key determinant of CVD risk factor status either before or after elective surgery in midlife.[65] Findings from CARDIA (Coronary Artery Risk Development in Young Adults Study) are similar.[66]

Menopause Stages

A cross-sectional analysis of a Korean cohort of 2037 women 44 to 56 years of age at different stages of the MT (premenopause, early and late MT, and postmenopause; see The MT section) reported significantly higher SBP and DBP only in late versus early MT,[67] whereas a longitudinal SWAN analysis found that total cholesterol, high-density lipoprotein (HDL) cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, and lipoprotein(a) peaked during late perimenopause and early postmenopause, with a relative

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odds of 2.1 (95% CI, 1.5–2.9 for an LDL-C ≥130 mg/dL) during the early postmenopausal compared with premenopausal stages.[68]

Metrics of vascular health also have been evaluated in relation to menopause stages. Progression rates of carotid intima-media thickness (cIMT) and adventitial diameter differed by menopause stage in a longitudinal SWAN analysis of repeated carotid scan measures over the MT, with structural carotid artery remodeling being most evident during the late perimenopausal stage compared with the premenopausal and early perimenopausal stages.[69] A later SWAN study reported that midlife women undergoing the MT had more rapid increases in aortic pulse wave velocity than women who remained premenopausal or were postmenopausal throughout an average of 2.3 years of follow-up.[70]

Endogenous Estrogens

Declining endogenous estradiol levels during the MT also have been associated with a wide range of cardiovascular risk factor changes. However, this literature has been limited by cross-sectional design and an overemphasis on postmenopausal women, thereby yielding complex and inconsistent associations.[13] In contrast, results from studies linking estradiol with subclinical measures of atherosclerosis have been more consistent. For example, in cross-sectional analyses of late perimenopausal and postmenopausal women, higher estradiol levels were related to a smaller carotid interadventitial diameter (suggesting less carotid remodeling), whereas higher estrone levels were related to a higher brachial flow-mediated dilation (ie, better endothelial function).[71] SWAN also reported an association between higher estradiol levels and lower progression of carotid interadventitial diameter over time.[72] Different associations were seen when trajectories of estradiol over the FMP were evaluated (Figure 2A). Specifically, compared with women with low estradiol before and after their FMP, SWAN participants with higher estradiol before their FMP but lower estradiol thereafter appeared to be less likely to develop carotid plaque after menopause.[73]

Vasomotor Symptoms

Vasomotor symptoms reported at midlife have been linked to an adverse lipid profile, insulin resistance, and greater risk for incident hypertension.[13,15] A cross-sectional SWAN analysis reported that women with hot flashes had reduced flow-mediated dilation and greater aortic calcification, independently of CVD risk factors and estradiol, compared with women reporting no hot flashes.[74] In a SWAN ancillary study, women who reported hot flashes at both baseline and follow-up visits, which were 2 years apart, had higher cIMT than those reporting no hot flashes, particularly among women who were overweight or obese.[75]

Some research indicates that vasomotor symptoms–CVD risk associations may be sensitive to the timing or duration of vasomotor symptoms. In a longitudinal SWAN analysis exploring trajectories of vasomotor symptoms, women with vasomotor symptoms early in the MT had higher mean and maximal cIMT than those with consistently low frequency of vasomotor symptoms across the transition.[76] A link between vasomotor symptoms and the development of CVD has also been reported. In this respect, a meta-analysis of 10 studies that included 213 976 women with a total of 10 037 CVD outcomes compared women with and without any menopausal symptoms reported that the presence of vasomotor symptoms and other menopausal symptoms was generally associated with increased risk of CHD, stroke, or CVD. Notably, only the association between menopausal symptoms and CHD persisted after adjustment for established CVD risk factors (RR, 1.28 [95% CI, 1.08–1.52]).[77]

Sleep Disturbance

Cross-sectional studies of women at different stages of the MT showed significant associations of objective measures of poorer sleep quality with greater risk of metabolic syndrome[78] and both carotid plaque and cIMT.[79] Self-reported poor sleep quality has been independently linked to a greater risk of aortic calcification in midlife women[80] and to higher arterial stiffness in perimenopausal, but not premenopausal, women.[81] In a recent exploratory analysis of the impact of menopause status on associations between subjective measures of sleep quality and cardiovascular health, as measured by the AHA Life's Simple 7 score, shorter sleep duration, poorer sleep quality, and greater severity of insomnia were associated with worse AHA Life's Simple 7 scores in postmenopausal, but not premenopausal, women.[82]

Depression

Depressive symptoms during the MT also have been strongly linked to increased CVD risk.[83–85] In healthy women 46 to 59 years of age in the SWAN Heart Study followed up for 5 years, having ≥3 versus no episodes of depression was significantly associated with elevated coronary artery calcification scores.[84] Among postmenopausal women enrolled in the WHI trials (Women's Health Initiative) with no history of CVD and followed up for an average of 4.1 years, depression was an independent predictor of CVD death and all-cause mortality after adjustment for demographics and established risk factors for CVD.[85]

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CARDIOMETABOLIC HEALTH CHANGES ACCOMPANYING THE MT BEYOND CHRONOLOGICAL AGING

As discussed below, key cohort studies, including SWAN,[69,72,86,87] the Melbourne Women's Midlife Health Project,[88–90] the Healthy Women Study,[91] the Penn Ovarian Aging Study,[92] and the Seattle Women's Health Study,[93] were specifically designed to address relative contributions of chronological and reproductive aging to cardiometabolic health. The Atherosclerosis Risk in Communities cohort,[94] the Nurses' Health Study II,[95] and other prospective cohorts,[96–99] although not designed for this primary purpose, have also offered important insights. In their efforts to disentangle the contribution of the MT beyond aging, longitudinal studies analyzed health measures anchored to time elapsed since menopause and tested whether a linear or a piecewise model better fit the analyzed data. The linear model was consistent with chronological aging, whereas the piecewise linear model suggested ovarian aging.

Lipids, Blood Pressure, Insulin, Glucose, and the Metabolic Syndrome

The SWAN study provided some of the strongest evidence on reproductive aging and changes in lipids, demonstrating that several lipid parameters (total cholesterol, LDL-C, and apolipoprotein B levels) increase dramatically within a relatively brief time span (from the year before to the year after the FMP) and that these associations were independent of the effect of aging alone.[86,100] On the other hand, HDL-C levels were found to have a complex relationship with menopause, with the quality or functional capacity of HDL undergoing alterations.[101] More specifically, the MT is associated with an apparent reversal in the direction of the association between HDL-C and CVD risk, with higher HDL-C levels associated with less carotid atherosclerosis before menopause but with greater carotid atherosclerosis after menopause.[102] The HDL changes observed during the MT include changes in HDL particle distribution and function. Moreover, preliminary work from SWAN suggests that a key antiatherogenic function of HDL particles,[103] the ability to promote the first step in the reverse cholesterol transport, may weaken during the MT.

Although menopause was not independently linked to increases in blood pressure, insulin, or glucose beyond age,[86,90] the prevalence of the metabolic syndrome (and the clustering of its components) appeared to increase with menopause, beyond the effects of chronological aging.[87,100,104] These associations have generally been consistent across cohort studies.[87,89,92,94] Moreover, a report from the Atherosclerosis Risk in Communities cohort documented that the progression and increase in severity of the metabolic syndrome were greatest during the late premenopausal and perimenopausal years rather than during the postmenopausal period ($P<0.05$).[94] The rate of change in metabolic syndrome severity during this reproductive stage was more pronounced in Black women than in White women in the cohort ($P<0.0001$ and $P=0.036$, respectively).[94]

Vascular Health Measures

Beyond changes in cardiometabolic risk factors, vascular imaging studies have shown adverse changes during the MT that extend beyond the effects of aging. In a longitudinal analysis from a SWAN ancillary study, marked increases in carotid atherosclerosis (eg, increases in cIMT and carotid adventitial diameter) were found during late perimenopause relative to premenopause that were independent of aging.[69] Most recently, a significant increase was reported in arterial stiffness (percent increase, 7.5% [95% CI, 4.1–11.1]), measured via carotid femoral pulse wave velocity, within 1 year of the FMP in SWAN participants, which was not explained by adjustment for traditional CVD risk factors.[105]

Weight Gain, Body Composition, and Ectopic Fat

Midlife weight gain, often accompanied by reduced energy expenditure, can be explained largely by changes in chronological age.[91] In SWAN, there was no difference in self-reported weight (or BMI) among premenopausal versus postmenopausal women after adjustment for age.[106] In both SWAN and the Healthy Women Study, change in body weight was prospectively assessed during the MT. In both studies and over the 3-year period, women gained an average of ≈2.0 to 2.3 kg, but these differences were not related to menopausal status.[91,100,106]

Although weight change was more closely related to chronological than reproductive aging, the MT was found to be independently associated with adverse changes in body composition and increases in visceral adipose tissue.[100] Using dual energy x-ray absorptiometry, SWAN investigators examined change in body composition over 18 years across the FMP (8 years before and 10 years after the FMP). Of note, ≈2 years before the FMP, the rate of fat gain doubled and lean mass declined, which continued until 2 years after the FMP, suggesting that accelerated gains in fat mass and losses of lean mass are menopause-related phenomena.[107] In a study of 23 women who underwent MRI assessments of body composition when they were premenopausal and then ≈8 years later when they were postmenopausal, there were statistically significant increases in total abdominal fat, subcutaneous adipose tissue, and visceral adipose tissue but no significant changes in weight, waist circumference, or

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lean mass after adjustment for age.[108] Other studies have had similar findings.[109–111] Ectopic fat deposition, defined as the accumulation of excess adipose tissue in organs such as the heart and liver, may relate to the MT. Research involving imaging of intrathoracic adiposity has suggested a link between paracardial fat depositions (the fat outside the parietal layer of the pericardium) with menopause and lower endogenous estradiol levels that are independent of age. Fat deposition around the heart may be particularly deleterious, given its close proximity to the myocardium and role in secreting inflammatory cytokines.[112] Indeed, mounting evidence supports its link with CVD risk,[113] as well as greater accumulations during late perimenopause and postmenopause compared with the premenopausal period, independently of age and other potential confounders.[114] New research from the KEEPS trial (Kronos Early Estrogen Prevention Study) of MHT use and atherosclerosis progression in recently menopausal women demonstrated a differential effect of MHT (based on the type of agent used or route of administration) on heart fat deposition[115] and its association with both coronary artery calcification[115] and cIMT.[116]

Compared with premenopausal women, postmenopausal women may be at a greater risk of fat deposition in the liver, although the literature has not been consistent.[117–120] An overnourished zebrafish model has shown that ovarian senescence triggers the development of hepatic steatosis and the fibrotic progression of liver disease,[118] suggesting that menopause-related hormonal changes contribute to fat accumulation in liver after menopause. However, a number of studies linking years from menopause[119] and timing of menopause (early [<45 years of age], normal [45–54 years of age], and late (≥55 years of age) postmenopause)[120] with risk of nonalcoholic fatty liver disease do not support this link.

WOMEN'S CARDIOVASCULAR HEALTH (LIFE'S SIMPLE 7) AT MIDLIFE: CURRENT STATUS

The AHA operationalizes cardiovascular health (referred to as Life's Simple 7) as ideal, intermediate, or poor according to 7 core health indicators: BMI, physical activity, smoking, diet, cholesterol, blood pressure, and fasting glucose.[121] At any age, women tend to have more metrics at ideal levels than men, yet only one-fifth of women ≥20 years of age have ≥5 metrics of ideal cardiovascular health according to the National Center for Health Statistics and NHANES (National Health and Nutrition Examination Survey) 2013 to 2014.[1] Data characterizing the current status of metrics of cardiovascular health in women transitioning through menopause are limited. Thus, data from postmenopausal women were presented as appropriate.

BMI and Adiposity

More than 42% of US women 40 to 59 years of age have a BMI ≥30 kg/m^2.[1,122] The age-adjusted prevalence of obesity is higher among middle-aged women (40–59 years of age, 42.1%) than younger women (20–39 years of age, 34.4%).[123]

In postmenopausal women with a BMI ≥40 kg/m^2, a waist circumference of 115.5 to 122 and >122 cm, compared with ≤108.4 cm, was associated with higher total mortality and incidence of both CHD and heart failure.[124] Moreover, postmenopausal women who had normal BMI with higher central adiposity (defined as waist circumference ≥88 cm) were at higher risk of mortality than those with normal BMI and no central adiposity.[125]

Physical Activity and Sedentary Behavior

Evidence demonstrates a strong inverse dose-response association between amount of physical activity and cardiovascular mortality.[126] Current recommendations encourage women to engage in ≥150 min/wk of moderate-intensity aerobic (or 75 min/wk of vigorous) physical activity.[127] Notably, only 7.2% of midlife women from the SWAN study self-reported physical activity levels that consistently met the current recommendations.[128] Among adults 20 to 59 years of age, 3.2% of women and 3.8% of men met recommendations to engage in moderate to vigorous physical activity for 30 minutes (in sessions of ≥10 minutes) on ≥5 of 7 days.[1] For objectively measured (eg, by accelerometer) moderate to vigorous physical activity, adherence to physical activity recommendations was 2.3% among women ≥60 years of age and 2.5% for men of the same age.[1]

A systematic review found that the association between sedentary behavior and all-cause mortality and CVD mortality was nonlinear.[129] Specifically, the risk for all-cause and CVD mortality risk increased more rapidly with >8 h/d of sedentary behavior.

Cigarette Smoking

Currently, ≈13.5% of adult women are smokers.[1] Conversely, data from the SWAN study showed that 62.2% of the study participants never smoked and remained in this status over time.[128] On the basis of age-adjusted estimates in 2015, among people ≥65 years of age, 9.7% of men and 8.3% of women were current smokers.[1]

Women who smoke die ≈11 years earlier than women who have never smoked.[130] A meta-analysis of prospective cohort studies suggests that the relative risk of CHD from smoking 1 cigarette per day is higher in

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women than in men.[131] Compared with women who never smoked, women who smoke have an increased risk of CHD and stroke incidence, as well as mortality from CHD and all causes.[132]

Diet

In a recent analysis from the SWAN study, only 17.8% of study participants consistently stayed in the top tertile of the alternate Healthy Eating Index, a well-established scale to quantify diet quality in 9 nutrient components (vegetables, fruit, nuts, white to red meat consumption, cereal fiber, *trans* fat, ratio of polyunsaturated/saturated fatty acids, multivitamins, alcohol consumption), with higher values indicating higher-quality diet, over the MT.[128] In the Netherlands Epidemiology of Obesity study, a prospective cohort study of 6671 individuals 45 to 65 years of age, dietary intake of fruit and vegetables and plant-based fats and oils was associated with less visceral fat, and intake of sweet snacks was associated with more liver fat.[133] More than half of the 3576 women in the study were postmenopausal.

Cholesterol

Among US adults ≥60 years of age, only 25.2% have a total cholesterol level <200 mg/dL.[1] The prevalence of LDL-C ≥130 among women ≥ 20 years of age is 30.4%. Some variation in mean LDL-C levels is noted between racial/ethnic groups of women, with the highest mean LDL-C levels for non-Hispanic White women at 114.9 mg/dL compared with 112.1 mg/dL for men. The mean LDL-C levels for women were 111.4 mg/dL for non-Hispanic Black women, 112.6 mg/dL for Hispanic women, and 110.3 mg/dL for non-Hispanic Asian women.[1]

Blood Pressure

Hypertension remains the most prominent modifiable CVD risk factor that increases with age among women.[134,135] Although a higher percentage of men had hypertension before 65 years of age (NHANES data 2013–2016), a higher percentage of women had hypertension thereafter, with the gap between men and women reaching its nadir at ≈55 to 64 years of age.[1] Women >60 years of age are less likely to have controlled blood pressure (49.2%) compared with younger women (40–49 years of age, 54.2%; 18–39 years of age, 62.6%).[136] According to NHANES 2010 to 2016 data among adults ≥20 years of age, 38.8% of non-Hispanic White women, 53.2% of non-Hispanic Black women, and 37.9% of Hispanic women had hypertension.[1] Pooled data from 124 prospective cohort studies that included 1.2 million individuals, of whom 44% were women, found that, after controlling for comorbidities, every 10–mm Hg increase in SBP was associated with a 15% increased risk of CVD for both men and women.[137]

Fasting Glucose

Diabetes is a stronger risk factor for CVD mortality in women than in men,[138,139] and some evidence suggests a link between menopause and higher risk of type 2 diabetes.[140] In a pooled analysis of >850 000 participants with diabetes, the risk of CVD was 44% greater in women compared with men.[141] Unfortunately, the prevalence of diabetes has increased significantly for both men and women over the past 2 decades. Clinically diagnosed diabetes was reported in 5.4% of both men and women ≥20 years of age in the 1988 to 1994 NHANES survey and in 10.9% of men and 8.9% of women in the 2013 to 2016 survey.[1]

EFFECT OF LIFESTYLE INTERVENTIONS ON CARDIOMETABOLIC HEALTH AND CVD RISK IN MIDLIFE WOMEN: INTERVENTION TIMING

To achieve ideal cardiovascular health, as presented in the 2011 AHA's classification of CVD risk in Women and Life's Simple 7,[6,121,142] lifestyle interventions should bring about smoking cessation in smokers, weight loss in overweight women, a DASH (Dietary Approaches to Stop Hypertension)–like eating pattern,[143,144] physical activity to recommended levels,[127] and optimization of total cholesterol, fasting blood glucose, and blood pressure levels.[145,146] Strong lines of evidence support the critical contribution of controlling these factors in reducing CVD burden. However, very limited research has focused on the timing of lifestyle interventions as related to the MT, when women are subjected to multiple adverse changes in several cardiometabolic health parameters simultaneously (see the Cardiometabolic Health Changes Accompanying the MT Beyond Chronological Aging section).

Randomized Clinical Trials of Lifestyle Interventions on Cardiometabolic Health in Women's Transition Through Menopause

Early randomized clinical trials (RCTs) examining the potential cardiovascular benefits of diet and exercise interventions in middle-aged women, including the SWCP-II (second Stanford Weight Control Project)[147] and the DEER trial (Diet and Exercise for Elevated Risk),[148] intentionally included or excluded participants by menopausal status. Both trials found significant lipid profile improvements and reduced central obesity

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from a reduced-fat (total and saturated) diet combined with increased physical activity.[147,148] Of note, these trials recruited women with different baseline lipid profiles and different phases of the MT. Therefore, any differences in the intervention effects on cardiovascular risk could not be directly attributed to differences in menopausal status.

The Pittsburgh WHLP (Women's Healthy Lifestyle Project) was probably the first and, to date, is the only RCT designed specifically to assess the effects of a diet and exercise intervention during the MT.[149] The WHLP trial randomized 535 healthy premenopausal women 44 to 50 years of age to an assessment-only control group or a 5-year cognitive-behavioral program that included a hypocaloric diet with reduced saturated fat and cholesterol combined with moderately increased leisure-time physical activity. An LDL-C increase in the control group during perimenopause to postmenopause was blunted in the intervention group. In addition, the intervention prevented weight gain from premenopause to perimenopause to postmenopause and reduced triglycerides, SBP, DBP, and blood glucose and insulin.[149] MHT use did not modify the associations between treatment groups and changes in LDL-C and other CHD risk factors. In addition, the intervention slowed cIMT progression among perimenopausal/postmenopausal (0.008 mm/y for the control group versus 0.004 mm/y for the intervention group; *P*=0.02), whereas no differences were seen in premenopausal women.[150]

Most lifestyle intervention trials of cardiovascular risk factors in middle-aged (between 40 or 45 and 64 years or up to 69 years of age) women published since the WHLP trial have also distinguished between premenopausal and postmenopausal women, with the specific intention of not including women in the MT. For example, a small single-arm (diet and physical activity) weight loss intervention study showed significantly fewer changes in metabolic risk factors between 22 premenopausal women (mean±SD age, 43.7±6.4 years) and 50 postmenopausal women (mean±SD age, 58.2±5.1 years).[151] Moreover, in a 2018 systematic review and meta-analysis of 17 small RCTs (a total of 792 women) on the effects of exercise on body composition, cardiovascular risk factors, and bone mineral density among menopausal women, exercise exerted significant benefits on body fat, waist circumference, and triglyceride levels. Of note, all participants were postmenopausal.[152]

We were unsuccessful in finding lifestyle RCTs that recruited participants or stratified randomization by menopausal stage or other menopausal characteristics associated with greater cardiovascular risk such as early age of menopause or vasomotor symptoms, discussed in the Menopause Characteristics Relevant to CVD Risk and Cardiometabolic Health Changes Accompanying the MT Beyond Chronological Aging sections.

Lifestyle Behaviors and Cardiometabolic Health in Midlife Women

With the growing body of literature supporting an acceleration of CVD risk and associated factors as women transition through menopause (Menopause Characteristics Relevant to CVD Risk and Cardiometabolic Health Changes Accompanying the MT Beyond Chronological Aging sections), increasing efforts have been directed at testing associations between healthy lifestyle behaviors and CVD risk in women in the observational study setting. The Nurses' Health Study provided some of the strongest and earliest evidence of the benefit of adherence to a healthy lifestyle, including diet, exercise, and abstinence from cigarette smoking, in reducing CHD risk in women.[153] Women who adhered to multiple healthy lifestyle parameters over 14 years of follow-up (only 3% of the study population) had an RR of coronary events of 0.17 (95% CI, 0.07–0.41) compared with all other women.[153]

A recent large systematic review and meta-analysis of 59 prospective cohort studies involving >5.3 million middle-aged and elderly (not defined) women evaluated associations between modifiable lifestyle factors and fatal and nonfatal CVD events.[132] In a comparison of women who currently smoked and never smokers, the pooled reduced risks were 3.12 (95% CI, 2.15–4.52) for CHD incidence, 2.09 (95% CI, 1.51–2.89) for stroke incidence, and 2.76 (95% CI, 1.62–4.71) for CVD mortality.[132] Studies comparing the effects of cigarette smoking cessation in perimenopausal and postmenopausal women with premenopausal women on CVD-related outcomes are rare.[154]

In the same meta-analysis described above, both lower BMI and greater leisure physical activity were associated with lower CVD risk.[132] Specifically, compared with women with a BMI <25 kg/m^2, CHD risk increased from 1.47 (95% CI, 1.20–1.81) for a BMI of 25 to 30 kg/m^2 to 1.67 (95% CI, 1.24–2.25) for a BMI of 30 to 35 kg/m^2. Moreover, women who reported leisure physical activity had a reduced risk of CHD (0.71 [95% CI, 0.67–0.75]), stroke (0.77 [95% CI, 0.70–0.85]), and CVD mortality (0.70 [95% CI, 0.58–0.84]).[132]

Despite voluminous literature showing that weight-reducing dietary changes may reduce CVD risk in obese adults,[143,155,156] we are unaware of a meta-analysis focusing on CVD risk in middle-aged women for a healthy eating pattern that emphasizes fruits, vegetables, and low-fat dairy products and reduced saturated fatty acids, red meat, sweets, and beverages containing added sugars and includes whole grains, poultry, fish, and nuts.

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In 1143 participants, the SWAN study prospectively tested associations of a composite healthy lifestyle score, constructed from self-reported data on cigarette smoking, diet, and physical activity, and subclinical atherosclerosis as common cIMT and interadventitial diameter, measured 14 years after baseline.[128] Compared with women in the lowest score level, those in the highest score level (indicating healthier lifestyle) had 0.024-mm-thinner cIMT (95% CI, −0.048 to 0.00) and 0.16-mm-smaller interadventitial diameter (95% CI, −0.27 to −0.04). Abstinence from cigarette smoking showed the strongest inverse associations with measures of subclinical carotid atherosclerosis (never smokers had 0.047-mm thinner-cIMT [95% CI, −0.07 to −0.024] and 0.24-mm-smaller interadventitial diameter [95% CI, −0.35 to −0.13]) and 49% lower odds of higher carotid artery plaque risk (odds ratio, 0.51 [95% CI, 0.35–0.73]) compared with those who smoked during follow-up.[128]

In another SWAN study that included 721 midlife women with prevalent metabolic syndrome at baseline, reversal of metabolic syndrome was observed in 16.7% of the included women. Eating fewer calories over the MT (HR, 0.96 [95% CI, 0.93–0.990] per 100 kcal] was associated with this reversal, whereas physical activity was associated with 60% lower risk of developing metabolic syndrome among 493 women without metabolic syndrome at baseline in the same study.[157]

EFFECTS OF MENOPAUSAL HORMONE THERAPY USE ON CARDIOMETABOLIC HEALTH AND CVD EVENTS

All high-quality evidence to date on the effects of MHT use on cardiometabolic health is based on clinical trials conducted among postmenopausal women. No data are available on the effects of MHT use on cardiometabolic health in women during perimenopause, who may need to use MHT to treat MT-related symptomatology. In fact, US Food and Drug Administration guidance on clinical trial design for new products to be approved for treating vasomotor symptoms recommends including only postmenopausal women, defined as those with 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone levels >40 mIU/mL or women 6 weeks after BSO with or without hysterectomy.[158]

Timing of MHT Initiation

Evidence suggests that the effects of MHT on the progression of atherosclerosis and CVD events vary by age or time since menopause when MHT is initiated. Specifically, beneficial effects on CVD outcomes and all-cause mortality may occur when MHT is initiated in women <60 years of age or <10 years since menopause, whereas null or harmful effects may occur when MHT is initiated at older ages or after greater time since menopause. Numerous observational studies before 1991, reflecting the clinical practice of initiation MHT use near the time of menopause, reported reduced rates of CHD in MHT users.[159] A 1991 analysis of prospective observational studies reported an overall summary relative risk of CHD events of 0.50 (95% CI, 0.43–56).[160] Analyses from the Nurses' Health Study (in women 30–55 years of age at baseline) showed a lower risk of mortality among current users compared with those who never used MHT (RR, 0.63 [95% CI, 0.56–0.70]), with the mortality reduction greater in women at higher risk.[161] Case-control and cross-sectional studies also found reduced CHD morbidity with MHT for women with angiographically defined CHD.[159,162–164]

Building on the above data, clinical trials of secondary prevention for CHD (HERS [Heart and Estrogen/Progestin Replacement Study]) and stroke (Women's Estrogen for Stroke Trial) were conducted in the 1990s with average ages at baseline of 67 and 72 years, respectively. Neither of these trials found benefit with MHT.[165,166] Moreover, the WHI trials shared the premise that, because MHT appeared protective against CVD in observational studies that included recently menopausal women,[167] it might be more effective in women at greater risk. The WHI trial of conjugated equine estrogens (CEEs) plus medroxy-progesterone acetate (MPA) found no CHD protection in the cohort overall (mean age, 63 years; 12 years postmenopausal; HR, 1.24 [95% CI, 1.00–1.57]).[168] However, trends were consistent with prior literature,[155,160] with HRs of 0.89 in women within 10 years of menopause and 0.95 in women 50 to 59 years of age with hot flashes. Notably, these results were not statistically significant in the limited sample in these age ranges (31% of the cohort) because the WHI was heavily weighted toward women distant from menopause.[168]

The WHI trial of CEEs alone in women with hysterectomy also reported no benefit for CHD in the overall cohort 50 to 79 years of age (HR, 0.95 [95% CI, 0.79–1.16]). In this arm, women 50 to 59 years of age had a reduced risk of a composite coronary outcome [HR, 0.66 [95% CI, 0.45–0.96]) but not of the primary outcome (myocardial infarction or coronary death), probably because of the low event rate in young women.[169] HRs for stroke were elevated by 35% to 40% with both MHT regimens in the overall WHI cohorts of women 50 to 79 years of age, without significant interaction by age. However, in women 50 to 59 years of age, stroke event rates were identical with CEE and placebo.[170,171]

In an overview of findings from the intervention and extended postintervention phases of the 2 WHI trials, results for CHD and stroke were similar to those of earlier reports.[172] Consistent with observational studies,

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all-cause mortality was reduced 31% relative to placebo in women 50 to 59 years of age only when the 2 MHT trials were pooled (because of their similar results for mortality). The test for trend by age was significant (*P*=0.01), indicating a contrast in mortality between younger and older women.[173] DOPS (Danish Osteoporosis Prevention Study) tested oral estradiol alone in women with hysterectomy and combined with norethisterone acetate in women with an intact uterus. Mean age was 50 years, and the primary end point was a composite of hospitalized heart failure, myocardial infarction, and death. After 10 years of treatment, the primary end point was reduced with MHT (HR, 0.48 [95% CI, 0.26–0.87]), and the effect on stroke was null.[174]

A meta-analysis of randomized trials in young postmenopausal women (mean age, 55 years) suggested a 27% reduction (RR, 0.73 [95% CI, 0.52–0.96]) in mortality with MHT compared with no treatment.[175] Similarly, meta-analyses limited to trial data stratified by either age or time since menopause showed that MHT may decrease CHD and all-cause mortality by 30% to 48% when initiated in women <60 years of age or <10 years since menopause.[176–179] In the most recent Cochrane systematic review evaluating RCTs of MHT for preventing CHD in postmenopausal women, among women initiating MHT at <60 years of age or <10 years since menopause, CHD risk was reduced by roughly half (RR, 0.52 [95% CI, 0.29–0.96]) and all-cause mortality by 30% (RR, 0.70 [95% CI, 0.52–0.95]). Venous thromboembolism was increased (RR, 1.74 [95% CI, 1.11–2.73]), but there was no evidence of an excess risk of stroke with MHT.[178] In contrast, in women initiating MHT at >60 years of age or >10 years since menopause, MHT had no effect on CHD or all-cause mortality.[178] Of note, risks for stroke and venous thromboembolism were increased.[178]

The timing effect was also examined with the use of nationwide registers of postmenopausal MHT use (n=498 105) in Finland (1994–2009) to evaluate CHD death among users of estradiol-based MHT according to age at the initiation of therapy.[180] The CHD standardized mortality ratio was lower among women who initiated MHT at <60 years of age compared with those initiating at older ages (for estradiol alone, 0.53 [95% CI, 0.47–0.59] versus 0.76 [95% CI, 0.71–0.82]; for estradiol/progestin, 0.45 [95% CI, 0.41–0.49] versus 0.74 [95% CI, 0.67–0.81]).[180]

Two trials have assessed the effect of MHT on the age-related increase in cIMT, an established measurement of atherosclerosis progression.[181–184] In the 4-year KEEPS trial, low-dose oral (CEE 0.45 mg/d) and patch (estradiol 50 µg/d) estrogen had no significant effect on cIMT progression in healthy newly menopausal women.[185] In contrast, the 5-year ELITE trial (Early Versus Late Intervention Trial With Estradiol) showed reduced cIMT progression with oral estradiol 1 mg daily in women <6 years, but not in women >10 years, postmenopausal (*P* for interaction=0.007).[186] The reasons for the outcome differences between KEEPS and ELITE are unclear, but a possibility is a higher dose of estrogen in the latter.[187]

Route of Administration and MHT Formulations

Clinical trial comparisons of MHT formulations and routes of administration with CVD outcomes are not available. Recent evidence from large observational studies suggests potential differential effects based on the type of estrogen, route of administration, or type of progestin agent in combined regimens. A report from the WHI observational study of 93 676 postmenopausal women (50–79 years of age at baseline) followed up between 1994 and 2009 compared CVD outcomes among various estrogen regimens. Nonsignificant trends for lower rates of CHD, stroke, and CVD mortality, but not all-cause mortality, were reported for transdermal estradiol compared with oral CEEs.[188] In a US matched-cohort study of health insurance claims between 1999 and 2011, transdermal estrogen preparations were associated with a lower incidence of CVD complications compared with oral estrogen preparations (incidence rate ratio, 0.81 [95% CI, 0.67–0.99]), regardless of the type of estrogen agent used.[189] Most recently, 2 large nested case-control studies using the QResearch and Clinical Practice Research Datalink database in the United Kingdom evaluated the associations between various MHT regimens and the risk of venous thromboembolism.[190] Oral MHT preparations were associated with increased venous thromboembolism, whereas transdermal preparations were not. CEE was associated with a higher risk than estradiol. Within the oral regimens, CEE+MPA had the highest risk, and estradiol+dydrogesterone had the lowest. Micronized progesterone was not evaluated.[190]

MHT Use as Related to Cardiometabolic and Vascular Health

Body Fat Distribution

After 3 years of treatment, lean soft tissue mass was preserved and upper body fat distribution, assessed as change in ratio of trunk to leg fat mass, was lower among WHI women in the CEE+MPA group compared with those in the placebo group.[191] In PEPI (Postmenopausal Estrogen/Progestin Interventions Study), women on CEE-based regimens averaged 1 kg less weight gain (*P*=0.006) and 1.2 cm less increase in waist circumference (*P*=0.01) than those given placebo after 3 years of follow-up.[192] In KEEPS, although no statistically significant differences were observed in BMI changes across

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treatment groups, women on oral CEE showed smaller increases in BMI compared with those on transdermal estradiol or placebo. There was also a trend for less increase in waist circumference.[193]

Metabolic Syndrome Components

In PEPI, CEE-based regimens were associated with decreases in fasting glucose (P=0.03) and fasting insulin (P=0.07), but there was no effect on SBP or DBP.[194] In KEEPS, transdermal estradiol was associated with decreases in fasting insulin and fasting glucose versus placebo, whereas oral CEE was not. However, both oral and transdermal treatments were associated with significant decreases in insulin resistance, measured via the Homeostatic Model Assessment of Insulin Resistance score, compared with placebo.[185] In both the WHI and HERS, CEE+MPA was associated with a reduced incidence of type 2 diabetes, as was CEE alone in the WHI.[172,195]

Vascular Health

ELITE showed lower cIMT progression with oral estradiol versus placebo in women <6 years postmenopausal.[186] However, at a lower dose of oral CEE or transdermal estradiol versus placebo, KEEPS showed no benefit in cIMT progression and no change in coronary artery calcium score in women <3 years postmenopausal.[185] Among WHI women 50 to 59 years of age, CEE alone was associated with lower mean coronary artery calcium score assessed ≈1 year after trial completion (P=0.02), and differences were larger in women at least 80% adherent to study treatment.[196]

Stopping MHT

To assess related risks of cardiovascular events and all-cause mortality after MHT is stopped, surviving participants from both WHI trials (CEE+MPA trial and CEE alone trial) were followed up after trial completion for a median of 8.2 years in the CEE+MPA trial and 6.6 years in the CEE alone trial. In both cases, postintervention results were neutral for CHD, stroke, pulmonary embolism, and all-cause mortality.[172] Conversely, a Finnish national study of 1.97 million women-years of follow-up (baseline age, 40–107 years) reported a >2-fold increase in cardiac and stroke deaths in the first year after stopping MHT use (median age at starting, 52 years; median age at stopping, 59 years).[197] Results were the same in a follow-up analysis that excluded women with nonfatal cardiac or stroke events within 1 year before stopping MHT.[198] Notably, the risks were greater in Finnish women <60 years of age or in those who used MHT for >5 years.[197,198] However, results from the randomized WHI trials and the observational Finnish studies are likely not comparable because of differences in study designs, characteristics of study populations, and the MHT regimens. The Finnish study did not have any data on the reasons why MHT was stopped or the cardiovascular risk factors during MHT use that may have led to stopping MHT.

In summary, positive early expectations for MHT on the prevention of CVD were based on data derived mostly from observational studies and 1 clinical trial (which focused on CVD risk factors) of newly menopausal women. Later, these were replaced by a concern for harm in trials that enrolled women who were on average a decade or more postmenopausal. Since then, evolving research has shown that timing of initiation is likely relevant to coronary benefit and that there may be differences by route of administration and treatment regimen. Current recommendations from leading specialty societies endorse the use of MHT in recently menopausal women with appropriate indications.[199–201] The evidence supports cardiovascular benefit for MHT initiated early among women with premature or surgical menopause and within 10 years of menopause in women with natural menopause. The benefits of MHT (ie, including lower rates of diabetes, reduced insulin resistance, and protection from bone loss) appear to outweigh risks for the majority of early menopausal women. Perimenopausal women should be provided individualized guidance on MHT and options for treatment, particularly when vasomotor symptoms are present.

LIPID-LOWERING MEDICATIONS IN WOMEN

Although an optimal lipid profile is a measurable objective in the prescription of lipid-lowering therapies for women with elevated risk, data for primary and secondary prevention of atherosclerotic CVD and improved survival with lipid-lowering interventions remain elusive for women. Nonpharmacological therapies that incorporate lifestyle modification (exercise, weight loss, smoking cessation, and heart-healthy diet) are recommended as the first-line strategy for improving lipid profiles.[202] In addition, dietary interventions, herbal products, and nutritional supplements have been used in holistic practices to promote health and to prevent the development of heart disease.[203] ω-3 and ω-6 polyunsaturated fatty acids have been evaluated extensively in this regard. For example, in a recent meta-analysis, ω-3 was significantly associated with reductions in CHD (RR, 0.93 [95% CI, 0.89–0.98]) and myocardial infarction (RR, 0.92 [95% CI, 0.85–0.99]) but not CVD mortality (RR, 0.98 [95% CI, 0.93–1.02]) or all-cause mortality (RR, 0.93 [95% CI, 0.86–1.01]).[203] Similarly, in a Cochrane analysis, ω-6 acids were found to lower total cholesterol (mean difference, –0.33 mmol/L [95% CI, –0.50 to –0.16]), but the reduction of myocardial infarction in high-risk individuals was

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not statistically significant (RR, 0.88 [95% CI, 0.76–1.02]).[204] Notably, the ω-3 and -6 studies included relatively few women, for whom menopausal status was unreported, challenging a general application of these results to this population.

Numerous studies have evaluated lipid-lowering medications for the prevention of atherosclerotic CVD, with most focusing on HMG-CoA reductase inhibitors (ie, statins). Limited RCT evidence for the primary prevention of CVD with statin therapy derives from a cohort of women (n=6801) with baseline LDL-C <130 mg/dL and high-sensitivity C-reactive protein >2 mg/dL studied in the JUPITER trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin).[205] Although fatal and nonfatal myocardial infarction and all-cause mortality were not reduced with statin therapy across the entire cohort of women in JUPITER, arterial revascularization was reduced in the subgroup of women >60 years of age.[205]

In the MEGA trial (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese), in which a large cohort of women (n=5356) were followed up for >5 years of statin therapy, the effect on CHD and all-cause mortality was null.[206] In a subgroup analysis, noncardiovascular mortality was reduced in women >55 years of age.[206] Furthermore, the sex-specific data from the online supplement of the HOPE-3 trial (Heart Outcomes Prevention Evaluation-3), a large RCT of women (n=5871) and men (n=6831) with intermediate risk for CHD, provide further evidence that statin therapy had a nonsignificant effect on CHD and all-cause mortality for primary prevention in women.[207]

Of the meta-analyses comparing primary prevention trials of statin therapy, primary prevention of CHD has been demonstrated in men (n=28 346; RR, 0.59 [95% CI, 0.48–0.74][208]; and n=26 921; RR, 0.72 [95% CI, 0.61–0.86][209]) but not in women (n=13 346; RR, 0.89 [95% CI, 0.79–1.00][208]; and n=20 817; RR, 0.79 [95% CI, 0.56–1.13][209]), whereas the results for all-cause mortality were null for both sexes.[208,209] In a large meta-analysis of primary and secondary prevention trials of the Cholesterol Treatment Trialists' database comprising 46 675 (27%) women, the effect size of primary prevention with statin therapy was smaller and nonsignificant in women compared with men (rate ratio of major vascular event, 0.72 [95% CI, 0.66–0.80] in men versus 0.85 [95% CI, 0.72–1.00] in women).[210] Simultaneous incorporation of both primary and secondary prevention trials into the analysis strengthened the finding of a CVD reduction in women. A meta-analysis that analyzed primary and secondary prevention trials with statin therapy separately in women showed a significant reduction in CHD events in secondary (n=6,185; RR, 0.80 [95% CI, 0.71–0.91]), but not in primary, prevention (n=9806; RR, 0.87 [95% CI, 0.69–1.09]). All-cause mortality in women was not reduced by statin therapy in primary (n= 7677; RR, 0.95 [95% CI, 0.62–1.46]) or secondary prevention (n=2393; RR, 1.00 [95% CI, 0.77–1.29]).[211]

Although statin therapy is first-line therapy to lower LDL-C, other treatments may be considered as adjuncts or alternatives to improve the lipid profile resulting from inadequate LDL-C control or statin intolerance. The most common nonstatin therapies are bile acid sequestrants, cholesterol absorption inhibitors (ezetimibe), and PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors. The relative safety and efficacy of ezetimibe have been shown in women and men.[212] The options for lipid-lowering therapies are evolving rapidly. PCSK9 inhibitors and other targeted therapies hold unique promise in the future of CVD risk reduction therapies, but clinical trials are needed to disaggregate sex differences for women versus men. Observational data suggest that serum PCSK9 levels are higher in postmenopausal women, but the clinical significance of this finding is unknown.[213–215] Available data suggest no sex-based difference in low-density lipoprotein reduction for the newly US Food and Drug Administration–approved ATP citrate lyase inhibitor bempedoic acid.[216] On the basis of the limitations in the effectiveness of statins in improving hard outcomes for women, the new lipid-lowering medications (PCSK9 inhibitors, bempedoic acid, siRNA [small interfering RNA] class of agents [eg, inclisiran], MTTP [microsomal triglyceride transfer protein] inhibitors [eg, lomitapide], antisense oligonucleotides, and others) warrant sex-specific trials to determine efficacy for hard end points. Although evidence-based data supporting a statistically significant reduction of CVD events and all-cause mortality in primary prevention in women are lacking for statins and other lipid-lowering therapies, the current guidelines for the prevention of CVD do not provide specific recommendations for women and men independently. Therefore, the most recent lipid-lowering guidelines recommend statins as first-line therapy for CVD risk reduction, regardless of sex or menopausal status.

LATEST AHA GUIDELINES ON CVD PREVENTION IN WOMEN

Summary of Guidelines

On the basis of a review of the literature on unique aspects of CVD in women, the AHA published scientific statements addressing prevention of CVD in women in 1997 and 1999.[217,218] Using clinical criteria or the Framingham global risk score,[219] an expert panel updated the 1999 statement in 2004 to develop the first AHA evidence-based guidelines for CVD prevention in women, emphasizing the spectrum of CVD and classifying women as being at high risk, intermediate risk, low risk, and optimal risk.[220] In 2007, a further update of these

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guidelines recommended a general approach to classify women as high risk, at risk, or optimal risk,[221] recognizing that the average lifetime risk for CVD was nearly 1 in 2 in women.[222] This scheme aligned the guidelines well with available clinical trial evidence, most of which was for women at high risk or apparently healthy women with a spectrum of risk.[221] The 2007 panel also acknowledged the growing appreciation of the limitations of risk stratification with the Framingham risk function in diverse populations of women.[223]

In 2011, another AHA panel updated the 2007 recommendations as effectiveness-based guidelines for the prevention of CVD in women, which considered benefits and risks of preventive therapies observed in clinical practice rather than limiting recommendations to evidence that documented efficacy.[6] The 2011 panel continued to emphasize categorical classification of CVD risk in women as high risk, at risk, and ideal cardiovascular health, which replaced the former optimal risk category. Ideal cardiovascular health was defined by the absence of clinical CVD and the presence of all ideal levels of total cholesterol (<200 mg/dL), blood pressure (<120/80 mm Hg), and fasting blood glucose (<100 mg/dL), as well as adherence to healthy behaviors, including having a BMI <25 kg/m^2; abstaining from smoking; engaging in moderate- or vigorous-intensity physical activity at ≥150 or ≥75 min/wk, respectively, or a combination; and following a healthy (DASH-like) diet.[121]

Although these national goals were not specific to women, available data on women were evaluated in their development,[121] and on the basis of these findings, the 2011 expert panel stated that "when achieved or maintained into middle age, the overall pattern of ideal cardiovascular health is associated with greater longevity" and "dramatic reductions in short-term, intermediate-term, and lifetime risks for CVD events."[6] Other notable modifications to the risk classification algorithm included acknowledging the availability of several risk equations for the prediction of 10-year global CVD risk such as the updated Framingham CVD risk profile and the Reynolds risk score for women[224,225] and adding factors to the at-risk status group that are known to be more prevalent among women and possibly making special contributions to CVD risk in women. Specifically, systemic autoimmune collagen–vascular disease (eg, systemic lupus erythematosus or rheumatoid arthritis) and history of preeclampsia, gestational diabetes, or pregnancy-induced hypertension were included (Table).[6] Notably, menopause and menarche were mentioned only as periods of potential vulnerability across women's life span, which should be evaluated by future research to identify women at risk and to determine the effectiveness of diagnostic and preventive interventions during these critical times.[6]

The 2011 guidelines retained the Class III recommendations from the 2007 guidelines[221] that MHT, selective estrogen-receptor modulators, antioxidant vitamin supplements (eg, vitamin E, vitamin C, and β-carotene), and folic acid (with or without vitamin B_6 and B_{12} supplementation) should not be used for primary or secondary prevention of CVD. The guidelines also stated that routine use of aspirin in healthy women <65 years of age is not recommended to prevent myocardial infarction.[6]

Table. Classification of CVD Risk in Women

Risk Status	Criteria
High risk (≥1 high-risk states)	Clinically manifest CHD
	Clinically manifest cerebrovascular disease
	Clinically manifest peripheral arterial disease
	Abdominal aortic aneurysm
	End-stage or chronic kidney disease
	Diabetes
	10-y Predicted CVD risk ≥10%
At risk (≥1 major risk factors)	Cigarette smoking
	SBP ≥120 mm Hg, DBP ≥80 mm Hg, or treated hypertension
	Total cholesterol ≥200 mg/dL, HDL-C <50 mg/dL, or treated for dyslipidemia
	Obesity, particularly central adiposity
	Poor diet
	Physical inactivity
	Family history of premature CVD occurring in first-degree relatives in men <55 y of age or in women <65 y of age
	Metabolic syndrome
	Evidence of advanced subclinical atherosclerosis (eg, coronary calcification, carotid plaque, or thickened IMT)
	Poor exercise capacity on treadmill test or abnormal heart rate recovery after stopping exercise
	Systemic autoimmune collagen–vascular disease (eg, lupus or rheumatoid arthritis)
	History of preeclampsia, gestational diabetes, or pregnancy-induced hypertension
Ideal cardiovascular health (all of these)	Total cholesterol <200 mg/dL (untreated)
	BP <120/<80 mm Hg (untreated)
	Fasting blood glucose <100 mg/dL (untreated)
	BMI <25 kg/m^2
	Abstinence from smoking
	Physical activity at goal for adults >20 y of age: ≥150 min/wk moderate intensity, ≥75 min/wk vigorous intensity, or combination
	Healthy (DASH-like) diet

BMI indicates body mass index; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; HDL-C; high-density lipoprotein cholesterol; IMT, intima-media thickness; and SBP, systolic blood pressure.

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The AHA guidelines for the prevention of stroke in women published in 2014[226] stated that no study had investigated the relationship between endogenous hormones and stroke as women transition through menopause. The authors referenced a review on the role of menopause and MHT in stroke risk, which is lower in women than men during middle age but doubles during the 10 years after menopause,[227] and a review of observational studies of the association of premature (before 40 years of age) or early (between 40 and 45 years of age) menopause and the risk of ischemic stroke.[228] These observational cohort studies demonstrated an increased risk of all types of stroke in women who underwent BSO before 50 years of age compared with women who retained their ovaries.[228] The AHA guidelines stated that neither postmenopausal MHT (specifically CEE with or without MPA) nor selective estrogen-receptor modulators should be used for the primary or secondary prevention of stroke in postmenopausal women.[226]

Sex-related differences in the cardiovascular system were outlined in a 2016 AHA scientific statement on preventing and experiencing ischemic heart disease as a woman,[229] but the discussion of menopause was limited to statements on the changes in body fat discussed in previous sections of this scientific statement and results from a blood pressure study showing no differences by menopausal status in blood pressure in 152 hypertensive women (40–60 years of age) versus 40 age-matched normotensive control subjects.[230] To date, the concurrence of advancing age and menopause with increasing blood pressure continues to raise doubt as to whether menopause is an independent risk factor for high BP,[231] a major risk factor for stroke.

Premature menopause has been recognized as a risk-enhancing factor favoring statin therapy initiation in the 2018 updated guidelines of blood cholesterol management.[202]

Implications of the Evolving Findings on Menopause and CVD Risk on These Guidelines

As presented in the Menopause Characteristics Relevant to CVD Risk section, an association between age at natural menopause and CVD risk has been observed in many, but not all, population cohorts, as has a higher CVD risk with surgical menopause with BSO, particularly in women <45 years of age. However, the 2011 classification of CVD risk in women does not include early menopause among categorical risk factors. As also presented in previous sections of this statement, adverse changes in lipids and body fat deposition and increases in metabolic syndrome risk have been related to the MT independently of aging. However, the most recent AHA guidelines for CVD prevention in women have not fully addressed menopause and its related cardiometabolic consequences as independent risk factors,[6] nor have more recent AHA statements on stroke in women.[226]

The North American Menopause Society published key points and recommendations for the clinical care of midlife women in 2014, including that all women be evaluated for CVD risk with the American College of Cardiology/AHA risk assessment tool and these risks managed accordingly.[232] Future risk assessment guidelines should include menopause among CVD risk factors in women. Until the next consensus guidelines are presented, we believe the North American Menopause Society recommendation should be promoted.

SUMMARY AND CONCLUSIONS

Menopause signifies the permanent cessation of ovarian reproductive function. The transition from any level of function, manifested by uterine menstruation, to the absence of menses is referred to as the MT and is characterized as the time when the menstrual cycles become significantly variable or other menopause-related symptoms begin. The MT is a period of significant symptomatic, hormonal, menstrual, and other physiological changes that are relevant to CVD risk. Accordingly, the purpose of this scientific statement was to provide a contemporary synthesis of the existing data on the MT and how these data relate to CVD, the leading cause of mortality in US women. Here, we summarize the salient content provided in the preceding sections:

1. The median age of natural menopause is 50 years. Natural menopause is considered premature if it occurs before 40 years of age and early if it occurs between 40 and 45 years of age.
2. Because of the trends for increases in overall life expectancy in the United States, a significant proportion of women will spend up to 40% of their lives postmenopausal.
3. Earlier age at natural menopause is generally reported as a marker of greater CVD risk and linked to being Black or Hispanic, having a short menstrual cycle length, having a low parity, being a smoker, and having a worse cardiovascular health profile during reproductive life. Of note, the studies on age of natural menopause and incident morbidity and mortality are not entirely consistent, which may be the result of different formulations of the composite outcomes.
4. Iatrogenically induced menopause (ie, BSO) during the premenopausal period is associated with higher CVD risk. Hysterectomy, regardless of ovarian status, does not influence CVD risk factors before or after menopause. Guidelines from the North American Menopause Society endorse MHT use among women with premature or early natural or surgical menopause, with treatment

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until at least the median age of menopause (in the absence of contraindications).

5. Vasomotor symptoms are associated with worse CVD risk factor levels and measures of subclinical atherosclerosis. These associations may depend on the timing of these symptoms during the MT.
6. Sleep disturbance, a common complaint during the MT, is linked to a greater risk of subclinical CVD and worse cardiovascular health indexes in midlife women.
7. Depression occurs more frequently during the perimenopausal and postmenopausal years and is related to both vasomotor symptoms and incident CVD.
8. The perimenopause stage begins with the onset of intermenstrual cycle irregularities or other menopause-related symptoms. This stage extends 12 months after menopause and has been identified as a stage of vulnerability accompanied by significant alterations in several cardiometabolic and vascular health parameters strongly linked to higher CVD risk.
9. Central/visceral fat increases and lean muscle mass decreases are more pronounced during the MT. The increased central adiposity is associated with an increased risk of mortality, even among those with normal BMI.
10. Paracardial fat volumes are higher after menopause, independently of age, and could be influenced by estradiol levels or MHT use.
11. Increases in lipids (LDL-C and apolipoprotein B), metabolic syndrome risk, and vascular remodeling at midlife are driven by the MT more than aging, whereas increases in blood pressure, insulin, and glucose are likely more influenced by chronological aging.
12. Novel data show a reversal in the associations of HDL-C with CVD risk over the MT, suggesting that higher HDL-C levels may not consistently reflect good cardiovascular health in midlife women.
13. Limited data exist on the current status of ideal cardiovascular health components in women during the MT. According to this limited literature, only 7.2% of women traversing menopause report a physical activity level that matches the current recommendation, and <20% consistently maintain a healthy eating diet.
14. Although the data are limited, randomized trial results suggest that a multidimensional lifestyle intervention can prevent weight gain while reducing triglycerides, SBP, and DBP, as well as blood glucose, insulin, and subclinical carotid atherosclerosis, among women undergoing the MT.
15. Regardless of the strong line of observational evidence showing the MT as a period of accelerated cardiovascular risk, RCTs of lifestyle and behavioral interventions have not adequately represented this high-risk population.
16. The literature supporting a critical role for the time of initiation of MHT use relative to menopause, with initiation at <60 years of age or within 10 years of menopause appearing to be associated with reduced CVD risk, strongly calls for further research assessing MHT use, including potential contrasts by form, route, and duration of administration, on cardiometabolic effects in women traversing menopause, a large proportion of whom experience menopausal symptoms before even reaching menopause.
17. Data for primary and secondary prevention of atherosclerotic CVD and improved survival with lipid-lowering interventions remain elusive for women, with further study required for evidence-based recommendations to be developed specifically for women.

As is evident from the information provided in this statement, the MT is a uniquely impactful period of time in most women's lives, which is associated with adverse changes in CVD risk. Trial results suggest that behavioral interventions can be used effectively during this time frame to reduce adverse CVD profiles. However, the number of randomized trials and observational studies including women during this transition is remarkably constrained. Therefore, definitive conclusions from the data are difficult to make with reasonable certainty. Unfortunately, this has left a substantial proportion of women and their healthcare providers unsure about how to proceed with interventions such as lipid-lowering medications and MHT use. Because the MT is a period of significant detrimental changes in several cardiometabolic risk factors (ie, lipids, vascular health, metabolic syndrome, visceral adiposity), healthcare practitioners may consider an aggressive prevention-based approach for women at this stage in their lives to decrease the probability of a future CVD event. On the basis of the data collected to date, a reasonable lifestyle intervention would target ideal body weight with low central adiposity and maintenance of skeletal muscle mass.

To further assist these practitioners and to reduce the burden of CVD while improving quality of life in this population of women, it is strongly recommended that future studies make a conscious effort to include or to focus on women who are undergoing the MT, especially those related to MHT and other therapeutic interventions. Studies that do so should carefully consider how to integrate women's reproductive aging into the study design vis-à-vis surveys, case report forms, etc. In addition, new studies may ponder the inclusion of more contemporary or emerging biomarkers of reproductive aging such as the anti-Müllerian hormone, which has

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been linked to the MT and the timing of menopause[233] and may complement information obtained from the more traditional hormone measures.

ARTICLE INFORMATION

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Disclosures

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*Modest.

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