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Body composition and cardiometabolic health across the menopause transition

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Abstract

Every year, 2 million women reach menopause in the United States, and they may spend 40% or more of their life in a postmenopausal state. In the years immediately preceding menopause—known as the menopause transition (or perimenopause)—changes in hormones and body composition increase a woman's overall cardiometabolic risk. In this narrative review, we summarize the changes in weight, body composition, and body fat distribution, as well as the changes in energy intake, energy expenditure, and other cardiometabolic risk factors (lipid profile, glucose metabolism, sleep health, and vascular function), that occur during the menopause transition. We also discuss the benefits of lifestyle interventions in women in the earlier stages of menopause before these detrimental changes occur. Finally, we discuss how to include perimenopausal women in research studies so that women across the life-span are adequately represented.

INTRODUCTION

Obesity is a major public health concern that affects women disproportionately more than men (1). In the United States, the prevalence of obesity in women was 39.7% among those aged 20 to 39 years, 43.3% among those aged 40 to 59 years, and 43.3% among those aged 60 years and over (2). During the menopause transition, women experience dramatic decreases in circulating estrogens—particularly estradiol (E_2)—and increases in

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CONFLICT OF INTEREST

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the gonadotropin follicle-stimulating hormone (FSH) (3). These hormonal changes are associated with changes in energy expenditure and energy intake that promote a positive energy balance, leading to weight gain (3–5). This weight gain is due to increased fat mass and, in particular, increased abdominal fat deposition (3–5), which contribute to increased cardiometabolic risk. Despite these known detrimental consequences of the menopause transition, many researchers avoid combining premenopausal, perimenopausal, and postmenopausal women in their studies or avoid enrolling perimenopause-aged women. Yet the menopause transition itself has much to teach us about how these adverse cardiometabolic profiles arise. Because all women will experience menopause and have the potential of spending much of their lives in the postmenopausal phase, understanding how the menopause transition affects body composition and cardiometabolic health is critically important to understanding the evolution of women's health across the life-span.

This narrative review details how the menopause transition imposes a significant health burden on women and affects total body weight, body composition, and body fat distribution, as well as how these changes impact cardiometabolic health. We also briefly review lifestyle interventions to improve cardiometabolic health in women. Finally, we call for further research during the menopause transition to identify the inflection points of risk accrual, as they are likely to be the time points at which interventions have the best chance of being effective.

DEFINING THE MENOPAUSE TRANSITION: STAGING AND STUDY DESIGN CONSIDERATIONS

The menopause transition—a brief overview

The menopause transition (i.e., perimenopause) is characterized by an increased rate of attrition of ovarian follicles. The initial result of this decrease in follicle number is reduced inhibin-B release from the ovaries. This reduction in inhibin-B signals the anterior pituitary to upregulate secretion of FSH which, in turn, stimulates ovarian E_2 production, with FSH continuing to increase as ovarian function declines. As women transition through perimenopause, the ovarian follicle supply becomes critically low, and the ovary can no longer respond to the increased FSH signaling with consistent output of E_2. Eventually, all functioning follicles are lost, and E_2 production by the ovary ceases, accompanied by a steady state of high FSH output. *Natural menopause* is typically defined after amenorrhea of 12 months in a woman aged 45 or older (6). Median age of natural menopause is 51.4 years (7), with an approximate 95% CI of 45 to 55 years, and it has been reported to be slightly higher at 52.5 years among longitudinally studied women (8). Although the length of the menopause transition typically encompasses 4 to 5 years, the length of the transition is highly variable and it can last from <1 to 10 years or longer (9). While 12% of women report sudden amenorrhea, the remainder of women experience changes in cycle length and variability in cycles during the transition (9). Approximately 5% of women experience early menopause, defined as having a final menstrual cycle between ages 40 and 45 years. A minority of women (~1%) experience *primary ovarian insufficiency* (*POI*), defined as hypergonadotropic amenorrhea before 40 years of age. A woman can also undergo *iatrogenic premature menopause* after having bilateral oophorectomy surgery or

iatrogenic ablation of ovarian function (e.g., chemotherapy, pelvic radiation) prior to natural menopause (10).

When classifying menopause stages, it is important to know that the menopause transition can be divided into early or late perimenopause stages (11). *Early perimenopause* is marked by increases in menstrual cycle length of 7 days or more, and some women report small but noticeable increases in common menopausal symptoms, such as vasomotor symptoms (e.g., hot flashes, night sweats). *Late perimenopause* is characterized by intervals of amenorrhea for at least 60 days and an elevated FSH >25 mIU/mL with a more sharply increased prevalence of menopausal symptoms. The Stages of Reproductive Aging Workshop (STRAW)+10 guidelines provide a comprehensive and easy to understand staging system for determining where a woman is in her menopause transition (Table 1) (11).

Considerations when studying the stages of the menopause transition

The menopause transition is difficult to study because of the inherent variability in the process of ovarian failure (initiation and duration), the confounding effects of chronological aging, and the variability of hormones (ovarian and gonadotropins) both between cycles and between women. These highly variable characteristics might explain why many studies exclude women in the perimenopausal age range. However, classification systems such as STRAW+10 criteria assist in identifying stages of the transition without relying on spot-check levels of hormones, which can lead to misclassification. It is helpful, in longitudinal studies, to organize changes around the final menstrual period (FMP) to better elucidate how and when changes in the parameters of interest relate to menopause. This approach does not, however, adequately account for variability in transition duration, which can be meaningful.

Even though the STRAW+10 criteria has simplified classification of women as they progress through the menopause transition, *early perimenopause* remains more difficult to identify than late perimenopause. Entry into the menopause transition is defined by the STRAW+10 criteria as increased variability in cycle length (i.e., a difference of ±7 days within 10 cycles). This change can be challenging to accurately measure as it requires a well-documented cycle history. Most women notice more obvious changes, such as a missed menstrual cycle. With the evolution of new menstrual period tracking apps, it may become easier for women to observe and report changes in menstrual cycle length and regularity (e.g., tracking of deviation in more than 7 days from “usual” menstrual cycle length) (12). Researchers often rely on self-reported cycle lengths, elevated early follicular phase FSH (cycle days 1 to 5), or serum E_2 to help define early perimenopause (11). Because of cycle-to-cycle variability in FSH and E_2, single measurements of these hormones are of limited value for classifying women in the early stage of the menopause transition. Anti-Müllerian hormone (AMH), which is secreted by small antral follicles (granulosa cells), is also a reliable marker of ovarian follicle reserve, with lower AMH indicative of being closer to the FMP. Although AMH can be predictive of age at FMP, there are several caveats. First, AMH is most predictive in women in their late 40s or early 50s. It is possible for women aged 35 to 39 years to have an undetectable concentration of AMH but still have regular menstrual cycles (13). Additionally, the lack of an international standard for AMH means that measurement techniques can vary (13). Nonetheless, AMH is one of the best predictors

of FMP (13–15). With greater population data, AMH could be a useful qualitative measure of the early menopause transition.

Late perimenopause is easier to characterize than early perimenopause, given that it is defined by the presence of at least 60 days of amenorrhea (11). An FSH concentration greater than 25 IU/L is now also considered to be characteristic of the late perimenopausal period (11). Although listed in the STRAW+10 criteria, using the presence of vasomotor symptoms to define the late perimenopausal period is not recommended because their appearance does not strictly follow changes in the menstrual cycle or hormones across the menopause transition (16). Additionally, not all women will experience vasomotor symptoms (16).

CHANGES IN WEIGHT AND BODY COMPOSITION

On average, women gain approximately 5 to 7 pounds (or 2 to 3 kg) over the course of the menopause transition (17,18), yet there is substantial interindividual variability. Increased weight and particularly abdominal fat are associated with more severe vasomotor symptoms (i.e., hot flashes and night sweats) and insomnia (19,20), as well as increased fatigue and decreased quality of life (21,22). Some women may not experience weight gain even though changes in body composition occur (i.e., increased fat mass, decreased fat-free mass, and decreased bone mineral density). The following section details the changes in body composition and fat distribution that have been reported in both animal and human (observational and clinical) studies focused on the loss of ovarian function. A summary of the known changes in body composition and cardiometabolic risk that occur during the menopause transition and into the postmenopausal years is included (Figure 1).

Findings from animal studies

Ovariectomy (OVX) is used as a model of menopause in laboratory animals to study how the loss of ovarian function causes fat mass accumulation. OVX eliminates ovarian estrogens and raises FSH due to the loss of negative feedback from E_2. OVX is associated with increased body weight and abdominal adiposity when compared with animals that undergo sham surgery (23–25). Although increased body weight and abdominal adiposity is caused by a combination of increased energy intake and/or decreased energy expenditure, the regulation of energy intake by E_2 appears to differ in mice and rats, such that OVX increased energy intake in rats but not mice. The increase in energy intake (+20%) in rats can last for several weeks (26–29), but in one study, returned to the level of energy intake of that in sham-operated controls (29). OVX also caused marked decreases in spontaneous physical activity (locomotor activity), metabolic rate, and energy expenditure in both mice (26–28,30) and rats (26,29,31). Another study reported that energy expenditure is lower in OVX mice than OVX+E_2 mice when activity is similar (28). Evidence also supports a strong, protective effect of E_2 against weight gain in OVX rodents, as weight gain was prevented in OVX rats treated with E_2 add-back or estrogen receptor (ER)-α agonist (25,32).

The metabolic actions of estrogens that cause alterations in body weight and adiposity are mediated through the ER. As a member of the nuclear receptor superfamily, ER regulates gene expression by binding to the estrogen response element (ERE) located on the promotor

sequence of target genes. ER has two main subtypes, ERα and ERβ, which are widely expressed through the body (e.g., brain, blood vessels, and adipose tissue). Much of our understanding on the molecular pathways that ER action regulates cardiovascular health and metabolism has been derived exclusively from rodent models (33). Evidence suggests that ERα is the primary mediator of the estrogen suppression of adiposity, as ERβ knockout (ERβKO) mice have stable body weight and percent fat (34). In contrast, ERα knockout (ERαKO) mice have increased fat mass, as well as adipocyte number and size (35). Brain-specific ERαKO mice have abdominal obesity mediated through hyperphagia and hypometabolism, produced by decreased heat production and decreased physical activity (36). There is a third known estrogen receptor that binds E_2 at the cell surface. This G-protein coupled estrogen receptor (GPER, formerly GPCR30) induces rapid, nongenomic signaling and, like the classical ERs, is expressed widely through the body (37). Mice lacking GPER are reported to have increased body weight and visceral adiposity (38), although this is not a consistent observation in female mice (39,40).

Although most differences in body composition between males and females have been attributed to E_2 and testosterone, more recently, FSH has been implicated as a mediator of abdominal adiposity. Liu and colleagues demonstrated that animals treated with an FSH beta-subunit-blocking antibody had a marked reduction in adiposity (41). The anti-obesity response to blocking FSH activity occurred in both sham and OVX animals, suggesting an effect of FSH even when FSH is in the normal range. Indeed, the anti-obesity effect of the FSH antibody was most pronounced in the abdominal visceral region (~70% difference in visceral fat volume vs. the comparator group), but differences were also apparent in abdominal subcutaneous fat volume (~30%) and total fat mass (~30%) (41).

Findings from human studies

Observational studies—Observational studies have shown that body weight and adiposity increase across the menopause transition. The Study of Women's Health Across the Nation (SWAN) provided very compelling evidence that an accelerated gain in fat mass and loss of fat-free (lean) mass were related to the menopause transition (42) rather than aging (43,44). Although an increase in fat mass and a decline in fat-free mass were observed during pre-menopause (prior to the menopause transition), these changes accelerated during perimenopause before stabilizing in the postmenopausal years (42). Other observational studies confirmed the increase in fat mass, particularly attributed to increased abdominal fat (subcutaneous and visceral), during the menopause transition (3–5,18). Changes in body composition may also vary depending on race or initial level of adiposity on entering perimenopause (18). These observed changes in body composition are partially the result of reductions in energy expenditure and fat oxidation (3), with the reduction in energy expenditure possibly explained by a reduction in regular physical activity during the perimenopausal years (45). The Healthy Transitions longitudinal study comprehensively phenotyped women across menopause and was the first study to demonstrate that women who completed the menopause transition had a greater reduction in 24-hour energy expenditure and sleep energy expenditure compared with women who did not complete the transition (3). Although resting energy expenditure (REE) was not measured in Healthy Transitions, average REE remained stable through menopause in the Montreal-Ottawa New

Emerging Team (MONET) study (46). Data from SWAN also indicated that bone mineral density declines at the greatest rate beginning 1 year before the FMP and decelerates (but does not cease) 2 years after the FMP at both the lumbar spine (7.38% loss) and femoral neck (5.8% loss) sites (47). Another study demonstrated that bone loss begins 2 to 3 years before the FMP and ends 3 to 4 years after the FMP, with spine, total body bone mineral, and femoral neck declining by 10.5%, 7.7%, and 5.3%, respectively (48). Supportive evidence suggests that the loss of estrogens is associated with or triggers the decreases in energy expenditure and physical activity (49,50), as well as bone mineral density (51). Because low rates of energy expenditure and fat oxidation at rest predict future fat gain (52–54), understanding the impact of menopause on human bioenergetics is critical. Although increased energy intake can also contribute to weight gain, longitudinal studies that assessed changes in energy intake across the menopause transition are limited (both by the lack of research examining energy intake across menopause, as well as the pitfalls surrounding self-reported energy intake (55)), but suggested energy intake decreased over the 3 to 4 years leading up to menopause onset (3).

An increase in fat mass (predominantly in the abdominal region) and decrease in fat-free mass during the menopause transition may result in little or no change in body weight yet will subsequently lead to increased cardiometabolic risk. The Women's Health Initiative demonstrated that central obesity (defined by a waist circumference >88 cm (56)) was detrimental regardless of weight status, as normal-weight central obesity (defined by BMI 18.5 to 24.9 kg/m^2 and waist circumference >88 cm) was associated with excess risk of mortality that was similar to women with BMI-defined obesity and central obesity (57). Thus, body fat distribution, rather than weight status alone, is a good determinant of cardiometabolic risk during the menopause transition.

Intervention studies—Several interventional studies indicated that hormone therapy initiated in the perimenopausal or early postmenopausal years attenuated weight gain (adiposity). In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, a randomized, placebo-controlled trial, women who received oral conjugated equine estrogens (CEE) gained less body weight and had smaller increases in waist girth than women randomized to placebo (58). The Danish Osteoporosis Prevention Study was a partially randomized study in which women who received sequential oral estrogen and progestogen gained less body weight, fat mass, and trunk fat than untreated women (59). In the Kronos Early Estrogen Prevention Study (KEEPS), increases in weight and waist circumference were attenuated in women randomized to either transdermal E_2 or CEE for 4 years (60).

The administration of gonadotropin-releasing hormone agonist ($GnRH_{AG}$) or GnRH antagonist ($GnRH_{ANT}$) in combination with E_2 versus placebo therapy is useful for isolating specific effects of the loss of ovarian E_2 in premenopausal women. Both $GnRH_{AG}$ and $GnRH_{ANT}$ reversibly suppresses ovarian function via the suppression of the hypothalamic-pituitary-ovarian axis, essentially creating a "medical menopause." Studies have shown that both acute and chronic ovarian hormone suppression with $GnRH_{AG}$ and $GnRH_{ANT}$ alters REE and total energy expenditure. In a small group of premenopausal women, REE was measured during the mid-luteal phase of the menstrual cycle (when E_2 was elevated), during the early follicular phase (when E_2 was low), and after 6 days of $GnRH_{ANT}$ treatment (when

E_2 was even lower) (49). REE across these 3 conditions paralleled the changes in E_2, with higher REE when E_2 was higher. In another study, REE decreased in premenopausal women randomized to 5 months of $GnRH_{AG}$ therapy, but this decrease in REE was attenuated in women who received transdermal E_2 add-back (50). Conversely, total energy expenditure measured by whole-room indirect calorimetry decreased in response to $GnRH_{AG}$ (−128 kcal/d) but was not prevented by E_2 add-back (50).

$GnRH_{AG}$ and $GnRH_{ANT}$ therapy also alters body composition. In brief, 4 months of $GnRH_{AG}$ therapy in premenopausal women resulted in no change in total body weight, but increased total body fat and trunk fat mass (61–63). Administering $GnRH_{AG}$ for shorter durations also resulted in no change in total body weight; however, visceral fat mass was increased in as little as 4 weeks, with estrogen add-back attenuating this effect (64). Althought body weight, fat mass, and trunk mass were all increased after 6 months of $GnRH_{AG}$ suppression in one study (65), some studies do not observe changes in overall fat mass after 3 to 5 months of suppression (51,66). Despite no change in total fat mass, one of these studies found that 5 months of $GnRH_{AG}$ resulted in an increase in visceral fat area measured by computerized tomography (CT) (51). Collectively, these studies suggest that the loss of ovarian E_2 promotes abdominal fat accumulation and a decline in energy expenditure.

CHANGES IN CARDIOMETABOLIC HEALTH

Changes in reproductive hormones and body composition across the menopause transition are associated with increased overall metabolic and cardiovascular disease (CVD) risk. These changes in cardiometabolic risk have led some researchers to suggest that obesity in women may be more appropriately diagnosed by a BMI ≥25 kg/m^2 (rather than 30 kg/m^2) later in life (67,68). Furthermore, the presence of central obesity is likely more detrimental to overall health and cardiometabolic risk than BMI-defined weight status alone (57). The following section details the changes in metabolic and cardiovascular health observed during the menopause transition and into the postmenopausal years and highlights how menopausal hormone therapy modifies cardiometabolic risk.

Metabolic health

Insulin sensitivity and glucose tolerance—Although the physiological effects of ovarian hormones on insulin metabolism are not clear, a role for estrogens (particularly E_2) in maintaining glucose homeostasis through effects on insulin secretion and clearance has been suggested (69). It is well-established that E_2 promotes peripheral (vs. central) fat distribution and improves insulin sensitivity in women (70).

In cross-sectional studies, evidence linking menopausal status and abdominal adiposity with insulin resistance and prevalent diabetes is mixed. Several of these studies found no associations between menopausal status and metabolic factors, including fasting glucose and insulin, insulin secretion rate, insulin sensitivity, and diabetes risk (71–74). Longitudinal studies, including the 6-year Pizarra Study (75), the 8-year Australian Longitudinal Study on Women's Health (76), and the 3-year Diabetes Prevention Program (77), also found no association between natural postmenopausal status and diabetes risk. Conversely, data from

SWAN indicated a progressive increase in the risk of metabolic syndrome development with menopause; this increased risk was primarily driven by worsening lipid profile rather than deleterious changes in glucose (78). In postmenopausal women without obesity, increase in abdominal fat during menopause was associated with decreased tissue insulin sensitivity and glucose tolerance (79). In a longitudinal study across the menopause transition, no changes in fasting glucose, fasting insulin, lipids, or insulin sensitivity were observed (3). However, a secondary analysis found that insulin sensitivity was reduced in women who gained the most abdominal adiposity (18). Although it was hypothesized that menopause status is associated with reduced insulin secretion and clearance (80), these associations are complicated by numerous factors that may be different between premenopausal and postmenopausal women. Increased BMI and abdominal adiposity, however, has always been strongly linked to insulin resistance and consequently, is associated with an increased risk for type 2 diabetes and CVD (81). Therefore, the increase in abdominal adiposity observed during the menopause transition is likely to be associated with insulin resistance and reduced glucose homeostasis.

Clinical studies involving exogenous E_2 administration provide insight into the mechanistic effects of menopause on insulin sensitivity and glucose tolerance. E_2 administration to postmenopausal women suggests a role for estrogens in maintaining glucose homeostasis through effects on insulin secretion and clearance (82). The risk of developing type 2 diabetes was significantly reduced in postmenopausal women who used hormone therapy in several randomized clinical trials, including the Women's Health Initiative and Heart and Estrogen/Progestin Replacement Study (HERS) (83–85). Compared with transdermal estrogens, the effects of oral estrogens are difficult to interpret because of the influences of first-pass metabolism in the liver (discussed in greater detail in this publication (83)). One recent study found that a short, 8-week treatment of orally administered CEE and the selective estrogen receptor modulator (SERM), bazedoxifene, did not alter insulin sensitivity or ectopic fat in postmenopausal women with obesity (86). Still, the effects of transdermal E_2 on glucose metabolism in postmenopausal women are conflicting. Although some studies of daily transdermal E_2 reported reduction in insulin concentrations during oral glucose tolerance testing (OGTT) (87,88), others did not (89–91). C-peptide concentrations during an OGTT have also been shown to be increased (89,91) or decreased (90) in response to transdermal E_2 therapy. One study found that acute administration (2.5-mg intravenous bolus) of conjugated estrogens increased insulin clearance and action in post-menopausal women during a constant rate of insulin infusion (92). However, a follow-up study revealed that 24-hour transdermal E_2 administration did not alter insulin secretion or clearance in postmenopausal women, yet longer time since menopause did reveal a reduced effect of transdermal E_2 to increase glucose uptake (93). It is likely that estrogen therapy has a beneficial effect on β-cell function and insulin secretion in postmenopausal women (83). Specifically, increased glucose-stimulated insulin secretion, as assessed by secretion of C-peptide and HOMA-β, and enhanced hepatic insulin clearance have been reported (94–96).

Although study findings do not currently support that menopausal hormone therapy consistently improves insulin sensitivity or glucose tolerance, the full extent of its potential risks and benefits needs further investigation. Importantly, the variability in treatments (estrogen only, estrogen plus progestins or SERM, etc.), treatment duration (weeks, months, or years), method of administration (oral vs. transdermal), and differences in metabolic

status on administration (normal vs. obesity weight status, insulin resistant vs. type 2 diabetic, etc.) is important to consider when evaluating the effect of such therapies on metabolic health.

Dyslipidemia—Postmenopausal abdominal fat gain is associated with an adverse lipid profile (97). Dyslipidemia develops 10 to 15 years later in women than in men (98), presumably due to the protective effect of ovarian hormones (particularly E_2). In SWAN, women had sharp increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and apolipoprotein (Apo)B concentrations within a 1-year interval surrounding the FMP (99). Furthermore, the menopause-related increase in LDL-C was associated with greater risk of carotid plaque later in life in follow-up analysis (99). Postmenopausal women also experience elevated concentrations of LDL-C and triglycerides, which contribute to the atherosclerotic process (99). In contrast to epidemiological studies supporting that high-density lipoprotein cholesterol (HDL-C) is cardioprotective, a number of studies have reported higher HDL-C as a CVD risk factor after menopause (100). Future longitudinal studies are needed to further evaluate the effect of HDL-C on CVD across menopause. Studies have shown that oral estrogen therapy resulted in decreased LDL-C and increased HDL-C (101–103); however, this was at the expense of an increase in triglycerides (102).

Sleep disruption—Disruptions in sleep health also become more prevalent in women as they age and particularly around the menopause transition with the decline of E_2 and progesterone. Sleep health is characterized by a number of sleep parameters that are affected by menopause, including changes in sleep duration, sleep times, awakenings, sleepiness, and sleep disorders (104). In SWAN, the prevalence of sleep disturbances ranged from 16% to 42% in premenopausal women and increased to 39% to 47% and 35% to 60% in perimenopausal and postmenopausal women, respectively (104). Vasomotor symptoms are associated with reduced sleep quality and increased waking, yet late perimenopausal and postmenopausal women still report more sleep difficulties compared with premenopausal women regardless of vasomotor symptom presence (99). Importantly, sleep disruption promotes increased energy intake (105) likely due to a combination of altered appetite hormones (i.e., decreased leptin and increased ghrelin, hunger, and appetite) (106), as well as altered sensitivity to food reward and disinhibited eating (105). Although sleep disruption is a well-recognized risk factor for metabolic abnormalities, including insulin resistance and glucose tolerance (107,108), the regulatory mechanisms linking sleep disruption and the changes in metabolic homeostasis that coincide with menopause have yet to be fully elucidated. Given the current breadth of literature, it is likely that women who experience sleep disruption during menopause may experience even greater weight and abdominal fat gain compared with women who do not.

Cardiovascular health

Postmenopausal women experience an increase in CVD risk that is primarily thought to be due to ovarian failure and the loss of E_2 that occurs across the menopause transition. CVD is the leading cause of mortality in postmenopausal women. The CVD risk factors that become more prevalent after menopause include vascular dysfunction, hypertension, and cardiac dysfunction.

Vascular dysfunction and hypertension—Aging is associated with vascular dysfunction, featuring endothelial dysfunction and large elastic arterial stiffening. The vascular endothelium is a single-cell layer that lines arterial walls and becomes dysfunctional during the aging process due, in part, to reduced nitric oxide (NO) availability, secondary to increased oxidative stress and inflammation. Oxidative stress is characterized by an excessive production of reactive oxygen species that scavenge NO and subsequently impairs endothelial function and increases large elastic arterial stiffness (109). Vascular inflammation and increased reactive oxygen species can also impair endothelial nitric oxide synthase (eNOS), further reducing NO bioavailability and worsening endothelial function and arterial stiffening.

In women, vascular function appears to be preserved up until the menopause transition, after which vascular function progressively deteriorates, possibly due to a shift in redox balance and inflammatory status. In postmenopausal women, the loss of the antioxidant and anti-inflammatory effects of E_2 are linked with a pro-oxidant and low-grade pro-inflammatory condition (110,111). Early observations noted that endothelial function, measured via brachial artery flow-mediated dilation (FMD), was preserved in women ≤40 years of age, decreased by 0.21% per year after age 40 years, and lowest in women ages 50+ years (by 0.49% per year) (112). A subsequent study found that the magnitude of difference in FMD between premenopausal women and late perimenopausal women was twice as great as the difference between premenopausal and early perimenopausal women (113); the greater difference was attributed to increased oxidative stress due to declines in E_2 (114). In postmenopausal women, FMD was improved with E_2 treatment, whereas FMD in placebo-treated women remained unchanged (115). Women with premature ovarian failure also had lower FMD compared with controls, which was rescued with oral CEE plus progestogen cyclic therapy (116). Oral CEE plus progestogen therapy did not improve FMD in postmenopausal women who already had coronary artery disease (117), in agreement with speculation that women who already have established coronary artery disease may not benefit from hormone therapy (118). Perimenopausal and postmenopausal women also exhibited greater arterial stiffness as indicated by an increase in pulse wave velocity (PWV) and reduced carotid artery compliance (inverse of stiffness) (119,120). However, adjusting for age eliminated the effect of menopausal status on arterial stiffness, suggesting that chronological aging may be more of a contributing factor to arterial stiffening than ovarian aging (121). This observation highlights the difficulty in separating the effects of chronological aging from the effects of ovarian aging and demonstrates the need for controlled interventions that can isolate the effects of age from female sex hormones.

Epidemiological data suggest that estrogen-based hormone therapy mitigates many risk factors for CVD (122), although the relative benefit of hormone therapy remains unclear and is the subject of ongoing debate. A current prevailing hypothesis is that postmenopausal women more than 10 years past menopause do not derive cardiovascular benefit from estrogen (122). The “timing hypothesis” posits that women who start menopausal hormone therapy within 10 years of their FMP derive protection from CVD, presumably because the intervention occurs before aging and lack of estrogen has resulted in too much vascular dysfunction to preclude the beneficial effects of estrogen (122). The “timing hypothesis” for

menopausal hormone therapy may also apply to effects of estrogens on body composition and cardiometabolic risk factors. Menopausal hormone therapy has been shown to increase NO production, decrease inflammation, and increase vascular smooth muscle cell growth and proliferation (118). The Early versus Late Estrogen Trial (ELITE) demonstrated that, compared with placebo, women randomized to E_2 who were less than 6 years past menopause had less progression of subclinical atherosclerosis as measured by carotid intimal-medial thickening (C-IMT), whereas there was no difference in atherosclerosis progression between the conditions in women who were 10 years past menopause (103). In contrast to ELITE, there were no changes in C-IMT or coronary artery calcium progression between early postmenopausal women (i.e., <6 years since menopause onset) randomized to estrogen or placebo in KEEPS. The reasons for the differential responses of C-IMT to estrogen may be related to the dose and type of estrogen used (i.e., 0.45 mg of conjugated equine estrogen and 0.05 ug/d of transdermal E_2 in KEEPS vs. 1.0 mg/d of oral E_2 in ELITE) and/or study population (103,123).

Endothelial dysfunction and arterial stiffness is also prognostic of hypertension in postmenopausal women (124). Age is a risk factor for hypertension as women experience increases in blood pressure as they get older. However, like vascular dysfunction, the age-related increases in blood pressure are more rapid in women, coinciding with the menopause transition (125). Pinpointing the mechanism behind the increase in blood pressure during this time is difficult because it is likely multifactorial; women gain weight and have increased incidence of metabolic syndrome, both of which increase the likelihood of hypertension and influence the response to traditional hypertensive treatments (124). Examining each of these facets is outside the scope of this review (more in depth review in (125)); however, estrogens are theorized to play a role.

Cardiac dysfunction—Concurrent with the shift in body composition, vascular dysfunction can contribute to pathophysiological changes to the heart that increase CVD risk. For example, arterial stiffening of the large elastic arteries can lead to increases in systolic and pulse pressures and aortic impedance (i.e., the resistance imposed on left ventricular [LV] ejection by the vasculature), consequently increasing the afterload and the amount of work performed by the LV to eject blood. These changes can contribute to LV hypertrophy, altered diastolic filling, and decrease LV systolic reserve (126). Evidence supporting a role for estrogens on LV hypertrophy induced by pressure overload come from studies of OVX mice that developed LV hypertrophy, which was rescued with E_2 replacement (127,128). Furthermore, women in heart failure are more likely to have heart failure with preserved ejection fraction (HFpEF) than men, which often has better outcomes than heart failure with reduced ejection fraction (HFrEF) (129). Compared with men, women also have increased LV mass as they age and thus, have increased diastolic dysfunction (130,131). Nonetheless, the extent to which menopause per se affects heart failure prevalence is still unclear.

Although the role of exogenous estrogens or other hormones in maintaining cardiovascular health remains to be elucidated, what is not controversial is that women experience an increase in CVD risk factors around the time of menopause and should be monitored and counseled accordingly. It has been suggested that menopause represents an ideal time point

to assess cardiovascular health and risk (132) and a perfect time to consider initiation of lifestyle interventions and careful monitoring of conventional risk factors for CVD including but not limited to cholesterol, diabetes, and hypertension.

LIFESTYLE INTERVENTIONS TO IMPROVE OVERALL HEALTH DURING MENOPAUSE

Current clinical guidelines do not recommend the use of menopausal hormone therapy for preventive indications; it is indicated only for the treatment of menopausal symptoms (133–135). Although menopausal hormone therapy has benefits—many of which (body composition, cardiovascular and metabolic health, and bioenergetics) have been reviewed here—not all women can or wish to take hormone therapy at the time of menopause transition. Even those who can take hormone therapy may experience a variety of side effects from different hormone treatment regimens. Introducing behavioral modifications that include diet (calorie restriction) and exercise (aerobic and/or resistance training) can help women limit weight gain and reduce cardiometabolic risk that arises during the menopause transition. Indeed, clinical trials provide ample evidence that diet and exercise—resistance or aerobic—can reduce body weight and notably, visceral fat mass accumulation, in many different populations. Even 5% weight loss in individuals with obesity has been shown to improve adipose tissue, liver and muscle insulin sensitivity, and β-cell function (136).

Despite the well-established evidence base that diet and exercise help limit weight gain, the vast majority of diet and exercise interventions have been conducted in postmenopausal women, and perimenopausal women have scarcely been studied (137). Longitudinal data from the SWAN study in women 47 to 57 years of age revealed an inverse association between percent body fat increased moderate or vigorous physical activity, particularly among White women (138). Similarly among postmenopausal women, there is a significant dose response for greater total body weight, fat, and intra-abdominal fat loss with increased exercise duration (139,140). Several studies addressed whether exercise or caloric restriction is more effective in reducing weight and targeting abdominal fat in postmenopausal women. The Sex Hormones and Physical Exercise (SHAPE)-2 study randomized postmenopausal women with overweight to either calorie restriction alone, calorie restriction plus exercise, or control (141). In brief, the SHAPE-2 exercise program combined both moderate-to-vigorous aerobic and resistance training 4 h/week (including two 1-hour fitness sessions plus 2 additional hours of walking), resulting in ~350 kcal/d exercise energy expenditure. Both intervention groups targeted 5 to 6 kg of body weight loss over a 10-to-14-week period and observed that subcutaneous fat loss was larger in the calorie restriction plus exercise group with no differences in intra-abdominal fat loss (141). In the Diet, Exercise, and Metabolism for Older Women Study, postmenopausal women with overweight were randomized to either a reduced calorie diet or a reduced calorie diet with aerobic exercise (3 d/week for 45-minutes at >85% heart rate reserve) for 6 months. Both groups lost similar amounts of weight, including similar subcutaneous abdominal and gluteal fat loss (142). Compared with premenopausal women, early postmenopausal women were equally capable of losing weight and reducing android fat when following a 3-month high-intensity exercise training

program (3 d/week for 1 hour of instructor-led spinning/cycling intervals) (143). Another important study from the Women's Healthy Lifestyle Project, a 4.5-year randomized clinical trial using long-term, dietary restriction (1,300 kcal/d) and increased physical activity (1,000 to 1,500 kcal/week of programmed moderate-intensity aerobic activity and additional activities of daily living) during peri- and post-menopause, demonstrated that waist circumference and fat mass were reduced, and fat-free mass was maintained (144). Subclinical markers of atherosclerosis, particularly C-IMT, were slowed with diet and exercise (145). Importantly, this long-term study demonstrated that continued behavioral modification among populations most susceptible to weight gain, such as perimenopausal women, is possible to implement.

A recent systematic review compared weight loss success across different lifestyle interventions and reported that postmenopausal women with obesity who were randomized to either diet or exercise modification alone had greater weight and fat mass loss compared with controls, whereas combining both diet and exercise resulted in the greatest weight and fat mass loss (137). Although only three of the aggregated studies had an exercise-only group as part of the lifestyle intervention, weight and fat mass loss appeared to be the greatest among women performing both aerobic and resistance training (146) versus aerobic or resistance training alone (147,148). Indeed, resistance training may help attenuate the loss in bone density that occurs with menopause, or the potential weight loss-associated bone loss with lifestyle interventions (149). In summary, initiating lifestyle modification programs that incorporate diet and exercise (aerobic and resistance training) for women during perimenopause may be timelier and have a higher yield in terms of reducing future risk of cardiometabolic than waiting until the postmenopausal years, after substantial weight gain and fat mass accrual have already occurred.

FUTURE DIRECTIONS AND CONSIDERATIONS

The menopause transition is accompanied by distinct changes in reproductive hormones, body composition, energy intake and expenditure, and other CVD risk factors. Intervention strategies that mitigate the negative effects that arise during the menopause transition are important to ensure that women maintain overall health as they age. First, behavioral (lifestyle) interventions targeting the perimenopausal period—possibly before detrimental changes in body composition and cardiometabolic health occur—are warranted. Few perimenopausal interventions exist that target weight loss (144,145), with most interventions focusing on the postmenopausal period (137). Second, given sleep disruption is one of the primary reasons why women seek medical care during menopause, future studies need to disentangle the degree to which sleep disruption (e.g., shortened sleep, interrupted sleep) alters individual behavior (i.e., energy intake and physical activity) and metabolism (i.e., whole-body and tissue-specific) across menopause and possibly exacerbates metabolic dysfunction and weight gain (107). Third, investigating racial and ethnic disparities in women across the menopause transition is also important and is lacking in the current literature. Black women have less visceral fat and intrahepatic lipid yet are paradoxically more insulin resistant compared with White women (150–152), suggesting that Black or non-White women are at greater risk of cardiometabolic dysfunction with menopause. Investigating racial and ethnic disparities in menopause-related health outcomes

is particularly important in the quest to maximize the “health span” and not just the life-span of women. Finally, although research is currently limited, studies of how the female gut microbiome modifies energy balance, calorie absorption, and fat storage during menopause should also be undertaken (153,154).

The North American Menopause Society (NAMS) is a resource to assist medical professionals in the management of menopause and it provides a body of evidence-based recommendations for the clinical care of women across the menopause transition (17). These recommendations range from managing common body changes (particularly weight gain) and disease risk to complementary and alternative medicine and prescription-based treatment approaches. If weight loss is indicated (i.e., BMI ≥ 30kg/m^2 or BMI ≥27 kg/m^2 with a comorbidity), NAMS recommends combining caloric restriction alongside an intensive behavioral lifestyle intervention (≥14 in-person counseling sessions in 6 months) (17,155). Of course, the prescribed caloric deficit is not a one-size-fits-all dictum and is particularly difficult to prescribe because of changes in body composition and a declining metabolic rate. Instead, caloric deficit targets (via diet, exercise, or both) need to be individualized to weight loss goals, current body composition, and health status. Furthermore, because women experience many changes in cardiometabolic health during the menopause transition, caring for women on an individual level is increasingly important —lifestyle changes may be best for some, whereas pharmacotherapy or pharmacogenomic analysis might be better for others. Readiness for initiating changes in lifestyle or treatment strategies should be considered.

Researchers looking to incorporate perimenopausal women into their investigations should consider:

- Characterizing women by menopause stage (11), including menstrual cycle tracking and measurement of sex steroids, FSH concentrations, and AMH;
- Documenting FMP to help guide menopause staging;
- Conducting a thorough review of medical history, including past surgeries (e.g., cesarean delivery, bariatric, hysterectomy, oophorectomy);
- Documenting sleep health, including relevant sleep parameters such as sleep duration, sleep times, awakenings, sleepiness, and specific sleep disorder symptoms;
- Documenting all medications, including current, recent, or past use of menopausal hormone therapy (or determining if these medications are deemed exclusion criteria) and medications used to treat menopause symptoms (e.g., depression, vasomotor symptoms, sleep disturbances);
- How the research findings will delineate the effect of aging from any changes in sex steroids or gonadotropins associated with menopause.O

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Study Importance

Study Importance What is already known?

- The menopause transition (i.e., perimenopause) is characterized by changes in hormones and body composition that increase overall cardiometabolic risk.

What does this review add?

- This review summarizes the changes in cardiometabolic health that occur during the menopause transition because of changes in hormones and body composition.
- This review provides considerations when incorporating perimenopausal women into clinical research studies.

How might these results change the direction of research?

- Researchers should consider including perimenopausal women in their future investigations to ensure adequate representation of women across the life-span.
- Research in perimenopausal women must properly characterize women by menopause stage, document current sleep health, and document current or past surgeries or medications used to treat menopausal symptoms.

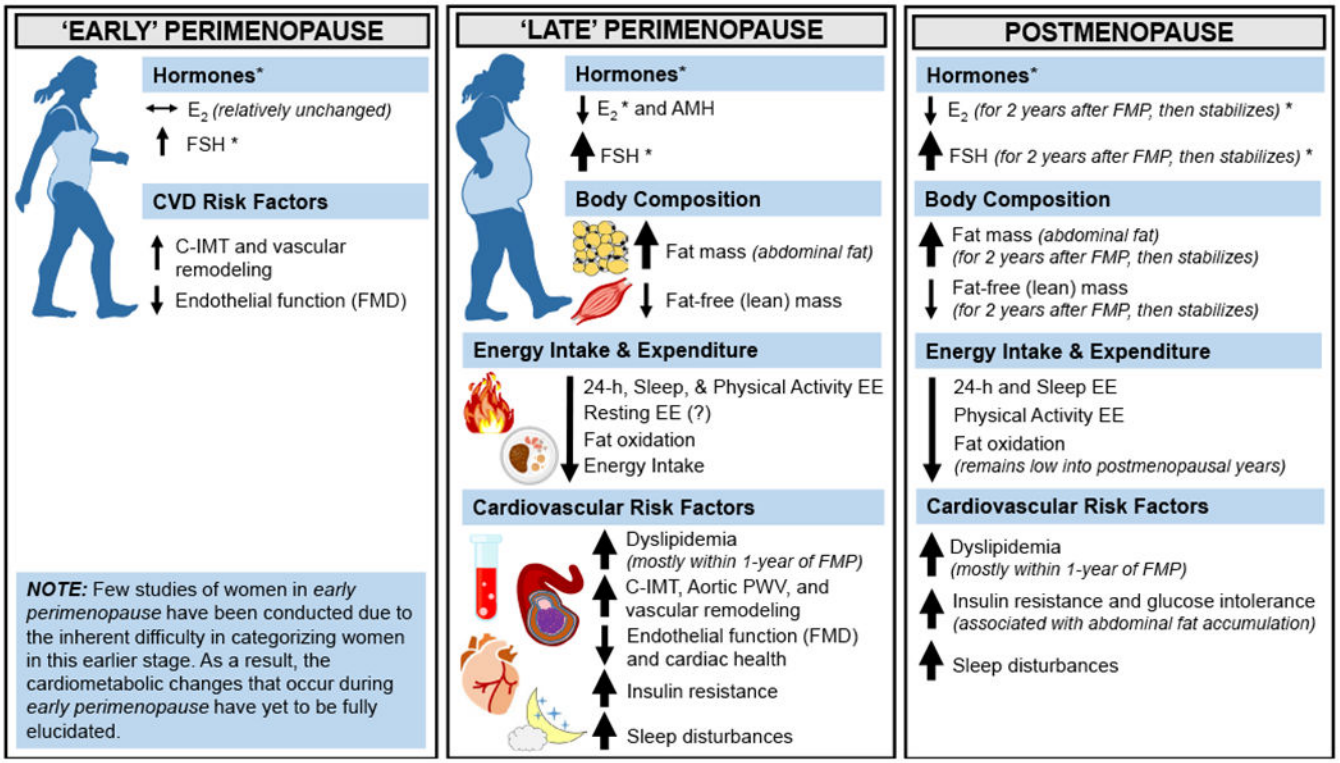

Figure 1.

Associated changes in cardiometabolic risk during the menopause transition. Changes in cardiometabolic risk factors occur during the menopause transition, which is separated into two subcategories (*early perimenopause* and *late perimenopause*) and into the postmenopausal years. Horizontal arrows (↔) indicate stability, and smaller or larger/thicker directional arrows (↑ or ↓) indicate smaller or larger changes that occur. *Although E_2 concentrations are lower at menopause onset compared with premenopausal concentrations, the patterns of E_2 decline and FSH rise during perimenopause are heterogenous across women. AMH, anti-Müllerian hormone; C-IMT, carotid intima-media thickness; E_2, estradiol; EE, energy expenditure; FSH, follicle-stimulating hormone; FMP, final menstrual period; PWV, pulse wave velocity

TABLE 1

The Stages of Reproductive Aging Workshop +10 staging system for reproductive aging in women

	Menarche						FMP (0)			
Stage	-5	-4	-3b	-3a	-2	-1	+1a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1-3 years	2 years (1+1)		3-6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	*Variable Length:* Persistent ≥7-day difference in length of consecutive cycles	Interval of amenorrhea of ≥60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			 Low Low	 Variable * Low Low	 ↑ Variable * Low Low	 ↑ >25 IU/L ** Low Low	 ↑ Variable * Low Low		 Stabilizes Very Low Very Low	
Antral Follicle Count			Low	Low	Low	Low	Very Low		Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

This table was adapted with permission from the previously published STRAW+10 staging guidelines (11).

Abbreviations: AMH, anti-Müllerian hormone; FMP, final menstrual period; FSH, follicle-stimulating hormone.

↑ = elevated.

* Blood draws during early follicular phase (cycle days 2-5).

** Approximate expected concentration based on assays using current international pituitary standard.