

Review article

Menopause and cardiometabolic diseases: What we (don't) know and why it matters



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ABSTRACT

This narrative review discusses the current understanding, knowledge gaps and challenges in expanding our knowledge of the association between menopause and the reproductive aging process and cardiometabolic disease (CMD) in women, with a focus on type 2 diabetes and cardiovascular disease. The physiological changes that occur at different stages of the reproductive life span, as well as type of menopause and timing, are factors widely associated with CMD risk; however, the underlying mechanisms remain either unclear or insufficiently studied. Decreased ovarian estrogen production and relative androgen excess around menopause onset are the most studied factors linking menopause and cardiometabolic health; nevertheless, the evidence is not persuasive and other hypotheses might explain the changes in CMD risk during menopausal transition. In this context, hormone therapy has been widely adopted in the treatment and prevention of CMD, although uncertainty regarding its cardiometabolic effects has raised the need to optimize therapeutic modalities. Mechanisms such as the "iron overload theory" and new "omics" platforms could provide new insights into potential pathways underlying the association between menopause and cardiometabolic health, such as the DNA damage response. Although it has been widely reported that environmental and lifestyle factors affect both menopause and cardiometabolic health, there is little evidence on the role of these exposures in menopause-associated CMD risk.

1. Introduction

Cardiometabolic diseases (CMD), including type 2 diabetes (T2D) and cardiovascular disease (CVD), and their associated factors, such as hypertension, dyslipidemia, insulin resistance and obesity are among the leading causes of morbidity and mortality in both sexes [1]. However, men and women experience different trajectories of cardiometabolic risk throughout the life course. At a young age, CMD prevalence is higher in men than women, but this female advantage gradually disappears with aging, particularly after menopause, when cardiometabolic risk factors accumulate [2,3]. However, the underlying biological pathways remain insufficiently studied, and disentangling the effect of age and menopause on cardiometabolic status worsening has been challenging [4,5]. Considering that the midlife period could be a critical window of opportunity to optimize cardiometabolic health and

initiate early prevention strategies, we conducted a narrative review in which we discuss the current understanding of the impact of menopause (timing, type and menopause stages) and associated modifying and/or mediating factors such as hormone therapy, genes, lifestyle and environment on CMD risk (e.g., risk factors such as blood pressure, lipid and glucose metabolism, obesity and T2D and CVD) in aging women.

2. Methods

PubMed was searched by four authors (ZMRD, PFR, JL, AB) to identify articles reporting on association between menopause characteristics (timing, type, stages), their modifying and mediating factors (hormone therapy, genes, lifestyle, environment) and CMD risk (blood pressure, lipid and glucose metabolism, obesity and T2D and CVD) from inception to 15th April 2021. The search strategy combined the terms

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related to menopause, menopause transition, female aging, hormone therapy, cardiovascular risk, diabetes risk, estradiol, testosterone, genetics, lifestyle and environmental, among others. Since this is a narrative review, we prioritized the inclusion of the latest and the most relevant publications among the available literature, as well as based on the knowledge expertise of co-authors.

3. Menopause characteristics and CMD risk

The Framingham study (1976) provided one of the first evidences on changes in CVD risk after menopause, reporting more cardiovascular events in post- as compared to pre-menopausal women of the same age [6]. Over the past four decades, great efforts have been put into understanding the determinants of increased CMD risk in postmenopausal women [7–15]. Besides the accumulation of CVD risk factors during menopausal transition (e.g., increased blood lipids, fasting glucose, and blood pressure, and accumulation of abdominal fat) [2,3,16,17], the prevalence of T2D, major CVD risk factor, also increases around this time. [18,19] In addition, menopausal transition is characterized by menopausal symptoms such as hot flashes, night sweats, sleep disturbances, depression, and anxiety, that have also been linked with adverse cardiometabolic profile and increased risk for CMD [20–22].

Thus, age at which women reach natural menopause (ANM) is considered as a marker/predictor of both reproductive and somatic aging, and of cardiometabolic and overall women's health. For instance, later ANM has been linked with both positive (e.g., longer life expectancy, reduced all-cause and CVD mortality) and negative health consequences (e.g., greater breast and ovarian cancer risk). (3) Factors such as race/ethnicity, reproductive factors, body composition, lifestyle, genetics and premenopausal cardiovascular health could affect ANM and are also linked with CMD risk. Indeed, in a cohort study including 3639 Dutch postmenopausal women experiencing natural menopause, women who experienced early natural menopause (ENM) had a 2.4-folds higher risk of T2D as compared to late menopause onset. In a later publication using data from the same cohort, women who experienced early natural menopause lived also shorter, and spent fewer years without T2D than women who experienced normal or late menopause [23]. A meta-analysis comprising 32 studies and 342,284 women reported that women going into EM, compared to women who reached menopause at 45 years or older, had a 50% increased risk for coronary heart disease (CHD). [24] These findings were replicated by a large study that pooled individual data from 301,438 women across five countries, reporting a 30% higher risk for CVD in women with EM than women having menopause at 50–51 years [25]. In addition, women who experienced EM had a significantly greater risk of heart failure [26]. However, a study involving 177,131 women from four different countries found that women with a CVD event before the age of 35 years, compared to women without CVD, had twice higher risk of EM [27]. Therefore, the associations may be bidirectional, and thus, worse premenopausal cardiovascular health profile could influence the onset of natural menopause.

Identification of biomarkers that can correctly forecast an individual's reproductive life span would have implications for the prevention of health conditions influenced by timing of menopause, such as CMD. Over the past decade, numerous studies attempted to measure the ovarian reserve to estimate individual ANM. Circulating anti-Müllerian hormone (AMH) is considered a reliable quantitative marker of ovarian reserve, and it has been linked with timing of ANM. Although AMH concentrations could predict the odds of menopause within the next years, among women in late reproductive age, the evidence remains conflicting with some studies reporting poor prediction performance of single and repeated AMH measurements [28,29]. In addition, validation and calibration of the prediction model based solely on AMH is lacking; calibration is an important step in prediction model because even a good-performing model based on its C-statistics, can over- or underestimate the outcomes risk. The ability to predict the onset of menopause

could improve by combining AMH with other factors such as women's age, number of full-term pregnancies, body mass index (BMI), other hormones or polymorphisms of genes included in ANM and sex steroid synthesis such as cytochrome P450 17 α -hydroxylase/17,20-lyase (CYP17). Besides exploring the accuracy of newer prediction models in predicting the 5- and 10-year risk of developing menopause, future studies may explore the value of these risk prediction models in prediction of menopause-associated disorders (e.g., osteopenia, atherosclerosis and CMD).

Limited number of cohorts have been designed to explore relative contributions of chronological and reproductive aging to cardiometabolic health changes. In favor of reproductive aging theory, studies have reported that women who experience surgical menopause (without estrogen therapy use) have a higher CMD risk compared to women with natural menopause. [30–32] Some studies suggest that the risk is higher if the surgery occurs at a younger age (before 40–45 years) [30,33,34]. However, studies exploring the mechanisms on how surgical menopause may affect CMD risk factors have provided contradicting findings. Some studies have reported poorer atherogenic lipid profile in women who experienced surgical than natural menopause [11,30], while longitudinal studies from the SWAN (Study of Women's Health Across the Nation) and CARDIA (Coronary Artery Risk Development in Young Adults Study) studies showed that hysterectomy was not a key determinant of CVD risk factors either before or after elective surgery in midlife [32,35]. Thus, it remains unclear whether the poorer CMD health profile seen in postmenopausal women is attributed to aging or it is a consequence of menopause-specific changes.

Overall, the current evidence on the impact of menopause on cardiovascular risk factors is limited, and suffers from important methodological limitations precluding synthesis and comparability of the results. First, available studies used different methods for the classification of menopause and reproductive stages [36–38]. The gold standard for the diagnosis of menopause remains clinical, and no biomarkers have been validated to help in an accurate diagnosis of menopause.(3) Moreover, there is no uniformity in the assessment of menopausal symptoms and physiological changes, which increases the challenge for a reliable definition of menopausal stages [22]. Second, only few longitudinal studies (Table 1) have explored the impact of menopause transition and reproductive stages on longitudinal changes in cardiometabolic risk factors. These studies consider the individual baseline risk and the changes in risk factors over time. Therefore, these designs are superior in determining the association between menopause and cardiometabolic risk factors. However, there is a huge disparity among the analytical framework in longitudinal studies (linear versus piecewise regression) and the covariates used, precluding comparability of results [17,39–43]. For example, a study that used linear regression model did not show any statistically significant difference in body composition among different reproductive ages, but changes became more apparent after piecewise regression across six time points [43]. In addition, longitudinal studies could be susceptible to bias, such as “immortal bias” [44]. Honigberg et al. provided an example of how studies conducted in postmenopausal women, which restrict inclusion to those who experience menopause or a CVD event after enrollment, could exclude an immortal time interval during which women could potentially experience CVD events (time from menopause to study enrollment), and censor the time intervals of women who have already gone through menopause and had a CVD event. Therefore, it is recommended to enroll women at a young age (30 years) with enough follow them for women to develop cardiometabolic events to accurately determine the time-to-incident events [44]. Third, the mechanisms underlying menopause transition and CMD associations are not well understood, data are mainly based on traditional risk factors, and few on novel pathways that explain the association between menopause and CMD [5,45,46]. Alternative mechanisms, such as iron metabolism, the role of environmental factors, and the possible role of DNA damage response mechanisms in the association of menopausal and CVD, are some of the emerging

Table 1
Summary of some selected studies evaluating the association between menopause stages and cardiometabolic diseases.

Author, year and citation	Cohort name (Country)	Outcome	Main results
Longitudinal Analysis			
Do KA (2000). [39]	Melbourne Women's Midlife Health Project (Australia)	Lipids, diastolic blood pressure (DBP), body mass index (BMI).	Women transitioning to menopause had lower levels of high-density lipoprotein (HDL) (largest decline at 9 months after menopause) No changes in other parameters Women in menopausal transition (first year of menopause) had an increase in cholesterol, low-density lipoprotein (LDL), and apolipoprotein B (ApoB) (with correction for age) No changes in other parameters
Matthews KA (2009). [41]	SWAN (US)	Lipids and lipoproteins, blood pressure (BP), insulin, glucose, and hemostatic and inflammatory factors	Women at the early postmenopause stage had higher levels of cholesterol, LDL, and HDL, compared with their premenopausal stage. No changes in other parameters
Karvinen S (2019). [17]	ERMA (Finland)	Lipids, glucose, inflammatory markers	Women at the early postmenopause stage had higher levels of cholesterol, LDL, and HDL, compared with their premenopausal stage. No changes in other parameters
Sowers M (2007). [43]	SWAN (US)	Body composition (Waist circumference, fat mass, fat percent, skeletal muscle mass)	There was an increased in fat mass and waist circumference not only related to chronologic aging but also ovarian aging (↓FSH). On the contrary skeletal muscle mass decrease across postmenopausal time
Razmjou S (2018). [42]	MONET (Canada)	Body weight, waist circumference, fat mass, % fat mass, total cholesterol, LDL and HDL, haptoglobin, Apo B, ferritin, adiponectin, inflammatory markers	Compering %fat mass at final menstrual period against early postmenopause status, changes were lower one year after final menopause compared with 5 years. Similarly, after menopause, women had higher levels of triglycerides and LDL. There was no postmenopausal increase in body weight and BMI Inflammatory markers including Hp, ApoB, ferritin, sCD14, and adiponectin levels increased, whereas sTNFR-1, sTNFR-2, and IL-8 levels decreased at 10-year follow-up after menopause
		Total cholesterol, LDL, HDL,	Postmenopausal women had higher TC

Table 1 (continued)

Author, year and citation	Cohort name (Country)	Outcome	Main results
Jensen J (1990). [40]	No specified cohort (Denmark)	cholesterol and triglycerides	and LDL levels compared to premenopause, the highest increment was observed 3–6 months following the final menopausal period. On the contrary HDL decreased after menopause; however, the decrease was gradual and started 2 years before menopause.
Cross-sectional analysis			
Stevenson JC (1993). [106]	UK	Lipids and lipoproteins	TG, LDL, and total cholesterol are all increased in postmenopausal women compared to premenopausal. On the contrary, HDL was lower in postmenopausal women.
Cho GJ (2008). [107]	South Korea	Lipids, BP, glucose, metabolic syndrome, abdominal obesity	Postmenopausal women are at increased risk for metabolic syndrome compared to premenopausal. The risk increment varies according to the years in menopause.
Peters HW (1999) [12].	Netherlands	Lipids, BP, glucose	Increased LDL, cholesterol, and ApoB (present within 3 years from the onset of menopause) for postmenopausal compared to age-matched premenopausal women. Insulin, glucose, and BP not significant
Pansini F (1993). [11]	Italy	Lipids	Postmenopausal women had higher LDL levels compared with premenopausal. CMD risk was higher in surgical compared to natural menopause. The changes in lipid profile gradually occurred during the months preceding the onset of natural menopause.
de Kat AC (2017). [16]	Netherlands (LifeLines Cohort)	Lipids, BP, BMI	Higher LDL, systolic and diastolic BP, total cholesterol, BMI for postmenopausal women compared to premenopausal women.

Abbreviations: BMI, body mass index; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FSH, follicle-stimulating hormone; TG, triglycerides; TC, total cholesterol; Hp, haptoglobin; ApoB, apolipoprotein B; sCD14, soluble cluster of differentiation 14 cells; sTNFR-1, sTNFR-2, soluble Tumor necrosis factor receptor subtype 1 or 2; IL-8, interleukin 8; CMD,

cardiometabolic disease; SWAN, Study of Women's Health Across the Nation; ERMA, Estrogenic Regulation of Muscle Apoptosis - ERMA study; MONET, Montreal-Ottawa New Emerging Team Study group;

hypotheses [47,48].

4. Mechanisms underlying cardiometabolic risk in menopause

4.1. Hormonal changes

Dramatic decline in estradiol levels and changes in estrogens to androgens ratio that occur during menopausal transition coincide with increased incidence of CVD and T2D, and thus decreasing estradiol has been suggested as the main determinant of increased CMD risk in menopausal women. (Fig. 1) [49,50]. Although, cross-sectional studies often provide inconsistent evidence, longitudinal studies reported positive association between higher estradiol levels and subclinical CVDs [51]. Furthermore, when comparing women with low estradiol before and after menopause, women with higher estradiol before their final menstrual period but lower estradiol thereafter appeared to be less likely to develop carotid plaque after menopause suggesting a potential shift in cardioprotective role of estradiol in women traversing to menopause [51]. In addition, high estrogenic exposure in premenopausal women, such as in case of pregnancy, was associated with adverse metabolic changes (hyperglycemia or increased blood pressure) which could impact the risk of developing T2D and hypertension later in life. [52,53] In line with this, in postmenopausal women, higher serum estradiol levels may be linked with pro-atherogenic lipid profile, blood pressure increase, impaired blood glucose, increased risk of T2D and stroke [18, 54–58]. The Three-City prospective study reported high levels of endogenous estradiol were predictor of the risk of CHD and stroke among postmenopausal women older than 65 years, while data from Rotterdam Study showed that among postmenopausal women with carotid atherosclerosis, high levels of circulating estradiol were associated with both increased likelihood of having unstable carotid plaque and increased risk of stroke [54,59]. Overall, this data may reinforce the timing hypothesis, that is, while estrogen can have beneficial cardiometabolic effects in younger women, it can have harmful effects in elderly with underlying atherosclerosis. [60,61]

Increased androgenicity in peri- and postmenopausal women was associated with an unfavorable cardiovascular risk profile [55,57,58,62,

63]. The findings from longitudinal MESA (Multi-Ethnic Study of Atherosclerosis) study may suggest that testosterone/estrogen ratio may provide an alternative better predictor of CVD risk than testosterone or estrogen levels alone, but the findings have not been replicated [64]. On the other hand, the impact of other androgens in CMD has been little explored; higher serum dehydroepiandrosterone (DHEA), and DHEA sulfate, the major circulating hormones in the human body, have been inversely associated with risk of T2D and with N-terminal pro b-type natriuretic peptide (NT-proBNP) levels (a biomarker of CVD). [65,66] Considering that levels of androgens, including testosterone and DHEA also change in aging women, the association between menopause and CMD risk could be more complex and depend on several hormonal pathways.

While the impact of estradiol and androgens on women's health remains debatable, Mendelian randomization (MR) studies tried to clarify some of the discrepancies. A recent MR study suggested that genetically predisposed higher testosterone levels may play a role in modifying both CVD risk factors and CMD events (i.e., thromboembolism, heart failure, coronary artery disease risk, and stroke). (primarily in male population). [67,68] In line with these findings, another MR study reported some indications that genetically-predisposed higher follicle-stimulating hormone (usually associated with higher androgen levels in men) was positively associated with coronary artery disease (CAD) risk, but genetically-predicted higher AMH and higher risk of testicular dysgenesis syndrome (usually associated with lower androgen levels in men) were negatively associated with CAD risk [69]. To our knowledge, there are no other studies to explore the causal association between estradiol or other sex steroids and cardiovascular health indices. The data on the biological function of genetic variants linked with increasing serum levels of sex hormones are scarce and pleiotropic effects between shared genetic variants among hormones make the research challenging. On the other hand, the discrepancies in the associations between sex hormones and CMD risk observed in previous observational studies could be driven by several methodological differences, such as (i) study design (cross-sectional, cohort, nested-cohort or case-control designs), (ii) lack of adjustment for important confounding factors or for upstream precursor sex hormones, (iii) variations in follow-up times ranging from 4 to almost 30 years, (iv) differences in sex hormone assays, (v) different measurements of CMD events, including self-reports, medical records or national patient registries, and (vi) inclusion of postmenopausal women mostly, while perimenopausal women remain largely underrepresented

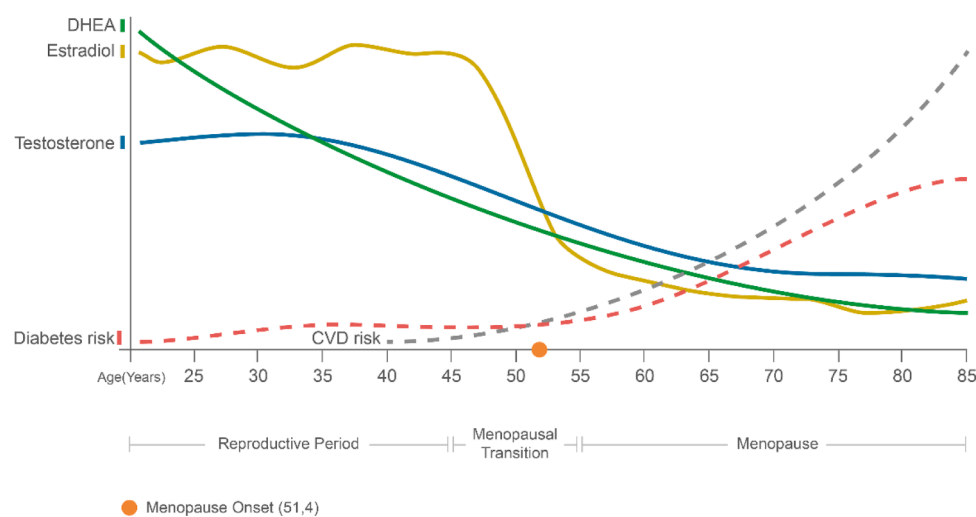


Fig. 1. Age-related variations in serum sex hormones and cardiometabolic risk in women.

The figure is adopted from Glisic, M. (2018, October 31). Sex Hormones and Cardiometabolic Risk. Erasmus University Rotterdam. Retrieved from <http://hdl.handle.net/1765/111755>.

in research. Considering that we lack studies exploring changes in hormones during menopausal transition and in first years of menopause, and whether these changes are linked to CMD, studies including premenopausal women with sufficiently long follow-up and repeated measures of sex hormones and CMD domains across different reproductive stages could help to understand the impact of hormone throughout women's life course. Furthermore, since estradiol/androgens ratio and extreme changes in hormonal levels may be more important determinants of cardiometabolic health rather than hormone levels solely, carefully planned longitudinal studies should explore how trajectories of sex hormones changes (androgens and estrogens) during menopausal transition and in the first years of menopause impact CMD risk later in life.

4.2. Hormone therapy

Menopausal hormone therapy (MHT) is considered to be the most effective treatment for relieving menopausal symptoms [70], but potential side effects could be present. Since the first data from the Women's Health Initiative (WHI) trial were published in 2012, followed by more studies linking hormone therapy with the development of several cancers, there is a decline in number of women willing to use hormone therapy from fear of its potential adverse effects [71–74]. However, factors such as therapy initiation and timing, duration, dose and administration route are determinants of its benefits and harms. [75] Oral HT preparations in women with baseline thromboembolic risk might increase the risk of venous thromboembolism (VTE) and stroke in a dose-dependent manner, but transdermal estradiol (alone or with micronized progesterone) was deemed safer [75]. Initiation of HT early into menopausal transition may be safer with regard to CVD risk, resulting to a lower absolute risk of VTE, CVD and stroke in the early menopausal years. Contrary, the current data show that late HT initiation (10 years after the menopause onset) should be given at the shortest time, with the lowest dose, and preferably using transdermal route (i.e., <50 µg/day of estrogen). Vaginal route could be a complementary approach as it was shown to have a lower risk for myocardial infarction and stroke risk, albeit the evidence is limited. [75] While women with baseline increased thromboembolic risk, low-dose oral and transdermal HT preparations were shown to be cardioprotective. [75]

In addition, large RCTs (PEPI, HERS, KEEPS) [76–78] have suggested that HT may reduce insulin resistance and incidence of T2D with oral preparations having stronger potential to improve glucose metabolism and decrease the risk of developing T2D [79]. Similarly, HT was also linked with improvements in glucose homeostasis and insulin resistance in diabetic women in meta-analysis of RCTs published in 2006 and results were supported by several RCTs that were published afterwards [80]. In placebo-controlled trials in postmenopausal women with T2D, conjugated estrogens and oral micronized estradiol treatment improved glucose metabolism, increased insulin suppression of hepatic glucose production, and insulin resistance without affecting postprandial glycemia [81–84]. Despite promising evidence, HT use is not recommended in the primary prevention of T2D due to the complex interplay between underlying conditions and other health risks (e.g., obese women with T2D may have higher risk of developing VTE with HT) [79].

There are important methodological differences among the studies with trials/studies focusing on women with T2D: (i) most studies used estrogens alone hormone preparations, and were performed over a shorter duration of time than studies in women without T2D, (ii) studies in women without T2D used both estrogens alone and combined hormone preparations but mainly were not designed to explore the effect of hormone therapy on T2D prevention as a primary end point, (iii) vasomotor symptoms remain the main clinical indication for HT, especially in perimenopause. However, studies focus on the effect of HT in postmenopause, neglecting data on the effect of HT on cardiometabolic risk during menopausal transition, [79] (iv) the role of underlying diseases and genetic traits (e.g., genetic variance in estrogen receptor,

genetic predisposition to higher estradiol levels) in mediating CVD risk in women taking hormones remains unclear.

Furthermore, most of the studies explore HT use on postmenopausal women. However, vasomotor symptoms remain the main clinical indication for HT and are usually given in perimenopausal women. Hence, we are losing important data on the effect of HT on cardiometabolic health indices in women during perimenopause who may be offered the treatment in order to relieve menopausal symptoms. Whereas the role of underlying diseases and genetic traits (e.g., genetic variance in estrogen receptor, genetic predisposition to higher estradiol levels) in mediating CVD risk in women taking hormones remains unclear. The paradigm that postmenopausal women have poorer cardiometabolic risk profile in comparison to premenopausal women lead to belief that HT can be used in chronic disease prevention. However, considering the narrow therapeutic index of estrogens, we still do not have enough evidence, nor proper therapeutic modalities to ensure the effect of estrogens in selected issues (such as bone, vasculature or brain) and at the same time avoid potential deleterious effects of estrogen on uterus, ovarian and breast tissues. Thus, future therapeutic modalities may hold the key on how to properly tailor hormonal therapy in women not only to treat vasomotor symptoms but to improve overall cardiometabolic health indices while avoiding potential health harms in high-risk women. In order to prevent harms and reduce the dose and time of estrogen exposure, alternative approaches could be recommended to women suffering from menopausal symptoms, such as phytoestrogen supplementation/nutritional intake, which has shown to have the potential not only to improve menopausal symptoms, but also to improve glucose homeostasis, reduce the risk of T2D and CVD [85,86].

4.3. Genes

Genome wide association studies (GWAS) have identified between 56 and 290 single nucleotide polymorphisms (SNPs) associated with timing of menopause and uncovered new pathways involved in the genetic expression of menopausal traits [47,48]. Many of the SNPs associated with ANM, were linked with DNA damage response pathways. For example, missense mutations in FANCD1 and FANCD2 genes, which plays an important role in the response to replication stress (removal of interstrand crosslinks, DNA-protein crosslinks and R loops), were associated with EM. In addition, results from pathway analyses implicate that some of the highlighted genes are involved in the meiotic phase of fetal oocytes, endocrine and metabolic mechanisms [48]. However, the role of these findings in the development and progression of CMD and/or CVD is still unknown.

Newer methodologies, such as MR analysis, have extracted evidence supporting the causal association between prolonged reproductive life and reduced risk of T2D, [48] however, causal associations between ANM and CVD and lipid levels have not been reported to date [48].

Some of the limitations of MR approaches implemented so far in menopause and CMD are their focus on estimating the total causal effects of combined pathways linked to early menopause, and limited attention on assessing individual pathways that might mediate the effect of menopause on CMD, if present. Future MR studies can explore whether genetic variants related to DNA damage can partially explain the association between menopause and CMD. Furthermore, methodologies such as bidirectional MR could reduce uncertainty about the association of menopause and CMD, as reverse causality has been little explored. In this regard, a recent study evaluated the link between genetic variants associated with coronary heart disease and T2D and age at natural menopause (ANM) in over 50,000 women from three large consortia (ITMAT/Broad/CARE (IBC), ReproGen and EPIC-InterAct). In this study, the association between CMD and earlier timing of menopause was not causal but did not exclude the possibility that the reverse association can be causal [87]. It should be noted that few studies consider that sex can modify the effect of genetic variants on CVD [4]. Other approaches such as epigenetic study suggested that women with

higher blood DNA methylation levels than expected based on her chronological age have an increased risk of EM [2].

The current understanding of the genetics underlying menopausal traits, pathways, and clinical relevance is limited. Multi "-omics" approach, including genomics, transcriptomics, proteomics, and epigenetics technologies can be used to reveal the intricate relationship of menopause and aging, which is one of the main challenges to identify the independent role of the later on CMD. For example, future research could focus on the linkage of each SNP identified with ANM and/or genetic risk score with metabolomics, and then search for associations between the identified metabolomics sites with CVD/T2D, which could potentiate the discover of new treatment targets that could be applied solely to women. Also, "-omics" platforms, including genetic distribution, could help to characterize different menopausal types, which could have different relations with CVD/T2D.

4.4. Environmental factors and lifestyle

Environmental and lifestyle-related factors, including diet, alcohol consumption, physical activity, BMI, smoking, environmental toxicant exposures, the built environment, socio-demographic, psychological, and social-cognitive factors, among others, are linked with both ANM and CMD risk [88–91]. Lifestyle and environmental factors may trigger mechanisms that underlie menopause-associated CMD, including their influence on DNA methylation and gene expression, induction of low-grade inflammation and oxidative stress, and many toxicants, that may act as endocrine-disrupting chemicals, interfering with hormone-related signaling, among other mechanisms [92,93].

Lifestyle factors play a role in both the onset of menopause and CMD. Specific diets may play a role, where for example, adherence to western dietary patterns have been associated with subclinical carotid atherosclerosis in women undergoing the menopausal transition [91]. The role of nutrition in menopausal age is not clear. In a prospective study of women in the UK, investigating the relationship of nutrient intake with ANM, intakes of oily fish and fresh legumes were associated with later ANM and intake of refined pasta/rice was associated with EM [94]. Additionally, in a follow-up study of the same participants, low-meat dietary patterns were associated with EM [95], through this was not supported in the Nurses' Health Study II in the US [96]. Studies assessing the effects of healthier lifestyles in modifying the association of ANM and CMD are limited. However, there is evidence that those who have a healthy lifestyle (i.e., smoking cessation, healthy diet, and regular physical activity) during menopause transition have lower levels of subclinical atherosclerosis later in life [97] and a favorable body composition profile [8]. Despite the importance of a healthy lifestyle, a recent study from 1656 Swiss women found that they did not change their dietary habits during the menopausal transition. [98] This highlights that the CVD risks differences between menopausal categories are not solely related to diet. Nevertheless, early introduction of dietary interventions could improve CMD risk, but we lack studies that focus on women, and explore dietary patterns that can improve women's health.

Exogenous environmental exposures can shorten the time to menopause onset, where toxicants, such as those found in personal care products, foods, water, and air, resulting in ubiquitous and continuous exposure, are associated with ANM [93]. In two cross-sectional studies the association between environmental mixtures was associated with ANM, where high serum levels of polyfluoroalkyl chemicals were associated with EM [99] and women exposed to mixtures of PCBs, phthalates, pesticides, and dioxins reached menopause 3 years earlier than those having lower levels of exposure [100]. More established, is the role of the environment on CMD. Air pollution and metals, such lead, cadmium, and arsenic, may play a prominent role in the development of CMD [101,102]. Additionally, other environmental stressors are associated with CMD, including social isolation, work stress, and noise exposure [103].

However, there are several limitations in previous studies assessing

the role of lifestyles and/or environmental exposures on ANM, CMD, and/or menopause-associated CMD. In majority of studies the role of lifestyle and environmental factors were assessed only in post-menopausal women. There is a need to evaluate the role of exposures also on menopausal transition and subsequent CMD across the life-course as life-long exposures are cumulative. Additionally, there are differences in susceptibility of the effects of exposures at critical and sensitive timepoints [104]. While the postmenopausal period remains important, earlier in life assessments, such as *in utero* where there is a strong imprint on both hormonal and egg development, need to be considered. Particularly, the prenatal period is critical, where exposures can lead to an insufficient quantity of germ cells formed during the establishment of the ovarian reserve, ensuing deficient ovarian follicle pool at birth and/or puberty [90]. Furthermore, there are differences in behaviors at various timepoints, which are not captured in studies assessing factors at single timepoint, undermining the effect of cumulative exposure on an individual, as has been demonstrated with diet, where a single dietary measurement may not accurately capture long-term dietary habits [105]. Lastly, there are populations that have different susceptibilities to environmental toxicants and lifestyle-behaviors, whereby many previous studies may not have captured this as many have focused on women of white, European descent. Excluding diverse populations fails to capture differences in exposure/disease susceptibility and limits generalizability of results of age at menopause-associated CMD on other racial and ethnic groups.

5. Conclusions and future outlook

Menopause has been, traditionally, associated with increased CMD disease risk because of its peculiar timing and health consequences in aging women. The current evidence, however, remains of limited methodological quality and often provides inconsistent or even conflicting evidence. In this review, we present an overview of the most important determinants of increased CMD risk in aging women and provide directions for future research (illustrative summary provided in Fig. 2). None of the available evidence sufficiently clarifies the dilemma on the independent and causal role of menopause in development of CMD, the lasting effects of menopause in older ages, its ethnic variations, and the interaction of menopause traits with traditional cardiovascular risk factors. We emphasize that more robust evidence is required to disentangle the complex mechanistic pathways mediating increased cardiometabolic risk after menopause. Considering that menopause transition may be a period when women are the most vulnerable, there is a need to develop 5- and 10-year risk prediction models that identify women who are at increased risk of developing early menopause and who may benefit from targeted preventive interventions.

Contributors

Zayne M. Roa-Díaz contributed to drafting and revision of the manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest.

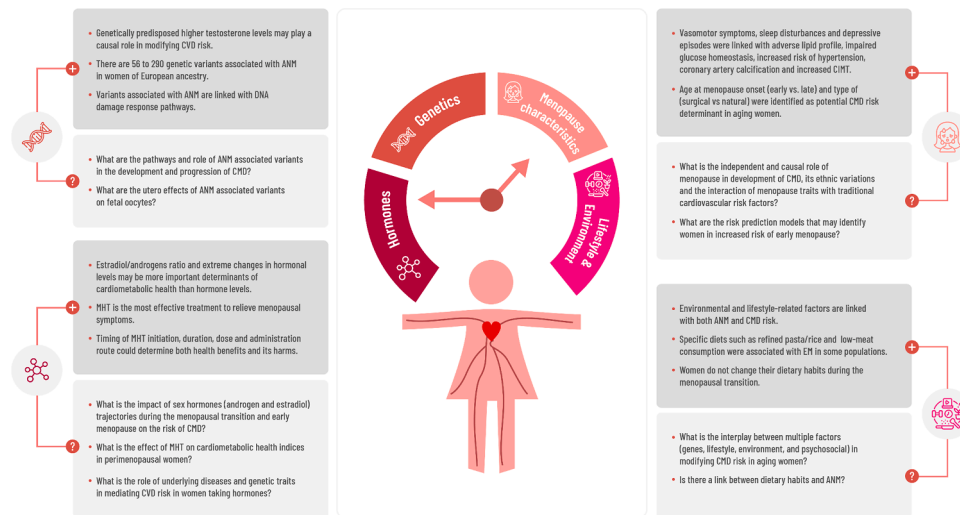


Fig. 2. Menopause and cardiometabolic disease: Illustrated summary of the most important findings

Abbreviations: CVD: cardiovascular disease, ANM: age at natural menopause, CMD: cardiometabolic disease, MHT: menopausal hormone therapy, CIMT: carotid intima media thickness, T2D: type 2 diabetes, EM: early menopause.

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