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REVIEW

Vasomotor symptoms in menopause: a biomarker of cardiovascular disease risk and other chronic diseases?

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ABSTRACT

Menopausal disorders may include shorter-term symptoms, such as hot flushes and night sweats (vasomotor symptoms, VMS) and longer-term chronic conditions such as cardiovascular disease (CVD), osteoporosis, and cognitive impairment. Initially, no clear link between the shorter-term symptoms and longer-term chronic conditions was evident and these disorders seemed to occur independently from each other. However, there is a growing body of evidence demonstrating that VMS may be a biomarker for chronic disease. In this review, the association between VMS and a range of chronic postmenopausal conditions including CVD, osteoporosis, and cognitive decline is discussed. Prevention of CVD in women, as for men, should be started early, and effective management of chronic disease in postmenopausal women has to start with the awareness that VMS during menopause are harbingers of things to come and should be treated accordingly.

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Introduction

The 20th century witnessed a major epidemiologic transition characterized by a shift in the leading causes of death from infectious diseases to chronic conditions[1]. Life expectancy at birth now exceeds 80 years in many countries, which means that many women spend over a third of their lives in a postmenopausal state and one in every two women will experience about 30 years of postmenopausal life. Menopause frequently coincides with the period when women are at the peak of their careers and, because women are postponing pregnancy until later in life, many will also have young children. Although the menopause is a natural transition, it has important physiological manifestations resulting from hormonal changes that have far-reaching short- and long-term consequences.

In general, menopausal disorders can be divided into two main groups: short-term symptoms, the most common of which are hot flushes and night sweats known as vasomotor symptoms (VMS) and longer-term chronic conditions including cardiovascular disease (CVD), osteoporosis, and cognitive impairment[2]. For many years, it was thought that short-term symptoms and long-term chronic conditions occurred independently with no causal link between them. However, there is now a body of evidence demonstrating that menopausal symptoms, in particular VMS, may be considered precursors or biomarkers of chronic disease.

In this Expert Opinion piece, a multidisciplinary group of Italian physicians, involved in the care of postmenopausal women, review and discuss the evidence and emerging findings for the link between VMS in menopause and a range of chronic postmenopausal conditions including CVD, osteoporosis, and cognitive decline.

Vasomotor symptoms: more than a nuisance

Of the core symptoms that make up the menopause, VMS (hot flushes or night sweats) are the most frequently reported, and most women experience VMS at some stage during the menopausal transition. In the Study of Women's Health Across the Nation (SWAN), one of the largest conducted in menopausal women, 60–80% of women experienced VMS during the menopausal transition[3]. A sizable portion of women report VMS earlier in midlife, before the onset of menstrual cycle changes, which continued for many years postmenopause[4,5]. VMS occur more frequently in women with premature menopause (occurring before the age of 40 years) than premenopausal women, and women

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with medically induced premature menopause (induced by oophorectomy, chemotherapy, or radiotherapy) may experience more severe symptoms[6]. The long-term consequences of premature or early menopause include adverse effects on cognition, mood, CVD, bones, and sexual health, as well as an increased risk of early mortality[7]. In fact, the 2016 IMS Recommendations on women's midlife health outline that women with POI should receive hormonal treatment after exclusion of contraindications to prevent an increase in the risk of cardiovascular disease, osteoporosis, cognitive decline, dementia and Parkinsonism [Grade B recommendation][8].

Hot flushes impair quality of life, disturb sleep, and have a negative effect on mood[2,3,9]. Untreated hot flushes are associated with higher health-care utilization, work loss, and total costs. Sarrel and colleagues compared over a quarter of a million (252 273) women with hot flushes with an equal number of matched control women without hot flushes and found that women with hot flushes made 1.5 million more patient visits than those without[10,11]. Untreated VMS were associated with a significantly higher frequency of outpatient visits and incremental direct and indirect costs. Furthermore, a recent study overturned the long-held belief that VMS last for a relatively short time (<2 years after the final menstrual period). Avis and colleagues showed that frequent VMS lasted in excess of 7 years for more than half of women in the SWAN, persisting for 4.5 years after the final menstrual period[12]. VMS can last for decades, and as such should be taken into account when making treatment decisions. For the purpose of this review, VMS are included in the 'short-term symptoms' category, but it should be remembered that they are anything but short-term in a significant percentage of women. Results of a population-based, cross-sectional study in 1548 older Australian women (aged 65–79 years) showed that VMS were common, but predominantly untreated, and the highest prevalence of VMS (39.2%; 95% confidence interval (CI) 35.4–43.2) was seen for women aged 65–69 years[13].

The physiology of hot flushes is not completely understood. VMS are thought to be endocrine and/or thermoregulatory events originating in the hypothalamus as the result of decreases in ovarian hormones. The fundamental role of estrogen deprivation is well known and underlined by the recent Global Consensus Statement on Menopausal Hormone Therapy stating that hormonal therapy, including tibolone and the combination of conjugated equine estrogens and bazedoxifene, is the most effective treatment for VMS associated with menopause at any age[14].

Women with severe hot flushes may have an increased sympathetic tone with vascular involvement[15]. What is, however, now clear is that hot flushes (previously thought to be solely due to decreased estrogen levels) are a complex multicausal phenomenon and reflect a combination of interconnected systems including genetic bases, diet, physical changes, use of medications, cultural influences, and individual experiences and expectations[16–18].

Cardiovascular disease in women

World-wide, 8.6 million women die from heart disease each year, accounting for a third of all deaths in women[19]. Historically, CVD was considered a male disease; however, since 1984, more women than men have died each year from heart disease and the gap between men and women's survival continues to widen[19]. In the USA, 267 000 women die each year from heart attacks, which kill six times as many women as breast cancer[19]. Likewise, in Europe, CVD is the leading cause of death and, despite recent decreases in mortality rates in many countries, it is still responsible for over 4 million deaths per year, with the proportion of deaths attributable to CVD greater in women (51%) than in men (42%)[20]. Because women have a longer life expectancy, larger numbers of older women mean that the absolute number of deaths due to CVD in women is actually rising and nearly half of all deaths in women over 50 years are due to some form of CVD[21,22].

Paradoxically, despite being the leading cause of death, persisting cultural misperceptions and lack of effective management of risk factors mean that CVD is frequently undetected and untreated in women, with fatal consequences. The processes involved in CVD start long before their clinical manifestation and it is important to begin to manage risk factors during the 'window of opportunity' to maximize reductions in CVD and overall mortality[23]. Effective primary prevention is therefore a critical health-care priority as stated by the most recent International Menopause Society guidelines[8].

The Framingham study provided evidence of the relationship between menopause and cardiovascular mortality, with a 103% increased risk of ischemic stroke in women who experienced natural menopause before the age of 42 compared with women with later menopause, and a trend of increasing risk of ischemic stroke with decreasing age at the time of natural menopause[24]. The study conducted in 2873 women who were followed for 24 years showed that no premenopausal woman developed a myocardial infarction or died from CVD, but that CVD in postmenopausal women was more than doubled that in premenopausal women (20 vs. 70 cardiovascular events)[25,26]. Similarly, the Nurses' Health Study including 121 700 females showed that, after adjusting for age, CVD risk among women with a natural menopause was increased compared with the risk among premenopausal women[27]. Women who had surgical menopause (bilateral oophorectomy) and did not use hormone replacement therapy were found to be at increased risk of coronary heart disease (CHD) compared with age-matched controls (risk ratio 2.2)[27].

Epidemiological studies of age at menopause and CHD have shown that women experiencing early menopause (between age 40 and 45 years) have an increased risk of future CVD, with one study showing a two-fold increased risk of CHD or ischemic stroke[28,29]. Shuster and colleagues reviewed the literature and concluded that data show an increased risk for CVD in women who undergo bilateral oophorectomy, inducing premature (age <40 years) or early (age 40–45 years) menopause[7]. Women with a natural premature menopause (<40 years) had a 2-year lower life expectancy compared with women with a normal or late menopause[30].

Cardiovascular aging is not the same in men and women. In men, the risk of coronary artery disease increases after the

age of 45 years, whereas in women the risk is 2–3 times higher after menopause (whether early or late, natural or surgically induced)[31]. It is not clear whether there is an inverse causality between early menopause and CVD. On the one hand, ovarian exhaustion in women who have an early menopause may occur as a result of an unfavorable cardiometabolic profile; on the other hand, it may be that ovarian exhaustion causes premature atherosclerosis of the ovarian vessels, thus impairing their function. To understand the etiology and evolution of CVD in women, a complete hormonal picture starting from menarche, through pregnancy, until menopause needs to be considered.

In a 2016 robust meta-analysis including 32 studies with 310 329 non-overlapping women, the role of menopause in CVD was clearly demonstrated[32]. In particular, premature or early-onset menopause in women younger than 45 years was associated with an increased risk of coronary artery disease and all-cause mortality. The relative risks (95% CIs) were 1.50 (1.28–1.76) for overall CHD, 1.11 (1.03–1.20) for fatal CHD, 1.23 (0.98–1.53) for stroke overall, 0.99 (0.92–1.07) for stroke mortality, 1.19 (1.08–1.31) for CVD mortality, and 1.12 (1.03–1.21) for all-cause mortality. In addition, in comparison with women who experienced menopause before the age of 50 years, those who were aged 50–54 years at the onset of menopause showed a decreased risk of fatal CHD (relative risk 0.87; 95% CI 0.80–0.96) and no effect on stroke.

Menopause, vasomotor symptoms, and cardiovascular disease

Current cardiovascular risk algorithms do not predict well for clinical CVD in middle-aged women and a better understanding of the role played by VMS in vascular health could help identify women with an increased risk. Women with VMS have less favorable cardiovascular markers than those without symptoms. In one study, in over 11 000 women (aged 45–50 years), those having frequent VMS had an increased risk of developing CHD over 14 years, even when the effects of age, menopause status, lifestyle, and other chronic disease risk factors were taken into account[17]. The SWAN and its follow-up, in an older cohort of women, showed that women with hot flushes had indices of greater subclinical CVD, including poorer endothelial function and poorer flow-mediated dilation (FMD), and greater aortic calcification, and intima media thickness than women without hot flushes[33,34]. Others have found similar findings for endothelial function[35]. The vascular endothelium regulates blood viscosity and coagulation, and vagal stimulation can weaken procoagulant responses to endotoxin. Hot flushes are also associated with a lower level of total plasma antioxidant activity and an increased cardiovascular response to stressful situations[36]. Vascular aging, endothelial dysfunction, and large artery stiffening seem to increase in women during the menopausal transition. It may be that the menopause acts as a trigger to decreased vascular function and increased vascular vulnerability as women age. It has been shown that, during the perimenopausal period, reduced ovarian function and decreased estrogen levels accelerate vascular aging[37]. Although more work needs to be done to elucidate the exact mechanisms leading to endothelial dysfunction and large artery stiffening, it has been suggested that a combination of oxidative stress, vascular inflammation, estrogen receptor alpha, and endothelial NOS dysfunction contribute to the process[37].

Analysis of the SWAN subgroup showed that VMS, particularly frequent hot flushes, were associated with increases in tissue plasminogen activator antigen (tPA-ag), and factor VIIc[38]. Altered inflammation and hemostasis have been related to CVD risk, and the endothelium (dysfunction of which has been linked to VMS) plays a central role in regulating blood coagulation and inflammation. Important additional findings from the SWAN show that hot flushes were associated with elevated factor VIIc (an important protein in the coagulation cascade) and tPA-ag (a fibrolytic protein largely derived from the endothelium and associated with elevated cardiovascular risk among women) after multivariable adjustment. The results suggest an association with hemostatic, as opposed to inflammatory processes but, because inflammatory and hemostatic processes are interrelated and several of the markers have both roles, the authors recommend caution in interpreting the results[38].

In the Women's Ischemia Syndrome Evaluation Study (WISE), endothelial function determined by brachial artery FMD, was assessed in 104 postmenopausal women (>50 years) with signs/symptoms of ischemia[39]. Receiver-operating curve analysis was used to determine VMS groups: symptoms beginning at age <42 years (early onset), beginning at ≥42 years (later onset), and never, which were examined in relation to cardiovascular events and FMD. Women who had VMS when they were young (≤42 years) had significantly lower FMD compared with women whose symptoms started after the age of 42 years ($p = 0.038$) and those who never had VMS. The MS Heart study enrolled 189 women (nonsmokers, intact uterus and ovaries, not using hormones) aged 40–60 years, without heart disease[40]. There was a significant relationship between hot flushes and FMD and age ($p = 0.03$). In younger women (<52 years), a higher number of hot flushes was associated with lower FMD ($p = 0.02$). FMD in younger women who had ≥10 hot flushes a day was reduced by almost half compared with younger women without hot flushes, indicating that the more hot flushes these women had, the more evidence of endothelial dysfunction and CVD risk there was.

Silveira and colleagues reported an inverse correlation between the intensity of hot flushes and postreactive hyperemia flow in two groups of women: those with recent (<10 years) and late (>10 years) menopause[41]. In both groups, hot flushes were associated with endothelial dysfunction and higher systolic and diastolic blood pressures, but the relationship between hot flushes and endothelial dysfunction was independent of blood pressure. Endothelial dysfunction, if not treated, may progress to atherosclerosis with subsequent increase in risk of myocardial infarction or stroke, currently the major causes of death in postmenopausal women[41].

Menopause and aging induce variations of some cardiometabolic parameters, but it is unknown whether this occurs

in a sex-specific manner. Campesi and colleagues analyzed markers of oxidative stress, systemic inflammation, and endothelial dysfunction in men younger and older than 45 years and in pre- and postmenopausal women[42]. They reported that, before body weight correction, men overall had higher creatinine, red blood cells, and hemoglobin and lower triglycerides than women. Men younger than 45 years had lower levels of tumor necrosis factor (TNF)-α and malondialdehyde and higher levels of arginine than age-matched women, whereas postmenopausal women had higher interleukin (IL)-6 concentrations than men, and higher total cholesterol, triglycerides, creatinine, and IL-6 levels than younger women. Oxidative stress, inflammation, and endothelial dysfunction were associated with aging/menopause status for women and aging for men. Aging/menopause status increased many more cardiovascular risk factors in women than aging in men, confirming that postmenopausal women had increased vascular vulnerability and indicating the need for early cardiovascular prevention in women[42]. VMS occurring early in the menopausal transition were not associated with increased CVD risk whereas late VMS were associated with increased CHD risk and all-cause mortality[43]. It is not known whether VMS occurring for the first time in late menopause are pathophysiologically distinct from classic perimenopausal VMS. There also appears to be a link (via the sympathetic nervous system) between VMS and high blood pressure in menopausal women, with those with hot flushes having a significantly higher incidence of essential hypertension and high systolic blood pressure than those without hot flushes[44,45]. Collins and colleagues, in a review published in 2016, discussed current knowledge of the importance of conventional CVD risk factors (smoking, hypertension, lipids, and diabetes mellitus) as well as the link between VMS and CVD risk[23]. They also discussed how menopausal VMS are associated with increased sympathetic and decreased parasympathetic function that may increase the risk of cardiovascular events, which may be particularly important during a hot flush episode in women with a propensity to severe arrhythmias[23].

Cagnacci and colleagues, in a series of studies, investigated the association between menopausal symptoms and CVD risk factors[46–49]. One studied the relationship between oxidative stress and climacteric symptoms in 50 apparently healthy postmenopausal women[47]. Results showed that blood antioxidant defense is mainly determined by climacteric complaints and, among the possible endocrine, metabolic, and body parameters, it was only climacteric symptoms (not high density lipoprotein cholesterol or other metabolic parameters) that were linearly related to the decrease of antioxidant defenses.

Oxidative stress is a risk factor for CVD and these data provide additional evidence of the causal link between VMS and CVD. In another study by the same group, the Greene Climacteric Scale score was associated with raised 24-h urinary cortisol levels[49]. The Greene Climacteric Scale is composed of 21 items that evaluate VMS (two items), anxiety (six items), depression (five items), somatic symptoms (seven items), and sexuality (one item). An increased cortisol level is believed to play an important role in the aging process as well as having a detrimental effect on the immune response. There is evidence that it is involved in degeneration of hippocampus neurons, impairs memory and cognitive function, and accelerates bone loss as well as promoting the metabolic syndrome and diabetes, which in turn increase the risk for atherosclerosis/CVD.

Two large-scale meta-analyses assessing the association of VMS with various cardiovascular risk markers in tens of thousands of perimenopausal, menopausal, and postmenopausal women were recently published[50,51]. In general, results showed that women with VMS have an unfavorable cardiovascular risk profile (increased risk of CVD, CHD, or ischemic stroke) compared with women without VMS. Women experiencing VMS have significantly higher systolic and diastolic blood pressures, higher circulating total cholesterol levels, and a higher body mass index than their counterparts with no symptoms. There was also a positive, albeit weak, association of VMS with hypertension.

Menopause, vasomotor symptoms, and osteoporosis

Postmenopausal osteoporosis affects up to 200 million women world-wide with 70% of hip fractures occurring in women[52,53]. Osteoporotic fractures can lead to chronic pain, deformity, depression, disability, and death as well as having huge economic consequences. In the UK alone, annual hospital costs associated with hip fractures are estimated to be £1.1 billion[54]. The prevention of fractures in postmenopausal women is, therefore, a vital public health priority world-wide[52,53].

The observation that VMS peak around the same time as accelerated bone loss has led researchers to examine whether there was a link between VMS and adverse bone health[55–66]. However, it was not until 2015 that the first prospective study in a large cohort of postmenopausal women was conducted[67]. The study analyzed the medical records of more than 23 000 US women (aged 50–79 years). Results showed that women with moderate/severe VMS had lower bone mineral density (at the femoral neck and lumbar spine) and increased rates of hip fractures during more than 8 years of follow-up compared with women who did not have VMS[67]. These results confirmed those of Gast and colleagues, who showed that VMS were associated with reduced bone density[57].

Lower estradiol levels in women with hot flushes may explain the associations between VMS and reduced bone density. During menopause, reduced hormone levels are linked to increases in serum levels of inflammatory cytokines (TNF-α, IL-4, IL-10, and IL-12) – cytokines that stimulate osteoclast and osteoblast formation, leading to increased bone turnover and eventually bone loss[68]. The mechanisms involved in the association between VMS and osteoporosis are complex, but it may be that, in menopause, decreases in the natural antioxidant estrogen together with increases in

the proinflammatory cytokines lead to oxidative stress and ultimately loss of bone density[69].

Menopause, vasomotor symptoms, and cognitive function

Women have long reported 'brain fog' or memory problems during menopause. As well as the short-term implications on work and everyday activities, women worry that these symptoms may be linked to future cognitive impairment – dementia is more common in women than men (16% vs. 11% aged >71 years). It is therefore important to understand the mechanisms mediating cognitive decline in women. In the SWAN, over 40% of perimenopausal and postmenopausal women reported that they suffered from forgetfulness/worsening memory compared with 31% of premenopausal women[70], whereas in the Seattle Midlife Women's Health Study that enrolled women between the ages of 35 and 55 years, over 60% of midlife women reported an undesirable change in memory[71].

Postmenopausal women have low levels of estrogens and these are linked with both cognitive changes and inflammation[72]. It appears that estrogens, via their effects on the hippocampus and prefrontal cortex, play a significant role in cognitive functioning[73–76]. Premenopausal women showed higher achievements in verbal memory performance during the phases of the menstrual cycle associated with high estrogen[2]. However, it is likely that these changes are multifactorial with the hallmark symptoms of menopause (depression, sleep disturbance, and hot flushes) playing independent or synergistic roles[77].

There are few studies directly addressing the relationship between hot flushes and cognitive performance; however, a study by Maki and colleagues in 29 peri- and postmenopausal women (mean age 53 years) showed that objective, rather than subjective (highly symptomatic women underreport the number of objective hot flushes by 43%) hot flushes impaired verbal memory in women with moderate to severe VMS. Interestingly, changes in memory appeared to be due to night-time rather than daytime hot flushes. These findings suggest that physiological, rather than psychological, factors associated with VMS relate to memory dysfunction in the menopause transition[76,78].

In a similar study by the same group in 68 menopausal women (mean age 53 years), the frequency of hot flushes was significantly related to performance on a test of episodic memory[79]. There is evidence that estrogen, and its estrogen receptor alpha isoform, exert their protective effect by acting as neuro-anti-inflammatories – when estrogen levels are reduced, such as in menopause, neuro-inflammatory processes persist. Estrogen in the microglia might influence the onset and progression of neurodegenerative diseases[80]. Although inflammation has been put forward as one of the potential mediators between low levels of estrogen and cognitive function, Maki and colleagues proposed that cortisol might mediate the relationship between objective hot flushes and cognitive performance in highly symptomatic women[78]. Levels of cortisol increase after hot flushes, and menopausal women with high levels of urinary cortisol are more likely to have severe hot flushes compared with those with lower cortisol levels. Several days of exposure to cortisol, at doses and plasma concentrations associated with physical and psychological stress in humans, reversibly decreased specific elements of memory performance in otherwise healthy individuals[81].

Conclusions

The climacteric syndrome, mainly, but not only, related to estrogen deprivation, leads most women to seek medical advice and this is an opportunity to provide support and implement therapy strategies. It is important that women are not left to 'suffer in silence' but are provided with up-to-date information on the long- as well as short-term implications of not treating menopausal symptoms in general and VMS in particular. The effective management of chronic disease in postmenopausal women starts with the awareness that VMS during menopause are harbingers of things to come and should be managed accordingly.

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