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Vasomotor Symptoms: Natural History, Physiology, and Links with Cardiovascular Health

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Abstract

Vasomotor symptoms (VMS), or hot flushes and night sweats, are the classic symptom of menopause. Recent years have brought key advances in the knowledge about VMS. VMS last longer than previously thought, on average 7–10 years for frequent or moderate to severe VMS. Although VMS have long been understood to be important to women's quality of life, research has also linked VMS to indicators of cardiovascular disease (CVD) risk, such as an adverse CVD risk factor profile, greater subclinical CVD, and in emerging work, CVD events. Relations between VMS and CVD are not typically accounted for by CVD risk factors. In newer work, VMS-CVD risk relations are demonstrated with state-of-the-art subjective and objective measures of VMS. Some research indicates that VMS-CVD risk relations may be sensitive to the timing or duration of VMS. Thus, research collectively supports relations between VMS and CVD risk independent of known CVD risk factors. Next steps include identifying the mechanisms linking VMS and CVD risk indicators, understanding any timing effects, and clarifying the precise nature of relations between VMS and CVD risk. Clinical implications are discussed.

Keywords

menopause; vasomotor symptoms; hot flashes; hot flushes; cardiovascular disease

Vasomotor Symptom (VMS) Epidemiology

Vasomotor symptoms (VMS), or hot flashes/flushes and night sweats, are among the most common symptoms of the menopause transition. VMS are reported by over 70% of midlife women at some point during the menopause transition, and for a third of women, VMS are very frequent or severe (1, 2). VMS were long thought to last the few years around the final menstrual period, but newer data indicate that they last much longer, on average 7–10 years for frequent or moderate-severe VMS, and much longer for less frequent or severe VMS (3–5).

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Longitudinal studies further indicate that women follow distinct patterns of VMS. In fact, both the Study of Women's Health Across the Nation (SWAN) in the United States (US) and the Australian Longitudinal Study of Women's Health found that VMS follow four trajectories as women transition through the menopause (6, 7). In SWAN (6), women fell into approximately equal proportions across the following four groups: the early onset group of women had their VMS early in the transition, before their menstrual periods have stopped, and then their VMS declined with their final menstrual period. A later onset group of women had their VMS largely after their menses stopped and the VMS continued well into their postmenopausal years. A third, mild VMS group had few or no VMS over the transition, and a fourth group of women, which we dubbed the "super flashers" started their VMS well before their final menstrual period, and their VMS continued well into the postmenopause. Broadly similar groups were identified in the Australian samples, yet with multiple postmenopausal onset groups differentiated by severity (7).

VMS vary by demographic factors. In the US, African American women are those who have the most prevalent, persistent, and bothersome VMS (1, 3, 4, 8). Asian women in the US also report VMS, but in lower proportions than White and African American women. Hispanic and non-Hispanic White women fall between African American and Asian groups with respect to VMS incidence and frequency. Further, women in lower socioeconomic positions tend to have more VMS, relations that are not accounted for by race/ethnicity (1).

VMS Physiology

The physiology of VMS is not fully identified, but likely represent a complex interplay between central and multiple peripheral physiologic systems. Changes in reproductive hormones are clearly relevant to VMS, as lower estradiol (E2) and higher follicle stimulating hormone (FSH) are consistent predictors of VMS (5, 9). However, whereas all women experience these hormonal changes, not all women have VMS, pointing to the importance of other physiologic systems in VMS. Thermoregulatory models of VMS underscore that women with VMS show a narrowed thermoneutral zone observed during menopause, and that small perturbations over this zone trigger a heat dissipation event in the form of a hot flash (10). In this model, VMS represent attempts for the body to dissipate heat in the context of altered thermoregulatory function. Other work has found changes in the autonomic nervous system with VMS, with elevated sympathetic or lower parasympathetic control over heart rate at the time of the VMS observed across multiple studies (11–14). A range of additional systems have been proposed in VMS. Newer work has further elucidated central nervous systems mechanisms likely involved in the VMS, and particularly the role of kisspeptin/neurokinin B/dynorphin neurons in the genesis of VMS (15), a system that has become the recent target for new VMS therapies (16).

Relations of VMS to CVD Risk

VMS have long been understood to be important to women's mental health, sleep, and quality of life, but only recently have they been understood to have implications for women's cardiovascular health. Early observations came from hormone therapy (HT) trials, including the Women's Health Initiative (WHI) and the Heart and Estrogen Replacement

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Study, both of which showed in post hoc analyses that the relation between HT and CVD risk was modified not only by age (in the case of the WHI) but also by VMS (17, 18). These initial findings suggested a difference in the underlying vasculature of women with VMS relative to their counterparts without them.

We examined associations between VMS and women's vascular health in SWAN Heart, a sub-study of SWAN that focused on cardiovascular health in which approximately 600 SWAN participants without clinical CVD underwent multiple measures of subclinical CVD, including measures of endothelial function, coronary and aortic calcification, and carotid intima media thickness (IMT). As clinical CVD typically begins to manifest beginning in women's sixth decade of life, subclinical CVD measures, which involve imaging the vasculature to assess CVD risk before clinical disease is present, are useful in assessing vascular risk in midlife women. In SWAN Heart (19), we found that women reporting hot flashes in the prior two weeks had poorer endothelial function as well as greater aortic calcification relative to women without VMS, associations that persisted with adjustment for multiple CVD risk factors as well as endogenous E2 and FSH. Later, we examined associations between VMS and IMT (20), another commonly used and well-validated subclinical CVD measure (21). In this analysis, we found that women reporting VMS six or more days in the prior two weeks had higher IMT than women without VMS, controlling for standard CVD risk factors or sex hormones. We further found that associations were most pronounced among women who were overweight or obese (the majority of this US sample).

We moved from cross-sectional work to the longitudinal context, examining VMS-IMT associations in the larger SWAN cohort. SWAN obtained prospective measures VMS for well over a decade and assessed subclinical CVD (carotid IMT) beginning in the 12th follow up visit. These data enabled us to examine the trajectories of VMS over 13 years in relation to later IMT in over 800 women (22). In unadjusted analyses, we found that both the early VMS onset group and the "super flashers" had higher IMT relative to their counterparts with few or no VMS. However, when adjusting for covariates such as blood pressure and race/ethnicity, only the early onset VMS group had elevated IMT.

Our findings linking VMS to indices of subclinical CVD extended beyond SWAN. For example, we considered these relations in the National Heart Lung and Blood Institute (NHLBI)-supported Women's Ischemia Syndrome Evaluation. We found that women recalling that their VMS began early in life (before age 42) had poorer endothelial function and elevated CVD mortality, adjusting for major risk factors such as BMI, smoking, or menopause timing (23). We further considered these relations in the Healthy Woman Study, an early major cohort study of the menopause, finding that a longer duration of reporting VMS over time was associated with higher aortic calcification later in life, particularly among HT users (24). Other investigators have also found associations between VMS and markers of CVD risk, including FMD (25), IMT (26, 27), and even CVD events (28, 29). Notable exceptions exist, particularly among women who are exceptionally low CVD risk such as in the Kronos Early Estrogen Prevention Study (KEEPS) (30). Finally, the WHI Observational Study (OS) using largely retrospective reports of VMS has shown complex findings that underscored the importance of VMS timing or HT use to potential relations of VMS to CVD risk (31, 32).

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These data indicate potentially important relations between VMS and markers of CVD risk. However, they are limited by the measurement of VMS. Typically, questionnaires are employed that ask women to recall their VMS from the weeks, months, and even decades prior to their visit. Memory for symptoms such as VMS is not strong, is subject to multiple biases, and degrades as time increases (33, 34). Further, standard VMS questionnaires confound VMS frequency, severity, and bother. Notably, appraisals of VMS including bother is highly subject to the influence of negative mood (8), which itself is related to CVD risk (35, 36). Thus, to understand the relation of VMS to CVD risk indicators, using state-of-the-art prospective self-report and physiologic measures of VMS is imperative. A further limitation of prior work is that the hormone assays employed in many of these large cohort studies typically cannot accurately quantify the low levels of estradiol observed among many postmenopausal women (37), leaving open what role endogenous sex steroid hormones play in relations between VMS and CVD risk.

To address these limitations, we conducted the National Institutes of Health / NHLBI - supported MsHeart Study. We recruited 300 nonsmoking midlife women (aged 40–60) in Pittsburgh, Pennsylvania, USA with and without daily VMS, who had their uterus and at least one ovary, who were free of clinical CVD, and who were not using HT, SSRI/SNRIs, other medications for VMS, or several major medications impacting cardiovascular function (e.g., beta blockers, calcium channel blockers). Women underwent three days of ambulatory VMS monitoring that included three days of subjective measures of VMS via electronic digital diary (38), 24 hours of physiologic monitoring of VMS (39), three days of wrist actigraphy measurements of sleep, and a 24-hour ambulatory electrocardiogram (ECG). Women also completed a fasting blood draw (for measurement of CVD risk factors, hemostatic factors, and liquid chromatography tandem mass spectrometry-assessed sex steroid hormones (37)), anthropometric measurements, and vascular ultrasounds for the measurement of carotid IMT, carotid plaque, and brachial artery endothelial function. Results indicated that despite having a relatively favorable CVD risk factor profile, almost half of the participants showed carotid plaque (40). Moreover, participants under-reported their VMS relative to physiologic monitoring (13). Importantly, among participants reporting VMS, the frequency of diary-reported or physiologically monitored VMS were associated with higher carotid IMT as well as higher carotid plaque in a dose response fashion (40). VMS-IMT/plaque associations persisted controlling for standard and novel CVD risk factors. In fact, the frequency of physiologic VMS was associated with more variance in IMT than any other standard CVD risk factor, second only to race/ethnicity. These findings further confirmed that VMS, when measured using state-of-the-art prospective physiologic and electronic diary VMS measures, were related to higher IMT and plaque, above CVD risk factors and sex steroid hormones.

Several additional findings emerged from MsHeart. First, examining the 24-hour ECG monitoring of over 2,300 physiologically assessed VMS across 215 women, we found acute reductions in cardiac vagal control during physiologic VMS (13). These associations were observed during wake and sleep, but were most pronounced during sleep. Many of the physiologically-detected VMS were not reported, yet even these un-reported VMS were accompanied by signature autonomic changes, supporting their validity as VMS. Another notable MsHeart finding was our analysis of endothelial function. We found a higher

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frequency of physiologically assessed VMS associated with poorer endothelial function, yet only among the younger tertile of women (aged 40–53) in the sample (41). Associations were not examined by CVD risk factors, mass spectrometry-assessed sex steroid hormones, or psychosocial factors. These findings further underscore the potential importance of timing in understanding relations between VMS and women's vascular health.

Finally, we considered whether the relations observed of VMS to the peripheral vasculature extended to the brain. In collaboration with Dr. Pauline Maki, we conducted a pilot ancillary study to MsHeart in which twenty MsHeart participants underwent structural and functional brain imaging. We found that more frequent physiologically-detected VMS were associated with greater white matter hyperintensities (42), a measure of small vessel disease in the brain, adjusting for confounders. We also found more frequent VMS associated with greater default mode network connectivity (43), particularly networks supporting the hippocampus. These findings begin to indicate that observations from the vasculature extend to the brain and point to other central nervous system processes that may be relevant to VMS as well as neurocognitive health. These findings serve as the platform for the ongoing National Institutes of Health / National Institute on Aging - funded MsBrain study in our laboratories.

One of the questions that emerge from this work is what are the mechanisms that link VMS to CVD risk. We have extensively considered CVD risk factors, as VMS are associated with a more adverse CVD risk factor profile. For example, in SWAN, more frequent VMS are related to higher blood pressure and greater subsequent hypertension (44), higher lipids (including LDL, triglycerides, Apo B, and surprisingly higher HDL and ApoA1) (45), and greater insulin resistance (46). Similar findings are noted in other work (47), including a recent finding from the WHI OS demonstrating an associations between VMS and diabetes risk (48). In SWAN, we found VMS associated with a more pro-coagulant profile (49), and in three other cohorts including MsHeart, VMS were associated with lower vagal control (11–13). Sleep and mood are also relevant when considering midlife women's CVD risk, as short sleep and negative mood are consistently associated with elevated CVD risk (36, 50). Many midlife women, particularly with VMS, report poor sleep (51) and negative mood (52). In MsHeart, we did find shorter sleep associated with subclinical CVD, independent of CVD risk factors (53), but it did not account for relations between VMS and subclinical CVD. Thus, we considered many potential explanatory pathways, including standard and novel CVD risk factors, mood, and sleep yet none explained the associations between VMS and indicators of CVD risk across the multiple cohorts, including SWAN, WISE, the Healthy Woman Study, and more recently, MsHeart.

Summary and Recommendations

The last several years have witnessed rapid growth in the research on VMS and their relation to markers of CVD risk. We have learned much about VMS. Some of the most striking findings are demonstrations of the persistence of VMS well into the postmenopause and the distinct trajectories they follow that have been replicated across cohorts. There have been recent advances in the understanding of the neurobiology of VMS. Further, across cohorts, we find the presence or frequency of VMS associated with greater subclinical CVD, and in initial work, CVD mortality. These associations are not explained by traditional or novel

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CVD risk factors. In fact, in some of our most rigorously-designed work, VMS are among the strongest predictors of subclinical CVD of the many covariates assessed. Further, we find relations between VMS and CVD risk to be sensitive to the timing of VMS, with three of our cohorts demonstrating the potential importance of early-occurring VMS. Together, these findings demonstrate associations between VMS and CVD risk and point to possible timing effects.

Several key critical questions remain. First, the mechanisms that may link VMS to indicators of CVD risk require clarification. We find VMS associated with a more adverse traditional CVD risk profile, poorer novel CVD risk profile, negative mood, disrupted sleep, and acute reductions in cardiac vagal control, yet these factors do not explain associations between VMS and subclinical CVD. Future work needs to further elucidate the mechanisms, and should consider additional potential physiologic pathways [e.g., (54–56)]. Although three of our cohorts point to early-occurring VMS as most relevant to CVD risk, other work points to late occurring or a longer duration of exposure to VMS. Any timing or duration effects of relations between VMS and CVD risk require further replication and explication. Further, we and others (57) find VMS associated with poorer cerebrovascular and neurocognitive health; further investigation of these relations should be undertaken, and this work is ongoing in our laboratories. Finally, and perhaps most critically, the precise nature of the relations between VMS and CVD risk require further elucidation, including whether VMS are a marker of CVD risk, are simply a cofactor, or are on the causal pathway linking VMS to CVD risk. Understanding any cardiovascular implications of treating VMS will yield insight into this question and translate this observational work to clinical intervention.

The clinical implications of this work are many. CVD is the leading cause of death for US women (58). Despite recent advances, CVD risk prediction among midlife women continues to lag behind that of men, in part because women manifest with many of their CVD events later than do men (59). Therefore, identification of midlife CVD risk markers in women remains an imperative to advancing CVD prevention in women; VMS may help identify those midlife women at elevated CVD risk who require aggressive risk factor reduction. These data also have implications for understanding the physiology of VMS, including a potential role for the vasculature and the autonomic nervous system, systems that may be the targets of future interventions to reduce VMS. Collectively, these data challenge long-held assumptions about the duration and implications of VMS, pointing to the persistence of VMS, the importance of VMS to women's quality of life, and the potential implications of VMS for women's physical health.

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