Published in final edited form as:
Obstet Gynecol Clin North Am. 2011 September ; 38(3): 489–501. doi:10.1016/j.ogc.2011.05.006.

Vasomotor Symptoms and Menopause: Findings from the Study of Women's Health Across the Nation

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Abstract

Vasomotor symptoms (VMS), or hot flashes and night sweats, are often considered the cardinal symptoms of menopause. SWAN, one of the largest and most ethnically diverse longitudinal studies of the menopausal transition, has allowed unique insights into VMS. Specifically, SWAN has helped yield important information about the prevalence of, racial/ethnic differences in, risk factors for, and implications of VMS for midlife women's mental and physical health. Below we review the literature on VMS, emphasizing findings which have emerged from SWAN and new areas of inquiry in the area of VMS.

Keywords

Hot flashes; hot flushes; vasomotor symptoms; menopause; climacteric symptoms; menopausal symptoms

SWAN is one of the largest and most ethnically diverse longitudinal studies of the menopausal transition. SWAN enrolled 3,302 midlife women across five racial/ethnic groups, and has followed these women for over 10 years. During this time, a wealth of information about SWAN participants was collected annually, including information about vasomotor and other menopause-related symptoms, health behaviors, social and psychological functioning, as well as a range of physiologic indices. Thus, SWAN, with its longitudinal design, multiethnic sample, and biopsychosocial perspective, has allowed unique insights into vasomotor symptoms (VMS), serving to advance the field of midlife women's health. Below we summarize some of the insights gained from SWAN about this common and often troublesome midlife symptom. Specifically, we review the epidemiology and physiology of VMS, risk factors for VMS, and associated quality of life and health conditions. We emphasize findings from SWAN given the wealth of information gained from this unique cohort study.

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Definition and epidemiology of VMS

VMS, or hot flashes and night sweats, are often considered the cardinal symptoms of menopause. VMS are episodes of profuse heat accompanied by sweating and flushing, experienced predominantly around the head, neck, chest, and upper back. VMS are experienced by the majority of women during the menopausal transition. In SWAN, 60-80% of women experience VMS at some point during the menopausal transition, with prevalence rates varying by racial/ethnic group.[1] Research from SWAN indicates that the occurrence and frequency of VMS peak in the late perimenopause and early postmenopausal years,[1] or the several years surrounding the final menstrual period. However, research from a range of studies has shown that a sizable minority of women report VMS earlier in midlife, before the onset of menstrual cycle changes,[2] and well into their 60's and 70's, decades after the menopause transition.[3, 4] Given the prevalence and duration of VMS among midlife women, it is critical to understand the underlying biology of this symptom, the extent to which VMS may impair quality- of-life, and whether VMS may serve as a marker for other important health conditions.

Physiology of VMS

Reproductive hormones

The physiology of hot flashes is not fully understood, and likely represents interplay between multiple central and peripheral physiologic systems. Reproductive hormones likely play an integral role, as evidenced by the onset of VMS occurring in the context of the dramatic reproductive hormone changes of the menopausal transition and by the therapeutic role of exogenous estrogen in their treatment. SWAN analyses show that levels of endogenous hormones are associated with VMS. On an annual basis, SWAN participants (N=3,302) reported on their experience of VMS over the prior two weeks and provided a blood sample for measurement of estradiol (E2), follicle stimulating hormone (FSH), testosterone (T), dehydroepiandrosterone sulfate (DHEAS), and sex hormone binding globulin (SHBG). Considered separately, higher FSH and lower E2 were associated with a greater likelihood of reporting VMS (over 5 years), whereas only higher FSH levels were associated with VMS when both hormones were considered together.[5]

A subset of SWAN women (N=742) also participated in the SWAN Daily Hormone Study, which involved annual urine collection over a complete menstrual cycle (or a comparable period of time for women without menstrual cycles) for assessment of urinary FSH, luteinizing hormone (LH), the progesterone metabolite pregnanediol glucuronide (PdG), and estrone conjugates (E1C). Women also completed a daily VMS diary during this time. In this analysis, findings were similar to those in the full cohort among women who had evidence of impaired ovulatory activity, with higher FSH and lower E1C associated with a greater likelihood of reporting VMS.[6] This pattern was not observed among women who appeared to be ovulatory, among whom the only hormone associated with VMS was higher PdG levels. Taken together, these findings indicate that lower estrogen and higher FSH levels are associated with VMS reporting, particularly for women with anovulatory cycles. However, while all perimenopausal women experience these hormonal changes, not all women have VMS. Therefore, other physiologic systems beyond the reproductive axis must be at play.

Thermoregulatory

Leading models characterize VMS, at least in part, as thermoregulatory heat dissipation events. There is some evidence of a narrowing of the thermoneutral zone in symptomatic postmenopausal women, or the zone in which core body temperature is maintained without triggering thermoregulatory homeostatic mechanisms such as sweating or shivering.[7]

Therefore, for symptomatic women, small fluctuations in core body temperature can exceed this zone and trigger heat dissipation mechanisms such as sweating and peripheral vasodilation (i.e., a hot flash). Research indicating that E2 administration reduces VMS and widens the thermoneutral zone adds support to this model.[8] While there is some empirical data to support this model, more research is needed. Other systems implicated in the etiology of hot flashes include central serotonergic, noradrenergic, opioid, adrenal, and autonomic systems, as well as vascular processes, but little evidence is available to clearly elucidate their role in the genesis of hot flashes.[9-13]

Genetics

SWAN and other studies have sought to characterize associations between genetic polymorphisms and VMS. To date, estrogen receptor (ER) polymorphisms and selected single nucleotide polymorphisms (SNPs) of genes involved in the biosynthesis and metabolism of different estrogens (i.e., E2, estrone, estriol) have been explored. Variants in genes that encode for ER alpha and in enzymes involved in synthesis of and conversion between more and less potent estrogens have been found to predict the likelihood of VMS in the different racial/ethnic groups studied in SWAN (n=1,538).[14, 15] Although there have been some inconsistencies between findings, similar results have been seen in other studies investigating SNPs involved in synthesis and metabolism of estrogens,[16-19] as well as ER alpha.[20] In general, these associations persist after adjusting for other important contributory factors, including reproductive hormone levels. Given established variability between race/ethnic groups in genetic polymorphisms, SWAN results provide an important contribution to our understanding of gene/VMS associations because of the inclusion of large numbers of women from different racial/ethnic minority groups. Taken together, these results suggest that the link between VMS and genetic polymorphisms may be due to polymorphisms that alter sex steroid hormone activity. However, it is not known whether these genetic determinants exert their effects centrally in the brain or peripherally on the autonomic nervous system, vasculature, or other systems potentially involved in the genesis of VMS.

Risk factors for VMS

Race/ethnicity

VMS show pronounced racial/ethnic variations. Of the five racial/ethnic groups studied in SWAN, African American women were most likely to report VMS. All women were also more likely to describe their VMS as bothersome, even after controlling for the increased rate of reporting VMS among African American women. Caucasian and Hispanic women in SWAN are broadly similar in their rates of reporting VMS. However, pronounced variation across different ethnic groups of Hispanic women has been noted in SWAN, with the highest rates of VMS reported among Central American women and lowest rates among Cuban women.[21] Chinese and Japanese women in SWAN are least likely to report VMS, with Japanese women least likely to report VMS and to describe them as bothersome.[1, 22]

The reasons for these racial/ethnic differences are likely varied and not fully understood. Although key factors associated with VMS show pronounced racial/ethnic variation, including BMI, E2 levels, smoking, hormone use, and socioeconomic position, racial/ethnic differences in VMS in SWAN persist after controlling for these factors.[1] Others have suggested that the low level of VMS among Asian versus Caucasian women is due to Asian women's relatively high soy intake. However, in SWAN, this does not appear to be the case,[1, 23] consistent with findings from randomized controlled trials which have produced mixed or inconclusive results regarding the use of soy or isoflavones for the management of VMS.[24-26] Moreover, experiencing and reporting of any physical symptom, including VMS, is complex and influenced by a range of perceptual and reporting processes. Cultural

variations in how women experience, interpret, label, and report VMS to others may also play a role in observed racial/ethnic differences in VMS.[27]

Obesity

A key risk factor for VMS is obesity. For many years, obesity was thought to be protective against VMS because androgens are aromatized into estrogens in body fat.[28] Women with more adipose tissue would be expected to have a lower risk of VMS because of higher levels of estrogen. One important finding from SWAN and other large observational studies is that obesity may be a risk factor, rather than a protective characteristic, for VMS during the perimenopause and early postmenopause. For example, in SWAN (N=3,302), women with no or infrequent VMS had an average BMI of 28 kg/m^2, whereas those with more frequent VMS (having VMS at least 6 days in the past two weeks) had an average BMI of 31 kg/m^2.[1] This association between VMS and higher BMI persisted after controlling for related risk factors. Findings of positive associations between BMI and VMS are more consistent with a thermoregulatory model of VMS, in which adipose tissue acts as an insulator, preventing the heat dissipating action of VMS, thereby increasing their occurrence or severity. However, the mechanisms responsible for links between obesity and VMS are not understood, and may include other physiologic mechanisms, including a possible role of other endocrine functions of adipose tissue.[29] Moreover, the positive associations between obesity and VMS may be most applicable to women earlier in the menopausal transition (e.g., in the perimenopause or early postmenopause).[30-34]

The analytic approaches used to examine the association between obesity and VMS primarily use calculated BMI, which encompasses both lean and fat mass, and thereby cannot discern the relative contributions of fat and lean mass as predictors of VMS. Since the contribution of adipose tissue to risk for VMS may result from its thermoregulatory properties or its endocrine products, understanding specifically how adiposity is related to VMS is important. SWAN analyses have examined the association of adiposity to VMS using three different approaches. The first of these investigations examined adiposity as measured by bioelectrical impedance analysis (BIA) (N=1,776), which yields measures of both fat and lean mass. A higher total percentage of body fat, but not lean mass, was related to an increased likelihood of VMS after controlling for confounding factors such as reproductive hormones, smoking, race/ethnicity, education and negative affect.[35] A second analysis from SWAN utilized computed tomography (CT) measures of abdominal adiposity (N=461). CT yields measures of total abdominal adiposity, including subcutaneous adiposity, or the adipose tissue between the skin and the abdominal muscle wall, and visceral adiposity, or the adipose tissue behind the abdominal muscle wall and in the peritoneal space around the organs. Notably, subcutaneous fat is particularly insulating.[36] Results indicated that higher abdominal adiposity, and particularly subcutaneous adiposity, was associated with an increased likelihood of hot flashes.[37] These associations were not accounted for by confounding factors or reproductive hormones (E2 and FSH). Finally, a third analysis from SWAN utilized measures of BIA over a four-year period, thereby allowing examination of change in adiposity over time in relation to VMS (N=1,659). This analysis is particularly relevant given that weight gain is common during midlife.[38] Findings indicated that, relative to women who maintained stable body fat, gains in body fat from one year to the next were associated with an increased likelihood of VMS at the subsequent visit.[39] These associations were independent of confounding factors and changes in reproductive hormones. Taken together, these findings indicate that among perimenopausal and early postmenopausal women, adiposity was associated with an increased likelihood of VMS, a finding consistent with both a thermoregulatory model of VMS and also an endocrine model of adiposity and VMS.

Health behaviors

The potential role of health behaviors in VMS has been of particular interest. One of the most consistently observed health behaviors associated with VMS is smoking. In SWAN, over the course of six years of follow up, current smokers had an over 60% increased likelihood of reporting VMS relative to nonsmokers,[1] adjusted for confounding factors such as education, BMI, menopausal status, and race/ethnicity. In fact, SWAN results show that both active smoking and passive smoke exposure are associated with a greater likelihood of VMS.[23] It has been hypothesized that the association between smoking and VMS is due to the anti-estrogenic effects of cigarette smoking.[40] However, challenging this explanation is evidence from SWAN indicating that differences in endogenous E2 levels did not account for the association between smoking and VMS.[23]

Other notable health behaviors, such as dietary factors and physical activity, have shown much weaker associations with VMS. In SWAN, dietary factors such as total kilocalorie, fat, fiber, caffeine, alcohol intake, or specific vitamin intake have not been associated with VMS, after accounting for confounding factors such as education, smoking, and BMI.[1, 23] Although initial reports showed a beneficial effect of the isoflavone, genistein, in relation to VMS,[23] this association was not observed in later longitudinal analyses.[1] Another health behavior of particular interest is physical activity.[41] Physical activity has also not been consistently associated with VMS in SWAN and other studies, after adjustment for confounding factors.[1, 41] It is notable that physical activity may have dual roles in relation to VMS, positively impacting factors such as mood and body weight, which may improve VMS, but also acutely raising core body temperature, which could theoretically increase the occurrence of VMS. Together, these SWAN investigations suggest that smoking is the health behavior most clearly related to VMS, with diet and physical activity showing much weaker or inconsistent associations with VMS.

Negative affect

Negative mood (affect) has consistently been associated with VMS across investigations. In SWAN (N=3302), higher levels of anxiety, depressive symptoms, and perceived stress at study entry have been associated with an increased likelihood of VMS occurring over the subsequent six years.[1] In fact, the psychological factor most consistently associated with hot flashes is anxiety, an association that has been observed in SWAN and other studies.[42] In addition to an increase in the occurrence and frequency of VMS, women with greater negative affect tend to rate their VMS as more bothersome, even after accounting for the higher frequency of their VMS. The relationships between negative affect and VMS are not fully understood, and may involve a complex interplay between physiologic and psychological factors. It is well-established that negative affect can influence symptom reporting, with a tendency towards elevated symptom reporting in the context of negative affect.[43] For example, women with a greater sensitivity to physical symptoms in general may be more likely to subsequently report VMS.[1] Research with physiological hot flash monitors has confirmed the importance of negative affect in the reporting of hot flashes, showing a greater likelihood that hot flashes are reported when they are not detected physiologically.[44, 45] However, the relationship between negative affect and VMS is bidirectional, as VMS also influence mood, as discussed below.

Other social and demographic factors

Multiple other social and psychological factors have been associated with an increased likelihood of VMS. Child abuse and neglect is prevalent in the SWAN population and is associated with a range of poor physical and mental health outcomes. VMS are no exception. Women who endorsed a history of child abuse or neglect (38% of the sample assessed) were more likely to report VMS during the menopausal transition even after

controlling for multiple factors, including negative affect, sociodemographic factors, and health behaviors.[46] Another important sociodemographic risk factor for VMS is low socioeconomic position. Women who are in lower socioeconomic positions, including women with lower educational attainment, lower income, or who endorse difficulty paying for basics are more likely to report VMS relative to their higher socioeconomic position counterparts.[1] The reasons for the association between socioeconomic position and VMS, an association observed across studies, are not well understood. Lower socioeconomic position is associated with smoking, higher BMI, higher perceived stress, and higher negative affect,[47, 48] and is concentrated among certain minority racial/ethnic groups.[49] However, in SWAN, the association between low socioeconomic position and VMS could not be accounted for by any of these potentially confounding factors. It is notable that the influence of low socioeconomic position or early exposures such as child abuse on health is likely the result of multiple social, psychological, and physiologic processes operating over a life course, presenting a challenge to explaining these associations with any set of assessments administered at midlife.[47, 50]

Associated quality-of-life symptoms

SWAN has investigated the association between VMS and key quality-of-life outcomes that may be influenced by the presence of VMS. These include sleep, mood, and cognitive function. As each of these symptom domains is covered separately in other sections of this special edition, we will briefly discuss available SWAN data that address specifically the association between VMS and these common symptoms affecting quality-of-life. In SWAN analyses, VMS have been strongly associated with reduced health-related quality-of-life (HRQL), although menopause stage itself was not associated with HRQL.[51, 52] The negative association between VMS and HRQL is strongest in those with more frequent VMS.[51]

Sleep

SWAN results have shown strong associations between VMS and perceived sleep disturbance in cross-sectional analyses,[53] longitudinal studies that follow women annually across the menopausal transition,[54] and in daily diary studies that capture a more detailed pattern of the close association between reported VMS and sleep problems.[55] VMS have been associated with all aspects of perceived sleep disturbance that contribute to poor sleep continuity and quality, including falling asleep, staying asleep, and early-morning awakening.[54] In all analyses, VMS reporting stands out as a consistent factor that contributes to reporting of poor sleep after controlling for other important predictive factors. These data are consistent with numerous other studies that have similarly described a strong association between reported VMS and perceived sleep disturbance. The SWAN Sleep Study has collected extensive data which will address the association between VMS and objectively measured sleep using polysomnography (PSG). Results of ongoing analyses bearing on the association between VMS and PSG-measured sleep are eagerly awaited given the more controversial extant literature on the association between VMS and objectively measured sleep parameters.

Mood

VMS and mood appear to be related in numerous and potentially complex ways. Initial evidence for links between VMS and depression comes from studies such as SWAN showing that high levels of depressive symptoms[56-58] as well as clinically significant depression[59-61] are most common during the perimenopause and early postmenopause, when VMS are most prevalent. SWAN and other studies have also found that perimenopausal women with VMS are more likely to develop depression following the onset of VMS than are perimenopausal women without VMS,[56, 59-64] although these links

may be due to other factors associated with having a depressive episode, such as a prior history of anxiety disorder and stressful life events.[59]

Studies have shown that VMS can both precede and follow, as well as occur concurrently with, depression,[65] indicating that the link between VMS and depression may be explained by a number of different causal pathways. When depression co-occurs with or follows VMS, VMS may result in mood disturbance because VMS can impair sleep, which is an important risk factor for depression. Alternatively, VMS may be an initial symptomatic manifestation of perturbations in neural systems that also underlie depression. Indirect evidence suggests that the serotonergic and noradrenergic systems, neurotransmitter systems commonly linked to depression, may be involved in the etiology of VMS,[10-13, 66] raising the possibility that central nervous system processes contribute to both VMS and depression vulnerability.

However, many women with VMS do not experience depression. The observation that VMS occur in the absence of depression and that depression occurs in midlife women without VMS indicates that neither condition is required for the other symptom to manifest. Further investigation is warranted to understand the causal relationship between these two common midlife symptoms.

Cognitive function

SWAN analyses (n=2362) have shown that there is a transient decrement in cognitive performance during the perimenopause, which is characterized by a diminished ability to learn that subsequently resolves as women become postmenopausal.[67] Additional SWAN analyses (n=1903) have indicated that this transient decrement is not explained by VMS.[68] These data are consistent with some,[69] but not all,[70] other smaller studies which similarly found an absence of an association between VMS and verbal memory performance when VMS are measured by self-report. In contrast, studies measuring VMS objectively show an inverse correlation between VMS and cognitive performance,[71] suggesting that physiologic changes underlying VMS may be linked directly and centrally to cognitive function.

Emerging links between VMS and disease outcomes

VMS have traditionally been conceptualized as an important quality of life issue during the menopausal transition, and they have generally not been assumed to have specific implications for physical health. However, emerging research from SWAN and other studies has begun to call this assumption into question.

Cardiovascular risk

Initial work from several large trials of hormone therapy, including the Women's Health Initiative (WHI) and the Heart and Estrogen Replacement Study (HERS), suggested links between VMS and cardiovascular disease (CVD) risk. In both studies the elevated coronary heart disease event risk associated with hormone therapy use were highest among women reporting moderate to severe VMS at the study entry, and in WHI, the older women with VMS.[72, 73] We have followed up these initial observations in SWAN, exploring potential links between VMS and CVD. Much of this research has been conducted in the context of the SWAN Heart Study (N=588), an ancillary study to SWAN which collected data on several measures of subclinical CVD, including brachial artery flow mediated dilation, a marker of endothelial dysfunction; coronary artery and aortic calcification, measures of calcified plaques in these arterial beds; and carotid intima media thickness (IMT), a well-established marker of atherosclerosis. These subclinical CVD measures are useful to understand risk for CVD among disease-free individuals, as all three measures have been prospectively associated with elevated cardiovascular event rates among individuals without clinical CVD.[74-76] Findings indicated that women reporting hot flashes, and in the case of

IMT, more frequent hot flashes, had poorer endothelial function, greater aortic calcification, and greater IMT as compared to their counterparts without hot flashes.[77, 78] These associations persisted after controlling for confounding demographic and other known cardiovascular risk factors as well as E2 levels. Findings for night sweats were similar to those for hot flashes, but somewhat attenuated. Notably, associations between hot flashes and IMT were most pronounced for women who were overweight or obese as well as for women who experienced hot flashes across multiple annual visits, suggesting that hot flashes may be most informative with respect to CVD risk when they are persistent and when they occur in individuals with other CVD risk factors, such as obesity. The precise reasons for and nature of the association between VMS and CVD risk require further investigation and explication. However, one interpretation of these findings is that hot flashes may be a symptomatic manifestation of underlying adverse changes in a woman's vasculature.

Bone health

Emerging research from SWAN and other studies has linked VMS and bone mineral density and bone turnover. In the first of these SWAN analyses (N=2213), women reporting VMS had lower bone mineral density.[79] This association was observed across women of all menopausal stages in the sample, but particularly among the postmenopausal women. The associations between VMS and bone mineral density varied by specific bone site studies, most apparent at the lumbar spine and hip among postmenopausal women, and at the femoral neck among women earlier in the menopausal transition. In a second set of SWAN analyses (N=2283), the occurrence of VMS was further examined in relation to a highly sensitive marker of bone turnover, urinary N-telopeptide. In these analyses, perimenopausal and postmenopausal women with VMS had higher bone turnover (higher urinary N-telopeptide) than their counterparts without VMS.[80] In both analyses of bone density and bone turnover, associations largely persisted after controlling for potential confounders, although E2 and FSH levels accounted for some, but not all of these associations. Potential reasons for associations between VMS and bone health require further investigation, including an exploration of the potential contribution of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system.[79] However, these results suggest that VMS may be an important indicator of some aspect of declining ovarian function that is not captured by menstrual cycle changes or annual reproductive hormone levels.

Summary and Conclusions

SWAN has yielded unique insights about VMS, the cardinal symptom of menopause. We have learned that VMS are experienced by most midlife women, but show pronounced racial/ethnic differences that cannot be explained by other known VMS risk factors. Key risk factors for VMS include low education, smoking, and negative affect. Obesity, previously thought to be protective against VMS, is actually a risk factor for VMS among perimenopausal and early postmenopausal women. Further, VMS are associated with poorer quality of life, negative mood, and sleep problems during midlife. The association between VMS and mood is complex, bidirectional, and possibly explained by multiple pathways, including sleep and neural mechanisms. Finally, emerging information from SWAN indicates that VMS may be linked to certain adverse physical health outcomes, including subclinical cardiovascular disease and lower bone density. Thus, SWAN has been a rich source of information about is common and often troublesome midlife symptom. Ongoing findings from SWAN will continue to yield important information about VMS in the years to come.

Acknowledgments

Disclosures: Thurston: none. Joffe (past 12 months): *Research Support*: Bayer HealthCare Pharmaceuticals (co-PI), Forest Laboratories (co-I), GlaxoSmithKline (co-I); *Advisory/Consulting*: Sunovion.

In addition to the SWAN funding described in the overview, this work was also supported by NIH grants AG029216 (Thurston) and NH082922 (Joffe).

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