Original article

# Vasomotor Menopausal Symptoms and Risk of Cardiovascular Disease: A pooled analysis of six prospective studies


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**Competing interests**

The authors report no conflicts of interest.

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**Condensation:**

Severity (rather than frequency) of VMS, and VMS with onset before or after menopause were associated with increased risk of CVD.

**Short Title:** Vasomotor menopausal symptoms and cardiovascular disease

**AJOG at a Glance:**

**A. Why was the study conducted?**

Menopausal vasomotor symptoms (VMS, i.e., hot flushes and night sweats) have been associated with unfavorable risk factors and surrogate markers of cardiovascular disease (CVD), but their association with clinical CVD events is unclear.

**B. What are the key findings?**

Compared with women who had no VMS, greater severity of both hot flushes and night sweats were associated with higher risk of CVD, and either early-onset (before menopause) or late-onset (after menopause) VMS were associated with increased risk of incident CVD.

**C. What does this study add to what is already known?**

This study helps to identify women who are at a higher risk for the development of CVD during menopause transition, and who may need close monitoring in clinical practice.

## Background

Menopausal vasomotor symptoms (VMS, i.e., hot flushes and night sweats) have been associated with unfavorable risk factors and surrogate markers of cardiovascular disease (CVD), but their association with clinical CVD events is unclear. We aimed to examine the associations between different component of VMS and timing of VMS and risk of CVD.

## Study Design

We harmonized and pooled individual-level data from 23 365 women in six prospective studies which contributed to the InterLACE consortium. Women who experienced CVD events before baseline were excluded. The associations between frequency (never, rarely, sometimes and often), severity (never, mild, moderate and severe), and timing (before or after age of menopause, i.e., early or late onset) of VMS and incident CVD were analysed. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI).

## Results

In the adjusted model, no evidence of association was found between frequency of hot flushes and incident CVD, while women who reported night sweats “sometimes” (HR 1.22, 95% CI 1.02-1.45) or “often” (1.29, 1.05-1.58) had higher risk of CVD. Increased severity of either hot flushes or night sweats was associated with higher risk of CVD. The hazards ratios of CVD in women with severe hot flushes, night sweats and any VMS were 1.83 (1.22, 2.73), 1.59 (1.07, 2.37) and 2.11 (1.62, 2.76) respectively. Women who reported severity for both hot flushes and night sweats had a higher risk of CVD (1.55, 1.24-1.94) than those with hot flushes alone (1.33, 0.94-1.88) and night sweats alone (1.32, 0.84-2.07). Women with either early onset (1.38, 1.10-1.75) or late onset (1.69, 1.32-2.16) VMS had an increased risk of incident CVD, compared with women who did not experience VMS.

## Conclusion

Severity rather than frequency of VMS (hot flushes and night sweats) was associated with increased risk of CVD. VMS with onset before or after menopause were also associated with increased risk of CVD.

## INTRODUCTION

Menopausal vasomotor symptoms (VMS: hot flushes, night sweats) are the cardinal menopausal symptoms during the course of menopausal transition.[1] About 60-80% of women experience VMS[1] and they typically increase markedly in the two years before menopause and peak one year after menopause.[2] The median duration of VMS among women has been shown to be 7.4 years, with many women experiencing VMS even longer.[3] VMS also vary in frequency and severity. More than 80% of women with VMS experience symptoms every day,[4] and the severity ranges from mild to severe.[5]

Greater frequency and severity of VMS have been linked to adverse cardiovascular disease (CVD) risk factors[6-8] and subclinical CVD, such as increased intima media thickness, aortic calcification, and reduced brachial artery flow-mediated dilation (FMD), a marker of endothelial dysfunction.[9,10] However, studies that examined the relationships between VMS and clinical CVD events have yielded mixed and inconclusive findings.[11-14] One longitudinal study found that both hot flushes and night sweats were associated with an increased risk of coronary heart disease (CHD),[11] while another study found that only night sweats was associated with higher risk of heart disease.[13]In a study that examined the timing of VMS, it was found that women with early onset VMS was associated with decreased the risk of CVD, while late-onset VMS increased the risk of CVD.[14] A systematic review of VMS and other menopausal symptoms and the risk of CVD concluded that a number of menopausal symptoms (including VMS and other symptoms) were associated with an increased risk of CVD, but this relationship was mainly explained by CVD risk factors. Of the 10 studies selected in that review, only two assessed the association between VMS

and CHD, one assessed VMS and stroke, and one assessed VMS and composite CVD.[15]

Two key gaps remain in the current evidence on the associations between VMS and incident CVD. One is which components of VMS increase the risk of CVD - hot flushes, night sweats, or both?[11,13] The other gap is what timing of VMS (e.g. before or after menopause) is associated with increased risk of CVD?[14,16] Thus, we aimed to examine the associations of hot flushes and night sweats with incident CVD (including CHD and stroke) after adjusting for CVD risk factors, and to investigate whether the timing of onset of VMS affected the associations.

## METHODS

### Study participants

We harmonized and pooled individual-level data from 23 365 women in six prospective studies (Table 1) which contributed to the International collaboration for a Life course Approach to reproductive health and Chronic disease Events (InterLACE). These studies collected survey data on key reproductive, sociodemographic, lifestyle, and disease outcome variables. A more detailed description of InterLACE has been published previously.[17,18] The data were obtained from studies participating in 2013. All participants were still alive and not lost to follow-up at their last data collection. All six studies included data on VMS (frequency or severity) and information on CVD events (experienced or not, and age when the CVD event occurred). The baseline survey of each study was defined as the first survey when data on the VMS status of the women was collected (Table 1). To examine the prospective association between VMS and incident CVD, women who experienced a CVD event before baseline were excluded from analyses (n=736).

Women who had missing data on any of the key covariates, including race/ethnicity, education, body mass index (BMI), and hypertension status at baseline, and smoking status, menopausal status, and menopausal hormone therapy (MHT) status at each survey were excluded (n=4414). Overall, 83% of the women were selected from the six studies for this analysis. The enrolled proportion from the source population ranged from 54.4% to 92.4% (ALSWH 92.4%, HOW 54.4%, NSHD 72.0%, NCDS 79.0%, WHITEHALL II 64.5%, SWAN 82.6%). Person-years of observation, number of CVD events, and percentage of missing data in each study are listed in Supplementary Table S1.

**Exposure variables and outcome events**

In each study, VMS (hot flushes and night sweats) were self-reported and collected at each survey. When frequency and severity of VMS were harmonized from multiple studies, original questionnaires were collapsed into a simple level of detail to incorporate useful information from as many studies as possible. For example, in SWAN study, to harmonize the data for the frequency of VMS *not at all* was categorized as "never", *1-5 days/2 weeks* as "rarely", *6-8 days/2 weeks* as "sometimes", *9-13 days/2 weeks* and *every day* as "often"). For studies that collected frequency of VMS (ALSWH and SWAN), we categorized frequency as never, rarely, sometimes, and often. For studies that collected severity of VMS (NSHD, NCDS, HOW and WHITEHALL II), we categorized severity as never, mild, moderate and severe. Onset of VMS was defined in relation to occurring before or after menopause (defined as 12 months since last menstrual period). Early-onset VMS was defined as hot flushes or night sweats that first occurred before menopause, and late-onset VMS was defined as hot flushes or night sweats that first occurred after menopause.

Women were also categorized into four groups: no VMS, only had hot flushes, only had night sweats, and had both hot flushes and night sweats.

The study endpoint was specified by the incidence of a self-reported physician-diagnosed CVD event, defined as the first occurrence of either CHD (including heart attack and angina) or stroke (including ischemic stroke or haemorrhagic stroke), or the time at last follow-up for those without a CVD event. We first analyzed all incident CVD (a composite outcome), followed by separate analyses for incident CHD and stroke.

**Covariates**

We included time-invariant covariates recorded at baseline and time-varying covariates recorded at subsequent surveys based on evidence from the literature.[19,20] Baseline covariates included race/ethnicity (Caucasian-European, Caucasian-Australian/New Zealand, and Caucasian-American/Canadian), years of education (≤10, 11-12, and >12 years), BMI (<18.5 kg/m$^2$, 18.5 to 24.9 kg/m$^2$, 25 to 29.9 kg/m$^2$ and ≥30 kg/m$^2$), hypertension status (self-reported or measured, divided into present or absent), parity (0, 1, 2 and ≥3 live births), and age at menarche (≤11, 12, 13, 14, and 15 years or more). Time-varying covariates included smoking status (current, former or never smoker), menopausal status (pre-/perimenopause, surgical menopause, and natural menopause) and MHT status (current user/non-user).

**Statistical analyses**

Baseline characteristics were presented as means and standard deviation (SD) for continuous variables and as percentages (%) for categorical variables. We used Cox proportional hazards models to estimate hazard ratios and 95% confidence intervals

(HR, 95% CI). The proportional hazards assumption was checked using log cumulative hazard plots and appeared to be reasonable.

The extent of VMS (categories of frequency and severity) was analyzed as a time-varying exposure variable. We determined the association of each interval of stable symptoms status (e.g., mild severity of hot flushes) with the incident CVD events (i.e., whether CVD occurred in that interval). To deal with time-varying symptoms, we reorganized the dataset into a long format. For each ID (a unique variable to identify each subject), every observation that indicated a change in VMS frequency status is a distinct data record for that ID and at that timepoint. Taking frequency of hot flushes for example, each woman might contribute multiple observations in the analysis if the frequency of her hot flushes changed during follow-up. Each observation represented an interval of time during which the status of hot flushes remained unchanged, i.e., the first interval was from baseline until the survey when her status changed; the second interval was from the end of the first interval until time when her status changed again, and so on. The time-to-event of each observation was defined from the beginning of the interval to the end of the interval if no CVD event was experienced in the interval, or to the year when a CVD event occurred. For each observation the values of the time-invariant covariates (race/ethnicity, education level, BMI, hypertension status) were those at baseline. For the time-varying covariates (age, smoking status, MHT status, and menopausal status), the values were those at the start of the interval. Because each woman could contribute multiple observations and each study contributed data from multiple women, identifiers for women and studies were included in the model as random effects. All the models were adjusted for both baseline covariates (race/ethnicity, years of education, BMI category, hypertension status, parity, and age at menarche) and time-varying covariates

(smoking status, menopausal status, and MHT status. In these fully adjusted models, when the association between hot flushes and risk of CVD was analyzed, night sweats status was included as a covariate, and vice versa.

We used SAS (version 9.4, SAS Institute Inc, Cary, NC) in all statistical analyses. The PHREG procedure was used to fit the Cox proportional hazards regression models. All statistical tests were based on the two-sided 5% level of significance.

Each study in the InterLACE consortium has been undertaken with ethical approval from the Institutional Review Board or Human Research Ethics Committee at each participating institution, and all participants provided consent for that study.

## RESULTS

### Participant characteristics

There were 23 365 women included in total. The mean (standard deviation, SD) age at baseline was 48.3 (2.8) years, with more than half of the women born between 1940 and 1949 (Table 1). The mean age at last follow up was 59.3 years (Table 1). There were 1947 (8.3%) CVD events reported, including 1726 (7.3%) CHD and 373 (1.6%) strokes. At baseline, 53.8% of women reported VMS (hot flushes and/or night sweats); 47.8% with hot flushes and 38.7% with night sweats. Overall, across the study period, 59.5% of women reported early-onset VMS, with mean age of 48.4 (2.3) years at onset; 30.9% women reported late-onset VMS, with mean age of 52.2 (3.8) years at onset. Women who were European, with lower education level, overweight/obese, current smokers, MHT users had a higher frequency of VMS (Table 2 and Table S2).

### The association between hot flushes, night sweats and incident CVD

*Frequency or severity of hot flushes*

Results for the fully adjusted models are shown in Table 3. Compared with women who

reported no hot flushes, no significant association was found between women who reported frequency of hot flushes rarely, sometimes, or often and incident CVD. There were, however, associations for severity of hot flushes: women who reported mild (HR 1.70, 95%CI 1.31-2.20) and severe (1.83, 1.22-2.73) hot flushes had increased risk of CVD. Similar results were found with the risk of CHD. Due to the relatively low number of participants who had stroke in studies that collected severity of hot flushes, no evidence of associations was detected for this outcome.

*Frequency or severity of night sweats*

Compared with women who reported no night sweats, women who reported night sweats sometimes (HR 1.22, 95%CI 1.02-1.45) or often (1.29, 1.05-1.58) had higher risk of CVD, and there was also a dose-response relationship between frequency of night sweats and incident CVD (p trend<0.01) (Table 3). Also, mild (1.41, 1.06-1.87), moderate (1.70, 1.24-2.33) or severe (1.59, 1.07-2.37) night sweats were associated with higher risk of CVD. Similar results were found with the risk of CHD and stroke.

*Any VMS*

For frequency of any VMS, women who reported symptoms sometimes (1.19, 1.02-1.38) or often (1.36, 1.16-1.59) had increased risk of CVD, compared with women who had no symptoms. For severity of any VMS, women who reported mild (1.78, 1.42-2.24), moderate (1.68, 1.30-2.16) or severe symptoms (2.11, 1.62-2.76) had higher risk of CVD. Similar results were found with the risk of CHD (Table 4).

**Individual or combined components**

For studies that reported frequency of symptoms, compared with women who had no VMS, the risk of CVD in women with both hot flushes and night sweats (1.17, 1.03-1.33) was higher than in those with hot flushes alone (0.87, 0.71-1.06) and was close to the risk in those with night sweats alone (1.16, 0.86-1.56). For studies that reported

severity there was some evidence that the risk of CVD in women with both symptoms (1.55, 1.24-1.94) was higher than in those with hot flushes alone (1.33, 0.93-1.88) or night sweats alone (1.32, 0.84-2.07) (Table 5).

**The association between timing of VMS and incident CVD**

Compared with women who had no VMS, both early-onset (1.38, 1.10-1.75) and late-onset (1.69, 1.32-2.16) VMS were associated with increased risk of incident CVD, with late-onset conveying a greater risk (Table 6). Similar results were found for both hot flushes and night sweats (Table 6). The estimates for stroke suggested higher risk, albeit with non-significant associations due to less statistical power.

## DISCUSSION

### Summary of results

In findings on the frequency of VMS, some evidence was found for the frequency of night sweats and increased risk of CVD, but no significant association was found regarding the frequency of hot flushes. In contrast, findings showed that the severity of hot flushes, night sweats, and any VMS were consistently associated with higher risk of CVD. Early or late onset VMS relative to menopause was also associated with higher risk of CVD.

### The presence of VMS and CVD

Results from previous studies about the association between VMS and subsequent risk of CVD have been mixed. Some studies have found a higher risk with incident CVD,[11,13] while others did not.[12,14] A recent systematic review concluded that for women with VMS, the relative risks (95% CI) for developing CHD, stroke and overall CVD were 1.28 (1.08, 1.52), 1.14 (0.82, 1.59) and 1.23 (1.00, 1.52) respectively after adjusting for established CVD risk factors, compared with women

without any menopausal symptoms.[15] However, this review had some limitations. It only included two studies on VMS and CHD, and one study on VMS and stroke. Hot flushes and night sweats were grouped together, so the effect of individual symptoms could not be assessed. Further, not all studies assessed the severity of VMS, and the review did not specify whether women with CVD before baseline were excluded. When hot flushes and night sweats were grouped as 'any VMS', we found the HR (95%CI) for incident CVD, CHD and stroke were 1.36 (1.16, 1.59), 1.35 (1.14, 1.60), and 1.43 (1.03, 1.98) respectively in women who reported VMS 'often' which are similar to the findings in the review.[15] Also, the associations with severity of VMS were stronger than the associations with frequency of VMS.

For individual symptoms, a prospective cohort study found that both hot flushes often [Odds ratio (OR) 1.70, 95% CI 1.16–2.51] and night sweats often (OR 1.84, 95% CI 1.24–2.73) were associated with higher risk of CHD, and no difference between these two associations were found.[11] However, a cross-sectional study found that the presence of night sweats rather than hot flushes were associated with increased risk of CHD after the adjustment of BMI, blood pressure, and total cholesterol.[13] Previous studies have suggested hot flushes and night sweats might have different aetiology with CVD.[21,22] Similar to the findings of Herber-Gast et al,[11] we found both hot flushes and night sweats were linked to increased risk of CVD, and the significant associations were mainly observed with severity. In addition, in the measure of severity there is some evidence that the combined effect of hot flushes and night sweats on risk of CVD was higher than each symptom alone.

**The timing of VMS**

In the Women's Health Initiative Observational Study (WHI-OS) study,[14] early-onset VMS were associated with decreased risk of stroke and overall CVD events, while late-onset VMS were associated with increased risk of CHD. However, the definitions of onset in that study differed from the ones used here. In the WHI-OS study, early-onset VMS was defined as VMS at menopause onset, while late-onset VMS was defined as VMS at enrolment but not at menopause onset. The mean age at enrolment was 63.3 years in WHI-OS study (i.e., the majority of women were postmenopausal), which means the definition of late-onset VMS was around 14.4 years after the average age of menopause. The difference in definition might explain why the number of women with late-onset VMS in the WHI-OS study was rather small. Also the study did not examine the effect of hot flushes and night sweats separately, and MHT use and smoking status were adjusted for using time-invariant variables at baseline rather than treating them as time-varying variables.

The Women's Ischemic Symptom Evaluation (WISE) study,[16] which defined timing of VMS as starting at age <42 years (early onset), >42 years (late onset, reference) and never, found women who reported early-onset VMS (HR 3.35, 95% CI 1.23-7.86) and women who never had VMS (HR 2.17, 95% CI 1.02-4.62) had higher CVD mortality than women with later-onset symptoms. However, all 254 participants in the WISE study were women who had undergone coronary angiography and had suspected myocardial ischemia. Also, the prevalence of non-fatal CVD events did not differ significantly among VMS groups. Further, women with early-onset VMS were more likely to be overweight/obese, smokers, and had a history of type 2 diabetes at baseline.

In contrast to the studies mentioned above, we defined timing of VMS as starting before or after menopause and we treated smoking and MHT status as time-varying

variables. We found both early onset and late onset VMS were associated with increased risk of CVD. It has been reported that the prevalence of VMS increases during the two years before menopause and peaks one year after menopause.[2] This might explain why the association with late onset VMS was somewhat stronger than that with early onset VMS.

**Mechanisms**

VMS have been associated with a less favorable cardiovascular risk profile and surrogate CVD endpoints.[23] Women with VMS have been found to have higher cholesterol, triglycerides, LDL, BMI, systolic blood pressure, diastolic blood pressure, insulin resistance,[6-8,24,25] and higher odds of hypertension and diabetes,[6,26] compared with asymptomatic women. However, controlling for these factors attenuated the observed associations of VMS with CVD only slightly, suggesting that other mechanisms play a role in the etiology of CVD. Additionally, studies have found that women with moderate to severe hot flushes had increased carotid intima media thickness compared to women with no or mild hot flushes.[27-29] Also, the Study of Women's Health Across the Nation (SWAN) found reduced flow-mediated dilation (a marker of arterial endothelial dysfunction) and increased coronary artery calcium and aortic calcification in women with hot flushes.[10]

VMS and CHD also share some common causes. The fluctuation and decline in estrogen levels that occur during and after the menopause transition can explain part of the occurrence of VMS,[30] and endogenous estrogen is protective against CHD.[31] Further, unfavorable cardiovascular risk profiles, which may lead to both VMS and CVD, may play a role. One study, however, has found that unfavorable cardiovascular risk profile was not associated with VMS.[32] VMS is also related to thermoregulatory

dysfunction,[33] which involves activity of the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis.[34] The disturbances in the ANS and HPA axis may serve as a common link between VMS and cardiovascular disease.[35,36]

Hot flushes and night sweats may lead to different physiological changes in women. In one study, women with daytime hot flushes were leaner and had lower systolic blood pressure than women with night sweats.[23] Systolic blood pressure was 2.4 mmHg higher for each additional occurrence of daily night sweat and 2.2 mm Hg lower for each additional occurrence of daily hot flush.[23] The different associations between hot flushes and night sweats and cardiovascular markers (such as BMI and blood pressure) may explain their divergent risk for CVD. For example, we found night sweats sometimes or often were associated with higher risk of CVD, but we found no association between hot flushes sometimes or often and risk of CVD. Also, night sweats may affect sleep quality, which may increase the risk of CVD,[37] but this potential mechanism needs further investigation.

The mechanisms underlying the association between early-onset VMS and late-onset VMS might be different. One possibility is that early-onset VMS before the menopausal transition represent a physiologic response to the normal perimenopausal hormonal fluctuations, while the late-onset VMS may be a marker of vascular instability or an early manifestation of cardiac ischemia.[14] Future studies are necessary to examine the pathophysiologic mechanisms underlying hot flushes and night sweats, which might be different.

**Strength and limitations**

First, the frequency and severity of VMS are affected by menopausal status and taking MHT, thus we used time-varying VMS as the exposure rather than a single time-

invariant variable, and we adjusted for time-varying menopausal status and MHT status. Second, unlike other studies that defined early or late onset VMS by using a fixed age,[16] or defined timing of VMS by using VMS status at enrolment age,[14] we defined early or late onset VMS in relation to age at menopause.

The present study also had several limitations. First, we used self-reported hot flushes and night sweats. Mann et al. found that self-reported VMS and sternal skin conductance measures of VMS were not always concordant, and night sweats tended to be under-reported.[38] Second, we also used self-reported CVD events as the outcome. However, studies have shown the self-reported CVD had high validity and agreement with medical records.[39] Also, several studies in InterLACE (e.g., ALSWH and Whitehall II study) have validated their self-reported outcomes with hospital records and found moderate to high agreement.[40,41] Third, we used BMI and hypertension reported at baseline (mid age) rather than treating them as time-varying covariates, which may cause some bias. Nonetheless, in studies of InterLACE that included women who reported BMI levels and hypertension status both before and after menopause (i.e., NSHD, NCDS, SWAN), the concordance was approximately 80%. Thus, we assume the bias caused by time-varying BMI and hypertension status is limited. Fourth, we lacked information on lipid levels and diabetes status during women's transition through menopause. These factors may confound or mediate the association between VMS and CVD events. However, evidence on links between VMS and CVD risk factors has been mixed, with some studies finding no association between lipid level or fasting plasma glucose level and VMS. [22,32,42] Thus, the potential bias due to lipid levels and diabetes status appears limited. Fifth, it should be noted that in determining the relationship between the extent of VMS and incident CVD event in that interval, the preceding level of VMS might be a confounder.

However, given that the intervals that describe different VMS levels were for at least two years, the preceding VMS level was not considered an important predictor of current VMS, compared with other concurrent factors including menopausal status, MHT use, and smoking behavior. Last, compared with the number of CHD events, the number of participants with strokes was limited in this research, especially in studies that reported severity of VMS. Thus, even this large multi-cohort study may lack sufficient statistical power to detect the associations with stroke.

## Conclusions

Severity rather than frequency of hot flushes and night sweats was associated with increased risk of CVD. Both VMS before menopause (early-onset) or after menopause (late-onset) were associated with increased risk of incident CVD. Our findings imply that identification of women with high severity of VMS during the menopausal transition offers a window of opportunity to implement active management of other CVD risk factors in these women in order to improve their overall cardiovascular health. These women may also need close monitoring in clinical practice.


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Table 1. Characteristics of individual studies in the InterLACE consortium

| Study | Country | N | Survey used for baseline | Age at baseline, Mean (SD) | Age at last follow-up, Mean (SD) | Women's year of birth (%) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | <1939 | 1940-49 | 1950-59 |
| Australian Longitudinal Study on Women's Health (ALSWH) | Australia | 12 667 | Survey 1 | 47.6 (1.5) | 61.6 (5.4) | . | 73.77 | 26.23 |
| Healthy Ageing of Women Study (HOW) | Australia | 472 | Survey 1 | 55 (2.8) | 62.6 (4.0) | . | 88.11 | 11.89 |
| MRC National Survey of Health and Development (NSHD)* | UK | 1131 | Survey 7 | 47.0 | 53.9 (0.3) | . | 100 | . |
| National Child Development Study (NCDS)* | UK | 4164 | Survey 8 | 50.0 | 54.4 (1.6) | . | . | 100 |
| Whitehall II study (WHITEHALL II) | UK | 2203 | Survey 3 | 50.1 (6.1) | 63.2 (6.7) | 39.81 | 48.07 | 12.07 |
| Study of Women's Health Across the Nation (SWAN) | USA | 2728 | Survey 1 | 46.9 (2.7) | 54.7 (3.7) | . | 40.76 | 59.24 |
| All | | 23 365 | | 48.3 (2.8) | 59.3 (5.9) | 3.75 | 55.91 | 40.34 |

*NSHD (1946 British Birth Cohort) and NCDS (1958 British Birth Cohort) are birth cohort studies and first collected information on vasomotor symptoms in 1993 (survey 7) and 2008 (survey 8), respectively.
Abbreviations: InterLACE, International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events; SD, standard deviation.

Table 2. Baseline characteristics of women with hot flushes and night sweats*

| | Hot flushes (%) | | | | Night sweats (%) | | | | VMS (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Never (n=12197) | Rarely/mild (n=3600) | Sometimes/ moderate (n=5041) | Often/ severe (n=2527) | Never (n=14320) | Rarely /mild (n=3173) | Sometimes /moderate (n=3987) | Often /severe (n=1885) | Never (n=10791) | Rarely /mild (n=4002) | Sometimes /moderate (n=5622) | Often /severe (n=2950) |
| Race/ethnicity | | | | | | | | | | | | |
| Australian | 5297 (51.6) | 1694 (16.5) | 2239 (21.8) | 1027 (10) | 6365 (62.1) | 1471 (14.3) | 1657 (16.2) | 764 (7.4) | 4783 (46.6) | 1837 (17.9) | 2477 (24.1) | 1160 (11.3) |
| European | 4539 (48.6) | 1118 (12) | 2464 (26.4) | 1216 (13) | 5423 (58.1) | 943 (10.1) | 2058 (22) | 913 (9.8) | 3998 (42.8) | 1167 (12.5) | 2731 (29.2) | 1441 (15.4) |
| American | 982 (67.8) | 303 (20.9) | 76 (5.2) | 88 (6.1) | 1020 (70.4) | 307 (21.2) | 68 (4.7) | 54 (3.7) | 839 (57.9) | 405 (28) | 99 (6.8) | 106 (7.3) |
| Others | 1379 (59.4) | 485 (20.9) | 262 (11.3) | 196 (8.4) | 1512 (65.1) | 452 (19.5) | 204 (8.8) | 154 (6.6) | 1171 (50.4) | 593 (25.5) | 315 (13.6) | 243 (10.5) |
| Education level | | | | | | | | | | | | |
| ≤ 10 years | 5121 (45.6) | 1621 (14.4) | 2957 (26.3) | 1543 (13.7) | 6408 (57) | 1388 (12.3) | 2302 (20.5) | 1144 (10.2) | 4579 (40.7) | 1669 (14.8) | 3210 (28.6) | 1784 (15.9) |
| 11-12 years | 2019 (54.3) | 607 (16.3) | 771 (20.7) | 320 (8.6) | 2334 (62.8) | 537 (14.4) | 600 (16.1) | 246 (6.6) | 1784 (48) | 678 (18.2) | 878 (23.6) | 377 (10.1) |
| > 12 years | 5057 (60.2) | 1372 (16.3) | 1313 (15.6) | 664 (7.9) | 5578 (66.4) | 1248 (14.8) | 1085 (12.9) | 495 (5.9) | 4428 (52.7) | 1655 (19.7) | 1534 (18.2) | 789 (9.4) |
| Body mass index (kg/m$^2$) | | | | | | | | | | | | |
| Underweight, < 18.5 | 513 (55.5) | 119 (12.9) | 183 (19.8) | 110 (11.9) | 560 (60.5) | 123 (13.3) | 157 (17) | 85 (9.2) | 443 (47.9) | 138 (14.9) | 208 (22.5) | 136 (14.7) |
| Normal, 18.5-24.9 | 6311 (57.4) | 1590 (14.5) | 2144 (19.5) | 952 (8.7) | 7044 (64.1) | 1449 (13.2) | 1780 (16.2) | 724 (6.6) | 5589 (50.8) | 1824 (16.6) | 2466 (22.4) | 1118 (10.2) |
| Overweight, 25.0-29.9 | 3280 (48.5) | 1079 (15.9) | 1549 (22.9) | 858 (12.7) | 4037 (59.7) | 911 (13.5) | 1181 (17.5) | 637 (9.4) | 2918 (43.1) | 1172 (17.3) | 1698 (25.1) | 978 (14.5) |
| Obese, ≥ 30 | 2093 (44.8) | 812 (17.4) | 1165 (24.9) | 607 (13) | 2679 (57.3) | 690 (14.8) | 869 (18.6) | 439 (9.4) | 1841 (39.4) | 868 (18.6) | 1250 (26.7) | 718 (15.4) |
| Smoking status | | | | | | | | | | | | |
| Never smoker | 6891 (55.8) | 1886 (15.3) | 2456 (19.9) | 1110 (9) | 8057 (65.3) | 1653 (13.4) | 1822 (14.8) | 811 (6.6) | 6173 (50) | 2153 (17.4) | 2730 (22.1) | 1287 (10.4) |
| Former smoker | 3409 (51.3) | 1042 (15.7) | 1497 (22.5) | 703 (10.6) | 3968 (59.7) | 942 (14.2) | 1225 (18.4) | 516 (7.8) | 2970 (44.7) | 1164 (17.5) | 1689 (25.4) | 828 (12.4) |
| Current smoker | 1897 (43.4) | 672 (15.4) | 1088 (24.9) | 714 (16.3) | 2295 (52.5) | 578 (13.2) | 940 (21.5) | 558 (12.8) | 1648 (37.7) | 685 (15.7) | 1203 (27.5) | 835 (19.1) |
| Hypertension status | | | | | | | | | | | | |
| No | 9973 (53.4) | 2826 (15.1) | 3917 (21) | 1944 (10.4) | 11608 (62.2) | 2502 (13.4) | 3115 (16.7) | 1435 (7.7) | 8851 (47.4) | 3186 (17.1) | 4360 (23.4) | 2263 (12.1) |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Yes | 2224 (47.3) | 774 (16.5) | 1124 (23.9) | 583 (12.4) | 2712 (57.6) | 671 (14.3) | 872 (18.5) | 450 (9.6) | 1940 (41.2) | 816 (17.3) | 1262 (26.8) | 687 (14.6) |
| MHT users | | | | | | | | | | | | |
| No | 10779 (54.6) | 3001 (15.2) | 4080 (20.7) | 1891 (9.6) | 12517 (63.4) | 2617 (13.2) | 3220 (16.3) | 1397 (7.1) | 9549 (48.3) | 3376 (17.1) | 4592 (23.2) | 2234 (11.3) |
| Yes | 1418 (39.2) | 599 (16.6) | 961 (26.6) | 636 (17.6) | 1803 (49.9) | 556 (15.4) | 767 (21.2) | 488 (13.5) | 1242 (34.4) | 626 (17.3) | 1030 (28.5) | 716 (19.8) |
| Menopausal status | | | | | | | | | | | | |
| Surgical | 1806 (42) | 665 (15.5) | 1135 (26.4) | 695 (16.2) | 2321 (54) | 587 (13.6) | 900 (20.9) | 493 (11.5) | 1616 (37.6) | 676 (15.7) | 1229 (28.6) | 780 (18.1) |
| Hormone use | 1465 (47.8) | 481 (15.7) | 744 (24.3) | 373 (12.2) | 1749 (57.1) | 409 (13.4) | 612 (20) | 293 (9.6) | 1300 (42.4) | 508 (16.6) | 830 (27.1) | 425 (13.9) |
| Pre- and peri-menopause | 8018 (59.8) | 2021 (15.1) | 2416 (18) | 950 (7.1) | 8972 (66.9) | 1785 (13.3) | 1887 (14.1) | 761 (5.7) | 7069 (52.7) | 2367 (17.7) | 2799 (20.9) | 1170 (8.7) |
| Post-menopause | 908 (35) | 433 (16.7) | 746 (28.7) | 509 (19.6) | 1278 (49.2) | 392 (15.1) | 588 (22.7) | 338 (13) | 806 (31) | 451 (17.4) | 764 (29.4) | 575 (22.1) |

Abbreviation: MHT, menopausal hormone therapy; VMS, Vasomotor symptoms.

*Covariates listed in Table 2 were all significantly related to the frequency/severity of VMS (Chi-square test, P<0.001).

Table 3. The association between hot flushes, night sweats and incident CVD, CHD and stroke

| | Vasomotor symptoms (VMS) | CVD | | | CHD | | | Stroke | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No. of CVD events | No. of cases per 1000 person-years | Adjusted hazard ratio (95% CI) | No. of CHD events | No. of cases per 1000 person-years | Adjusted hazard ratio (95% CI) | No. of stroke events | No. of cases per 1000 person-years | Adjusted hazard ratio (95% CI) |
| Frequency (ALSWH, SWAN) | Hot flushes | | | | | | | | | |
| | Never | 563 | 5.4 | 1.00 | 494 | 4.7 | 1.00 | 131 | 1.2 | 1.00 |
| | Rarely | 232 | 5.8 | 0.88 (0.73, 1.05) | 198 | 5.0 | 0.87 (0.71, 1.06) | 48 | 1.2 | 0.75 (0.50, 1.12) |
| | Sometimes | 314 | 5.7 | 0.92 (0.77, 1.09) | 281 | 5.1 | 0.94 (0.78, 1.12) | 64 | 1.1 | 0.80 (0.55, 1.16) |
| | Often | 240 | 6.5 | 0.93 (0.76, 1.12) | 204 | 5.5 | 0.93 (0.76, 1.15) | 65 | 1.7 | 0.93 (0.62, 1.38) |
| | Night sweats | | | | | | | | | |
| | Never | 657 | 5.1 | 1.00 | 575 | 4.4 | 1.00 | 146 | 1.1 | 1.00 |
| | Rarely | 228 | 6.1 | 0.96 (0.80, 1.16) | 197 | 5.3 | 0.93 (0.76, 1.14) | 54 | 1.4 | 1.04 (0.71, 1.53) |
| | Sometimes | 280 | 6.5 | 1.22 (1.02, 1.45) | 245 | 5.7 | 1.19 (0.98, 1.43) | 60 | 1.4 | 1.27 (0.87, 1.85) |
| | Often | 184 | 7.0 | 1.29 (1.05, 1.58) | 160 | 6.0 | 1.25 (1.00, 1.56) | 48 | 1.8 | 1.57 (1.05, 2.37) |
| Severity (NSHD, NCDS, HOW, WHITEHALL) | Hot flushes | | | | | | | | | |
| | Never | 294 | 9.6 | 1.00 | 259 | 8.5 | 1.00 | 43 | 1.4 | 1.00 |
| | Mild | 137 | 13.5 | 1.70 (1.31, 2.20) | 133 | 13.1 | 1.80 (1.38, 2.35) | 7 | 0.7 | 0.80 (0.29, 2.22) |
| | Moderate | 90 | 11.4 | 1.23 (0.88, 1.70) | 88 | 11.1 | 1.30 (0.93, 1.81) | 5 | 0.6 | 0.48 (0.10, 2.27) |
| | Severe | 77 | 19.1 | 1.83 (1.22, 2.73) | 69 | 17.1 | 1.78 (1.17, 2.70) | 10 | 2.3 | 3.03 (0.94, 9.78) |
| | Night sweats | | | | | | | | | |
| | Never | 337 | 9.7 | 1.00 | 303 | 8.7 | 1.00 | 45 | 1.2 | 1.00 |
| | Mild | 106 | 13.1 | 1.41 (1.06, 1.87) | 99 | 12.3 | 1.37 (1.02, 1.83) | 9 | 1.0 | 1.24 (0.45, 3.42) |
| | Moderate | 95 | 15.4 | 1.70 (1.24, 2.33) | 93 | 15.1 | 1.72 (1.25, 2.37) | 4 | 0.6 | 0.96 (0.25, 3.68) |
| | Severe | 60 | 16.6 | 1.59 (1.07, 2.37) | 54 | 15.0 | 1.51 (1.00, 2.29) | 7 | 1.8 | 1.90 (0.53, 6.86) |

All HRs were adjusted for age at beginning of the interval, race/ethnicity, education, body mass index, smoking status, hypertension status, menopausal hormone therapy status, and menopausal status. When the association with hot flushes was analyzed, night sweats status was further adjusted, and vice versa.
Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease.

Table 4. The association between any VMS and incident CVD, CHD and stroke

| | Vasomotor symptoms (hot flushes and/or night sweats) | CVD | | | CHD | | | Stroke | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No. of CVD events | No. of cases per 1000 person-years | Adjusted hazard ratio (95% CI) | No. of CHD events | No. of cases per 1000 person-years | Adjusted hazard ratio (95% CI) | No. of stroke events | No. of cases per 1000 person-years | Adjusted hazard ratio (95% CI) |
| Frequency (ALSWH, SWAN) | Never | 492 | 5.2 | 1.00 | 433 | 4.6 | 1.00 | 115 | 1.2 | 1.00 |
| | Rarely | 242 | 5.7 | 0.98 (0.82, 1.17) | 206 | 4.9 | 0.98 (0.81, 1.19) | 53 | 1.2 | 0.86 (0.59, 1.26) |
| | Sometimes | 344 | 5.8 | 1.19 (1.02, 1.38) | 303 | 5.1 | 1.18 (1.01, 1.39) | 71 | 1.2 | 1.10 (0.79, 1.53) |
| | Often | 271 | 6.7 | 1.36 (1.16, 1.59) | 235 | 5.8 | 1.35 (1.14, 1.60) | 69 | 1.7 | 1.43 (1.03, 1.98) |
| Severity (NSHD, NCDS, HOW, WHITEHALL) | Never | 262 | 9.4 | 1.00 | 230 | 8.3 | 1.00 | 40 | 1.4 | 1.00 |
| | Mild | 131 | 12.5 | 1.78 (1.42, 2.24) | 125 | 11.9 | 1.87 (1.48, 2.37) | 9 | 0.8 | 0.95 (0.43, 2.13) |
| | Moderate | 115 | 12.6 | 1.68 (1.30, 2.16) | 112 | 12.2 | 1.81 (1.40, 2.34) | 6 | 0.6 | 0.47 (0.14, 1.57) |
| | Severe | 90 | 17.3 | 2.11 (1.62, 2.76) | 82 | 15.7 | 2.12 (1.61, 2.81) | 10 | 1.8 | 2.09 (0.97, 4.49) |

All HRs were adjusted for age at beginning of the interval, race/ethnicity, education, body mass index, smoking status, hypertension status, menopausal hormone therapy status, and menopausal status.

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease

Table 5. Individual or combined component of VMS and risk of CVD

| | | CVD | | | CHD | | | Stroke | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Vasomotor symptoms (VMS) | No. of CVD events | No. of cases per 1000 person-years | Adjusted hazard ratio (95% CI) | No. of CHD events | No. of cases per 1000 person-years | Adjusted hazard ratio (95% CI) | No. of stroke events | No. of cases per 1000 person-years | Adjusted hazard ratio (95% CI) |
| Frequency (ALSWH, SWAN) | No VMS | 774 | 5.7 | 1.00 | 674 | 4.9 | 1.00 | 176 | 1.3 | 1.00 |
| | Only had night sweats | 155 | 5.0 | 1.16 (0.86, 1.56) | 137 | 4.4 | 1.14 (0.83, 1.57) | 34 | 1.1 | 1.15 (0.62, 2.11) |
| | Only had hot flushes | 63 | 7.6 | 0.87 (0.71, 1.06) | 55 | 6.6 | 0.89 (0.72, 1.09) | 11 | 1.3 | 0.66 (0.42, 1.05) |
| | Both had hot flushes and night sweats | 415 | 6.8 | 1.17 (1.03, 1.33) | 362 | 5.9 | 1.16 (1.01, 1.32) | 100 | 1.6 | 1.15 (0.89, 1.49) |
| Severity (NSHD, NCDS, HOW, WHITEHALL) | No VMS | 393 | 8.5 | 1.00 | 355 | 7.6 | 1.00 | 49 | 1.2 | 1.00 |
| | Only had night sweats | 50 | 6.2 | 1.32 (0.84, 2.07) | 47 | 5.8 | 1.42 (0.89, 2.26) | 5 | 1.0 | 0.44 (0.06, 3.29) |
| | Only had hot flushes | 38 | 10.6 | 1.33 (0.94, 1.88) | 37 | 10.3 | 1.46 (1.02, 2.07) | 1 | 0.4 | 0.57 (0.13, 2.45) |
| | Both had hot flushes and night sweats | 117 | 7.6 | 1.55 (1.24, 1.94) | 110 | 7.1 | 1.58 (1.25, 2.01) | 10 | 1.3 | 1.36 (0.72, 2.59) |
| Frequency or severity | No VMS | 1167 | 6.4 | 1.00 | 1029 | 5.6 | 1.00 | 225 | 1.3 | 1.00 |
| | Only had night sweats | 205 | 5.3 | 1.27 (1.00, 1.63) | 184 | 4.7 | 1.29 (0.99, 1.67) | 39 | 1.1 | 1.07 (0.60, 1.91) |
| | Only had hot flushes | 101 | 8.5 | 0.96 (0.81, 1.14) | 92 | 7.7 | 1.00 (0.83, 1.20) | 12 | 1.1 | 0.66 (0.43, 1.02) |
| | Both had hot flushes and night sweats | 532 | 6.9 | 1.24 (1.11, 1.38) | 472 | 6.1 | 1.23 (1.10, 1.39) | 110 | 1.6 | 1.18 (0.93, 1.50) |

All HRs were adjusted for age at beginning of the interval, race/ethnicity, education, body mass index, smoking status, hypertension status, menopausal hormone therapy status, and menopausal status.
Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease.

Table 6. The association between early onset (i.e., before menopause), late onset (i.e., after menopause) VMS and incident CVD, CHD and stroke

| Vasomotor symptoms (VMS) | CVD | | | CHD | | | Stroke | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of CVD events | No. of cases per 1000 person-years | Adjusted hazard ratio (95% CI) | No. of CHD events | No. of cases per 1000 person-years | Adjusted hazard ratio (95% CI) | No. of stroke events | No. of cases per 1000 person-years | Adjusted hazard ratio (95% CI) |
| Hot flushes | | | | | | | | | |
| Never | 128 | 8.1 | 1.00 | 113 | 7.2 | 1.00 | 21 | 1.5 | 1.00 |
| Early onset | 1082 | 10.1 | 1.35 (1.09, 1.66) | 959 | 8.9 | 1.41 (1.13, 1.77) | 215 | 2 | 1.11 (0.69, 1.78) |
| Late onset | 633 | 11.5 | 1.64 (1.32, 2.05) | 559 | 10.1 | 1.68 (1.33, 2.14) | 120 | 2.3 | 1.45 (0.88, 2.37) |
| Night sweats | | | | | | | | | |
| Never | 131 | 7.6 | 1.00 | 119 | 6.9 | 1.00 | 18 | 1.2 | 1.00 |
| Early onset | 1077 | 12.1 | 1.56 (1.26, 1.93) | 955 | 10.7 | 1.56 (1.24, 1.96) | 214 | 2.4 | 1.57 (0.95, 2.60) |
| Late onset | 630 | 12.8 | 2.03 (1.62, 2.54) | 554 | 11.1 | 1.99 (1.57, 2.53) | 122 | 2.5 | 1.99 (1.18, 3.37) |
| VMS (hot flushes or/and night sweats) | | | | | | | | | |
| Never | 101 | 8 | 1.00 | 90 | 7.1 | 1.00 | 15 | 1.4 | 1.00 |
| Early onset | 1111 | 9.4 | 1.38 (1.10, 1.75) | 984 | 8.3 | 1.43 (1.12, 1.84) | 222 | 1.9 | 1.26 (0.73, 2.17) |
| Late onset | 613 | 11.5 | 1.69 (1.33, 2.16) | 541 | 10.1 | 1.73 (1.33, 2.24) | 115 | 2.2 | 1.57 (0.89, 2.76) |

All HRs were adjusted for age of VMS, race/ethnicity, education, body mass index, smoking status, hypertension status, menopausal hormone therapy status, and menopausal status.
Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease