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**Original Articles**

# Hot Flash Frequency and Blood Pressure: Data from the Study of Women's Health Across the Nation

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## Abstract

***Background:*** Vasomotor symptoms (VMS) are highly prevalent among midlife women and have been associated with subclinical cardiovascular disease (CVD). However, the association between VMS frequency and risk factors such as hypertension (HTN) remains unclear.

***Materials and Methods:*** We examined VMS frequency and blood pressure (BP) among 2839 participants of the Study of Women's Health Across the Nation (SWAN), a multiethnic, prospective, study of women enrolled from seven U.S. sites between November 1995 and October 1997. Women were age 42–52, with no history of CVD, and not postmenopausal at baseline. VMS was defined by the number of days a woman reported VMS over the 2-week period before each annual visit. Frequent VMS was defined as ≥6 days of VMS; less frequent VMS was defined 1–5 days of symptoms with asymptomatic women the reference group. BP was measured at each visit in addition to demographic and clinic factors.

***Results:*** At baseline, 298 women reported frequent VMS, 794 less frequent VMS and 1747 no VMS. More frequent baseline VMS was associated with higher BP. Compared to no VMS, baseline VMS was associated with HTN (odds ratio [OR] 1.47, 95% confidence interval [CI]; 1.14–1.88 for infrequent VMS, and OR 1.40, (95% CI; 0.97–2.02 for frequent VMS). Risk for incident pre-HTN or HTN during follow-up was increased among women with frequent VMS (hazard ratio of 1.39, 95% CI; 1.09–1.79) after adjustment for multiple covariates.

***Conclusion:*** Women with VMS may be more likely to develop HTN compared to women without VMS. Further research related to VMS including frequency of symptoms is warranted.

## Introduction

Hot flashes and night sweats, frequently experienced by women transitioning through menopause, are collectively termed vasomotor symptoms (VMS). The prevalence of VMS during the menopausal transition ranges from 42% to 79%.[1–4] VMS can occur up to 20 or more episodes per day in some women, and are associated with changes in vasodilatation and autonomic function.[5] VMS frequency may influence vascular changes in women as they age and thus may influence a woman's blood pressure (BP) as well. Since hypertension (HTN) is common among women, particularly in the peri and postmenopausal years, and is a major risk factor for cardiac events and stroke,[6,7] examining VMS in association to BP may improve current understanding of BP during the midlife transition.

To provide information on BP in relation to VMS, we examined the associations between VMS frequency and BP among participants enrolled in the Study of Women's Health Across the Nation (SWAN), a multiethnic prospective cohort study of women transitioning through menopause. We hypothesized that frequency of VMS would be positively associated with BP and increase the risk for developing HTN over time.

## Materials and Methods

### *Study population*

SWAN is a community-based longitudinal study designed to examine women's health through the menopausal transition. Study design and procedures, including recruitment and enrollment have been described in detail elsewhere.[8] Between November 1995 and October 1997, 3302 women were

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enrolled at 7 geographic sites. Sites used various sampling frameworks and recruitment strategies to enroll women from the surrounding communities. All sites enrolled non-Hispanic Caucasians and a specific minority racial/ethnic group. For the Boston, Chicago, Pittsburgh, and Detroit sites, African American women were enrolled, while Chinese, Hispanic, and Japanese women were enrolled at the Oakland, CA, Newark, NJ, and Los Angeles, CA, sites respectively. Eligibility requirements included age between 42 and 52 years upon entry, menses within the 3 months before enrollment, and the presence of a uterus and at least one ovary. Methods used in SWAN were approved by the Institutional Review Board at each study site. Each participant read and signed an informed consent document.

Of the 3302 SWAN participants, women who reported a baseline history of cardiovascular disease (CVD) (stroke, angina, or heart attack; $n=92$), and women missing information on baseline VMS frequency ($n=21$), BP ($n=10$), or covariates ($n=340$) were excluded. The remaining 2839 women were included in cross-sectional analysis of baseline data. For analysis of within-woman change in BP since baseline, additional women were excluded if they were on antihypertensive medications at baseline and/or follow-up visit 1 ($n=365$), had a hysterectomy or bilateral oophorectomy (BSO) at follow-up visit 1 ($n=21$), and had incident CVD at follow-up visit 1 ($n=9$). An additional 107 women who did not have follow-up visits with complete data and/or missing information on exogenous hormone use (HT) were excluded. The remaining 2367 women provided 1 or more observations through follow-up visit 10. For analysis of incident pre-HTN/HTN, of the 2839 women in baseline analysis, women were excluded if they were not normotensive at baseline ($n=1385$), had a hysterectomy or BSO at follow-up visit 1 ($n=7$), had incident CVD at follow-up visit 1 ($n=5$), or had incomplete data and/or missing information on exogenous hormone use (HT) use ($n=89$). The remaining 1353 women were included in analysis of incident pre-HTN/HTN through follow-up visit10. For both longitudinal analysis, a woman's data were censored at hysterectomy or BSO or at a reported CVD event, and visits with HT were omitted. For analysis of change in BP, data also were censored at first use of antihypertensive medication, which results in a shorter follow-up time for this analysis (mean follow-up time was 4.3 years).

### *Measures*

Vasomotor symptoms. Information on VMS (*i.e.*, hot flashes and night sweats) was collected by self-report *via* the SWAN questionnaires during each annual study visit. Participants were asked how many days over the 2-week period immediately before the annual visit they experienced any VMS (not at all, 1–5 days, 6–8 days, 9–13 days, every day). For the present analysis, VMS frequency was categorized into three groups (frequent VMS: six or more days with symptoms; infrequent VMS:1–5 days with symptoms; no VMS; prior 2 weeks without symptoms), consistent with prior SWAN analyses.[9]

Blood pressure. BP was measured according to a standardized protocol, with readings taken on the right arm, with the respondent seated and feet flat on the floor for at least 5 minutes before measurement. Respondents were asked to refrain from smoking or consuming any caffeinated beverage within 30 minutes of BP measurement. Appropriate cuff size was determined based on arm circumference. A standard mercury sphygmomanometer was used to record systolic and diastolic pressures at the first and fifth phase Korotkoff sounds. Two sequential BP values were completed, with a minimum 2-minute rest period between measurements. The average of the two measures was used in this analysis.

In addition to examining BP levels as a continuous variable, categorical variables were created based on the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High BP (JNC VII).[10] HTN was defined as SBP ≥140 mmHg, or DBP ≥90 mmHg, or current use of antihypertensive medications (queried at each annual visit). Pre-HTN was defined as SBP 120–139 mmHg or DBP 80–89 mmHg without medication use, and normotension was defined as SBP <120 mmHg and DBP <80 mmHg without medication use.

Covariates. Premenopausal status was defined as a menstrual period within the past 3 months with no change in cycle regularity. Early perimenopause was defined as a menses within the past 3 months with a change in cycle regularity. Late perimenopause was defined as no menses for three or more months, but at least one period within the last 12 months. Postmenopause was defined as no menses for 12 or more consecutive months with no other reason for the amenorrhea. Surgical menopause (occurring during follow-up) was defined as having had a hysterectomy or BSO. By design, all women were pre- or early perimenopausal at baseline.

Demographic information was collected at baseline including race/ethnicity, education level, and parity (any live births). Information on a number of known risk factors for HTN was collected at baseline and during follow-up, including age, body mass index (BMI, kg/m$^2$), smoking status (current versus former and never), alcohol consumption (abstainer, <2 servings/week, 2–7 servings/week, and >7 servings/week), and[11]anxiety, computed as the sum of frequency of four symptoms (irritability or grouchiness, feeling tense or nervous, pounding or racing heart, fearful for no reason) in the past 2 weeks, with scores for each item ranging from 0 (no days) to 4 (every day); the sum was dichotomized at the ~75th percentile, 4+ vs. <4.[12] Level of physical activity was assessed at baseline and follow-ups 3, 5, and 9 using the Kaiser Physical Activity Survey adapted from the Baecke questionnaire.[13,14] Because both alcohol consumption and physical activity were stable over time within woman (intra-class correlation = 0.75 and 0.64, respectively), analysis used baseline rather than time-varying values.

### *Statistical analysis*

Characteristics of the analytic sample at baseline were compared by baseline VMS frequency groups using chi-square testing for categorical variables and analysis of covariance for continuous variables. The covariate- adjusted association of baseline VMS frequency with categorized HTN (normotensive, prehypertensive, and hypertensive) at baseline was estimated using multinomial logistic regression.

Linear mixed models,[15,16] were used to examine the associations of VMS frequency reported at each visit with the changes in systolic and diastolic BP (change from baseline to

BP measures at the concurrent visit as the VMS reported), adjusting for baseline age, time since baseline, study site, race, education level, current menopausal status, baseline parity, baseline alcohol consumption, baseline physical activity, smoking status, current anxiety score, current BMI, and baseline VMS. Associations of time-varying VMS with incident pre-HTN or HTN among normotensive participants at baseline, before and after adjustment for covariates, were estimated using logistic regression with a complementary log-log link for discrete survival analysis, to account for the interval censoring due to assessment of HTN only at annual visits.[17] In sensitivity analysis, we interpolated missing values of the time-varying covariates for gaps of 1–2 visits based on covariate values at prior and subsequent visits, analogous to prior SWAN analysis;[18] results were similar to those presented (data not shown).

## Results

At baseline 298 (10.5%) women reported frequent VMS (six or more days in the prior 2 weeks), 794 (28.0%) women reported infrequent VMS (between 1 and 5 days of symptoms), and 1747 (61.5%) reported no VMS. (Table 1) Mean and median years of follow-up were 8.2 and 10.0, respectively. Compared with women providing follow-up data, women with no follow-up visits had slightly higher baseline mean systolic (119.2 mmHg vs. 115.3 mmHg) and diastolic BP (76.3 mmHg vs. 74.3 mmHg) and were somewhat more likely to have pre-HTN or HTN at baseline (58.4% vs. 48.2%).

Women reporting frequent VMS at baseline were on average older, more likely to be African American, and less educated compared with those with fewer symptoms. As expected, women who reported frequent VMS at baseline were more likely to be early perimenopausal than premenopausal. Women who reported frequent VMS at baseline were also heavier, less physically active, more anxious, and more likely to be current smokers compared to asymptomatic women. Among women not on antihypertensive medications, mean SBP and DBP were higher among the more symptomatic women in age-adjusted models. Women with VMS were also more likely to be prehypertensive or hypertensive at baseline, as defined by JNC VII criteria compared to asymptomatic women.

Women who reported frequent VMS at baseline were more than twice as likely to have HTN at baseline, compared to asymptomatic women. (Table 2) Frequent VMS was also significantly associated with pre-HTN. These associations remained significant when adjusting for age. Further adjustment for multiple demographic factors and CVD risk factors attenuated these associations. In multivariable models VMS frequency was no longer associated with either pre-HTN or HTN. However, having VMS 1–5 days, remained associated with HTN, which likely reflects the larger sample of women reporting VMS in the past 1–5 days, compared to the smaller sample of women reporting frequent VMS.

Table 1. Baseline Characteristics by Baseline Frequency of Vasomotor Symptoms, ($N = 2839$)

| | *Number of days reported hot flashes/night sweats in the past 2 weeks* | | | |
|---|---|---|---|---|
| *Characteristics* | *0 days* n = *1747* | *1–5 days* n = *794* | *6 or more* n = *298* | p |
| Age in years, mean (SE) | 46.2 (0.1) | 46.5 (0.1) | 47.2 (0.2) | <0.0001 |
| Race/ethnicity, *n* (%) | | | | <0.0001 |
| African American | 393 (22.5) | 222 (28.0) | 105 (35.2) | |
| Caucasian | 907 (51.9) | 373 (47.0) | 136 (45.6) | |
| Chinese | 159 (9.1) | 50 (6.3) | 13 (4.4) | |
| Hispanic | 121 (6.9) | 84 (10.6) | 29 (9.7) | |
| Japanese | 167 (9.6) | 65 (8.2) | 15 (5.0) | |
| Menopausal status, *n* (%) | | | | <0.0001 |
| Premenopausal | 1058 (60.6) | 362 (45.6) | 113 (37.9) | |
| Early peri-menopausal | 689 (39.4) | 432 (54.4) | 185 (62.1) | |
| Any live births, *n* (%) | 1413 (80.9) | 685 (86.3) | 253 (84.9) | 0.0023 |
| College degree, *n* (%) | 872 (49.9) | 303 (38.2) | 100 (33.6) | <0.0001 |
| Alcohol consumption, *n* (%) | | | | 0.2670 |
| Abstainer | 857 (49.1) | 377 (47.5) | 163 (54.7) | |
| Infrequent (<2 servings/week) | 176 (10.1) | 88 (11.1) | 30 (10.1) | |
| Light to moderate (2–7 servings/week) | 473 (27.1) | 205 (25.8) | 63 (21.1) | |
| Heavy (>7/week) | 241 (13.8) | 124 (15.6) | 42 (14.1) | |
| High anxiety (score ≥4), *n* (%) | 247 (14.1) | 226 (28.5) | 155 (52.0) | <0.0001 |
| BMI, kg/m$^2$ (SE) | 27.6 (0.2) | 28.6 (0.3) | 30.4 (0.4) | <0.0001 |
| Current cigarette smoking, *n* (%) | 245 (14.0) | 144 (18.1) | 68 (22.8) | <0.0001 |
| Physical activity, mean (SE)[a] | 7.8 (0.04) | 7.7 (0.1) | 7.4 (0.1) | 0.0398 |
| Systolic BP, mmHg, mean (SE)[b] | 114.2 (0.4) | 117.3 (0.6) | 118.5 (1.0) | <0.0001 |
| Diastolic BP, mm Hg, mean (SE)[b] | 73.9 (0.2) | 75.4 (0.4) | 75.5 (0.6) | 0.0023 |
| Blood pressure categories, *n* (%) | | | | <0.0001 |
| Normotensive | 974 (55.8) | 364 (45.8) | 116 (38.9) | |
| Prehypertensive | 477 (27.3) | 237 (29.9) | 96 (32.2) | |
| Hypertensive | 296 (16.9) | 193 (24.3) | 86 (28.9) | |

[a]Kaiser physical activity survey total score ranges from 3 to 15, with 15 being highest level of activity.
[b]Excluding subjects on antihypertensive medications at baseline.
BMI, body mass index; BP, blood pressure; SE, standard error.

Table 2. Estimated Odds Ratios from Multinomial Logistic Regression for Baseline Prehypertension or Hypertension by Baseline VMS Categories ($N=2839$)

| | *Odds ratio (95% confidence interval)* | *Odds ratio (95% confidence interval)* | p |
|---|---|---|---|
| Unadjusted | Prehypertensive vs. normotensive | Hypertensive vs. normotensive | |
| None | Reference | Reference | <0.0001 |
| 1–5 days | 1.32 (1.09, 1.62) | 1.75 (1.40, 2.17) | |
| 6+ days | 1.69 (1.26, 2.26) | 2.44 (1.79, 3.32) | |
| Model 1 | | | |
| None | Reference | Reference | <0.0001 |
| 1–5 days | 1.31 (1.08, 1.60) | 1.69 (1.36, 2.11) | |
| 6+ days | 1.60 (1.19, 2.14) | 2.15 (1.57, 2.94) | |
| Model 2 | | | |
| None | Reference | Reference | <0.0341 |
| 1–5 days | 1.17 (0.94, 1.46) | 1.47 (1.14, 1.88) | |
| 6+ days | 1.27 (0.91, 1.76) | 1.40 (0.97, 2.02) | |

Model 1 = baseline age-adjusted; Model 2 = adjusted for baseline age, study site, race/ethnicity, education, baseline menopausal status, parity, baseline alcohol consumption, baseline physical activity, baseline smoking status, baseline anxiety score, and baseline BMI.
VMS, vasomotor symptoms.

Table 3. Estimated Change in Mean BP by VMS Categories from Mixed Effect Models ($N=2369$)

| | *Change in systolic blood pressure (mmHg)* | | |
|---|---|---|---|
| *Frequency* | *Unadjusted, mean (SE)* | *Model 1, mean (SE)* | *Model 2, mean (SE)* |
| Concurrent VMS | | | |
| None | 1.54 (0.27) | 1.61 (0.27) | 2.10 (0.42) |
| 1–5 days | 1.49 (0.26) | 1.54 (0.26) | 2.01 (0.42) |
| 6+ days | 1.97 (0.28) | 2.00 (0.28) | 2.44 (0.42) |
| Trend p value | 0.16 | 0.22 | 0.31 |
| | *Change in diastolic blood pressure (mmHg)* | | |
| *Frequency* | *Unadjusted, mean (SE)* | *Model 1, mean (SE)* | *Model 2, mean (SE)* |
| Concurrent VMS | | | |
| None | –0.20 (0.20) | –0.13 (0.20) | 0.09 (0.31) |
| 1–5 days | 0.06 (0.19) | 0.10 (0.19) | 0.29 (0.31) |
| 6+ days | 0.34 (0.21) | 0.35 (0.20) | 0.46 (0.31) |
| Trend p value | 0.003 | 0.009 | 0.046 |

VMS was assessed concurrently with each visit and VMS was treated as a time-varying covariate. Change in BP at concurrent visit–baseline BP. Observations were censored at first use of HTN medications, excluding missing changes in BP, VMS, and covariates ($n=2369$ women with 13,947 observations over a mean follow-up time of 4.3 years); Estimated changes in mean BP were calculated at means of all included covariates in each model; Unadjusted model includes time since baseline, adjusting for baseline VMS; Model 1: adjusted for age at baseline, time since baseline, study site, and baseline VMS; Model 2: adjusted for covariates in model 1 and race, education level, current menopausal status, baseline parity, baseline alcohol consumption, baseline physical activity, current smoking status, current anxiety score, current BMI.

Table 4. Estimated HR for Incident Prehypertension/Hypertension by VMS Categories, 1353 Women Normotensive at Baseline

| *Unadjusted* | *HR (95% CI)* | p | *No. observations/ No. events* |
|---|---|---|---|
| None | Reference | 0.0001 | 6385/620 |
| 1–5 days | 1.22 (1.01, 1.48) | | |
| 6+ days | 1.62 (1.30, 2.03) | | |
| Model 1 | | | |
| None | Reference | 0.0024 | 6385/620 |
| 1–5 days | 1.20 (0.98, 1.46) | | |
| 6+ days | 1.50 (1.19, 1.89) | | |
| Model 2 | | | |
| None | Reference | 0.0443 | 6257/589 |
| 1–5 days | 1.08 (0.87, 1.33) | | |
| 6+ days | 1.39 (1.08, 1.79) | | |

VMS was assessed concurrently with each visit and VMS was treated as a time-varying covariate. Unadjusted: model includes only current VMS frequency and time since baseline; Model 1: adjusted for baseline age and site; Model 2: variables including in Model 1, race, education level, current menopausal status, baseline parity, baseline alcohol consumption, baseline physical activity, current smoking status, current anxiety score, current BMI; Prehypertension (SBP 120–139 mmHg or DBP 80–89 mmHg); hypertension (use of an antihypertensive agent or SBP ≥140 mmHg or DBP ≥90 mmHg) per JNC VII.
HR, hazard ratio.

We next examined the relation between VMS frequency and change in BP over time (Table 3). Baseline VMS was not associated with change in SBP or DBP (data not shown). After adjusting for baseline VMS, and other factors, women who reported frequent VMS during follow-up had greater increases in DBP during follow-up. VMS was not related to changes in SBP.

We also examined the incidence of pre-HTN or HTN by VMS frequency (Table 4). Compared with absence of VMS, incidence of pre-HTN or HTN was more likely with occurrence of both 1–5 days of VMS and frequent VMS (six or more days of VMS). After adjustment for covariates, frequent VMS remained associated with a higher risk for pre-HTN or HTN compared to asymptomatic women.

## Discussion

In this large multi-ethnic cohort of midlife women, more frequent VMS at baseline were associated with higher BP and HTN at baseline. During follow-up incident pre-HTN and HTN was associated with frequent VMS. However, change in BP over time did not appear to be associated with VMS frequency during follow-up.

Our study represents one of the largest prospective cohorts in which VMS and BP has been examined. Other smaller studies have shown a similar relationship between VMS and BP. In a study of 20 women, in which BP was measured *via* ambulatory BP monitoring, higher SBP levels were observed among women who reported having VMS compared to women with no symptoms.[19] However, frequency of VMS was not collected. A similar positive association was observed in data from the Neighborhood Health Study[20] in which 154 midlife women wore an ambulatory BP monitor for 24 hours. Women who reported VMS had significantly higher SBP (both daytime and nocturnal) compared to women who

reported no symptoms, after controlling for age, race/ethnicity, BMI, and menopausal status. In contrast, a more recent study of 202 women, aged 45–55 observed no significant difference in mean SBP between women who reported hot flashes compared to those who were asymptomatic.[21] However, the investigators did observe a significant and transient increase in SBP during the 10 minutes before individual hot flashes episodes. In a cross-sectional analysis of 5523 women, Gast et al. showed evidence for a positive association between reported VMS and BP. These associations were in part, but not fully accounted for, by confounders such as BMI.[22]

Prior studies suggest an association between VMS and cardiovascular risk parameters that may also influence BP. Thurston and colleagues, using data from SWAN Heart, observed that women who reported having any hot flashes over a 2-week period were more likely to have reduced flow-mediated dilation, a marker of subclinical CVD.[23] Using the same study population, these symptomatic women were 63% more likely to have aortic calcification compared with women who reported no symptoms.[23] Other subclinical markers of CVD such as carotid intimal thickness also appear to be associated with hot flash symptoms in women.[9] Although findings are mixed, additional studies suggest higher rates of coronary heart disease among women who report VMS compared with those who do not.[24,25]

VMS is highly prevalent among women transitioning through menopause; with many women reporting increased frequency during late peri-menopause and early postmenopause.[1–4] The exact physiologic mechanisms behind VMS are not clearly understood. However, data suggest that changes in core body temperature and vascular function occur transiently around the time of a VMS episode.[5] As peripheral temperature increases, skin vasodilation occurs, resulting in an increase in skin blood flow and dispersion of heat.[5] Additional studies have observed that the main metabolite of norepinephrine, 3-methoxy-4-hydroxyphenylglycol (MHPG), is increased in women with VMS,[26,27] while women without VMS demonstrate no such increase in MHPG. Current knowledge regarding the physiology of VMS in the menopausal transition suggests the role of autonomic regulation may be important.[28–31] Given these relationships, along with observational studies, VMS may be associated with incident HTN; however, we did not observe a strong relationship between VMS frequency over time and increases in BP. Over time, small increases in BP may contribute to the development of preHTN and HTN. However, the differences may also reflect the examination of continuous BP measures versus BP categories. Understanding the relationship between VMS and BP including duration of VMS warrants further study.

Several strengths and limitations exist in this study. At each annual visit, women were asked about the number of days in the prior 2 weeks in which they experienced hot flashes and/or night sweats, without specification of how many VMS events they were having on those days. Although this method of asking about VMS is widely used, it would lead to reduced precision in regard to VMS frequency and a bias toward the null hypothesis that BP does not differ by VMS frequency. Thus, differentiating between women with 20 VMS per day and those with three per day is not possible; however, SWAN's longitudinal design and multi-ethnic cohort does allow an examination of days of symptoms over several years.

## Conclusion

Among a multi-ethnic cohort of midlife women, those who experienced frequent VMS had an increased risk for incident pre-HTN and HTN, although a change BP level over time was not associated with VMS. Further research is needed to understand the relationship between VMS and BP as women age.

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## Author Disclosure Statement

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