Published in final edited form as:
Menopause. 2011 October ; 18(10): 1044–1051. doi:10.1097/gme.0b013e31821f5d39.

Are Vasomotor Symptoms Associated with Alterations in Hemostatic and Inflammatory Markers? Findings from the Study of Women's Health Across the Nation

Rebecca C. Thurston, PhD[a,b], **Samar R. El Khoudary, PhD, MPH**[b], **Kim Sutton-Tyrrell, DrPH**[b], **Carolyn J. Crandall, MD, MS**[c], **Ellen Gold, PhD**[d], **Barbara Sternfeld, PhD**[e], **Faith Selzer, PhD**[b], and **Karen A. Matthews, PhD**[a,b]

[a] Department of Psychiatry, University of Pittsburgh School of Medicine

[b] Department of Epidemiology, University of Pittsburgh Graduate School of Public Health

[c] Department of Medicine, David Geffen School of Medicine, University of California Los Angeles

[d] Department of Public Health Sciences, University of California Davis School of Medicine

[e] Kaiser Permanente Division of Research

Abstract

Objective—Emerging research suggests links between menopausal hot flashes and cardiovascular risk. The mechanisms underlying these associations are unclear, due in part to the incomplete understanding of the physiology of hot flashes. We aimed to examine the longitudinal associations between hot flashes/night sweats and both inflammatory and hemostatic markers, controlling for cardiovascular risk factors and estradiol concentrations.

Methods—Participants in the Study of Women's Health Across the Nation (SWAN) (N=3199), a longitudinal cohort study, were ages 42–52 years at cohort entry. Women completed interviews (hot flashes, night sweats: none, 1–5, 6 days in past 2 weeks), physical measures (blood pressure; height; weight), and a blood draw (C-reactive protein, high sensitivity; plasminogen activator inhibitor-1; Factor VIIc, tissue plasminogen activator antigen (tPA-ag); fibrinogen; glucose; serum estradiol) yearly for 8 years. Hot flashes/night sweats were examined in relation to each inflammatory/hemostatic marker in linear mixed models adjusting for demographic factors, cardiovascular risk factors, and medication use, and additionally serum estradiol.

Results—Compared to experiencing no flashes, reporting hot flashes was associated with higher $tPA\text{-}ag_{log}$ (hot flashes 1–5 days: % change (95%CI): 3.88(2.22–5.58), $p<0.0001$; ≥6 days: % change (95%CI): 4.11(1.95–6.32), $p<0.001$) and higher Factor $VIIc_{log}$ (hot flashes ≥6 days: % change (95%CI): 2.13(0.80–3.47), $p<0.01$) in multivariable models. Findings persisted after adjusting for estradiol. Findings for night sweats were similar but attenuated with adjustment.

Conclusions—Frequent hot flashes were associated with higher Factor VIIc and tPA-ag. Hemostatic pathways may be relevant to understanding hot flashes physiology and links between hot flashes and cardiovascular risk.

Keywords

Menopause; vasomotor symptoms; hot flashes; inflammation; coagulation; hemostasis

Corresponding Author: Rebecca C. Thurston, PhD; 3811 O'Hara St; Pittsburgh, PA 15213; tel: (412) 648-9087; fax: (412) 648-7160; thurstonrc@upmc.edu.

Disclosures: None

Vasomotor symptoms (VMS; hot flashes and/or night sweats), are experienced by most women transitioning through the menopause.[1] VMS are associated with sleep disturbance,[2] depressed mood,[3] and overall decrements in physical, social, and emotional quality.[4] Most women with menopausal symptoms, principally VMS, seek treatment for them.[5]

Despite their prevalence and impact on women's lives, the physiology of VMS is not well understood. Leading etiologic models cite VMS as thermoregulatory heat dissipation events occurring in the context of the menopausal withdrawal of gonadal hormones.[6] However, many other central and peripheral systems have been implicated in VMS, and the need for better understanding of the physiology of VMS has been recognized.[7]

In addition to the quality of life implications of VMS, emerging evidence is linking VMS to cardiovascular risk. In the Women's Health Initiative (WHI)[8] and the Heart and Estrogen/Progestin Replacement Study (HERS),[9] older postmenopausal women with moderate-severe VMS at the study baseline were at greatest cardiovascular risk with hormone use. Our findings from the Study of Women's Health Across the Nation Heart Study (SWAN Heart) further showed that midlife women with hot flashes had indices of greater subclinical cardiovascular disease, including poorer endothelial function,[10] greater aortic calcification,[10] and greater intima media thickness[11] than women without hot flashes. Others have found similar findings for endothelial function.[12] Associations generally persist with adjustment for standard cardiovascular risk factors.

The reason(s) for links between VMS and cardiovascular risk is not fully understood. One study has suggested that hot flash severity may be associated with alterations in inflammatory processes.[13] Altered inflammation and hemostasis, two inter-related systems,[14] play key roles in the pathogenesis of CVD. These alterations have been related, in many cases prospectively, to CVD risk.[15] In fact, the endothelium, dysfunction of which has been linked to VMS, plays a central role in regulating blood coagulation and inflammation.[16]

The primary study aim was to examine the associations between VMS and inflammatory and hemostatic markers in SWAN, a large, longitudinal study of women transitioning through the menopause. We assessed the longitudinal relations of VMS to hs-CRP (high sensitivity C-reactive protein), an acute phase reactant prospectively associated with CVD risk,[17] the procoagulant/anti-fibrinolytic hemostatic markers, plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator antigen (tPA-ag), and Factor VIIc (FVIIc), and the acute-phase reactant protein, fibrinogen,[18] all of which have been linked to CVD risk.[15, 18–19] We hypothesized that VMS would be associated with adverse alterations in inflammation and hemostasis after adjusting for potential confounding/explanatory factors (e.g., smoking, obesity, educational attainment) as well as serum estradiol (E2), a gonadal hormone associated with both VMS [20–21] and inflammation/hemostasis.[22] We also evaluated any modification of these associations by menopausal stage as well as race/ethnicity, given the importance of these factors to VMS and cardiovascular risk.

Methods

Sample

The Study of Women's Health Across the Nation (SWAN) is a multiethnic cohort study designed to characterize biological and psychosocial changes over the menopausal transition. Details of the SWAN design and recruitment procedures are reported elsewhere.[23] Briefly, each SWAN site recruited non-Hispanic White women and women belonging to a predetermined racial/ethnic minority group (African American women in

Pittsburgh, Boston, Michigan, Chicago; Japanese in Los Angeles; Hispanic in New Jersey; Chinese in Oakland area of California). Los Angeles, Pittsburgh and New Jersey sites used random-digit-dialed sampling from banks of telephone numbers, and Boston, Chicago, Michigan, and Oakland sites selected randomly from lists of names or household addresses. Select sites supplemented primary sampling frames to obtain adequate numbers of racial/ethnic minority women. SWAN protocols were approved by the institutional review boards at each site, and each participant provided written informed consent.

Baseline eligibility criteria for SWAN included being aged 42–52 years, having an intact uterus and ≥one ovary, not being pregnant or lactating, not using oral contraceptives or hormone therapy, and having ≥one menstrual cycle in the 3 months prior to the interview. Seventy-three percent of the women selected were contacted and provided information to determine eligibility; 51% (N=3,302) of eligible women enrolled. Annual clinic assessments began in 1996–1997. This investigation was a longitudinal analysis of associations between vasomotor symptoms and inflammatory/hemostatic markers from baseline through study visit 7 (visits in which inflammatory/hemostatic markers were assessed).

Of the 3302 women enrolled in SWAN, 92 women were excluded from this analysis due to a history of stroke/myocardial infarction at baseline, and 11 women were excluded due to having no data for VMS or hemostatic/inflammatory markers at any visit. Data were censored during the follow-up period at the time of hysterectomy/oophorectomy (N=221 participants) or reported stroke/heart attack (N=55 participants), and data from visits in which pregnancy or hormone use (hormone therapy (HT), oral contraceptives) within the previous year was reported were excluded. Thus, 3199 women were included in primary analyses. Women excluded from this analysis had lower education, higher BMI, more VMS, higher depressive symptom scores, less physical activity, and higher hs-CRP, PAI-1, tPA-ag, and fibrinogen concentrations, and were more likely perimenopausal, parous, nondrinkers, diabetic, and taking cardiovascular, psychotropic, or steroid medications, than women included (all p's<0.05).

Design and procedures

Vasomotor symptoms—Hot flashes and night sweats were assessed via questionnaire at each SWAN visit. Women responded to two questions which separately asked how often they experienced 1) hot flashes and 2) night sweats in the past two weeks (not at all, 1–5 days, 6–8 days, 9–13 days, every day; categorized as none, 1–5, ≥6 days in the past two weeks for analysis). Hot flashes and night sweats were considered separately in all analyses due to the differential pattern of associations of hot flashes versus night sweats with markers investigated here.

Blood Assays—Phlebotomy was performed in the morning following an overnight fast. Participants were scheduled for venipuncture on days 2–5 of a spontaneous menstrual cycle. Two attempts were made to obtain a day 2–5 sample. If a timed sample could not be obtained (as menstrual cycles became less regular, samples tied to the early follicular phase were not feasible), a random fasting sample was taken within 90 days of the annual visit. Blood was maintained up to an hour at 4° C until separated and then frozen (−80°C) and sent on dry ice to the Clinical Laboratory Improvement Amendments-certified CLASS laboratory at the University of Michigan (E2) and Medical Research Laboratories (hs-CRP, PAI-1, tPA-ag, FVIIc, fibrinogen) for analysis. For budgetary reasons, hemostatic/inflammatory assays were completed at baseline and SWAN study years 1, 3, 4, 5, 6, and 7 for hs-CRP, PAI-1, and tPA-ag, and at baseline, years 1, 3, 5, and 7 for FVIIc and fibrinogen.

Inflammatory/hemostatic markers: Hs-CRP, FVIIc activity, PAI-1, tPA-ag, and fibrinogen were measured in plasma. The hs-CRP was quantitated using an ultrasensitive rate immunonephelemetric method (hs-CRP, Dade-Behring, Marburg, Germany). The sensitivity of the assay was 0.03 mg/dl and interassay coefficients of variations (CVs) at CRP concentrations of 0.05 and 2.2 mg/dl were 10–12% and 5–7%, respectively. Fibrinogen and FVIIc were measured in frozen citrated plasma (MLA ELECTRA 1400C, Medical Laboratory Automation Inc., Mt. Vernon, NY) using a turbidometric detection system. Fibrinogen monthly interassay CVs were 2.3–3.5% and 2.6–3.6% at mean concentrations of 250 and 140 mg/dl, respectively, and FVIIc monthly interassay CVs were 7.8%, 5%, and 4% for mean activities of 8%, 45%, and 99%, respectively. PAI-1 was measured with a sandwich procedure using a solid phased monoclonal antibody and enzyme labeled goat second antiserum for detection (IMUBIND plasma PAI-1 ELISA, American Diagnostica, Greenwich, CT). PAI-1 monthly interassay CVs were 5–9% and 4–9% at mean concentrations of 7 and 22.5 ng/dl, respectively. TPA-ag was measured in plasma using a double antibody in an enzyme linked immunosorbant assay (IMUBIND tPA ELISA, American Diagnostica, Greenwich, CT). The assay uses human single chain t(PA) as a standard calibrated against an international standard (NIBSAC, Hertfordshire, UK). Monthly interassay CVs were 4.7–8.7% and 3.8–7.8% at mean concentrations of 5.6 and 11 ng/dl, respectively.

Consistent with published guidelines,[24] hs-CRP values >10 were excluded (8.6% of observations). For all other markers, to identify extreme values/those likely reflecting acute illness, values outside of mean ±3SD after log transformation were excluded (of available observations: 0.65% for PAI-1, 0.95% for tPA-ag, 1.1% for FVIIc, 1.3% for fibrinogen).

Estradiol (E2): E2 assays were performed on the ACS-180 automated analyzer (Bayer Diagnostics Corporation, Tarrytown, NY) utilizing a double-antibody chemiluminescent immunoassay with a solid phase anti-IgG immunoglobulin conjugated to paramagnetic particles, anti-ligand antibody, and competitive ligand labeled with dimethylacridinium ester (DMAE). The E2 assay modifies the rabbit anti-E2-6 ACS-180 immunoassay to increase sensitivity, with a LLD of 1.0 pg/mL and inter- and intra-assay coefficients of variation of 10.6% and 6.4%, respectively.[25] Duplicate E2 assays were conducted and results reported as the arithmetic mean.

Covariates—Race/ethnicity, parity (number of live births; any vs. none), and educational attainment (years of completed education categorized as < vs. ≥college degree) were derived from the SWAN screening interview. Age, smoking status (current vs. past/never),[26] depressive symptoms, physical activity, alcohol use, menopausal status, and medication use/health conditions were derived from questionnaires and interviews that used standard instruments administered during annual visits. Age, smoking, physical activity, menopausal status and medication use/health conditions were considered as time varying covariates. Race/ethnicity was determined in response to the question “How would you describe your primary racial or ethnic group?” Depressive symptoms were assessed via the Center for Epidemiologic Studies Depression scale.[27] Physical activity was assessed via a modified Kaiser Permanente Health Plan Activity Survey[28] at baseline, visits 3, 5, 6, with visits 1, 4, and 7 values carried forward from the last completed assessment. Alcohol use was the reported current consumption of beer, wine, liquor, or mixed drinks, categorized as any versus none. Menopausal status was obtained from reported bleeding patterns over the prior year, categorized as premenopausal (bleeding in the previous 3 months with no change in cycle predictability in the past year) early perimenopausal (bleeding in the previous 3 months with decrease in cycle predictability in the past year), late perimenopausal (<12 and >3 months of amenorrhea), or postmenopausal (≥12 of amenorrhea) at each visit.

Several medications/health conditions were considered. Psychotropic medication use was reported use of medication for a nervous condition (e.g., antidepressants) since the last study visit. Diabetes status was the reported diagnosis of or reported use of medications to treat diabetes. Women were censored at the time of stroke or heart attack. Other cardiovascular conditions (hypertension, angina) and use of CVD medications (any reported use of medication for a heart condition, an anticoagulant, or for blood pressure lowering in the past year) were combined into a single variable and covaried. Steroid and pain medication use was reported (including medications for headaches and arthritis). Body mass index (BMI) was derived from annual physical measures.

Data Analyses

Baseline differences between included and excluded participants were estimated using Wilcoxon rank-sum test for continuous variables and chi-square tests for categorical variables. Univariate associations between covariates and each marker were estimated at baseline using linear regression. All variables were examined for conformation to assumptions of normality and hs-CRP, FVIIc, PAI-1, tPA-ag, and E2 log transformed to normalize their distributions. Longitudinal associations between hot flashes/night sweats and each inflammatory/hemostatic marker, considered separately, were estimated in a random intercepts linear mixed model. An auto-regressive error correlation structure was selected based upon standard model fit statistics. For all log transformed outcomes, regression coefficients were back transformed using the formula $(100*(\exp^{(beta)}-1)$ to calculate the percentage change in the outcome per unit change in the predictor.[29] Models were first adjusted for age and site, and next additionally for covariates selected based upon previously-documented associations with the outcome and present association at $p<0.10$. Finally, serum E2 was added to each covariate-adjusted model along with cycle day of blood draw (in vs. out of the 2–5 day window). Since cycle day of blood draw and menopausal status were collinear (only early peri- and premenopausal women could provide timed sample), they were considered as a composite variable (premenopausal timed sample, premenopausal untimed sample, early perimenopausal timed sample, early perimenopausal untimed sample, late perimenopausal, postmenopausal). For time-varying covariates, values concurrent with the time point of the inflammatory/hemostatic marker were used. Interactions between hot flashes/night sweats and both race/ethnicity and menopausal status in relation to each marker were examined as cross product terms in both simple and multivariable models. Residual analysis and diagnostic plots were conducted to verify model assumptions of normality. Analyses were performed with SAS v9.2 (SAS Institute, Cary, NC). All models were 2-sided, alpha=0.05.

Results

At baseline, most participants were premenopausal, nonsmokers, overweight, and without hot flashes or night sweats (Table 1). Baseline factors associated with higher values of most inflammatory/hemostatic markers were Hispanic or African American race/ethnicity, low education, smoking, no alcohol consumption, higher BMI, lower physical activity, higher depressive symptoms, lower serum E2, and reporting hot flashes or night sweats (Table 2). Reporting of hot flashes and night sweats increased throughout the follow up period, from 26.3% (N=837) and 29% (N=924) of women reporting hot flashes and night sweats, respectively, at baseline, to 53.5% (N=943) and 38% (N=670) of women reporting hot flashes and night sweats, respectively, at annual visit 7.

In age and site-adjusted longitudinal models, hot flashes were associated greater tPA-ag, PAI-1, and FVIIc, and for women experiencing hot flashes ≥6 days in the past two weeks, higher hs-CRP and fibrinogen (Table 3). Associations between hot flashes and tPA-ag (any hot flashes) and FVIIc (hot flashes ≥6 days) remained with adjustment for covariates (Table

4). Findings persisted with additional adjustment for E2 (tPA-ag, 1–5 days: % change (95%CI) =3.80(2.14, 5.50), p<0.0001; ≥6 days: % change (95%CI)=3.87(1.70, 6.08), p<0.001; FVIIc, 1–5 days: % change (95%CI)=0.68(−0.30, 1.67); ≥6 days: % change (95%CI)=1.68(0.36, 3.03), p<0.05; relative to no hot flashes). A similar yet attenuated pattern of night sweats was observed in multivariable models (Table 3; with adjustment for E2 all nonsignificant except FVIIc: 1–5 nights, % change (95%CI)=0.41(−0.56, 1.38); ≥6 nights: 1.68(0.18, 3.20), p<0.05; relative to no night sweats).

No significant interactions between hot flashes or night sweats and menopausal status were observed for any of the markers. Further, no interactions were observed between race/ethnicity and hot flashes or night sweats in relation to any marker. The one exception was a significant interaction between race and night sweats in relation to fibrinogen (p=0.03), whereby the association between night sweats and fibrinogen appeared strongest among Hispanic women (data not shown). Given the large number of interactions tested, few Hispanic participants, lack of suggestion of interactions by race/ethnicity for any of the other markers, and lack of any interactions for hot flashes, this finding must be viewed with caution.

Discussion

These results showed that VMS, particularly hot flashes, were associated with elevated FVIIc and tPA-ag, and these associations persisted after we controlled for potential confounding factors as well as for serum E2 concentrations. Associations between VMS and hs-CRP, fibrinogen, and to a lesser extent PAI-1, were largely explained by their shared risk factors.

These findings may be relevant to understanding the physiology of VMS. VMS may be thermoregulatory events, or dramatic heat dissipation events occurring in the context of menopause-related declines in reproductive hormones.[6] However, understanding of the physiology of hot flashes is incomplete. Other systems have been implicated in hot flashes, including changes in neurotransmitters, the vascular endothelium, as well as the autonomic nervous system.[30] This study also suggests potential changes in hemostasis associated with VMS. Notably, hemostasis, the vascular endothelium, and the autonomic nervous system are interrelated systems. The vascular endothelium is an important regulator of blood viscosity and coagulation,[16] and vagal stimulation can attenuate procoagulant responses to endotoxin.[31] Thus, this research suggests that hot flashes may be more than an endocrine or a thermoregulatory event, but also an autonomic and vascular event.

These findings may also contribute to the understanding of emerging links between VMS and cardiovascular risk. Although not entirely consistent,[32] several investigations have found VMS to be linked to subclinical CVD,[10–12] and in the context of HT use, to clinical CVD events.[8–9] For subclinical CVD measures, the most consistent associations are observed between hot flashes and endothelial dysfunction markers.[10, 12] Notably, a key role of the endothelium is regulating blood coagulation and inflammatory responses.[16] In contrast to prior work showing associations between VMS and cardiovascular risk only apparent with HT use[8–9] or among women in the later postmenopause,[8] associations between VMS and hemostasis were observed in the absence of HT use and across several menopausal stages. These findings are consistent with our prior work[10] showing relations between hot flashes and subclinical CVD among women earlier in the transition.

Hot flashes were associated with elevated FVIIc and tPA-ag after multivariable adjustment. The reason(s) for the more pronounced associations for FVIIc and tPA-ag only is not clear. FVIIc is an important protein in the coagulation cascade[33] and the antigen to tPA, a

fibrolytic protein, is associated with elevated cardiovascular risk among women.[34] In addition, tPA is largely derived from endothelium,[33] notable given previously observed associations between hot flashes and endothelial indices. Thus, results suggest a clearer set of associations with hemostatic, as opposed to inflammatory, processes. However, this interpretation must be made with caution, as inflammatory and hemostatic processes are interrelated,[14–15] several of the markers have both roles, and the full range of inflammatory markers were not measured here.

For hs-CRP, PAI-1, and fibrinogen, associations with hot flashes were reduced when controlling for shared risk factors. One important risk factor is overweight/obesity. Overweight/obesity is a risk factor for VMS,[1] possibly due to body fat's insulating properties. Moreover, overweight/obesity is strongly associated with inflammation and hemostasis.[15] The majority of women in this cohort, similar to the US population, were overweight/obese. Thus, obesity was an important factor in (although not fully accounting for) associations between inflammation/hemostasis and VMS.

Another potentially important factor in links between VMS and inflammatory and hemostatic processes is E2. Although oral HT use is associated with pro-thrombotic/inflammatory states (e.g., elevated CRP),[22] endogenous estrogens have more favorable associations.[35] Further, E2 withdrawal is likely one precipitating factor for VMS, and lower endogenous E2 is consistently, although sometimes modestly,[21] associated with VMS.[20] Lower serum E2 was associated with elevations in most markers assessed here; however, control for E2 did not sizably reduce associations beyond other risk factors. Given that E2 was assessed yearly, and some of the women likely had fluctuating hormone concentrations, E2 exposure may not have been fully quantified, and further investigation of E2 in these associations is merited. However, these findings do not support low E2 as a primary pathway linking VMS to hemostasis.

Findings were most notable for hot flashes reported ≥six days in the past two weeks. Thus, a larger symptom burden may be more related to adverse health indices. Other work has found only more frequent[11] or severe VMS[8–9, 12–13] to be associated with cardiovascular risk and/or inflammation. However, findings have not been entirely consistent.[10] More detailed VMS measures, such as VMS severity or physiologic VMS measures were not available in this epidemiologic investigation. Further work with more detailed measures of VMS is important to more clearly identifying symptom thresholds associated with adverse cardiovascular profiles.

Findings were most pronounced for hot flashes, and slightly weaker for night sweats. With some notable exceptions,[36] prior evidence suggests more consistent associations between hot flashes and certain cardiovascular risk factors[37] and vascular changes[10, 12] than night sweats. Notably, night sweats may be reported less reliably given their occurrence during sleep,[38] and thereby their reporting may incorporate more non-VMS related factors. Further, whether the physiologies of hot flashes and night sweats are interchangeable has not been demonstrated. Thus, because reported hot flashes and night sweats may not be identical, their associations with hemostatic indices may vary as well.

Several limitations deserve mention. First, although an extensive set of inflammatory/hemostatic markers were assessed here, other relevant markers, such as IL-6 or IL-8, were not assessed. Future work should consider these markers. Although women with heart disease or stroke were excluded, relevant medical conditions and medications controlled, and careful consideration of outlying values was undertaken, not all medications were queried, and it is possible that women in this investigation were taking medications or had medical conditions not assessed here that could affect inflammation/hemostasis. The

grouping of medical conditions and certain medications, while important to reduce the number of parameters in the model and account for the correlations between these factors, may have masked some important relations and over-controlled for others. Additionally, the large number of markers may have increased the risk of detecting spurious associations. Further, although this was a population-based investigation, SWAN participants may not be fully representative of the US population of midlife women. Although many potential confounders were assessed, given that this is an observational study, the possibility of residual confounding by unmeasured factors (e.g., genetic factors) remains. Although this was a longitudinal investigation, the directionality or causal nature of these associations cannot be inferred. Further work in future studies to better understand the precise nature of these relations, as well as any potential clinical significance of these associations, is warranted.

This study had several strengths. This study is the first to examine longitudinal associations between VMS and inflammatory/hemostatic markers. It investigated a large, longitudinal, community-based investigation of women transitioning through the menopause. It allowed investigation of associations between VMS and inflammatory/hemostatic markers within a woman transitioning through the menopause, a considerably stronger design than solely conducting between-woman comparisons that are more vulnerable to confounding. Additionally, the sample included women from several different ethnic groups, allowing investigation of the consistency of associations across groups. Moreover, a wide range of potential confounders were assessed and controlled. Finally, this study assessed a wide range of inflammatory/hemostatic markers and across several time points, allowing investigation of the consistency of associations over time and across markers.

Conclusion

This study found VMS, particularly frequent hot flashes, to be associated with elevations in tPA-ag and FVIIc, above and beyond relevant risk factors and serum E2 concentrations. Frequent VMS are experienced by many midlife women and associated with impairments in quality of life during midlife, yet their underlying physiology as well as implications for health outcomes is not fully understood. The findings of the present study are relevant to further understanding the physiology of VMS. Further, whether VMS are associated with cardiovascular risk and by what mechanism is currently unclear. These findings may contribute to this emerging work linking this menopausal symptom to cardiovascular risk.

Acknowledgments

Funding support: This work was supported by National Institutes of Health (NIH) Grants NR004061; AG012505, AG012535, AG012531, AG012539, AG012546, AG012553, AG012554, AG012495, and AG029216

SWAN has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants NR004061; AG012505, AG012535, AG012531, AG012539, AG012546, AG012553, AG012554, AG012495). The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH.

Clinical Centers: University of Michigan, Ann Arbor–MaryFran Sowers, PI; Massachusetts General Hospital, Boston, MA–Joel Finkelstein, PI 1999–present; Robert Neer, PI 1994–1999; Rush University, Rush University Medical Center, Chicago, IL–Howard Kravitz, PI 2009-present; Lynda Powell, PI 1994–2009; University of California, Davis/Kaiser–Ellen Gold, PI; University of California, Los Angeles–Gail Greendale, PI; Albert Einstein College of Medicine, Bronx, NY–Rachel Wildman, PI 2010; Nanette Santoro, PI 2004–2010; University of Medicine and Dentistry–New Jersey Medical School, Newark–Gerson Weiss, PI 1994–2004; and the University of Pittsburgh, Pittsburgh, PA–Karen Matthews, PI.

NIH Program Office: National Institute on Aging, Bethesda, MD–Sherry Sherman 1994–present; Marcia Ory 1994–2001; National Institute of Nursing Research, Bethesda, MD–Project Officer.

Central Laboratory: *University of Michigan, Ann Arbor–Daniel McConnell* (Central Ligand Assay Satellite Services).

Coordinating Center: University of Pittsburgh, Pittsburgh, PA–Kim Sutton-Tyrrell, PI 2001–present; New England Research Institutes, Watertown, MA-Sonja McKinlay, PI 1995–2001.

Steering Committee: Susan Johnson, Current Chair, Chris Gallagher, Former Chair

We thank the study staff at each site and all the women who participated in SWAN

This work was also supported by NIH grant AG029216 (Thurston).

References

1. Gold E, Colvin A, Avis N, et al. Longitudinal analysis of vasomotor symptoms and race/ethnicity across the menopausal transition: Study of Women's Health Across the Nation (SWAN). Am J Public Health. 2006; 96:1226–1235. [PubMed: 16735636]
2. Kravitz HM, Ganz PA, Bromberger J, Powell LH, Sutton-Tyrrell K, Meyer PM. Sleep difficulty in women at midlife: a community survey of sleep and the menopausal transition. Menopause. 2003; 10:19–28. [PubMed: 12544673]
3. Bromberger JT, Matthews KA, Schott LL, et al. Depressive symptoms during the menopausal transition: the Study of Women's Health Across the Nation (SWAN). J Affect Disord. 2007; 103:267–272. [PubMed: 17331589]
4. Avis NE, Colvin A, Bromberger JT, et al. Change in health-related quality of life over the menopausal transition in a multiethnic cohort of middle-aged women: Study of Women's Health Across the Nation. Menopause. 2009; 16:860–869. [PubMed: 19436224]
5. Williams RE, Kalilani L, DiBenedetti DB, Zhou X, Fehnel SE, Clark RV. Healthcare seeking and treatment for menopausal symptoms in the United States. Maturitas. 2007; 58:348–358. [PubMed: 17964093]
6. Freedman RR. Physiology of hot flashes. Am J Human Biol. 2001; 13:453–464. [PubMed: 11400216]
7. Sherman S, Miller H, Nerurkar L, Schiff I. Research opportunities for reducing the burden of menopause-related symptoms. Am J Med. 2005; 118:166–171. [PubMed: 16414344]
8. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007; 297:1465–1477. [PubMed: 17405972]
9. Huang AJ, Sawaya GF, Vittinghoff E, Lin F, Grady D. Hot flushes, coronary heart disease, and hormone therapy in postmenopausal women. Menopause. 2009; 16:639–643. [PubMed: 19325499]
10. Thurston RC, Sutton-Tyrrell K, Everson-Rose SA, Hess R, Matthews KA. Hot flashes and subclinical cardiovascular disease: Findings from the Study of Women's Health Across the Nation Heart Study. Circulation. 2008; 118:1234–1240. [PubMed: 18765392]
11. Thurston RC, Sutton-Tyrrell K, Everson-Rose S, Hess R, Powell L, Matthews K. Hot flashes and carotid intima media thickness among midlife women. Menopause. 2011 Jan 14. [Epub ahead of print].
12. Bechlioulis A, Kalantaridou SN, Naka KK, et al. Endothelial function, but not carotid intima-media thickness, is affected early in menopause and is associated with severity of hot flushes. J Clin Endocrinol Metab. 2010; 95:1199–1206. [PubMed: 20080857]
13. Yasui T, Uemura H, Tomita J, et al. Association of interleukin-8 with hot flashes in premenopausal, perimenopausal, and postmenopausal women and bilateral oophorectomized women. J Clin Endocrinol Metab. 2006; 91:4805–4808. [PubMed: 17018658]
14. Levi M, van der Poll T, Buller HR. Bidirectional relation between inflammation and coagulation. Circulation. 2004; 109:2698–2704. [PubMed: 15184294]
15. Tracy RP. Thrombin, inflammation, and cardiovascular disease: an epidemiologic perspective. Chest. 2003; 124:49S–57S. [PubMed: 12970124]
16. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA. The clinical implications of endothelial dysfunction. J Am Coll Cardiol. 2003; 42:1149–1160. [PubMed: 14522472]

17. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med. 2000; 342:836–843. [PubMed: 10733371]

18. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA. 1998; 279:1477–1482. [PubMed: 9600484]

19. Folsom AR. Hemostatic risk factors for atherothrombotic disease: an epidemiologic view. Thromb Haemost. 2001; 86:366–373. [PubMed: 11487026]

20. Freeman EW, Sammel MD, Lin H, Gracia CR, Kapoor S, Ferdousi T. The role of anxiety and hormonal changes in menopausal hot flashes. Menopause. 2005; 12:258–266. [PubMed: 15879914]

21. Randolph JF Jr, Sowers M, Bondarenko I, et al. The relationship of longitudinal change in reproductive hormones and vasomotor symptoms during the menopausal transition. J Clin Endocrinol Metab. 2005; 90:6106–6112. [PubMed: 16144949]

22. Cushman M. Effects of hormone replacement therapy and estrogen receptor modulators on markers of inflammation and coagulation. Am J Cardiol. 2002; 90(1A):7F–10F.

23. Sowers, M.; Crawford, S.; Sternfeld, B., et al. SWAN: A multicenter, multiethnic, community-based cohort study of women and the menopausal transition. In: Lobo, RA.; Kelsey, J.; Marcus, R.; Lobo, AR., editors. Menopause: Biology and Pathology. New York: Academic Press; 2000. p. 175-88.

24. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003; 107:499–511. [PubMed: 12551878]

25. England BG, Parsons GH, Possley RM, McConnell DS, Midgley AR. Ultrasensitive semiautomated chemiluminescent immunoassay for estradiol. Clin Chem. 2002; 48:1584–1586. [PubMed: 12194939]

26. Ferris B. Epidemiology Standardization Project (American Thoracic Society). Am Rev Respir Dis. 1978; 118:1–120. [PubMed: 742764]

27. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. Applied Psychological Measurement. 1977; 1:385–401.

28. Ainsworth BE, Sternfeld B, Richardson MT, Jackson K. Evaluation of the kaiser physical activity survey in women. Med Sci Sports Exerc. 2000; 32:1327–1338. [PubMed: 10912901]

29. Singer, J.; Willett, J. Applied longitudinal analysis: Modeling change and event occurrence. New York: Oxford University; 2003.

30. Thurston R, Christie I, Matthews K. Hot flashes and cardiac vagal control: A link to cardiovascular risk? Menopause. 2010; 17:456–461. [PubMed: 20042892]

31. van Westerloo DJ, Giebelen IA, Meijers JC, et al. Vagus nerve stimulation inhibits activation of coagulation and fibrinolysis during endotoxemia in rats. J Thromb Haemost. 2006; 4:1997–2002. [PubMed: 16805873]

32. Tuomikoski P, Ebert P, Groop PH, et al. Evidence for a role of hot flushes in vascular function in recently postmenopausal women. Obstet Gynecol. 2009; 113:902–908. [PubMed: 19305337]

33. Saigo M, Hsue PY, Waters DD. Role of thrombotic and fibrinolytic factors in acute coronary syndromes. Prog Cardiovasc Dis. 2004; 46:524–538. [PubMed: 15224258]

34. Pradhan AD, LaCroix AZ, Langer RD, et al. Tissue plasminogen activator antigen and D-dimer as markers for atherothrombotic risk among healthy postmenopausal women. Circulation. 2004; 110:292–300. [PubMed: 15238458]

35. Sowers MR, Matthews KA, Jannausch M, et al. Hemostatic factors and estrogen during the menopausal transition. J Clin Endocrinol Metab. 2005; 90:5942–5948. [PubMed: 16105968]

36. Gast GC, Pop VJ, Samsioe GN, et al. Vasomotor menopausal symptoms are associated with increased risk of coronary heart disease. Menopause. 2011; 18:146–151. [PubMed: 21127438]

37. Thurston RC, Sowers MR, Sutton-Tyrrell K, et al. Abdominal adiposity and hot flashes among midlife women. Menopause. 2008; 15:429–434. [PubMed: 18204407]

38. Thurston RC, Blumenthal JA, Babyak MA, Sherwood A. The association between hot flashes, sleep complaints, and psychological functioning among healthy menopausal women. Int J Behav Med. 2006; 13:163–172. [PubMed: 16712434]

Table 1

Baseline sample characteristics

Age, years, mean±SD	45.84 ± 2.68
Race/ethnicity, %(n)	
African American	27.6 (882)
Chinese	7.7 (247)
Hispanic	8.5 (271)
Japanese	8.7 (280)
White	47.5 (1519)
Education, %(n)	
≤High school	24.6 (780)
Some College	31.9 (1010)
College graduate/postgraduate degree	43.5 (1378)
Menopausal status, %(n)	
Premenopausal	53.9 (1686)
Early peri-menopausal	46.1 (1439)
Parity, %(n)	
0 children	17.2 (547)
≥1 children	82.8 (2635)
Body Mass Index, kg/m^2, mean±SD	28.2 ± 7.2
Current smoker, %(n)	16.7 (535)
Current alcohol consumption, %(n)	
None	49.5 (1580)
Any	50.5 (1610)
Total physical activity score, mean±SD[a]	7.7 ± 1.8
Health history, %(n)	
Angina/heart medication use	1.8 (57)
Hypertension/anti-hypertension use	19.7 (619)
Psychotropic medication use	9.7 (308)
Steroid medication use	1.7(53)
Pain medication use	26.0 (827)
Diabetes/medication use	4.8 (149)
Frequency of hot flashes, %(n)	
None	73.7 (2350)
1–5 Days	19.0 (604)
≥6 Days	7.3 (233)
Frequency of night sweats, %(n)	
None	71.0 (2262)
1–5 Days	22.6 (719)
≥6 Days	6.4 (205)
Depressive symptoms (CES-D score), Median (IQR)	8.0 (3, 15)
Estradiol, pg/ml, Median (IQR)	55.3 (33.2, 88.7)

hs-CRP, mg/l, Median (IQR)	1.3 (0.5, 3.4)
PAI-1, ng/ml, Median (IQR)	20.5 (12.1, 33.8)
tPA-ag, ng/ml, Median (IQR)	7.3 (5.2, 9.7)
FVIIc, %, Median (IQR)	115.0 (98.0, 133.0)
Fibrinogen, mg/dl, Mean±SD	289.1 ± 60.8

[a]Possible range: 3–14

CES-D: Center for Epidemiologic Studies for Depression Scale; hs-CRP:high senstivity C-reactive protein; PAI-1:plasminogen activator inhibitor-1, tPA-ag:tissue plasminogen activator antigen, FVIIc:factor VIIc

Table 2

Univariate associations between study outcomes and covariates at baseline

	hs-CRP[a]	tPA-ag[a]	PAI-1[a]	FVIIc[a]	Fibrinogen
	β(SE)	β(SE)	β(SE)	β(SE)	β(SE)
Age, Yr	0.01(0.01)	0.01(0.003)[c]	0.01(0.01)	0.01(0.001)[b]	0.65(0.41)
Race					
African American	0.42(0.05)[b]	0.17(0.02)[b]	0.18(0.03)[b]	−0.04(0.01)[c]	18.90(2.56)[b]
Chinese	−0.53(0.08)[b]	−0.10(0.03)[c]	−0.08(0.05)	−0.04(0.02)[e]	−15.33(4.14)[c]
Hispanic	0.43(0.08)[b]	0.21(0.03)[b]	0.40(0.05)[b]	0.04(0.02)[e]	−2.37(3.98)
Japanese	−1.00(0.08)[b]	−0.07(0.03)[d]	−0.11(0.05)[e]	−0.03(0.02)[f]	−33.97(3.89)[b]
White	---	---	---	---	---
Menopausal status					
Premenopausal	---	----	---	---	---
Early peri-menopausal	0.08(0.04)[f]	0.04(0.02)[e]	0.05(0.03)[f]	0.02(0.01)[d]	6.88(2.23)[d]
Parity					
0 Live children	−0.19(0.06)[d]	−0.05(0.02)[e]	−0.06(0.04)[f]	−0.01(0.01)	1.77(2.93)
≥1 Live children	---	--	----	---	----
Education					
≤High school/Some College	0.30(0.04)[c]	0.12(0.02)[b]	0.19(0.03)[b]	0.03(0.01)[c]	8.47(2.22)[b]
College/postgraduate	---	---	-----	----	----
Current smoker					
No	−0.19(0.06)[d]	−0.10(0.02)[b]	−0.11(0.04)[d]	−0.001(0.01)	15.50(2.95)[b]
Yes	---	----	---	---	---
Hot flashes					
None	−0.43(0.09)[b]	−0.15(0.03)[b]	−0.27(0.05)[b]	−0.05(0.02)[e]	16.59(4.28)[b]
1–5 Days	−0.20(0.10)[f]	0.004(0.03)	−0.05(0.06)	−0.02(0.02)	−9.33(4.81)[e]
≥6 Days	---	---	---	---	---
Night sweats					
None	−0.44(0.10)[b]	−0.19(0.03)[b]	−0.33(0.06)[b]	−0.06(0.02)[d]	14.84(4.57)[c]

	hs-CRP[a]	tPA-ag[a]	PAI-1[a]	FVIIc[a]	Fibrinogen
	β(SE)	β(SE)	β(SE)	β(SE)	β(SE)
1–5 Days	−0.27(0.10)[d]	−0.13(0.03)[c]	−0.25(0.06)[b]	−0.04(0.02)[e]	−8.50(4.96)[f]
≥6 Days	---	---	---	---	---
Alcohol consumption					
None	0.16(0.04)[c]	0.03(0.02)[e]	0.12(0.03)[b]	0.04(0.01)[b]	12.46(2.19)[b]
Any	---	---	----	---	---
BMI	0.10(0.003)[b]	0.03(0.001)[b]	0.05(0.001)[b]	0.01(0.001)[b]	3.40(0.14)[b]
Physical activity score	−0.12(0.01)[b]	−0.06(0.004)[b]	−0.08(0.01)[b]	−0.01(0.002)[b]	−6.13(0.62)[b]
Depressive symptoms	0.01(0.002)[b]	0.003(0.001)[c]	0.01(0.001)[b]	0.002(0.0004)[c]	0.40(0.11)[c]
Serum Estradiol (pg/mL)[a]	−0.08(0.03)[d]	−0.06(0.01)[b]	−0.11(0.02)[b]	−0.02(0.006)[b]	−1.79(1.44)

[a] log transformed for analysis

[b] p<0.0001,

[c] p<0.001,

[d] p<0.01,

[e] p<0.05,

[f] p<0.10

hs-CRP: high senstivity C-reactive protein; PAI-1:plasminogen activator inhibitor-1, tPA-ag:tissue plasminogen activator antigen, FVIIc:factor VIIc

Menopause. Author manuscript; available in PMC 2012 October 1.

Table 3

Age and site-adjusted associations between frequency of hot flashes and night sweats and inflammatory/hemostatic markers

	hs-CRP[a] % change (95% CI)	**tPA-ag[a] % change (95% CI)**	**PAI-1[a] % change (95% CI)**	**FVIIc[a] % change (95% CI)**	**Fibrinogen β (95% CI)**
Hot Flashes[g]					
None[h]	---	---	---	---	---
1–5 days	1.59 (−1.79, 5.09)	4.74 (3.08, 6.42)[b]	3.79 (0.62, 7.06)[e]	1.59(0.63, 2.56)[d]	1.88(−0.46, 4.22)
6+ days	5.22 (0.65, 10.00)[e]	5.12 (2.99, 7.31)[b]	4.34 (0.26, 8.58)[e]	3.23(1.95, 4.53)[b]	5.64(2.54, 8.75)[c]
P value[i]	0.03	<0.0001	0.01	<0.0001	0.0005
Night Sweats[g]					
None[h]	---	---	---	---	---
1–5 days	4.72 (1.24, 8.32)[d]	1.32 (−0.28, 2.94)	4.24 (1.06, 7.51)[d]	0.99(0.05, 1.94)[e]	1.38(−0.94, 3.69)
6+ days	2.36 (−2.79, 7.77)	2.83 (0.43, 5.28)[e]	5.50 (0.76, 10.46)[e]	2.89(1.43, 4.37)[b]	4.30(0.74, 7.85)[e]
P value[i]	0.07	0.01	0.004	<0.0001	0.02

hs-CRP: high senstivity C-reactive protein; PAI-1:plasminogen activator inhibitor-1, tPA-ag:tissue plasminogen activator antigen, FVIIc:factor VIIc

[a] hs-CRP, tPA-ag, PAI-1, FVIIc log transformed. Regression coefficients back transformed using (100*(exp$^{(beta)}$-1) to calculate % of change in the outcome associated with a one unit change in the predictor and 95%CI

[b] p<0.0001,

[c] p<0.001,

[d] p<0.01,

[e] p<0.05,

[f] p<0.10

[g] Frequency in past two weeks

[h] Reference group

[i] Linear trend p value

Table 4

Covariate-adjusted associations between frequency of hot flashes and night sweats and inflammatory/hemostatic markers

	hs-CRP[a] % change (95% CI)	tPA-ag[a] % change (95% CI)	PAI-1[a] % change (95% CI)	FVIIc[a] % change (95% CI)	Fibrinogen β (95% CI)
Hot Flashes[g]					
None[h]	---	---	---	---	---
1–5 days	0.11 (−3.16, 3.48)	3.88 (2.22, 5.58)[b]	2.72 (−0.45, 5.98)	0.91(−0.07, 1.90)[f]	0.22(−2.17, 2.61)
6+ days	2.57 (−1.83, 7.17)	4.11 (1.95, 6.32)[c]	3.71 (−0.42, 8.01)	2.13(0.80, 3.47)[d]	1.72(−1.48, 4.92)
P value[i]	0.3	<0.0001	0.05	0.001	0.4
Night Sweats[g]					
None[h]	---	---	---	---	---
1–5 days	2.58 (−0.75, 6.02)	0.64 (−0.96, 2.26)	3.50 (0.34, 6.77)[e]	0.62(−0.34, 1.60)	0.78(−1.57, 3.13)
6+ days	−0.46 (−5.36, 4.68)	1.62 (−0.78, 4.09)	4.33 (−0.41, 9.30)[f]	2.11(0.61, 3.63)[d]	0.76(−2.86, 4.39)
P value[i]	0.6	0.2	0.02	0.007	0.5

Adjusted for age, site, race, education, menopausal status, parity, alcohol consumption, physical activity, smoking status, CES-D score, BMI, CVD status/medication use; psychotropic medication use; steroid/pain medication use; diabetes status/medication use. hs-CRP: high senstivity C-reactive protein; PAI-1:plasminogen activator inhibitor-1, tPA-ag:tissue plasminogen activator antigen, FVIIc:factor VIIc

[a] CRP-hs, tPA-ag, PAI-1, FVIIc log transformed. Regression coefficients back transformed using (100*(exp$^{(beta)}$-1) to calculate % of change in the outcome associated with a one unit change in the predictor and 95%CI

[b] p<0.0001,

[c] p<0.001,

[d] p<0.01,

[e] p<0.05,

[f] p<0.10

[g] Frequency in past two weeks

[h] Reference group

[i] Linear trend p value