Trajectories of Vasomotor Symptoms and Carotid Intima Media Thickness in the Study of Women’s Health Across the Nation

Rebecca C. Thurston, PhD; Samar R. El Khoudary, PhD; Ping Guo Tepper, PhD; Elizabeth A. Jackson, MD; Hadine Joffe, MD, MS; Hsiang-Yu Chen, MS; Karen A. Matthews, PhD

Background and Purpose—Emerging work has linked menopausal vasomotor symptoms (VMS) to subclinical cardiovascular disease (CVD) among women. However, VMS are dynamic over time. No studies have considered how temporal patterns of VMS may relate to subclinical CVD. We tested how temporal patterns of VMS assessed over 13 years were related to carotid intima media thickness (IMT) among midlife women.

Methods—The Study of Women’s Health Across the Nation is a longitudinal cohort study of midlife women. Eight hundred and eleven white, black, Hispanic, and Chinese participants with a well-characterized final menstrual period completed measures of VMS, a blood draw, and physical measures approximately annually for 13 years. Women underwent a carotid artery ultrasound at study visit 12.

Results—Four trajectories of VMS were identified by trajectory analysis (consistently high, early-onset, late-onset, persistently low VMS) and tested in relation to carotid indices in linear regression models. Results indicated that women with early-onset VMS had both greater mean IMT (beta, b [standard error, SE]=0.03 [0.01], \(P=0.03\)) and greater maximal IMT (b [SE]=0.04 [0.01], \(P=0.008\)) than women with consistently low VMS, adjusting for demographics and CVD risk factors.

Conclusions—This is the first study to test trajectories of VMS in relation to subclinical CVD. Women with VMS early in the menopause transition had higher mean IMT and maximal IMT than those with consistently low VMS across the transition. Associations were not accounted for by demographic factors nor by CVD risk factors. Results can signal to women in need of early CVD risk reduction. (Stroke. 2016;47:12-17. DOI: 10.1161/STROKEAHA.115.010600.)

Key Words: atherosclerosis ■ epidemiology ■ menopause ■ sex ■ women

Cardiovascular disease (CVD) is the leading cause of death among women, with its incidence increasing post-menopausally. An understanding of how menopause-related factors may be related to CVD risk among women has long been of interest. Vasomotor symptoms (VMS) are the classic menopausal symptom, experienced by over 70% of women. Although VMS are known to be associated with poorer quality of life, VMS have been linked to physical health outcomes, including CVD risk. Multiple studies show relations between VMS and subclinical CVD and CVD risk factors. However, the literature is not entirely consistent, and further understanding of VMS–CVD risk relations is warranted.

Although most women will experience VMS during the menopause transition, the patterns of VMS vary dramatically. Some women experience VMS early when they are still menstruating; others only postmenopausally; and still others have VMS for decades. These variations may reflect different etiologies of VMS with varying physiological sequelae. Preliminary work indicates that the timing of VMS may be important to CVD risk. However, these studies were modest in size, had few assessments, or asked women to recall their VMS occurring years earlier. They were not adequately designed to address variations in trajectories of VMS over the transition. To do so, a large cohort study with prospective assessments of VMS is needed.

The Study of Women’s Health Across the Nation (SWAN) is a large longitudinal cohort study of women transitioning through the menopause. Women were recruited in the pre- or early perimenopause and have been followed for over a decade. VMS have been assessed approximately annually, making SWAN an ideal cohort to prospectively characterize trajectories of VMS over the menopause transition. At visit 12, participants underwent a carotid ultrasound to assess carotid artery IMT, a well-validated subclinical CVD index predictive of later clinical CVD. We tested whether different trajectories

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of VMS over the menopause transition were related to later IMT and considered whether associations were accounted for by standard CVD risk factors.

Methods

SWAN is a prospective cohort study of women conducted at 7 sites: Boston; Chicago; the Detroit area; Los Angeles; Newark, New Jersey; Pittsburgh, Pennsylvania; and Oakland, California.\(^1\) Each site recruited white women and one additional racial/ethnic group. The 6 sites participating in carotid measurements recruited white women plus black (Pittsburgh, Chicago, Michigan, Boston), Chinese (Oklahoma), or Hispanic (Newark) women. Women were recruited from lists of names or household addresses, and select sites supplemented primary sampling frames to obtain adequate numbers of racial/ethnic minority women. Baseline eligibility criteria included being aged 42 to 52 years, having a uterus and ≥1 ovary, not being pregnant or lactating, not using oral contraceptives/hormone therapy (HT), and having ≥1 menstrual cycle in the prior 3 months. Fifty-one percent (N=3302) of eligible women enrolled. Annual clinic assessments began in 1996 to 1997. Ultrasound data were collected at visit 12. SWAN protocols were approved by the institutional review boards at each site, and each participant provided written informed consent. This study investigated associations between VMS trajectories from baseline through the 12th annual SWAN visit and carotid outcomes at visit 12. Of the 1512 women who had valid carotid data, 637 women were excluded from analyses because of a lack of a discernible final menstrual period (FMP; because of surgery or hormone use) or <3 visits with VMS data (required to construct trajectories). An additional 64 women were excluded because of a history of stroke or myocardial infarction. Eight hundred and eleven women were included in analyses. Women excluded differed from women included in that they were less often Chinese and more often black or white (P<0.001) and, consistent with the CVD exclusion, had a poorer risk factor profile (higher body mass index [BMI], higher systolic blood pressure, lower high-density lipoprotein, higher triglycerides, higher homeostatic model assessment, more often diabetic, and more often taking cardiovascular medications, P≤0.05).

Vasomotor Symptoms

VMS were assessed via questionnaire at each of 12 annual visits. Women responded to 2 questions which asked separately how often they experienced (1) hot flashes and (2) night sweats in the past 2 weeks (not at all, 1–5 days, 6–8 days, 9–13 days, every day). For each visit, women were categorized as having VMS if they reported any hot flashes or night sweats at that visit. Patterns of experiencing VMS (trajectories) across visits were identified (see data analyses).

Ultrasound Measures

At each site, centrally trained and certified sonographers obtained carotid ultrasound images using a Terason 3000 Ultrasound System (Teratech Corp, Burlington, MA) equipped with a variable frequency 5 to 12 MHz linear array transducer. Two digitized images were obtained of each of the left and right distal common carotid artery. From each of these 4 images, using the AMS semiautomated edge detection software, near and far wall common carotid artery IMT measures were obtained by electronically tracing the lumen–intima interface and the media–adventitia interface across a 1-cm segment proximal to the carotid bulb; one measurement was generated for each pixel over the area, for a total of ≥140 measures for each segment. The average and maximal values for these measures were recorded, with the mean of the average and maximal readings of all 4 images used in analyses. Common carotid artery interadventitial diameter was measured directly as the distance from the adventitial–medial interface on the near wall to the medial–adventitial interface on the far wall at end-diastole across the same common carotid artery segments used for IMT measurement. Images were read centrally at the SWAN Ultrasound Reading Center (University of Pittsburgh Ultrasound Research Laboratory). Technicians at study sites were trained by the University of Pittsburgh Ultrasound Research Laboratory and monitored during the study for reliability. Reproducibility was excellent (intraclass correlation coefficients ≥0.77 between sonographers) and intraclass correlation coefficients ≥0.90 (between readers).\(^1^\)

Covariates

At baseline, race/ethnicity was reported and education assessed (high school, some college/vocational, 2 college). Other covariates were taken from visit 12 (concurrent with the carotid ultrasound). Age, smoking (current versus past/never), anxiety, and medication use were derived from questionnaires/interviews. Use of cardiovascular medications (blood pressure lowering, lipid-lowering, blood thinning) was classified. Height and weight were measured and BMI calculated (kg/m\(^2\)). Blood pressure was averaged from 2 seated measurements, and the measure with the strongest association with the outcome included as a covariate (systolic). Women were considered diabetic if they reported diabetes mellitus or had fasting glucose levels ≥126 mg/dL or reported any use of insulin/anti-diabetic agents at ≥70% of the visits or for ≥3 consecutive visits.

Phlebotomy was performed after overnight fast within 90 days of the annual visit. Blood was separated, frozen (−80°C), and sent to the University of Michigan Pathology Laboratory, CLIA-certified, and accredited by the College of American Pathologists. Measurements were performed on a Siemens ADVIA 2400 automated chemistry analyzer utilizing Siemens ADVIA chemistry system reagents. Glucose was measured using a 2-step enzymatic reaction and serum insulin measured using radioimmunoassay. Homeostatic model assessment was calculated ([insulin×glucose]/22.5). Lipid fractions were determined from EDTA-treated plasma.

Data Analyses

Group-based growth trajectory modeling\(^1^\) was used (Proc Traj in SAS) to identify trajectories of VMS over time. Preliminary analyses in the full SWAN cohort identified 4 distinct trajectories.\(^1^\) For the present analyses, VMS trajectories were reidentified among participants who had a carotid ultrasound, a discernible FMP, and ≥3 visits with VMS data. Visits in which women reported HT use were dropped. Trajectories were adjusted for study site and age. The time scale was anchored to the FMP, with a maximum time before and after the FMP of 8.74 and 10.41 years, respectively. Trajectories were based on model fit statistics and scientific plausibility; 4 VMS trajectories were identified that each woman occupied based on her highest posterior (predicted) probability

The 4 VMS trajectories were next linked to carotid outcomes.

Associations between VMS trajectories and outcomes were estimated in linear regression adjusted for age, race/ethnicity, education, and site and covariates associated with outcomes at P<0.05. IMT, homeostatic model assessment, and triglyceride values were natural log-transformed. Interactions between VMS trajectories and race/ethnicity and BMI were examined as cross product terms. In sensitivity analyses, 24 women reporting using medications that could impact VMS (selective estrogen receptor modulators, aromatase inhibitors, selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors, gabapentin) were excluded. Residual analysis and diagnostic plots were used to verify model assumptions. Analyses were performed with SAS v9.2 (SAS, Cary, NC).

Results

At visit 12, the participants were on average 59 years old, overweight, non-smoking, and normotensive (Table 1). Four trajectories of VMS were identified: (1) consistently low probability of having VMS, (2) consistently high probability of having VMS, (3) VMS early in the transition that decreased shortly after the FMP, and (4) VMS that developed largely after the FMP (Figure), similar to the full SWAN cohort.\(^1^\) Black women and women with lower education were most likely to have consistently high VMS, and Non-Hispanic
white, Chinese, and more highly educated women were more likely to have consistently low VMS (Table 1). Women with consistently high VMS and early-onset VMS also had a more adverse CVD risk factor profile.

We next considered trajectories of VMS in relation to IMT. Women with consistently high VMS or early-onset VMS had higher IMT than women with consistently low VMS (Table 2). Early-onset VMS remained associated with higher mean and maximal IMT when adjusting for demographic and CVD risk factors (Table 3).

We next tested for interactions between VMS trajectory group and race/ethnicity or BMI in relation to IMT. None of these interactions were significant ($P'>0.05$). We also considered adventitial diameter given its association with vascular remodeling and sensitivity to reproductive hormones. Although women with early-onset VMS had higher adventitial diameter ($B$ [SE]=0.14 [0.07], $P=0.04$ versus consistently low VMS) in minimally adjusted models, relations did not persist when additionally adjusting for CVD risk factors ($B$ [SE]=0.06 [0.07], $P=0.40$). Finally, we conducted analyses excluding women taking medications that might impact VMS (selective estrogen receptor modulators, aromatase inhibitors, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, gabapentin). Findings were unchanged (data not shown).

**Discussion**

This is the first study to examine trajectories of VMS over the course of the menopause transition in relation to subclinical CVD. SWAN is uniquely able to address this question, given the repeated prospective assessment of VMS over a decade, the well-characterized cohort, and the measurement of IMT. Although women with persistent VMS over the menopause transition had the worst CVD risk factor profile, it was the women with early-onset VMS (VMS occurring up to a decade before the FMP and declining several years after the FMP) who had the highest IMT. Associations were not accounted for by demographics or by CVD risk factors.

A notable aspect of VMS is that they are dynamic, changing dramatically as women progress through the menopause.
Emerging work suggests that VMS may be related to higher subclinical CVD cross-sectionally. However, given the dynamic nature of VMS, a single assessment is inadequate to characterize a woman’s true burden of VMS. The few studies that have considered VMS over time in relation to CVD risk generally show more persistent VMS associated with subclinical CVD. However, these studies had few assessments, limited sample sizes, lack of ethnic diversity, or failed to capture the early transition. The Women’s Health Initiative reports have shown complex relations between VMS and CVD risk over time, yet analyses were limited by exclusion of women with high burden of VMS or reliance upon women recalling their VMS up to a decade earlier, the accuracy of which is likely low. Thus, the relation of VMS over time to subclinical CVD has not been rigorously tested.

As most women get VMS, refining the understanding of what types of VMS are most relevant to cardiovascular health is warranted. Like other research on reproductive factors and midlife women’s cardiovascular health, timing matters. These data indicate that early-occurring VMS (starting up to a decade before the FMP) seem to have specific implications for a woman’s cardiovascular health. The magnitude of the effects observed here is clinically significant, comparable to >4 years of aging in the present cohort. Prior work has shown that some women start experiencing VMS early in the transition (often when they are still cycling), particularly black or obese women. However, the present results controlled for race/ethnicity and BMI. Other work has indicated that VMS are associated with a more adverse adipokine profile, reduced cardiac vagal control, more adverse inflammatory or hemostatic profile, and poorer endothelial function. A closer examination of mechanisms linking early-onset VMS to CVD risk is warranted.

This study had several limitations. VMS were self-reported and recalled over the prior 2 weeks, reports which may contain more error than diaries or physiological VMS indices. To characterize VMS trajectories relative to the FMP, women without a discernable FMP because of HT use, hysterectomy, or oophorectomy were excluded. Results may not generalize to these women. Other conditions relevant to development of atherosclerosis (eg, chronic obstructive pulmonary disease, autoimmune disorders) were not rigorously assessed. Aspects of vessel morphology linked to CVD risk (ie, dolichocarotids) were not systematically assessed and should be considered in future work. Further, IMT was assessed once at visit 12; thus, trajectories of IMT could not be characterized. IMT was assessed only at the common carotid artery and not at other sites. This approach is consistent with guidelines because IMT at the common carotid artery is most reliably measured and predictive of events, yet atherosclerosis at other sites would not have been captured here.

SWAN has multiple strengths, including it being a large cohort of women who have been assessed prospectively and repeatedly over the course of the menopause transition. VMS are measured approximately annually ≤13 times, allowing the unique opportunity to characterize VMS trajectories. The FMP, menopausal stage, and HT are rigorously assessed, allowing anchoring of VMS trajectories relative to the FMP.

| Table 2. Unadjusted IMT by Vasomotor Symptom Group |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Consistently Low | Early Onset | Late Onset | Consistently High | Overall P Value |
| IMT, M (SD), mm | 0.77 (0.11) | 0.82 (0.12)* | 0.77 (0.11) | 0.80 (0.12)* | 0.0001 |
| Maximal IMT, M (SD), mm | 0.90 (0.13) | 0.96 (0.15)* | 0.90 (0.13) | 0.94 (0.14)* | <0.0001 |

IMT indicates intima media thickness; and M, mean. *P<0.05 relative to consistently low vasomotor symptoms.

| Table 3. Multivariable Associations Between Vasomotor Symptom (VMS) Trajectories and IMT |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Mean IMT | Maximum IMT |
| β (SE) | P Value | β (SE) | P Value |
| Model 1 VMS trajectory | Consistently low | ... | ... |
| Early onset | −0.01 (0.01) | 0.50 | −0.01 (0.01) | 0.50 |
| Late onset | 0.04 (0.01) | 0.004 | 0.05 (0.01) | 0.0006 |
| Consistently high | 0.01 (0.01) | 0.30 | 0.02 (0.01) | 0.20 |
| Model 2 VMS trajectory | Consistently low | ... | ... |
| Early onset | 0.03 (0.01) | 0.03 | 0.04 (0.01) | 0.008 |
| Late onset | −0.002 (0.01) | 0.90 | −0.001 (0.01) | 0.90 |
| Consistently high | −0.001 (0.01) | 0.90 | 0.002 (0.01) | 0.90 |

Model 1 covariates: site, age, ethnicity, education. Model 2 covariates: Adjusted for site, age, ethnicity, education, body mass index, systolic blood pressure, high-density lipoproteins; low-density lipoproteins, triglycerides, homeostatic model assessment, smoking status, diabetes mellitus, anxiety, use of cardiovascular medications. IMT indicates intima media thickness; and VMS, vasomotor symptoms.
and reducing confounding effects of HT. SWAN included a group of ethnically diverse women. Finally, carotid ultrasound were included in this large cohort, and multiple CVD risk factors were assessed repeatedly and prospectively.

This study was the first to examine trajectories of VMS over the menopause transition in relation to subclinical CVD, showing that women with VMS beginning a decade before the FMP had the highest IMT. Associations were not accounted for by CVD risk factors. Findings underscore that work investigating relations between VMS and CVD risk should consider the timing of VMS. Findings on VMS and CVD may ultimately be used to further understand the pathophysiology of CVD in women, as well as to assist in CVD risk prediction among middle women.

Appendix


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Study of Women’s Health Across the Nation (SWAN) における
血管運動症状の軌跡と頸動脈内膜中膜複合体厚

Trajectories of Vasomotor Symptoms and Carotid Intima Media Thickness in the Study of
Women’s Health Across the Nation

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脳卒中の予防における血管運動症状（VMS）と潜在性の心血管疾患（CVD）との関連が明らかになっている。しかし、VMSは経時的に
変化するものである。VMSの時間的パターンが潜在性のCVDとどのように関連しているかを検討した研究はこれまで行われていない。本研究では、13年間におけるVMSの時間的パターンが中年女性における頸動脈内膜中膜複合体厚（IMT）とどのように関連するかを検討した。

方法：Study of Women’s Health Across the Nation (SWAN) は中年女性を対象とした緩断的コホート研究である。最終の月経期間が正確に判明している白人、黒人、hisパニック系、中国系の参加者811名において、VMSの評価、採血、身体測定を約年1回、13年間にわたって実施した。12回目の来院時に頸動脈超音波検査を施行した。

結果：軌道解析により4種類のVMSの軌跡（持続高密度型、早発型、遅発型、持続低密度型）を特定し、線形回帰モデルでIMTとの関連性を検討した。その結果を入力統計学的特徴およびCVDの危険因子で調整すると、早発型VMSの女性では平均IMT [β（標準誤差：SE）= 0.03（0.01），P = 0.03] および最大IMT [β（SE）= 0.04（0.01），P = 0.008] ともに持続低密度VMSの女性よりも高いことが示された。

結論：本研究はVMSの軌跡と潜在性CVDとの関連性を検討した最初の研究である。早期の初期にVMSが見られた女性では、更年期を通じてVMSが一貫して低度であった女性と比較して平均IMTおよび最大IMTが高値であった。この関連は、入力統計学的因子またはCVDの危険因子によって説明できなかった。本研究の結果は、早期のCVDリスク低減が必要な女性を特定するのに役立つ可能性がある。

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表2 血管運動症状群別の無調整IMT

<table>
<thead>
<tr>
<th></th>
<th>持続低密度型</th>
<th>早発型</th>
<th>遅発型</th>
<th>持続高密度型</th>
<th>全体のP値</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT (M(SD)) mm</td>
<td>0.77 (0.11)</td>
<td>0.82 (0.12)*</td>
<td>0.77 (0.11)</td>
<td>0.80 (0.12)*</td>
<td>0.0001</td>
</tr>
<tr>
<td>最高 (M(SD)) mm</td>
<td>0.90 (0.13)</td>
<td>0.96 (0.15)</td>
<td>0.90 (0.13)</td>
<td>0.94 (0.14)*</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

IMT：頸動脈内膜中膜複合体厚，M：平均値
*P<0.05，血管運動症状が持続低密度型との比較による。

図1 更年期における血管運動症状（VMS）の軌跡（811例）。
試験実施時および年齢で調整。