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

Downloaded from http://ahajournals.org by on March 4, 2022

Cardiovascular disease (CVD) is the leading cause of death among women, with its incidence increasing postmenopausally.[1] 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.[2] Although VMS are known to be associated with poorer quality of life,[3] VMS have been linked to physical health outcomes, including CVD risk. Multiple studies show relations between VMS and subclinical CVD[4–7] and CVD risk factors.[8–10] However, the literature is not entirely consistent,[11,12] 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.[13,14] Some women experience VMS early when they are still menstruating; others only postmenopausally; and still others have VMS for decades.[14] 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.[5,6,12] 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.[15] We tested whether different trajectories

Received January 26, 2015; final revision received October 13, 2015; accepted October 15, 2015.

From the Department of Psychiatry, University of Pittsburgh School of Medicine (R.C.T., K.A.M.), Department of Epidemiology, University of Pittsburgh Graduate School of Public Health (R.C.T., S.R.E.K., P.G.T., H.-Y.C., K.A.M.), PA; Department of Medicine, Division of Cardiovascular Medicine, University of Michigan School of Medicine, Ann Arbor (E.A.J.); and Department of Psychiatry, Brigham and Women's Hospital and Dana Farber Cancer Institute, Boston, MA (H.J.).

Correspondence to Rebecca C. Thurston, PhD, 3811 O'Hara St, Pittsburgh, PA 15213. E-mail thurstonrc@upmc.edu

© 2015 American Heart Association, Inc.

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.115.010600**

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.[16] 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 (Oakland), 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 discernable 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 trigycerides, higher homeostatic model assessment, more often diabetic, and more often taking cardiovascular medications, P's<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 t3000 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,[17] 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]).[18]

Covariates

At baseline, race/ethnicity was reported and education assessed (high school, some college/vocational, ≥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[19] was used (Proc Traj in SAS) to identify trajectories of VMS over time. Preliminary analyses in the full SWAN cohort identified 4 distinct trajectories.[14] 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 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 norepinepherine 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, nonsmoking, 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.[14] Black women and women with lower education were most likely to have consistently high VMS, and Non-Hispanic

Downloaded from http://ahajournals.org by on March 4, 2022

Table 1. Characteristics of Women by Vasomotor Symptom Trajectory Group

	Consistently Low	Early Onset	Late Onset	Consistently High	Overall *P* Value
Age, y, mean±SD	59.8±2.6	59.7±2.6	59.2±2.6	59.5±2.8	0.06
Race, n (%)					<0.0001
Black	30(13.2)	43(32.1)	67(29.8)	98(43.8)	
White	125(54.8)	63(47.0)	116(51.6)	86(38.4)	
Chinese	60(26.3)	22(16.4)	33(14.7)	22(9.8)	
Hispanic	13(5.7)	6(4.5)	9(4.0)	18(8.0)	
Education, n (%)					<0.0001
High school	43(19.3)	29(21.8)	45(20.1)	69(30.9)	
Some college/vocational	51(22.9)	39(29.3)	67(29.9)	86(38.6)	
≥College	129(57.9)	65(48.9)	112(50.0)	68(30.5)	
BMI, kg/m^2, mean±SD	28.3±7.3	30.5±7.4*	28.0±6.2	31.3±7.7*	<0.0001
SBP, mm Hg, mean±SD	117.9±15.5	124.5±18.5*	119.0±15.7	125.2±19.0*	<0.0001
DBP, mm Hg, mean±SD	73.0±9.8	75.6±11.1*	72.8±10.1	74.5±9.7*	0.03
HDL, mg/dL, mean±SD	64.6±17.2	60.3±15.0*	64.5±16.7	60.0±14.2*	0.002
LDL, mg/dL, mean±SD	123.9±34.6	126.4±29.5	128.7±36.6	123.3±35.6	0.40
Triglycerides, mg/dL, median (Q1,Q3)	91.5 (71.0, 125.5)	101.0 (76.0, 145.0)*	87.0 (69.0, 126.0)	103.0 (76.0, 140.0)*	0.03
HOMA index, median (Q1,Q3)	1.7 (1.1, 3.4)	2.6 (1.5, 4.0)*	1.7 (1.1, 3.0)	2.6 (1.4, 4.2)*	<0.0001
Anxiety, median (Q1,Q3)	1.0 (0.0, 3.0)	2.0 (0.0, 4.0)	1.0 (0.0, 3.0)	3.0 (1.0, 6.0)*	<0.0001
Smoker, n (%)	11 (4.9)	9 (6.8)	15 (6.7)	30 (13.6)	0.004
Diabetes mellitus, n(%)	22 (9.7)	15 (11.2)	7 (3.1)	39 (17.4)	<0.0001
Cardiovascular medication use, n (%)†	103 (45.4)	75 (56.4)	103 (46.4)	144 (64.6)	<0.0001

BMI indicates body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA, homeostatic model assessment; LDL, low-density lipoprotein; Q, quartile; SBP, systolic blood pressure; and SD, standard deviation.

*Significant (P<0.05) difference compared with consistently low VMS.

†Ever use during the study; Cardiovascular medications: antihypertensive, lipid lowering, or anticoagulants.

Downloaded from http://ahajournals.org by on March 4, 2022

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's>0.05). We also considered adventitial diameter given its association with vascular remodeling[20] and sensitivity to reproductive hormones.[21] 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 norepinepherine reuptake inhibitors, gabapentin). Findings were unchanged (data not shown).

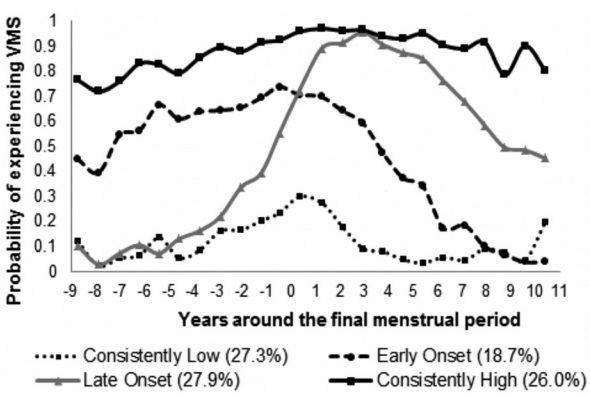

Figure. Trajectories of vasomotor symptoms (VMS) over the menopause transition (N=811). Adjusted for study site and age.

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.

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.

Emerging work suggests that VMS may be related to higher subclinical CVD cross-sectionally.[4,5,7,22] 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.[5,6] However, these studies had few assessments,[5] limited sample sizes,[5,6] lack of ethnic diversity,[6] or failed to capture the early transition.[6] The Women's Health Initiative reports have shown complex relations between VMS and CVD risk over time,[12,23] 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,[24] 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.[25] However, the present results controlled for race/ethnicity and BMI. Other work has indicated that VMS are associated with a more adverse adipokine profile,[26] reduced cardiac vagal control,[27] more adverse inflammatory or hemostatic profile,[28] and poorer endothelial function.[4,7] 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[29,30]) 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,[15] 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 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	0.04 (0.01)	0.004	0.05 (0.01)	0.0006
Late onset	−0.01 (0.01)	0.50	−0.01 (0.01)	0.50
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.

Downloaded from http://ahajournals.org by on March 4, 2022

and reducing confounding effects of HT. SWAN included a group of ethnically diverse women. Finally, carotid ultrasounds 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 midlife women.

Appendix

Clinical Centers: University of Michigan, Ann Arbor—Siobán Harlow, PI 2011–present, MaryFran Sowers, PI 1994–2011; 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; UCLA—Gail Greendale, PI; Albert Einstein College of Medicine, Bronx, NY—Carol Derby, PI 2011–present, Rachel Wildman, PI 2010–2011; Nanette Santoro, PI 2004–2010; University of Medicine and Dentistry–NJ Medical School, Newark—Gerson Weiss, PI 1994–2004; and the University of Pittsburgh, Pittsburgh, PA—Karen Matthews, PI. NIH Program Office: NIA, Bethesda, MD—Winifred Rossi 2012–present; Sherry Sherman 1994–2012; Marcia Ory 1994–2001; NINR, Bethesda, MD–Program Officers. Central Laboratory: University of Michigan, Ann Arbor—Daniel McConnell (Central Ligand Assay Satellite Services). Coordinating Center: University of Pittsburgh, Pittsburgh, PA—Maria Mori Brooks, PI 2012–present; Kim Sutton-Tyrrell, PI 2001–2012; New England Research Institutes, Watertown, MA—Sonja McKinlay, PI 1995–2001. Steering Committee: Susan Johnson, Current Chair; Chris Gallagher, Former Chair.

Acknowledgments

The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH.

Sources of Funding

The Study of Women's Health Across the Nation (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 U01NR004061; U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, U01AG012495).

Disclosures

Dr Jackson—Consulting: McKesson, American College of Cardiology; Authorships/editorial: American Journal of Medicine, Up-To-Date, Spry Publishing. Dr Joffe: Grant support: Cephalon/Teva, Merck Advisory board/consulting: Merck, Noven, Tanaka Mitsubishi. The other authors report no conflicts.

References

1. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. *Circulation*. 2011;124:2145–2154. doi: 10.1161/CIRCULATIONAHA.110.968792.
2. Gold EB, Colvin A, Avis N, Bromberger J, Greendale GA, Powell L, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: Study of Women's Health Across the Nation. *Am J Public Health*. 2006;96:1226–1235. doi: 10.2105/AJPH.2005.066936.
3. Avis NE, Colvin A, Bromberger JT, Hess R, Matthews KA, Ory M, 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. doi: 10.1097/gme.0b013e3181a3cdaf.
4. 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. doi: 10.1161/CIRCULATIONAHA.108.776823.
5. Thurston RC, Sutton-Tyrrell K, Everson-Rose SA, Hess R, Powell LH, Matthews KA. Hot flashes and carotid intima media thickness among midlife women. *Menopause*. 2011;18:352–358. doi: 10.1097/gme.0b013e3181fa27fd.
6. Thurston RC, Kuller LH, Edmundowicz D, Matthews KA. History of hot flashes and aortic calcification among postmenopausal women. *Menopause*. 2010;17:256–261. doi: 10.1097/gme.0b013e3181c1ad3d.
7. Bechlioulis A, Kalantaridou SN, Naka KK, Chatzikyriakidou A, Calis KA, Makrigiannakis A, 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. doi: 10.1210/jc.2009-2262.
8. Gast GC, Grobbee DE, Pop VJ, Keyzer JJ, Wijnands-van Gent CJ, Samsioe GN, et al. Menopausal complaints are associated with cardiovascular risk factors. *Hypertension*. 2008;51:1492–1498. doi: 10.1161/HYPERTENSIONAHA.107.106526.
9. Thurston RC, El Khoudary SR, Sutton-Tyrrell K, Crandall CJ, Gold EB, Sternfeld B, et al. Vasomotor symptoms and lipid profiles in women transitioning through menopause. *Obstet Gynecol*. 2012;119:753–761. doi: 10.1097/AOG.0b013e31824a09ec.
10. Thurston RC, El Khoudary SR, Sutton-Tyrrell K, Crandall CJ, Sternfeld B, Joffe H, et al. Vasomotor symptoms and insulin resistance in the Study of Women's Health Across the Nation. *J Clin Endocrinol Metab*. 2012;97:3487–3494. doi: 10.1210/jc.2012-1410.
11. Tuomikoski P, Ebert P, Groop PH, Haapalahti P, Hautamäki H, Rönnback M, et al. Evidence for a role of hot flushes in vascular function in recently postmenopausal women. *Obstet Gynecol*. 2009;113:902–908. doi: 10.1097/AOG.0b013e31819cac04.
12. Szmuilowicz ED, Manson JE, Rossouw JE, Howard BV, Margolis KL, Greep NC, et al. Vasomotor symptoms and cardiovascular events in postmenopausal women. *Menopause*. 2011;18:603–610. doi: 10.1097/gme.0b013e3182014849.
13. Freeman EW, Sammel MD, Lin H, Liu Z, Gracia CR. Duration of menopausal hot flushes and associated risk factors. *Obstet Gynecol*. 2011;117:1095–1104. doi: 10.1097/AOG.0b013e318214f0de.
14. Tepper P, Randolph J, Jones B, Crawford S, Gold E, El Khoudary S, et al. Trajectory patterns of vasomotor symptoms over the menopausal transition in the Study of Women's Health Across the Nation (abstract). *Menopause* 2013;20:1356.
15. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al; American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr*. 2008;21:93–111; quiz 189. doi: 10.1016/j.echo.2007.11.011.
16. Sowers M, Crawford S, Sternfeld B, Morganstein D, Gold EB, Greendale GA, 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, eds. *Menopause: Biology and Pathology*. New York: Academic Press; 2000:175–188.
17. Wendelhag I, Gustavsson T, Suurküla M, Berglund G, Wikstrand J. Ultrasound measurement of wall thickness in the carotid artery:

Downloaded from http://ahajournals.org by on March 4, 2022

fundamental principles and description of a computerized analysing system. *Clin Physiol*. 1991;11:565–577.
18. Sutton-Tyrrell K, Wolfson SK, Jr, Thompson T, Kelsey SF. Measurement variability in duplex scan assessment of carotid atherosclerosis. *Stroke*. 1992;23:215–220.
19. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol*. 2010;6:109–138. doi: 10.1146/annurev.clinpsy.121208.131413.
20. Kiechl S, Willeit J. The natural course of atherosclerosis. Part II: vascular remodeling. Bruneck Study Group. *Arterioscler Thromb Vasc Biol*. 1999;19:1491–1498.
21. El Khoudary SR, Wildman RP, Matthews K, Thurston RC, Bromberger JT, Sutton-Tyrrell K. Endogenous sex hormones impact the progression of subclinical atherosclerosis in women during the menopausal transition. *Atherosclerosis*. 2012;225:180–186. doi: 10.1016/j.atherosclerosis.2012.07.025.
22. Lambrinoudaki I, Augoulea A, Armeni E, Rizos D, Alexandrou A, Creatsa M, et al. Menopausal symptoms are associated with subclinical atherosclerosis in healthy recently postmenopausal women. *Climacteric*. 2012;15:350–357. doi: 10.3109/13697137.2011.618564.
23. Allison MA, Manson JE, Aragaki A, Langer RD, Rossouw J, Curb D, et al. Vasomotor symptoms and coronary artery calcium in postmenopausal women. *Menopause*. 2010;17:1136–1145. doi: 10.1097/gme.0b013e3181e664dc.
24. Lenfant F, Trémollières F, Gourdy P, Arnal JF. Timing of the vascular actions of estrogens in experimental and human studies: why protective early, and not when delayed? *Maturitas*. 2011;68:165–173. doi: 10.1016/j.maturitas.2010.11.016.
25. Freeman EW, Sammel MD, Grisso JA, Battistini M, Garcia-Espagna B, Hollander L. Hot flashes in the late reproductive years: risk factors for Africa American and Caucasian women. *J Womens Health Gend Based Med*. 2001;10:67–76. doi: 10.1089/152460901750067133.
26. Thurston RC, Chang Y, Mancuso P, Matthews KA. Adipokines, adiposity, and vasomotor symptoms during the menopause transition: findings from the Study of Women's Health Across the Nation. *Fertil Steril*. 2013;100:793–800. doi: 10.1016/j.fertnstert.2013.05.005.
27. Thurston RC, Christie IC, Matthews KA. Hot flashes and cardiac vagal control during women's daily lives. *Menopause*. 2012;19:406–412. doi: 10.1097/gme.0b013e3182337166.
28. Thurston RC, El Khoudary SR, Sutton-Tyrrell K, Crandall CJ, Gold E, Sternfeld B, et al. Are vasomotor symptoms associated with alterations in hemostatic and inflammatory markers? Findings from the Study of Women's Health Across the Nation. *Menopause*. 2011;18:1044–1051. doi: 10.1097/gme.0b013e31821f5d39.
29. Matteo Ciccone M, K Sharma R, Scicchitano P, Cortese F, Salerno C, Berchialla P, et al. Dolichocarotids: Echo-color doppler evaluation and clinical role. *J Atheroscler Thromb*. 2014;21:56–63.
30. Ciccone MM, Scicchitano P, Palumbo V, Cortese F, Valecce R, Dentamaro I, et al. Dolichocarotids and dilated cardiomyopathy: is there a relationship? *Int J Cardiol*. 2012;158:123–125. doi: 10.1016/j.ijcard.2012.04.052.

Downloaded from http://ahajournals.org by on March 4, 2022