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Hot Flashes and Subclinical Cardiovascular Disease
Findings From the Study of Women's Health Across the Nation Heart Study

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Background—Although evidence suggests adverse vascular changes among women with hot flashes, it is unknown whether hot flashes are associated with subclinical cardiovascular disease. The aim of this study was to examine relations between menopausal hot flashes and indices of subclinical cardiovascular disease. We hypothesized that women with hot flashes would show reduced flow-mediated dilation and greater coronary artery and aortic calcification compared with women without hot flashes.

Methods and Results—The Study of Women's Health Across the Nation Heart Study (2001 to 2003) is an ancillary study to the Study of Women's Health Across the Nation, a community-based cohort study. Participants were 492 women (35% black, 65% white) 45 to 58 years of age who were free of clinical cardiovascular disease and had a uterus and at least 1 ovary. Measures included a brachial artery ultrasound to assess flow-mediated dilation, electron beam tomography to assess coronary artery and aortic calcification, reported hot flashes (any/none, previous 2 weeks), and a blood sample for measurement of estradiol concentrations. Cross-sectional associations were evaluated with linear regression and partial proportional odds models. Hot flashes were associated with significantly lower flow-mediated dilation ($\beta=-1.01$; SE, 0.41; $P=0.01$) and greater coronary artery (odds ratio, 1.48; 95% confidence interval, 1.04 to 2.12) and aortic (odds ratio, 1.55; 95% confidence interval, 1.10 to 2.19) calcification in age- and race-adjusted models. Significant associations between hot flashes and flow-mediated dilation ($\beta=-0.97$; SE, 0.44; $P=0.03$) and aortic calcification (odds ratio, 1.63; 95% confidence interval, 1.07 to 2.49) remained in models adjusted for cardiovascular disease risk factors and estradiol.

Conclusions—Women with hot flashes had reduced flow-mediated dilation and greater aortic calcification. Hot flashes may mark adverse underlying vascular changes among midlife women. **(*Circulation*. 2008;118:1234-1240.)**

Key Words: aging ■ atherosclerosis ■ calcium ■ endothelium ■ epidemiology ■ hormones ■ women

Hot flashes are reported by most black and white women during the menopausal transition.[1] The occurrence of hot flashes peaks in the late perimenopause and early postmenopause periods, although they also are experienced by a sizable minority (20% to 40%) of late-reproductive-age premenopausal women[1,2] and postmenopausal women in their 60s and 70s.[3] Hot flashes are episodes of intense heat, sweating, and flushing associated with impaired quality of life,[4] disturbed sleep,[5] irritability, and depressed mood.[6] They are a leading reason that women seek menopause-related health care.[7] Leading models of the physiology of hot flashes characterize them as thermoregulatory events occurring in the context of altered thermoregulatory functioning,[8] with additional hormonal involvement.[9] In the wake of termination of the Women's Health Initiative (WHI) hormone arms[10] and search for nonhormonal treatments, hot flashes have gained increased scientific and clinical interest. However, they are viewed largely as a symptom with quality-of-life, but not medical, implications.

Clinical Perspective p 1240

Emerging research suggests underlying vascular changes among women with hot flashes. WHI findings indicated that incident coronary heart disease risk with hormone therapy (HT) was concentrated among older women reporting vasomotor symptoms at study baseline.[11] Moreover, estrogen withdrawal, likely involved in the physiology of hot flashes,[9] has widespread impact on vessel structure and function. Hypoestrogenic states are associated with impaired endothelial functioning,[12,13] and estrogen use among younger postmenopausal women has been associated with fewer calcified plaques in the coronary arteries.[14] Furthermore, potent vaso-

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dilators such as calcitonin gene-related peptide are released during hot flashes but not during exercise or sweating.[15,16] Finally, risk factors for hot flashes also are cardiovascular risk factors, including obesity and smoking.[1]

This study examined associations between hot flashes and several indices of subclinical cardiovascular disease (CVD), including flow-mediated dilation (FMD), coronary artery calcification (CAC), and aortic calcification (AC). Impaired FMD, a marker of endothelial dysfunction characteristic of early atherosclerosis, has been associated prospectively with incident CVD.[17,18] Calcified plaques of atherosclerotic lesions can be quantified by electron beam tomography.[19] CAC and AC have been prospectively linked to clinical CVD events, including stroke, incident coronary heart disease, and CVD mortality.[19–21] We hypothesized that hot flashes will be associated with lower FMD, higher AC, and higher CAC. We examined associations controlling for relevant cardiovascular risk factors. The role of serum estradiol (E2) concentrations in these associations and interactions by race/ethnicity, menopausal stage, and age were examined in an exploratory fashion.

Methods

Study Population

The Study of Women's Health Across the Nation (SWAN) is a multiethnic cohort study designed to characterize the menopausal transition. SWAN is being conducted across 7 sites in the United States. Details of study design and procedures have been reported previously.[22] At enrollment (1996 to 1997), SWAN participants (n=3302) were 42 to 52 years of age, had an intact uterus and at least 1 ovary, were not pregnant or breast feeding, had menstruated within 3 months, and were not using oral contraceptives or HT. The study was approved by the institutional review board at each site. Each participant provided written informed consent.

A subcohort of participants at Pittsburgh and Chicago SWAN sites participated in SWAN Heart, an ancillary study designed to assess cardiovascular risk over menopause. The present analysis is a cross-sectional analysis from the baseline SWAN Heart examination, occurring once during SWAN study years 4 through 7 (2001 to 2005) within 3 months after the corresponding annual core SWAN assessment. By design,[22] the Pittsburgh and Chicago sites recruited only non-Hispanic white and black women. Therefore, all SWAN Heart participants described themselves as white or black. All eligible SWAN participants were invited to participate in SWAN Heart; of these women, 76% enrolled. SWAN Heart exclusions included pregnancy, hysterectomy or bilateral oophorectomy, reported CVD (history of myocardial infarction, angina, intermittent claudication, cerebral ischemia, revascularization), and medications for diabetes, hypertension, or heart arrhythmias. Hormone use (HT, oral contraceptives) was an exclusion criterion for SWAN Heart with 1 exception. Although most participants were screened and enrolled in SWAN Heart during annual SWAN visits 4 through 7, at the Pittsburgh site, limited SWAN Heart enrollment began during the first annual SWAN visit. By the time these women underwent subclinical CVD assessments (SWAN years 4 through 7), 58 women were using HT. HT use was considered a covariate in all analyses.

Of the 588 SWAN Heart participants, 491 and 374 women provided information on hot flashes and underwent electron beam tomography (for calcification) or B-mode ultrasound (for FMD), respectively. Ultrasound data were more limited because of fiscal constraints on ultrasound collection and reading. Twenty-five women were excluded from CAC and AC models because of missing values on ≥1 covariates (education, n=17; low-density lipoprotein [LDL], n=6; high-density lipoprotein [HDL], n=4; triglycerides, n=4; glucose, n=2; physical activity, n=1; 9 women had >1 missing value). Two women undergoing electron beam tomography were missing AC data because of technical problems. In FMD models, 22 women missing values on ≥1 covariates (education, n=13; baseline lumen diameter, n=1; LDL, n=6; HDL, n=4; triglycerides, n=4; glucose, n=2; physical activity, n=1; 9 women had >1 missing value) were excluded. Women missing data had higher triglycerides than women without missing data ($P<0.01$). Missing body mass index (BMI) and blood pressure values were carried forward from the last completed assessment for 12 and 10 women, respectively. The final samples for evaluating primary hypotheses were 467 women in CAC models, 465 in AC models, and 352 in FMD models. Calcification and FMD models including hormone measures excluded an additional 21 and 19 women, respectively, missing hormonal data.

Design and Procedures

Participants completed a standard protocol at SWAN entry and annually thereafter, including questionnaires, fasting blood specimens, anthropometric measures, and blood pressure readings. Subclinical CVD measures were initiated during the SWAN Heart baseline during core SWAN years 4 through 7.

Subclinical CVD

Flow-Mediated Dilation

FMD of the right brachial artery was assessed by B-mode ultrasound images of the right brachial artery, 4 to 10 cm proximal to the antecubital crease, with a Toshiba (Toshiba American Medical Systems, Tustin, Calif) SSA-270A scanner and a 7.5-MHz linear-array transducer according to standardized protocol. Images were obtained after 10 minutes of supine rest (baseline) and 4 minutes of forearm blood flow occlusion (postdeflation) with a pneumatic tourniquet set to 50 mm Hg above the participant's systolic blood pressure (SBP). Baseline images were captured continuously for 20 seconds and postdeflation images for 3 minutes. The arterial diameter was measured as the distance between the proximal and distal arterial wall intima-media interfaces by 1 of 2 trained sonographers. All images were read by 1 of 2 readers blinded to the participant's hot flash status. FMD was calculated as the maximum percentage of change in arterial diameter relative to the resting baseline. Images were stored on magnetic optical disk. This protocol produced reproducible results with an intraclass correlation of 0.72. FMD values were normally distributed, and FMD was treated as a continuous variable in all analyses.

Calcification

Calcification of the aorta and coronary arteries was assessed by electron beam tomography with an Imatron C-150 Ultrafast CT scanner (Imatron, South San Francisco, Calif) administered by a trained technician. Three passes were performed. The first pass provided landmarks for scans. The second provided the coronary artery images; 30 to 40 contiguous 3-mm-thick transverse images from the level of the aortic root to the apex of the heart were obtained during maximal breath holding. ECG triggering was used so that each 100-millisecond exposure was obtained during the same phase of the cardiac cycle (60% of the RR interval). The third pass provided the aortic evaluation, acquiring cross-sectional 6-mm images from the aortic arch to the iliac bifurcation with a 300-millisecond exposure time during maximal breath holding. All scans were scored centrally at the University of Pittsburgh with a DICOM workstation and software by AcuImage, Inc (South San Francisco, Calif) with the method established by Agatston et al.[23] Scans were read by a trained technician blinded to hot flash status. Calcification was considered present if at least 3 contiguous pixels showed >130 Hounsfield units. AC was obtained from the single aortic score. Because AC clinical thresholds are not available, AC scores were categorized into approximate tertiles based on the sample distribution. The CAC score was the sum of scores for each of the 4 major epicardial coronary arteries. Because CAC was low, CAC was categorized as 0, >0 to 10, and >10, corresponding to none, minimal, and mild to moderate CAC.[19]

Hot Flashes

At the annual core SWAN interview corresponding to the SWAN Heart baseline, participants reported the number of days in which hot flashes were experienced (not at all, 1 to 5 , 6 to 8 days, 9 to 13 days, every day) in the 2 weeks before the interview. Women were categorized as experiencing any or no hot flashes. Although hot flashes also were considered categorized as a 3-level variable (not at all, 1 to 5 days, ≥6 days), hot flashes were dichotomized because of an indication of a threshold at any versus no hot flashes.

Hormone Assays

E2 was the primary hormonal covariate. However, given their association with cardiovascular risk[24] and/or hot flashes,[25] follicular-stimulating hormone (FSH), sex hormone–binding globulin (SHBG), and the free estradiol index (FEI) also were considered. Measures were obtained from a single morning fasting blood sample during the annual core SWAN visit corresponding to SWAN Heart baseline. Subjects were scheduled for venipuncture on days 2 through 5 of a spontaneous menstrual cycle. Two attempts were made for a timed sample, obtained on 35% of participants. If a timed sample could not be obtained, a random fasting sample was taken. Blood was refrigerated before centrifugation 1 to 2 hours after phlebotomy, and serum was placed in aliquots, frozen, and batched for shipment to the central laboratory. Samples were catalogued on arrival and assayed in a batch monthly. E2 assays were conducted in duplicate; and FSH and SHBG were done in singular. Assays were performed on the ACS-180 automated analyzer (Bayer Diagnostics, Tarrytown, NY) using 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. The assay modifies the rabbit anti–E2-6 ACS-180 immunoassay to increase sensitivity, with a lower limit of detection of 1.0 pg/mL. Duplicate assays were conducted with results reported as the arithmetic mean for each subject with a coefficient of variation of 3% to 12%. FSH assays were performed with a 2-site chemiluminometric immunoassay, with interassay and intra-assay coefficients of variation of 11.4% and 3.8%, respectively, and a lower limit of detection of 1.1 mIU/mL. The 2-site chemiluminescent SHBG assay was developed on site using rabbit anti-SHBG antibodies with a lower limit of detection of 1.95 nmol/L and interassay and intra-assay coefficients of variation of 9.9% and 6.1%, respectively. FEI was calculated as follows: 100×E2 (pg/mL)/272.11×SHBG (nmol/L).[26]

Covariates

Race/ethnicity and education (less than or high school, some college/vocational, college degree or higher) were derived from the baseline SWAN interview. All other covariates were derived from the annual SWAN interview or examination most closely corresponding to the SWAN Heart baseline. Race/ethnicity was determined in response to “How would you describe your primary racial or ethnic group?” Menopausal status, obtained annually from reported bleeding patterns in the year preceding the visit, was categorized as premenopausal (bleeding in previous 3 months with no past year change in cycle predictability), early perimenopausal (bleeding the previous 3 months with decrease in cycle predictability in the past year), late perimenopausal (<12 to >3 months of amenorrhea), or postmenopausal (≥12 months of amenorrhea). Women last classified as premenopausal or perimenopausal who reported taking hormones (oral contraceptives, oral estrogens and/or progestins, estrogen injections or patch) in the past year were considered indeterminate status because of the impact of hormone use, even if discontinued, on bleeding patterns. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression scale.[27] Physical activity was assessed with a modified Kaiser Permanente Health Plan Activity Survey, a validated measure designed to assess physical activity among women.[28,29] Women who reported taking hormones within the past month (relevant only to the subset of participants described earlier) were classified as HT users. Antidepressant use was reported as use of medications for a nervous condition (eg, antidepressants) since last study visit, and lipid-lowering medication use was reported use of medications for cholesterol/fats in the blood since last study visit. Diabetes history was the report at any prior or current study visit of having diabetes. Total serum cholesterol, HDL, LDL, triglycerides, and glucose were determined from a fasting blood sample with standard methods described previously.[30] Anthropometric measures (height, weight, SBP, diastolic blood pressure [DBP]) were obtained by standardized methods, with BMI calculated as weight in kilograms divided by height in meters squared.

Statistical Analysis

Associations between FMD, AC, and CAC (considered continuous variables) were examined with Spearman correlation coefficients. Multiple linear regression was used to estimate associations between hot flashes and FMD. Associations between hot flashes and AC and CAC were initially estimated with ordinal logistic regression. Because AC models and multivariable CAC models failed assumptions of proportionality, partial proportional odds models were used. Models were first estimated with the covariates site, age, and race; with covariates associated with the outcome at $P<0.10$; and finally with all potential cardiovascular risk factor confounders. Age, race, site, HT use, and BMI were included in all multivariable models. Because of their high correlation ($r=0.77$), SBP and DBP were not included together in models; the measure most strongly associated with the outcome was included. Hormonal models included transformed E2 (log), FSH (log), FEI (log), or SHBG (square root) values added to risk factor–adjusted models, with sample timing also covaried. Interactions by age, race, HT use, and menopausal stage were evaluated in all models. R^2 change values associated with hot flashes and covariates were calculated for linear regression models (relevant only to FMD). Analyses were performed with SAS (version 8.2, SAS Institute, Inc, Cary, NC) and STATA (version 9, Stata Corp, College Station, Tex). All tests were 2 sided at $\alpha=0.05$.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Participant characteristics by reported hot flashes are presented in Table 1. Almost half of the sample reported hot flashes. Although participants had a fairly favorable cardiovascular risk profile, it was slightly more adverse among women with hot flashes. FMD was high (mean percentage, 7.0; SD, 3.8). AC (mean, 122.8; SD, 345.9; range, 0 to 4234) and CAC (mean, 12.6; SD, 43.6; range, 0 to 598) scores were low. Although AC and CAC were significantly correlated ($\rho=0.49$; $P<0.0001$), FMD was not correlated with AC ($\rho=-0.04$; $P=0.49$) nor CAC ($\rho=-0.06$; $P=0.31$).

Women with hot flashes had significantly lower FMD than women without hot flashes in minimally adjusted and risk factor–adjusted models (Table 2). Associations remained significant with adjustment for E2. Baseline lumen diameter explained the greatest portion of the variance in FMD, although hot flashes were associated with a proportion of variance in FMD exceeding that of most of the traditional cardiovascular risk factors (Table 3).

Hot flashes were associated with significantly increased odds of AC and CAC in minimally adjusted models (Table 4). For AC, associations were significant with further adjustment for risk factors and E2. Associations between hot flashes and CAC were significant in minimally adjusted but not risk factor–adjusted models.

Several additional analyses were conducted. Interactions by age, race, HT use, and menopausal stage were included in

Table 1. Participant Characteristics by Reported Hot Flashes

	Hot Flashes	
	None (n=263)	Any (n=229)
Age, mean (SD), y§	50.0 (2.8)	50.7 (2.9)
Race, n (%)		
Black‡	78 (29.7)	92 (40.2)
White	185 (70.3)	137 (59.8)
Education, n (%)§		
≤High school	39 (14.8)	39 (17.0)
Some college/vocational	66 (25.1)	83 (36.3)
≥College	158 (60.1)	107 (46.7)
Menopausal status, n (%)‖		
Premenopausal	37 (14.1)	9 (3.9)
Early perimenopausal	141 (53.6)	86 (37.6)
Late perimenopausal	21 (8.0)	31 (13.5)
Postmenopausal	49 (18.6)	91 (39.7)
Indeterminate	15 (5.7)	12 (5.3)
BMI, mean (SD), kg/m^2‡	28.6 (6.1)	29.8 (6.2)
SBP, mean (SD), mm Hg†	117.8 (16.3)	120.4 (16.5)
DBP, mean (SD), mm Hg	75.4 (10.0)	76.3 (9.7)
HDL, mean (SD), mg/dL	56.4 (14.4)	58.1 (13.9)
LDL, mean (SD), mg/dL‡	116.1 (32.0)	122.3 (32.3)
Triglycerides, mean (SD), mg/dL	113.2 (63.7)	117.1 (66.0)
Glucose, mean (SD), mg/dL†	90.6 (18.7)	94.4 (28.0)
Antidepressant use, n (%)	37 (14.1)	25 (10.9)
HT use, n (%)	32 (12.2)	26 (11.4)
Smoking, n (%)	36 (13.7)	40 (17.5)
Physical activity, mean (SD), n (%)	8.1 (1.7)	7.9 (1.8)
Depressive symptoms, mean (SD), n (%)*‡	6.7 (7.6)	7.5 (7.3)
Baseline lumen diameter, mean (SD), mm	3.2 (0.5)	3.2 (0.5)
FMD, mean (SD), %§	7.5 (3.9)	6.4 (3.6)
AC score, n (%)§		
0	86 (35.0)	52 (23.7)
>0–<44	93 (37.8)	82 (37.5)
≥44	67 (27.2)	85 (38.8)
CAC score, n (%)‡		
0	145 (58.7)	102 (46.3)
>0–<10	61 (24.7)	60 (27.3)
≥10	41 (16.6)	58 (26.4)
E2, mean (SD), pg/mL*‖	80.6 (101.8)	48.3 (69.5)
FSH, mean (SD), mIU/mL*‖	39.8 (35.6)	66.8 (52.4)
FEI, mean (SD)*‖	0.94 (2.6)	0.51 (1.3)
SHBG, mean (SD), nmol/L*	48.7 (28.4)	48.4 (29.1)

*Statistical comparisons conducted with transformed depressive symptoms (log), E2 (log), FSH (log), FEI (log), and SHBG (square root) values.
†$P<0.10$, ‡$P<0.05$, §$P<0.01$, ‖$P<0.0001$, any versus no hot flashes.

all models. None of these interactions were significant ($P>0.15$), nor did exploratory analyses yield any clear pattern of results by age, race, HT use, or menopausal stage (Tables I through V of the online-only Data Supplement). A sensitivity analysis excluding HT users showed results consistent with primary results (supplementary Tables III and IV). When FSH, FEI, and SHBG were added individually to risk factor–adjusted FMD and AC models, associations remained significant in FMD and AC models additionally adjusted for FSH (FMD: $\beta=-0.98$, SE=0.44, $P=0.03$; AC: odds ratio [OR] =1.57, 95% confidence interval [CI] =1.03 to 2.39, $P=0.04$), FEI (FMD: $\beta=-0.93$, SE=0.44, $P=0.03$; AC: OR=1.55, 95% CI=1.02 to 2.37, $P=0.04$), or SHBG (FMD: $\beta=-1.01$, SE=0.43, $P=0.02$; AC: OR=1.58, 95% CI=1.04 to 2.41, $P=0.03$).

Table 2. Association Between Hot Flashes and FMD

	FMD	
Model	β (SE)*	P
1	−1.01 (0.41)	0.01
2	−1.02 (0.39)	0.01
3	−0.99 (0.41)	0.02
4	−0.97 (0.44)	0.03

Model 1: age, site, and race. Model 2: model 1 covariates plus baseline lumen diameter, BMI, education, DBP, and HT use. Model 3: model 2 covariates plus education, menopausal status, HDL, LDL, triglycerides, glucose, diabetes history, lipid medication use, smoking status, and physical activity. Model 4: model 3 covariates plus $E2_{log}$ and blood draw timing.
*Regression coefficient for any versus no hot flashes.

Discussion

The present findings indicate that hot flashes were associated with lower FMD and increased calcified plaques in the aorta. Associations persisted after controlling for relevant risk factors and E2 concentrations as assessed here. These find-

Table 3. R^2 Change Values for Association Between Hot Flashes and FMD

	FMD, R^2 Change %
Age	0.2
Race	0.0
Baseline lumen diameter	5.7‡
Education	1.8†
BMI	1.7†
DBP	0.9*
HT use	0.1
HDL	0.5
LDL	0.0
Triglycerides	0.1
Lipid medication use	0.1
Glucose	0.1
Diabetes history	0.6
Menopausal status	2.0†
Smoking	0.0
Physical activity	0.0
Blood sample timing	0.3
E2	0.6
Hot flashes	1.3†

Model was adjusted for site and covariates listed. Total model R^2=19.1%.
*$P<0.10$, †$P<0.05$, ‡$P<0.0001$.

Table 4. Hot Flashes and Odds of AC and CAC

	AC		CAC	
Model	OR (CI)*	*P*	OR (CI)*	*P*
1	1.55 (1.10–2.19)	0.01	1.48 (1.04–2.12)	0.03
2	1.53 (1.02–2.29)†	0.04	1.34 (0.88–2.05)‡	0.17
3	1.53 (1.02–2.29)§	0.04	1.33 (0.87–2.03)‖	0.19
4	1.63 (1.07–2.49)	0.02	1.31 (0.84–2.05)	0.24

*OR for any vs no hot flashes.

Model 1: age, site, and race.

†Model 2a: model 1 covariates plus BMI, smoking, education, SBP, LDL, HDL, triglycerides, glucose, physical activity, antidepressant use, depressive symptoms, HT use, lipid medication use, and menopausal status.

‡Model 2b: model 1 covariates plus BMI, education, SBP, LDL, HDL, triglycerides, glucose, diabetes history, antidepressant use, depressive symptoms, HT use, and menopausal status.

§Model 3a: model 2a covariates plus diabetes history.

‖Model 3b: model 2b covariates plus diabetes history, smoking, physical activity, and lipid medication use.

Model 4: model 3 covariates plus $E2_{log}$ and blood draw timing.

ings suggest that hot flashes may be a marker of adverse vascular changes and that the vasculature may play an important role in the physiology of hot flashes.

The clinical significance of hot flashes has been related largely to their impact on quality of life rather than an association with physical health risk. However, in the WHI, Rossouw et al[11] found the greatest coronary heart disease risk associated with HT to be concentrated among older women at baseline reporting moderate to severe vasomotor symptoms. In the present investigation, associations between hot flashes and subclinical CVD were observed for the sample as a whole rather than only for older women. It is notable that the SWAN Heart participants were younger than WHI participants and that use of subclinical CVD indices rather than clinical events enabled detection of early evidence of CVD. Impaired FMD is a marker of endothelial dysfunction that promotes atherosclerosis by regulating vascular tone, inflammatory, and thrombotic processes.[18] CAC and AC are measures of calcified plaques in the aorta and coronary arteries, with calcification a marker of calcified atheroma and total plaque burden and AC also a marker for arteriosclerotic arterial remodeling.[19] FMD, CAC, and AC have been prospectively linked to CVD morbidity and mortality.[17,18,20,21] Considered together, these findings suggest potential adverse vascular changes among women with hot flashes.

One postulated pathway linking hot flashes to subclinical CVD is low endogenous E2 concentrations. Although the precise mechanisms are unknown, E2 is likely 1 factor involved in the cause of hot flashes. Several[2,9,25] (but not all[31]) investigations have shown associations between lower or declining endogenous E2 and hot flashes. E2 also has a cardiovascular impact. Higher endogenous estrogen concentrations are associated with improved fibrinolytic activity,[30,32] reduced arterial diameter,[33] lower waist circumference,[24] and, although inconsistently,[34] more positive lipid profiles.[24] Hypoestrogenic states are associated with poorer endothelial functioning, poorer arterial distensibility, intima-media thickening, and CVD risk.[13,35,36] Relations between estrogens in CVD are complex and may vary by factors such as age, hormonal status, CVD status, and endogenous hormone concentrations versus exogenous supplementation. However, among younger postmenopausal women without CVD, estrogen supplementation may improve endothelial function.[12,13] In a WHI ancillary study, coronary heart disease–free midlife women randomized to receive conjugated equine estrogens had lower CAC 8.7 years later,[14] although these findings may not generalize to older women or women with existing coronary heart disease. In this initial examination, controlling for E2 concentrations obtained via annual blood draw did not eliminate relations between hot flashes and FMD or AC. Associations also were evident with concurrent control for menopausal status, which may in part (but not entirely[25]) share a common pathway with E2 to hot flashes. Moreover, findings were similar with adjustment for FEI, an estimate of the portion of E2 unbound to SHBG, and FSH, a strong correlate of hot flashes.[25]

Another possible mechanism linking hot flashes to CVD is shared risk factors. Hot flashes occur during a time characterized by adverse CVD risk factor changes. Women who are obese, smokers, and black and have less education also show increased hot flash reporting.[1] However, findings of impaired FMD and increased AC among women with hot flashes were robust to adjustment for traditional CVD risk factors. Therefore, these shared risk factors may account for some, but not all, of the observed associations.

The physiology of hot flashes is incompletely understood. Current models of hot flashes postulate a hypothalamic origin, serving a thermoregulatory function as heat dissipation events.[8] Vascular involvement is clearly present, given the marked peripheral vasodilatation with hot flashes. The endothelium may play a particularly important role. Pronounced alterations in plasma calcitonin gene-related peptide, a potent and partly endothelium-dependent vasodilator, are observed among women with hot flashes[15] and acutely during hot flashes[15] but not during other sweating.[16] However, the role of the vasculature in hot flashes has received limited attention. These findings point to the potential importance of the peripheral vasculature in understanding hot flashes.

Significant associations were observed for AC. However, CAC findings did not persist in multivariable models. CAC was low, with 53% of women showing no calcification and the remainder largely in the mild range. The clinical significance of these CAC levels is not well established. These low levels are not surprising given the age of the sample, the exclusion of women with CVD and medications affecting key risk factors, and the traditionally low CAC among women relative to men of the same age.[19] This limited range likely restricted the ability to detect CAC differences. Greater calcification was observed in the aorta, consistent with previous findings among women.[20]

Several limitations deserve mention. First, this analysis is cross-sectional and observational. The causal or directional nature of associations could not be assessed. Although many relevant risk factors were assessed and statistically controlled, the possibility of residual confounding cannot be ruled out. Several measurement issues should be considered. Hot flashes were self-reported, recalled over 2 weeks. Although common in the epidemiological literature, these measures do not allow detailed characterization of hot flashes. Future research should examine relations with more detailed hot flash measures. Although FMD is a widely used measure, FMD is a marker of, rather than a direct measure of, disease, and technical and physiological factors can increase variability that standard protocols can decrease but not completely eliminate.[37] Hot flashes were associated with a significant portion of variance in FMD, although other factors (eg, baseline lumen diameter, education) were stronger predictors. The model accounted for <20% of variance in FMD, suggesting key determinants not assessed here. Finally, this study included a single annual blood draw to measure E2. E2 concentrations can fluctuate dramatically during perimenopause; E2, and not other estrogens, was assessed here; and detailed daily hormonal assessments were not feasible in this population-based investigation. Thus, total estrogen exposure may not have been fully controlled. Given that the main study aim was to determine associations between hot flashes and subclinical CVD, future work should further examine the role of hormonal factors with more detailed hormonal assessments.

This investigation has numerous strengths. It is the first investigation to examine the association between hot flashes and markers of subclinical CVD. This study allowed investigation of relations between hot flashes and disease early in the atherosclerotic process among relatively young women. Moreover, including several subclinical CVD markers allowed comparison across measures. This study included black and white women, with a lack of interaction indicating findings extending to both groups. Finally, this study included a well-characterized sample of women followed up throughout the menopausal transition.

Hot flashes occur during a time of life characterized by adverse changes in cardiovascular risk factors and increased CVD risk. Despite the suggestion of vascular involvement in hot flashes, there has been little examination of the relation between hot flashes and CVD. The present investigation found that women with hot flashes had evidence of lower FMD and greater AC not fully accounted for by cardiovascular risk factors. These links between hot flashes and markers of subclinical CVD also have implications for more completely understanding the physiology of hot flashes. Thus, in addition to their impact on quality of life, hot flashes may signal underlying adverse vascular changes among women transitioning through menopause. Casting doubt on the assertion that hot flashes are solely a quality-of-life issue, the present findings raise intriguing links between hot flashes and subclinical CVD markers worthy of further investigation.

Appendix

Clinical centers: Rush University, Rush University Medical Center, Chicago, Ill: Lynda Powell, principal investigator. University of Pittsburgh, Pittsburgh, Pa: Karen Matthews, principal investigator. National Institutes of Health (NIH) program office: National Institute on Aging, Bethesda, Md: Marcia Ory, 1994 to 2001; Sherry Sherman, 1994 to present. National Institute of Nursing Research, Bethesda, Md: program officers. Central laboratory: University of Michigan, Ann Arbor: Daniel McConnell (Central Ligand Assay Satellite Services). Coordinating center: New England Research Institutes, Watertown, Mass: Sonja McKinlay, principal investigator, 1995 to 2001. University of Pittsburgh, Pittsburgh, Pa: Kim Sutton-Tyrrell, principal investigator, 2001 to present. Steering Committee: Chris Gallagher, chair; Susan Johnson, chair.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The present study found impaired flow-mediated dilation and higher aortic calcification among women at midlife reporting menopausal hot flashes. Hot flashes, common during the menopausal transition, have been viewed largely as a quality-of-life issue, not a medical issue. Hot flashes have been of increased clinical interest since findings of health risk associated with hormone therapy. Although the cause of hot flashes remains incompletely understood, recent findings from previous investigations have suggested increased cardiovascular risk among subsets of women reporting hot flashes. The present study examined associations between hot flashes and several indices of subclinical cardiovascular disease among 492 black and white midlife women. Results indicated that relative to women not reporting hot flashes, women reporting hot flashes had evidence of lower flow-mediated dilation, a marker of poor endothelial function, and higher aortic calcification, a measure of calcified plaques and arteriosclerotic remodeling of the artery. These associations were evident in the sample as a whole and were robust to adjustment for demographic and known cardiovascular risk factors, as well as for serum estradiol concentrations. Although the observed associations deserve further replication and investigation, these findings suggest that in addition to their impact on quality of life, hot flashes may signal underlying adverse vascular changes among women transitioning through menopause.