Menopausal Hot Flashes and White Matter Hyperintensities

Running title: Hot Flashes and White Matter Hyperintensities

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Abstract

Objective: Hot flashes are the classic menopausal symptom. Emerging data links hot flashes to cardiovascular disease (CVD) risk, yet how hot flashes are related to brain health is poorly understood. We examined the relationship between hot flashes - measured via physiologic monitor and self-report - and white matter hyperintensities (WMH) among midlife women.

Methods: Twenty midlife women ages 40-60 without clinical CVD, with their uterus and both ovaries, and not taking hormone therapy were recruited. Women underwent 24 hours of ambulatory physiologic and diary hot flash monitoring to quantify hot flashes; magnetic resonance imaging to assess WMH burden; 72 hours of actigraphy and questionnaires to quantify sleep; and a blood draw, questionnaires, and physical measures to quantify demographics and CVD risk factors. Test of a priori hypotheses regarding relations between physiologically-monitored and self-reported wake and sleep hot flashes and WMH were conducted in linear regression models.

Results: More physiologically-monitored hot flashes during sleep were associated with greater WMH, controlling for age, race, and body mass index [beta(standard error)=.0002 (.0001), p=.03]. Findings persisted controlling for sleep characteristics and additional CVD risk factors. No relations were observed for self-reported hot flashes.

Conclusions: More physiologically-monitored hot flashes during sleep were associated with greater WMH burden among midlife women free of clinical CVD. Results suggest that relations between hot flashes and CVD risk observed in the periphery may extend to the brain. Future work should consider the unique role of sleep hot flashes in brain health.

Key Words: hot flashes; vasomotor symptoms; menopause; white matter hyperintensities; brain

Introduction

Hot flashes are the cardinal symptom of the menopausal transition, experienced by over 70% of women during the menopausal transition.[1] They have long been understood to be associated with reductions across all domains of quality of life.[2] However, hot flashes have recently been shown to be associated with decreased physical health.

Several studies have shown hot flashes to be associated with elevated subclinical cardiovascular disease (CVD), including poorer endothelial function, higher intima media thickness, and aortic calcification.[3, 4] Hot flashes have also been linked to an adverse CVD risk factor profile, including elevated blood pressure,[5] higher lipids,[6] a more insulin resistant profile,[7] and a more pro-coagulant hemostatic profile.[8] Further, hot flashes, particularly those measured physiologically, have been associated with decreased cardiac vagal control.[9] Notably, associations between hot flashes and CVD risk indices persist after adjusting for other standard CVD risk factors.

The existing literature on hot flashes has largely focused on changes in peripheral physiology. Although hot flashes are conceptualized as largely a central nervous system event,[10] very few studies have examined hot flashes in relation to brain health. Elevated traditional and novel CVD risk factors, such as hypertension, insulin, and autonomic nervous system dysfunction have been associated with adverse changes in the brain, notably lesions in the white matter.[11-13] These lesions appear as white matter hyperintensities (WMH) on T2-weighted magnetic resonance imaging (MRI) scans and are thought to develop due to small vessel disease in the brain.[14] WMH are linked to later stroke, cognitive decline and dementia, and mortality.[15] No studies have examined whether hot flashes are linked to WMH in the brain.

We tested whether wake and sleep hot flashes were associated with WMH. We tested these hypotheses in a sample of midlife women who underwent both brain imaging and detailed ambulatory diary and physiologic hot flash monitoring. We considered the role of a range of potential explanatory factors and confounders in observed associations.

Materials and Methods

Study Sample

Twenty women who were a subcohort of a larger parent study of 300 women about hot flashes underwent brain imaging and cognitive assessments. Parent study inclusion criteria included being age 40-60; nonsmoking; having a uterus and at least one ovary; not pregnant; being late perimenopausal or postmenopausal status (no menstrual period in the prior two months); without a history of heart disease, stroke, arrhythmia, or breast cancer; and not taking hormone therapy, SSRI/SNRI antidepressants, clonidine, beta blockers, calcium channel blockers, gabapentin, or insulin within three months. Additional criteria for inclusion in the brain imaging sub-study included no metal in the body and no history of chronic migraines, concussion, stroke, brain injury, or Parkinson's disease. Of the twenty women who underwent the brain imaging protocol, one woman experienced hot flash monitor failure; thereby 19 women are included in analyses.

Design and Procedures

The parent study protocol included anthropometric measures, questionnaires, blood specimens, and a 3-day ambulatory hot flash assessment protocol. Women in the brain imaging substudy additionally underwent a magnetic resonance imaging (MRI) of the brain. Procedures were approved by the University of Pittsburgh Institutional Review Board. All participants provided written informed consent.

Hot flashes

Hot flash monitoring was conducted with an ambulatory sternal skin conductance monitor, which women wore for 24 hours, and an electronic hot flash diary which women carried for three days (the first day of which coincided with physiologic hot flash monitoring). Sternal skin conductance was recorded via the VU-AMS monitor (Amsterdam, the Netherlands), a

portable device worn in a pouch around the waist. This device measures sternal skin conductance sampled at 1 Hz from the sternum via a 0.5 Volt constant voltage circuit passed between two Ag/AgCl electrodes (UFI) filled with 0.05M KCL Velvachol/glycol paste.[16] Participants were instructed to avoid exercising and showering during monitoring. Physiologic hot flashes were classified via standard methods, with skin conductance rise of 2 μmho in 30 seconds[17] flagged automatically by UFI software (DPSv3.6; Morro Bay, CA) and edited for artifact.[18] Given that some women show submaximal hot flashes failing to reach the 2 μmho criterion,[19, 20] all potential hot flash events (submaximal hot flashes that show the characteristic hot flash pattern[18]) were also visually inspected, and events showing the characteristic hot flash pattern yet <2 micro mho/30 sec rise were coded as hot flashes and independently verified by two coders, a coding approach that has been shown to be reliable (κ=.86).[19, 20] A 20-minute lockout period was implemented after the start of the flash during which no hot flashes were coded. To report hot flashes over the three-day monitoring period, participants were instructed to 1) complete a portable electronic diary (Palm Z22, Palm, Inc.) and 2) press event mark buttons on their wrist actigraph and the hot flash monitor (24 hours only) when experiencing a hot flash. For reporting nighttime hot flashes, women were instructed to report hot flashes via button-press.

Brain imaging

MRI scanning was performed at the MR Research Center of the University of Pittsburgh. A 3T Siemens Tim Trio MR scanner was used, with a Siemens 12-channel head coil. Two series of MR images were analyzed for the current study: a Magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted sequence and T2-weighted Fluid-attenuated inversion recovery (FLAIR) sequence. MPRAGE images were acquired in the axial plane: TR=2300 ms; TE=3.43 ms; TI=900 ms; Flip angle= 9 deg; Slice Thickness=1mm; FOV= 256*224 mm; voxel size= 1mm*1mm; matrix size= 256*224; and number of slices=176. FLAIR images were acquired in the axial plane: TR=9160 ms; TE=89 ms; TI=2500 ms; FA=150 deg; FOV= 256*212

mm; slice thickness=3 mm; matrix size=256*240; number of slices=48 slices; and voxel size= 1mm*1mm.

The WMH volume was obtained from the MPRAGE and T2-weighted FLAIR image using an automated method for quantification and localization of WMH.[21] The WMH quantification was done using a fuzzy connected algorithm.[22] The total WMH volume was normalized by total brain volume.

Sleep

Participants wore a wrist actigraph and completed a sleep diary for three days over the monitoring period. Actigraphy data were collected with a Minimitter Actiwatch-2 (Respironics, Inc., Murrysville, PA) in 1-min epochs and analyzed with the Actiware (Version 6.0.1) software program. Sleep diary data for bedtime and rise time were entered for calculation of sleep-wake variables. Actigraphy outcome variables included total sleep time (within the bedtime and rise time interval), sleep latency (bedtime to first sleep period), wakefulness after sleep onset (WASO; total minutes of wakefulness between sleep onset and final wake time) and sleep efficiency (100%*total sleep time/time in bed). Participants also completed the Pittsburgh Sleep Quality Index,[23] the Epworth Sleepiness Scale,[24] and the Berlin Questionnaire,[25] widely-used and well-validated measures of sleep quality, daytime sleepiness, and sleep apnea respectively.

Covariates

Height was measured via fixed stadiometer and weight via balance beam scale, and BMI was calculated as weight (kg)/height (m).[2] Systolic and diastolic blood pressure was the average of the second and third of three seated measurements taken via a Dinamap v100. Demographics, medical history, and health behaviors were assessed by questionnaires and interview. Menopausal status was obtained from reported bleeding patterns, categorized as perimenopausal (>2-<12months amenorrhea), or postmenopausal ($\underline{\geq}$12 months amenorrhea). Race/ethnicity was self-reported by the participant. Education was assessed as years of completed education and due to small cell sizes classified as less than or greater than a college

for analysis. Self-rated health was rated on a 6-point likert scale from excellent to very poor. Depressive symptoms were assessed via the Center for Epidemiologic Studies Depression Survey.

Participants provided a morning fasting blood sample for assessment of glucose, insulin, and lipids assessed via direct reagent/antibody measurement or indirect calculation methods. Glucose, total cholesterol, and triglycerides were determined enzymatically in serum (Vital Diagnostics; Lincoln, RI). HDL was determined after selective precipitation by heparin/manganese chloride and centrifugal removal of VLDL and LDL. LDL was calculated indirectly using the Friedewald equation.[26] Insulin was measured by cross-reactivity of human proinsulin antibody via radioimmunoassay (EMD Millipore, St Charles, MO). HOMA, an index reflecting insulin resistance, was calculated [(fasting insulin*fasting glucose)/ 22.5].[27] High sensitivity C-reactive protein (CRP-hs) was measured using goat anti-CRP-antibodies (Beckman-Coulter, Brea, CA) and turbidimetrically measuring the increase in absorbance (AU400 from Olympus America, Inc., Melville, NY), with intra- and inter-assay coefficients of variation of 5.5% and 3.0%, respectively. Interleukin 6 (IL-6) was measured using a high sensitive ELISA kit (Minneapolis, MN), with intra and inter-assay coefficients of variation of 9.1% and 10.2%, respectively. Serum E2 was assessed using liquid chromatography-tandem mass spectrometry, with inter- and intra-assay coefficients of variation of 5.0 and 8.1%, respectively and a lower limit of detection of 1.0 pg/ml.[28]

Statistical analysis

Variables were examined for distributions, outliers, and cell sizes. To account for variations in monitoring times, hot flash rates were calculated, with the number of hot flashes divided by monitoring time and standardized to a 24-hour period. They were also separated into sleep and wake hot flashes defined by actiwatch sleep and wake times. For women without hot flashes their hot flash rates were set to 0. Associations between hot flashes, and WMH were

tested in linear regression models, controlling for a priori selected covariates age, race/ethnicity, and body mass index. Additional covariates were added in secondary models. WMH was considered both as an untransformed variable and log transformed; results were comparable and thereby untransformed data are presented here. Estradiol, HOMA, IL6, and hsCRP values were log transformed to conform to assumptions or normality. All tests were two tailed with an alpha set to 0.05. Analyses were conducted using SAS v9.4 (SAS Institute, Cary, NC).

Results

Participants were on average 55 years old and approximately a quarter of the women were African American, with the remainder non-Hispanic White. The participants were on average normotensive, overweight and postmenopausal. Nine women reported having hot flashes, yet on physiologic monitoring 14 women showed physiologic hot flashes, a finding that is consistent with prior findings that women tend to under-report hot flashes relative to physiologic monitoring.[29] For the sample as a whole, women reported an average of 3 hot flashes/24 hours, and showed 8 hot flashes/24 hours on physiologic monitoring.

When considered categorically, women with hot flashes (physiologically-verified) had marginally higher WMH [relative to women without hot flashes: beta, b (standard error, SE)=0.0009 (0.0004), p=0.07], controlling for age, race, and BMI. Considered continuously, more physiologic hot flashes, particularly during sleep, were associated with significantly greater WMH. (Table 2; Figure 1). Notably, in these models the magnitude of the effect size for sleep hot flashes [for each additional hot flash: b(SE)=0.0002 (0.0001), p=0.03] was larger than that for age [per year: b(SE)=0.000007 (0.00005), p=0.90] or race [White vs African American: b(SE)=0. 0005 (0.0005), p=0.31], and comparable to that of BMI [per unit increase in BMI: b(SE)=0.0002 (0.00004), p=0.001], the only other significant variable in the model. No significant associations were observed between self-reported hot flashes and WMH [24-hour self-reported hot flashes, per additional hot flash: b(SE)=-0.000013 (0.00006), p=0.83; self-

reported hot flashes during waking hours, per additional hot flash: b(SE)=-0.000017 (0.0001), p=0.86; self-reported hot flashes during sleep, per additional hot flash: b(SE)=-0.00001 (0.0001), p=0.91, controlling for age, race, BMI].

Because findings were observed for hot flashes occurring during sleep, we also adjusted for sleep characteristics, including actigraphy-assessed sleep time, waking after sleep onset, sleep efficiency, and fragmentation; and questionnaire-assessed sleep apnea, sleep quality, or daytime sleepiness. Only higher daytime sleepiness was related to more WMH [per increase in Epworth scale score: b(SE)=0.0001 (0.00004), p=0.02, adjusted for age race, and BMI]. However, controlling for sleepiness in relations between overnight physiologic hot flashes and WMH had little impact on associations [per additional hot flash: b(SE)=0.0003(.00008) p=0.008, adjusted for age, race, BMI, sleepiness].

We performed several additional analyses to determine whether other potential covariates that might relate to hot flashes and might modify the relationship between hot flashes and WMH. These covariates included education, SBP, DBP, menopause stage, lipids, HOMA, blood pressure-lowering medication use, prior hormone therapy use, self-rated health, depressive symptoms, IL6, and hsCRP. Higher LDL cholesterol [per unit increase in LDL: b(SE)=0.00003 (0.000008), p=0.01] and higher $hsCRP_{log}$ [per unit increase in $hsCRP_{log}$: b(SE)=0.0005 (0.0002), p=0.01] was associated with more WMH (both models adjusted for age, race, BMI, sleep physiologic hot flashes). None of the other factors (education, SBP, DBP, menopause stage, HDL, triglycerides, HOMA, blood pressure-lowering medication use, prior hormone therapy use, self-rated health, depressive symptoms, IL6) were significantly related to WMH. Further, inclusion of any these factors (including LDL and hsCRP) in models between sleep physiologic hot flashes and WMH did not substantially alter findings (data not shown). Further, we considered $E2_{log}$ concentrations in relations between sleep physiologic hot flashes and WMH in models adjusted for age, race, and BMI; relations between sleep physiologic hot flashes and WMH persisted [per additional hot flash: b(SE)=0.0002 (0.0001), $p<0.05$].

Discussion

This study was the first to investigate the relation between menopausal hot flashes and WMH. We showed that more physiologically-monitored hot flashes during sleep were associated with greater WMH burden among midlife women free of clinical cardiovascular or cerebrovascular disease. These associations were not accounted for demographic factors, CVD risk factors, sleep, E2, or other potential confounding factors. These findings demonstrate a link between menopausal hot flashes and brain health, specifically structural abnormalities associated with ischemic disease.

Some studies have linked hot flashes to elevated subclinical CVD as well as a more adverse CVD risk factor profile.[3-8] Notably, a more adverse CVD risk profile, particularly hypertension and diabetes, has been associated with more WMH which may reflect small vessel disease in the brain.[11, 12] Greater WMH burden in turn has been linked to elevated risk of stroke, dementia, and mortality.[15] Thus, these data suggest that the adverse CVD profile observed in the periphery in some work may extend to the brain. Importantly, the direction of relations cannot be assumed here - hot flashes may serve as a marker for underlying white matter changes, they may be etiologically involved in these changes in women, or the relations between WMH and hot flashes may be explained by a third factor. The precise nature of relations between hot flashes and WMH should be investigated in future work, including in longitudinal studies.

Prior work has considered other reproductive and hormonal factors, such as hormone therapy use, pregnancy, and preeclampsia in relation to WMH.[30-32] However, no prior work has considered menopausal hot flashes in relation to WMH. WMH can be observed among relatively healthy midlife women, and some evidence indicates that WMH may be particularly related to novel CVD risk factors as compared to traditional CVD risk factors in this group.[33] Further, prior work has demonstrated that reproductive factors, such as bilateral oophorectomy during pre or

perimenopause (which typically induces hot flashes), has been linked elevated risk for cognitive impairment, dementia, and parkinsonism.[34, 35] Midlife reproductive phenomena such as hot flashes may be particularly relevant to consider in relation to later brain health. Future work should extend these findings to a wider range of clinical and functional (i.e. cognitive) outcomes as well as populations such as women undergoing oophorectomy.

Findings were observed primarily for physiologically-assessed hot flashes. Physiologically-monitored hot flashes differ from self-reported hot flashes in several important ways. Physiologic hot flash measures have the advantage of not relying upon attention, perception, emotional influences, or adherence to hot flash reporting protocols[36]. These issues are particular relevant in the ambulatory setting which presents many distractions and competing activities. Thus, typically more hot flashes are detected than are reported in the ambulatory setting.[9, 29, 37] Physiologic hot flash measures may be particularly useful for measuring sleep hot flashes, when reporting may be particularly difficult and impacted by the quality of sleep itself.[38] Finally, as compared to self-reported hot flashes, physiologically-monitored hot flashes have been shown to be more strongly related to other indices such as cardiac vagal control[9] and cognitive indices such as verbal memory.[37]

Findings were most pronounced for physiologically-monitored hot flashes detected during sleep. These relations did not appear to be accounted for by sleep characteristics assessed both by actigraphy and by questionnaire. In fact, only daytime sleepiness was related to greater WMH burden, and sleepiness did not account for the observed associations. Notably, sleep apnea in other work has been related to WMH,[39] but was not related to WMH here, and sleep apnea is not typically related to hot flashes.[40] Although sleep was rigorously assessed here, without polysomnography measures of sleep, a role for sleep cannot be definitively ruled out. However, the evidence here does not support a major role for sleep in these associations. It is also notable that relations between physiologic hot flashes and other relevant outcomes, such as cardiac vagal control [9] and cognition,[37] appear most pronounced for sleep hot flashes.

Whether sleep hot flashes and waking hot flashes have different underlying physiologies is not known, and further investigation of the unique relation of sleep hot flashes to WMH is warranted.

The mechanisms that may link hot flashes to WMH are not entirely clear, yet the findings here were not altered when controlling for CVD risk factors, such as blood pressure, BMI, or lipids. Inflammation has been tied to WMH[41] and possibly hot flashes.[42] We considered IL6 and CRP here, and although CRP was related to WMH, neither marker explained the association between hot flashes and WMH. Further, hot flashes typically occur in the context of E2 withdrawal,[10] which may have implications for brain health.[32, 43] However, findings persisted controlling for E2, which was measured via gold standard methods that are sensitive to the low levels of E2 observed in postmenopausal women. Notably, as the timing of E2 withdrawal may be relevant to brain health,[43] future work with larger sample sizes should consider variations in the timing of hot flashes in relation to WMH. Other work has shown autonomic nervous system profile characterized by increased sympathetic and/or decreased vagal control of the heart associated with hot flashes[9] and WMH,[13] which may be a candidate pathway linking these two phenomena. Future work should further consider the mechanisms by which hot flashes may be associated with WMH.

This study has several limitations. The main limitation of the study was its small size, which may have limited power to detect associations. It is notable that such consistent findings were noted between WMH and hot flashes despite this small sample, and findings should be replicated in future work. The majority of women included here were postmenopausal and thereby any differences by menopausal stage could not be investigated. Although extensive sleep indices were included, future work should examine the role of sleep in these relations using additional measures such as polysomnography.

This study had several strengths. This is the first study to investigate menopausal hot flashes in relation to WMH. Hot flashes were investigated via both physiologic monitoring and prospective diary report and during wake and sleep as a woman went about her daily activities.

Women completed a detailed brain imaging procedure. Moreover, other related important indices, including sleep, depression, CVD risk factors, and rigorously-measured endogenous E2 concentrations were assessed and their roles considered.

Conclusions

More menopausal hot flashes, particularly hot flashes occurring during sleep hours, were associated with greater WMH burden among midlife women free of clinical cardiovascular or cerebrovascular disease. This study is the first to investigate hot flashes in relation to WMH, showing that changes in white matter can occur early in life among women with hot flashes during sleep. These findings underscore the importance of continued investigation of the brain in investigating the propensity towards, underlying physiology of, and sequelae of hot flashes.

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Table 1. Sample characteristics

N	19
Age, M(SD)	55.2 (3.5)
Race, N (%)	
White	14 (73.7)
African American	5 (26.3)
Education, N (%)	
< college	6 (31.6)
≥ college	13 (68.4)
Menopause status, N (%)	
Perimenopausal	3 (15.8)
Postmenopausal	16 (84.2)
SBP, mmHg, M(SD)	121.3 (12.1)
DBP, mmHg, M(SD)	69.6 (7.8)
BMI, M(SD)	28.7 (4.9)
HOMA, Median (IQR)	1.9 (1.8)
hsCRP, mg/dL, Median (IQR)	2.3 (2.7)
IL6, pg/dL, Median (IQR)	1.6 (1.4)
CESD score, M(SD)	7.4 (7.6)
Serum estradiol, pg/mL, Median (IQR)	5.0 (13.0)
Actigraphy-assessed sleep time, hours, M(SD)	6.2 (1.3)
Physiologic hot flash rate, number, M (SD)	
24-hr	7.9 (7.2)
Waking*	5.9 (5.9)
Sleep*	2.0 (1.9)

Self-report hot flash rate, number, M (SD)	
24-hr	2.8 (3.5)
Waking*	1.7 (2.2)
Sleep*	1.1 (1.7)
White matter hyperintensity ratio (WMH/Total Brain Volume), M (SD)	.0013 (.001)

*Standardized to sleep and wake periods of 17 and 7 hours respectively for ease of interpretation

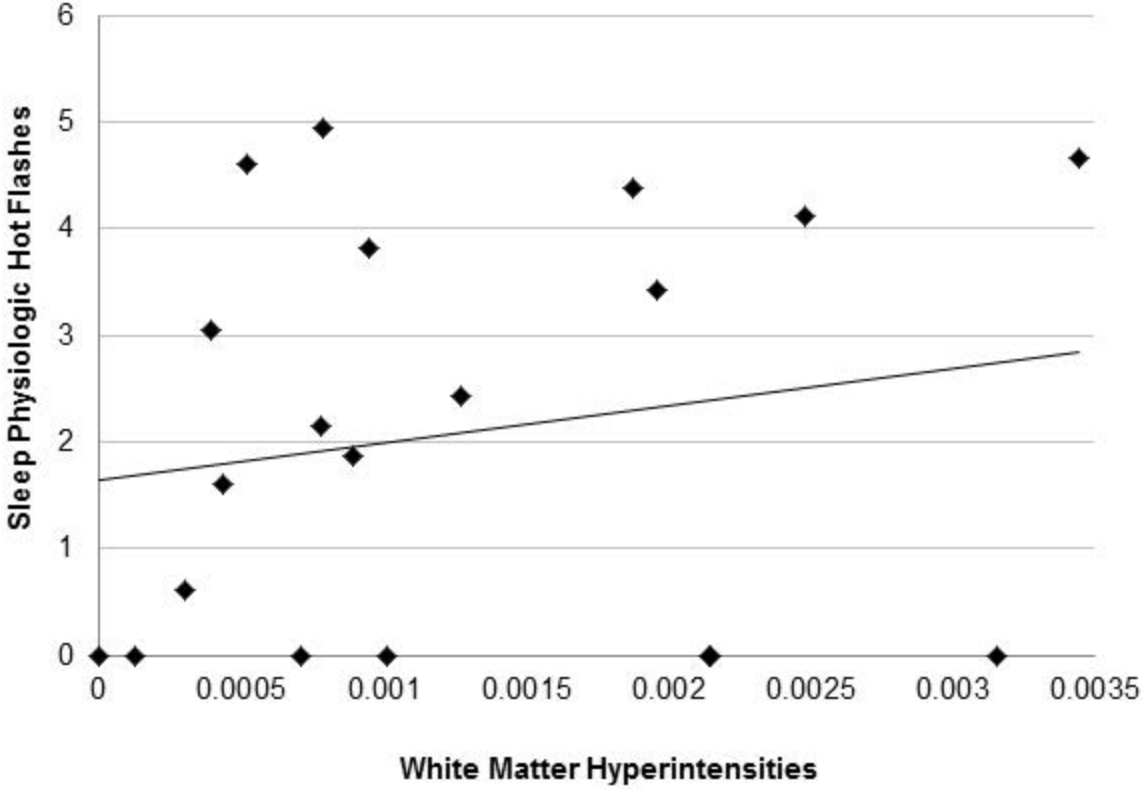
Table 2. Relation between physiologic hot flashes and white matter hyperintensities

	White matter hyperintensities	
	Beta (Standard Error)†	P value
Physiologic hot flash rate		
24-hr	.00004 (.00003)	.24
Sleep	.0002 (.0001)	.03
Wake	.00002 (.00004)	.75

Covariates: age, race, body mass index

† Beta indicates average increase in white matter hyperintensities associated with each additional hot flash

Figure 1. Relations between sleep hot flashes and WMH


Sleep Physiologic Hot Flashes
6
5
4
3
2
1
0
0
0.0005
0.001
0.0015
0.002
0.0025
0.003
0.0035
White Matter Hyperintensities