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Risk factors for hot flashes among women undergoing the menopausal transition: baseline results from the Midlife Women's Health Study

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Abstract

Objective—The aim of this study was to examine the associations between demographic characteristics, health behaviors, hormone concentrations, and the experiencing of any, current, more severe, and more frequent midlife hot flashes.

Methods—Baseline data were analyzed from 732 women aged 45 to 54 years enrolled in the Midlife Women's Health Study. A clinic visit was conducted to collect blood samples for hormone assays and to measure ovarian volume using transvaginal ultrasound. A self-administered questionnaire ascertained information on demographic factors, health habits, and hot flashes history. Multivariable logistic regression was conducted to examine the associations between potential risk factors and the hot flashes outcomes.

Results—Approximately 45% of participants reported experiencing midlife hot flashes. In the covariate-adjusted models, older age, peri-menopausal status, current and former cigarette smoking, and depressive symptoms were significantly associated with increased odds of all of the hot flashes outcomes. In addition, history of oral contraceptive use was associated with increased odds of any hot flashes. In contrast, higher current alcohol intake was significantly associated with decreased odds of any, current, and more severe hot flashes. Higher estradiol and progesterone concentrations were significantly associated with decreased odds of all hot flashes outcomes.

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Conclusions—Although the temporalities of such associations are not known due to the cross-sectional nature of the data, these observed relationships can help to identify women at risk for hot flashes.

Keywords

hot flashes; estrogen; progesterone; ovarian volume

INTRODUCTION

Hot flashes are the most prevalent and bothersome symptom reported by women during the menopausal transition. Recent estimates suggest up to 80% of women experience hot flashes during midlife¹ and, that on average, symptoms last for approximately 10 years from symptom onset through the menopausal transition.² Hot flashes consistently have been shown to be associated with discomfort, sleep disturbances, fatigue, and decreased quality of life.³ In addition, a recent study showed that, because of the negative effects of hot flashes on women's lives, women with hot flashes have lower work productivity and greater healthcare resource use than women without hot flashes.⁴ There is also some indication that hot flashes are associated with an increased risk of more serious adverse health outcomes, including cardiovascular disease⁵ and depression.⁶

Despite the impact that hot flashes can have on a woman's life, little remains known, to date, about risk factors for hot flashes or the events that precipitate them. Several characteristics and health behaviors have more often than not been reported to be significantly associated with an increased risk of hot flashes during midlife, including cigarette smoking⁷⁻⁹, obesity^{7, 10-12}, and lower levels of education^{9, 12-14}; however, these associations have not been observed in all studies examining these relationships.¹⁵ Other factors such as physical activity, alcohol intake, and reproductive history have also been examined in association with hot flashes; however, results pertaining to these risk factors have been less consistent than those reported for smoking, body mass index (BMI), and education (reviewed in: Ziv-Gal & Flaws¹⁶). There are a number of possible reasons why the results of studies examining the associations between risk factors and hot flashes have been inconsistent, including that the populations under study were composed of women of different race and ethnic backgrounds and that the measurement of hot flashes varied from a single question to a more detailed hot flashes history.

Starting in 2006, the longitudinal Midlife Women's Health Study has been conducted with the purpose of examining risk factors for hot flashes in a large population-based cohort study of women undergoing the midlife transition. In the Midlife Women's Health Study, detailed information on the experiencing of hot flashes is collected annually by self-report and a clinic visits are conducted to measure height and weight, to collect blood samples for hormone measurements, and a obtain ovarian volume measurement using a transvaginal ultrasound. The objective of this analysis was to describe the baseline characteristics of the cohort and to report, using the data collected at baseline, the associations between demographic characteristics, health behaviors, hormone concentrations, and the experiencing of any, more severe, and more frequent hot flashes.

METHODS

Study participants

The Midlife Women's Health Study is a cohort study of hot flashes among midlife women (45 to 54 years of age) that began in 2006, enrolling residents of the Baltimore metropolitan region, which includes Baltimore city and its surrounding counties. Detailed methods of this study are described in Gallicchio *et al.*¹⁵ All participants gave written informed consent according to procedures approved by the University of Illinois and Johns Hopkins University Institutional Review Boards.

Briefly, women in the selected age range were recruited through mass mailings in the targeted region. Women who were interested in participating in this study, which was presented as a general "Midlife Health Study" to avoid reporting bias, were invited to call the clinic to obtain more information. During this call, the clinic staff determined whether the woman met the eligibility criteria. Women were eligible if they were between 45 and 54 years of age, had intact ovaries and uteri, and were either pre- or peri-menopausal. Women were excluded if they were pregnant, had a history of cancer, or were postmenopausal. Women were also excluded if they were taking exogenous female hormones or herbal/plant substances so that we could study risk factors for hot flashes without the confounding effects of known treatments for hot flashes. Menopausal status was defined as follows: pre-menopausal women were those who experienced their last menstrual period within the past 3 months and reported 11 or more periods within the past year. Peri-menopausal women were those who experienced 1) their last menstrual period within the past year, but not within the past 3 months, or 2) their last menstrual period within the past 3 months and experienced 10 or fewer periods within the past year. Post-menopausal women were those women who had not experienced a menstrual period within the past year.

If a woman was eligible and interested in participating in the study, she was asked to make a clinic visit (the baseline visit) to a Johns Hopkins clinical site. During this baseline clinic visit, the participant completed the detailed 26-page baseline study survey, donated blood and urine samples, was weighed and measured (height), had her blood pressure measured, and received a transvaginal ultrasound to measure ovarian volume. Each participant was then asked to visit the clinic once per week for the three weeks following the baseline visit so that the study staff could obtain additional blood and urine samples. Women also completed a brief questionnaire at the last of the three weekly visits following the baseline visit. These four consecutive weekly clinic visits were then repeated on a yearly basis throughout the woman's participation in the study. Only data from the baseline clinic visit were analyzed in this study.

Through April 2014, 736 women were enrolled in the study of which 734 completed the baseline clinic visit and questionnaire. Two of these women were determined to be post-menopausal, and, thus, ineligible, at baseline after enrolling into the study and completing the clinic visit. Therefore, the final analytic dataset was comprised of 732 pre- and peri-menopausal women.

Study variables

On the study questionnaires, hot flashes were defined for participants as “a sudden feeling of heat in the face, neck, or upper part of the chest. Hot flashes are often accompanied by reddening or flushing of the skin followed by sweating and chills.” At baseline, a detailed hot flash history was obtained through a series of questions on the survey that asked for information on the following: whether the woman had ever experienced hot flashes, whether she had a hot flash in the past 30 days, the usual severity of hot flashes, the frequency of hot flashes, and the length of time that the woman experienced hot flashes. Women who responded no to ever experiencing hot flashes were prompted to skip the more detailed hot flash questions. The hot flashes questions chosen for inclusion on the questionnaires have been used to collect data on hot flashes in the Midlife Health Studies for over 10 years.

In terms of severity, each woman was asked to describe her hot flashes as: mild (sensation of heat without sweating), moderate (sensation of heat with sweating), or severe (sensation of heat with sweating that disrupts usual activity). In terms of frequency of hot flashes, each woman was asked to describe her hot flashes as occurring: every hour, every 2-5 hours, every 6-11 hours, every 12-23 hours, 1-2 days per week, 5-6 days per week, 2-3 days per month, 1 day per month, less than 1 day per month, or never. For analysis of the data, the following hot flash variables were examined as dependent variables (outcomes): ever experienced hot flashes (yes versus no); experienced any hot flashes in the past 30 days (yes versus no); moderate or severe hot flashes (yes versus no); and weekly or daily hot flashes (yes versus no).

Height and weight measured at the clinic visit were used to calculate BMI, which was categorized as less than 25 kg/m², 25 to 29.9 kg/m², and 30 kg/m² or greater. Smoking was categorized as current, former, and never using the questions: “Have you ever smoked cigarettes?” and “Do you still smoke cigarettes?” Similarly, alcohol use data were collected using the following questions: “During your entire life, have you had at least 12 drinks of any kind of alcoholic beverage?” and “In the last 12 months have you had at least 12 drinks of any kind of alcoholic beverage?” Further queries for those responding that they had had at least 12 drinks in the last 12 months were made regarding the number of days per month, on average, that the woman drank and the number of drinks that the woman drank on those days. Physical activity was assessed by the participant's response to the question: “In comparison with others my own age, I think my physical activity leisure time is: [choices: much more, more, as much, less, and much less].” Employment status was categorized as employed (either full-time or part-time) and not employed. Medication use information was provided by the participant. The presence of depressive symptoms was assessed using the Centers for Epidemiologic Studies – Depression Scale (CES-D).¹⁷ Individuals with a score > 16 were identified as having depressive symptoms. Data on race, education, and reproductive history were also collected on the questionnaire.

Ovarian volume

The transvaginal ultrasound examinations to collect data on ovarian volume were performed using the 7.5 MHz transvaginal probe on a GE transvaginal ultrasound machine. Examination of the ovary was established by scanning from the outer to the inner margin.

All of the transvaginal ultrasounds were conducted by highly trained physicians in the Department of Gynecology and Obstetrics at Johns Hopkins University. The physicians used a highly standardized protocol for the measurements on calibrated equipment. In pilot studies, the ultrasound measurements were determined to be highly repeatable. For example, when two different physicians performed ovarian size measurements on the same participant, the values were very close to each other (e.g., physician 1: right ovary, $2.98 \times 2.05 \times 2.04$ cm and physician 2: right ovary, $2.75 \times 1.95 \times 1.71$ cm). Given the extensive training and experience of the physicians performing the transvaginal ultrasounds, the use of calibrated equipment, and the repeatability of the results, solid quality controls were in place for transvaginal ultrasound measurements in the study.

Hormone assays

Serum concentrations of estradiol, testosterone, and progesterone were measured in blood samples collected at each clinic visit. Women were asked to donate blood at four clinic visits over four weeks during year 1 (baseline) and each subsequent year of participation in the study; however, not all women were able to attend all four clinic visits in year 1 or in follow-up years. In year 1, 82.0% of participants completed all four visits; 12.2% completed three visits, 2.3% completed two visits, and 3.5% completed only one visit. A single concentration value for year 1 and for each subsequent follow-up year was calculated using the average value of the hormone concentrations that were measured in each year.

Estradiol, testosterone, and progesterone concentrations were measured using enzyme-linked immunosorbent assays (ELISA). ELISA kits were obtained from Diagnostic Systems Laboratories, Inc. (Webster, TX) and the assays were run using the manufacturers' instructions.¹⁸ All assays were conducted in the same laboratory. All samples were run in duplicate and mean values for each participant were used in the analysis. The laboratory personnel were blind with respect to any information concerning study subjects. For quality control purposes, samples from both women with hot flashes and women without hot flashes were run within the same laboratory batches. In addition, positive controls containing known amounts of estradiol, testosterone, and progesterone were included in each batch. Further, some samples were run in multiple assays to ensure that the assay values did not dramatically shift over time.

The minimum detection limits and intra-assay coefficients of variation were as follows: estradiol 7pg/ml, $3.3 \pm 0.17\%$; testosterone 0.04ng/ml, $2.2 \pm 0.56\%$; and progesterone 0.1ng/ml, 2.1 ± 0.65 . The average inter-assay coefficient of variation for all assays was less than 5%.

Statistical analysis

Hormone concentration data were log-transformed because the values were not normally distributed. Normality was assessed by examining the distribution of hormone concentrations among women with and without hot flashes. Univariate analyses were done by calculating frequencies for categorical variables and geometric means for the continuous log-transformed hormone variables. Differences in demographic, reproductive, and health habit characteristics by hot flash status (ever versus never) were examined using chi-square

tests for categorical variables; differences in hormone concentrations by hot flash status were examined using generalized linear models.

To examine the age- and covariate-adjusted associations between participant characteristics, hormone concentrations, and each hot flash outcome, odds ratios (ORs) and 95% confidence intervals (CI) were estimated using logistic regression models. Variables included in all covariate-adjusted models were those that have been reported consistently in the published literature to be associated with hot flashes as well as those shown in the bivariate analyses to be significantly associated with a history of hot flashes at $p < 0.05$. Hormone concentrations were not included as covariates in the covariate-adjusted models, as hormone concentrations may represent the mechanism by which certain risk factors are associated with hot flashes. Further, models examining the association between a hormone and a hot flash outcome were not adjusted for other hormone concentrations.

All analyses were conducted among the total sample and also by race (white and black); however, race was not determined to be an effect modifier of the associations and the race-stratified results are not presented. Analyses were performed with SAS, version 9.2 (SAS Institute, Inc., Cary, North Carolina). A two-sided p -value of less than 0.05 was considered statistically significant.

RESULTS

At baseline, 45.4% of the study participants reported experiencing midlife hot flashes. Characteristics of women with and without a history of hot flashes are presented in **Table 1**. Women with a history of hot flashes were more likely to be older, to have graduated college, to be current or former smokers, to be of peri-menopausal status, to have depressive symptoms, and to be taking an anti-hypertensive medication compared to women without hot flashes. Mean estradiol and progesterone concentrations were significantly lower among women reporting hot flashes compared to those not reporting hot flashes. Similarly, mean ovarian volume was lower among women with hot flashes compared to women without hot flashes.

Among the women who had a history of midlife hot flashes, the majority reported experiencing hot flashes in the previous 30 days (72.3%) (**Table 2**). Approximately 9% reported their hot flashes as usually being severe, with 55.7% reporting them as being moderate in severity. About a quarter of those with hot flashes reported experiencing them daily and 26.2% reported experiencing hot flashes weekly. The majority of women with hot flashes in the study had experienced them for one to four years (44.9%).

The age- and covariate-adjusted associations between the participant characteristics, hormone concentrations, and the hot flashes outcomes (history of hot flashes, current hot flashes, moderate to severe hot flashes, and weekly or daily hot flashes) are shown on **Tables 3 and 4**. In the covariate-adjusted models, older age, peri-menopausal status, current and former cigarette smoking, and depressive symptoms were significantly associated with increased odds of all of the hot flashes outcomes. Peri-menopausal status was the factor that was most strongly related to the hot flashes outcomes, with ORs ranging from 5.34 (history

of hot flashes) to 12.42 (weekly or daily hot flashes) comparing peri-menopausal to pre-menopausal women. In addition, after adjustment for covariates, history of oral contraceptive use was associated with increased odds of ever experiencing hot flashes (OR 1.89; 95% CI 1.16, 3.08). In contrast, higher current alcohol intake (more than one drink per day) was significantly associated with decreased odds of ever experiencing hot flashes, currently experiencing hot flashes, and moderate to severe hot flashes.

Higher estradiol and progesterone concentrations were significantly associated with decreased odds of all of the hot flashes outcomes after adjustment for age, race, education, BMI, smoking, alcohol consumption and menopausal status. Testosterone concentration was not significantly associated with any of the hot flashes outcomes. Ovarian volume was significantly associated with all outcomes in the age-adjusted but not the covariate-adjusted analyses.

DISCUSSION

This study examined risk factors for experiencing any, current, more severe, and more frequent hot flashes among women aged 45 to 54 years participating in the Midlife Women's Health Study. Results of this study showed that older age, peri-menopausal status, cigarette smoking, and depressive symptoms were associated with a statistically significant increased risk of all of the hot flash outcomes. Conversely, greater alcohol intake and higher estradiol and progesterone concentrations were associated with a decreased risk of hot flashes. In general, the strength of the associations associated with each risk factor were similar across all outcomes except for menopausal status, where the OR for more frequent hot flashes was twice that of the other hot flashes outcomes. The consistency of the ORs suggests that the hot flashes the women report in the study that are associated with certain risk factors are likely be consistent in nature themselves – primarily moderate to severe in nature and experienced on a weekly or daily basis. Further, the stronger association between menopausal status and frequency of hot flashes confirms both clinical and research findings that the frequency of hot flashes increases during peri-menopause. In total, the results of this study add to previously published findings in that more detailed data on hot flashes were collected than in previous studies, allowing for a more thorough understanding of the role of certain factors in the development of midlife hot flashes.

Cigarette smoking has been the factor that has been most consistently reported to be associated with midlife hot flashes in previously published studies.^{7-9, 13, 19} Results from the present study confirm these previous findings. Specifically, current smoking was associated with a 2.6 fold increase in odds of ever experiencing hot flashes and, further, 3.4 to 3.8 increased odds of experiencing current, more severe, and more frequent hot flashes. Former smokers were also at significantly increased risk of all hot flashes outcomes, although the increase in odds was not as great as current smokers when compared to never smokers. A number of mechanisms for the increased risk of hot flashes associated with cigarette smoking have been postulated, including the anti-estrogenic effect of smoking.²⁰ However, in this study, consistent with what has been reported in several other previously published studies^{8, 21}, addition of estradiol as a covariate in the multivariable adjusted models for cigarette smoking did not attenuate the OR estimates (data not shown), indicating that other

mechanisms may be involved. Such mechanisms could include alterations in neurotransmitter metabolism within the dopaminergic system, as hypothesized by Butts *et al.*²²

In the present study, alcohol intake was significantly associated with decreased odds of experiencing any, current, and more severe hot flashes after adjustment for other risk factors and covariates, although there was little evidence of a dose-response relationship observed in terms of drinks per day in the analyses. Alcohol intake is a factor that has been shown in published studies to be associated with both increased^{19, 23, 24} and decreased risk^{25, 26} of midlife hot flashes. There is some evidence that alcohol consumption increases estrogen concentrations^{27, 28}, which would support our finding of a decreased risk of hot flashes with more alcohol intake, as hot flashes are thought to be associated with low estradiol levels. However, similar to cigarette smoking, the OR estimates for the hot flashes outcomes associated with alcohol intake did not change after the addition of estradiol, or progesterone, to the multivariable model (data not shown). An alternative mechanism is that perhaps most of the alcohol consumed by participants of this study was in the form of wine, and that a major component of wine, resveratrol, exerts health benefits such as lowering oxidative stress²⁹, leading to a decreased risk of hot flashes. We did not collect data on type of alcohol consumed (e.g., beer, wine, spirits, etc); thus, wine as the most common type of alcoholic beverage consumed is speculative based on the demographic characteristics of this study sample. Further, it unknown if there is a relationship between oxidative stress and hot flashes, although there are some data that suggest such an association.³⁰ The relationship between alcohol intake and hot flashes could also be bi-directional, with women having hot flashes increasing the amount of alcohol consumed.

Depressive symptoms were also significantly associated with the occurrence of hot flashes in this study. As this analysis was cross-sectional in nature, the temporality of the association between depressive symptoms and hot flashes is not clear. A recently published systematic review by Worsley *et al.*³¹ on the association between vasomotor symptoms and depression during the menopausal transition concluded that there is a positive, bidirectional association between vasomotor symptoms and depression during peri-menopause, with women with depressive symptoms more likely to develop vasomotor symptoms and women with vasomotor symptoms more likely to develop depressive symptoms. The systematic review was based on 17 cross-sectional studies and 12 cohort studies, although three large longitudinal studies accounted for a large percentage of the reviewed publications [The Study of Women's Health Across the Nation (SWAN), the Seattle Midlife Women's Health Study (SMWH), and the Penn Ovarian Aging Study (POA)]. A positive association between depressive symptoms and hot flashes could indicate a common etiology or that a depressed mood, or stress, might lower the threshold for reporting vasomotor symptoms.^{32, 33} Adjustment for hormone concentrations in the covariate-adjusted model did not attenuate the OR estimates between hot flashes and depressive symptoms (data not shown), suggesting that hormones do not mediate the association.

It should be noted that BMI was not associated with any of the hot flashes outcomes in this study. This finding, and a more in-depth discussion of the BMI results, was reported in a previous publication from the same cohort.¹⁵ In brief, it is unclear why the findings for this

study are different than those reported in similar types of studies. One possibility is that the perimenopausal women in our cohort study were later in peri-menopause than women in other similar studies of midlife women. Data collected in the study allowed for the determination of whether a woman was pre-menopausal, peri-menopausal, or post-menopausal; however, it is not possible to know from our data how early the participants were in each stage and how this compares to different studies. Thus, we can only speculate that reported differences in the association between BMI and hot flashes among studies are due to differences in where participants are in each stage of the menopausal transition.

Similarly, physical activity and reproductive factors such as having ever been pregnant, number of pregnancies, age at menarche, and age at first birth, were also not significantly associated with midlife hot flashes in this study. Findings in the published literature in regards to hot flashes and both physical activity and reproductive history have been inconsistent^{13, 16, 34-42} and, therefore, have not contributed to the identification of risk factors that could help provide clues to the etiology of hot flashes or measures to prevent the onset of hot flashes.

There has been much controversy about the etiology of midlife hot flashes. Numerous studies have examined the role of sex steroid hormones in hot flash etiology, with much of the focus being on estradiol. As shown in this study, and other longitudinal investigations^{9, 43, 44}, the risk of hot flashes increases over the menopausal transition, a time period when estradiol concentrations decline dramatically. The finding of a statistically significant increase in the odds of hot flashes associated with a decrease in estradiol concentration in this study is consistent with previous cross-sectional and longitudinal studies⁴⁵⁻⁴⁹, and it is thought that estrogen is involved in the thermoregulatory homeostasis in the hypothalamus.⁵⁰ In contrast to the numerous studies reporting on estradiol and hot flashes, the association observed in the present study between lower progesterone concentrations and an increased risk of hot flashes has only been reported in one previous study, conducted by our research group⁴⁷, although many studies have shown that progestin therapies are effective in reducing or preventing hot flashes in perimenopausal women (examples: Prior *et al.*⁵¹, Hitchcock *et al.*⁵², Ruiz *et al.*⁵³). There is some evidence that progestins, similar to estrogens, interact with several neurotransmitter pathways in the hypothalamus responsible for thermoregulation.⁵⁴ There is a paucity of information on progesterone and the etiology of menopausal symptoms; thus, future work should be conducted in this area.

There are several limitations of this study that should be considered. First, this analysis was cross-sectional in nature; thus, we are unable to determine the temporality of the associations observed with hot flashes. Second, the study sample, although relatively large, was well-educated and included mostly African-American and white women. Therefore, there may be selection bias in this study, and the results may not be generalizable to all midlife women. Finally, most of the data collected in this study, including the data on hot flashes, were based on self-report and not on objective measurements. We elected to use self-reported occurrence of hot flashes rather than a physiologic assessment of their occurrence primarily because physiological measurement of hot flashes is technically difficult and has not been validated in large populations. Most population-based studies have

used self-report as a valid measure of hot flashes,^{2, 8} and the National Institutes of Health accept self-report as a valid indicator of hot flashes.⁵⁵

A major strength of this study was the collection of detailed data on hot flashes, pertaining to both the present and past experiencing of any, more severe, and more frequent, hot flashes. Few studies examining risk factors of hot flashes have collected such detailed data; most have relied on a single hot flash question or have focused on the hot flash experience within a brief time period (i.e. the previous four weeks). A second strength was the collection of multiple blood samples over a four week period for each participant. The hormone concentrations for these samples were averaged for each participant and analyzed, reducing variability due to the time in menstrual cycle of the clinic visit.

CONCLUSIONS

This study shows that older age, peri-menopausal status, cigarette smoking, and depressive symptoms are factors associated with a statistically significant increased risk of the experiencing of any, current, more severe, and more frequent hot flashes among midlife women. Conversely, greater alcohol intake and higher estradiol and progesterone concentrations are associated with a decreased risk of hot flashes. Although the temporality of such associations are not known due to the cross-sectional nature of the data, these observed relationships can help to identify women at risk for menopausal hot flashes and can provide intervention strategies (e.g. quitting cigarette smoking) to reduce risk. As the Midlife Women's Health Study cohort continues to be followed, future analyses from this study will examine the factors investigated in this study, including hormone concentrations, and their relation to hot flashes over the menopausal transition.

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Table 1

Baseline characteristics by self-reported history of hot flashes

<i>Demographic characteristics and health habits</i>	Yes (n = 332)		No (n = 400)		p-value^a
	n	%	n	%	
Age, years					<0.0001
45 to 49	177	53.3	303	75.7	
50 to 54	155	46.7	97	24.3	
Education					0.001
Some college or tech school or less	143	43.1	125	31.3	
Graduated college or more	188	56.6	272	68.0	
Race					0.18
White	209	63.0	275	68.8	
Black	110	33.1	107	26.8	
Other	13	3.9	16	4.0	
Employed					0.51
Yes	259	78.0	320	80.0	
No	72	21.7	79	19.8	
Body mass index (kg/m ²)					0.4
<25	128	38.6	163	40.7	
25 to <30	87	26.2	114	28.5	
30	117	35.2	123	30.8	
Cigarette smoking					0.0002
Current	45	13.6	29	7.2	
Former	133	40.1	129	32.3	
Never	153	46.1	242	60.5	
Alcohol use in past year					0.07
Yes, more than 1 drink per day	118	35.5	153	38.3	
Yes, 1 drink or less per day	85	25.6	118	29.5	
No	127	38.3	127	31.8	
Leisure time activity compared to others of own age					0.07
More	112	33.7	144	36.0	
As much	102	30.7	121	30.3	
Less	116	34.9	128	32.0	
<i>Reproductive characteristics</i>					
Age at menarche					0.5
<10 years	26	7.8	22	5.5	
11 or 12 years	126	38.0	160	40.0	
13 or 14 years	140	42.2	159	39.8	
15	39	11.7	53	13.3	
Menopausal status					<0.0001
Pre-menopausal	146	44.0	334	83.5	

<i>Demographic characteristics and health habits</i>	Yes (n = 332)		No (n = 400)		p-value^a
	n	%	n	%	
Peri-menopausal	186	56.0	66	16.5	0.07
History of oral contraceptive use					
Yes	290	87.3	331	82.7	
No	41	12.3	69	17.3	0.1
Ever been pregnant					
Yes	302	91.0	350	87.5	
No	29	8.7	50	12.5	0.4
Number of pregnancies					
Never been pregnant	29	8.7	50	12.5	
1 or 2	104	31.3	131	32.7	
3 or 4	136	41.0	150	37.5	
5	62	18.7	69	17.3	0.5
Age at first birth					
No live births	61	18.4	91	22.8	
20 years	44	13.3	42	10.5	
21 to 25 years	71	21.4	79	19.8	
26 to 30 years	75	22.6	83	20.8	
30 years	79	23.8	103	25.8	0.0002
Health and medication use					
Depressive symptoms					
Yes	85	25.6	59	14.8	0.1
No	236	71.1	329	82.3	
Diabetes medication					0.04
Yes	18	5.4	12	3.0	
No	313	94.3	387	96.8	0.3
Hypertension medication					
Yes	59	17.8	49	12.3	0.0001
No	272	81.9	350	87.5	
Depression medication					0.3
Yes	43	13.0	41	10.3	
No	288	86.7	358	89.5	0.0001
Hormones and ovarian volume	GM	95% CL	GM	95% CL	
Estradiol, pg/mL (n = 726)	43.2	(40.2, 46.3)	62.7	(58.9, 66.8)	
Testosterone, ng/mL (n = 727)	0.28	(0.26, 0.30)	0.29	(0.27, 0.31)	
Progesterone, ng/mL (n = 668)	0.54	(0.47, 0.64)	1.53	(1.33, 1.76)	
Ovarian volume, cm ³ (n = 628)	3.56	(3.29, 3.97)	4.49	(4.09, 3.70)	

GM = Geometric mean; 95% CL = 95% confidence limits

^aChi-square p-values for categorical variables; t-test p-values for continuous variables

Table 2

Hot flash experience at baseline among women reporting a history of hot flashes (n = 332)

	n	%
Experienced hot flashes in last 30 days		
Yes	240	72.3
No	86	25.9
I don't know	3	0.9
Severity of hot flashes		
Mild	108	32.5
Moderate	185	55.7
Severe	31	9.3
Hot flash frequency		
Daily	77	23.2
Weekly	87	26.2
Monthly	140	42.2
I don't know	22	6.6
Length of time experiencing hot flashes		
< 1 year	97	29.2
1 to 4 years	149	44.9
5 years	60	18.1
I don't know	19	5.7

Table 3

Age- and covariate-adjusted odds ratios (ORs) and 95% confidence intervals (CI) for the associations between demographic characteristics, health habits, reproductive factors, and hormones, with a history of hot flashes and hot flashes experienced in the last 30 days

	History of hot flashes		Current hot flashes (Hot flashes in last 30 days)	
	Age-adjusted OR (95% CI)	Covariate-adjusted ^a OR (95% CI)	Age-adjusted OR (95% CI)	Covariate-adjusted ^a OR (95% CI)
Age, years				
45 to 49	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
50 to 54	2.74 (2.00, 3.75)	1.75 (1.22, 2.52)	3.28 (2.33, 4.62)	1.95 (1.30, 2.94)
Education				
Some college or tech school or less	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Graduated college or more	0.61 (0.45, 0.83)	0.77 (0.54, 1.12)	0.56 (0.40, 0.79)	0.83 (0.54, 1.25)
Race				
White	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Black	1.37 (0.98, 1.91)	1.15 (0.76, 1.74)	1.58 (1.10, 2.27)	1.02 (0.64, 1.64)
Other	1.03 (0.47, 2.24)	1.10 (0.47, 2.58)	1.23 (0.54, 2.82)	1.44 (0.57, 3.62)
Employed				
Yes	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
No	0.89 (0.62, 1.29)	1.18 (0.77, 1.81)	0.75 (0.50, 1.11)	1.02 (0.64, 1.63)
Body mass index (kg/m ²)				
<25	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
25 to <30	0.89 (0.61, 1.29)	0.64 (0.42, 0.98)	1.16 (0.77, 1.76)	0.76 (0.48, 1.27)
30	1.16 (0.82, 1.66)	0.75 (0.49, 1.14)	1.47 (0.99, 2.19)	0.96 (0.59, 1.56)
Cigarette smoking				
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Former	1.58 (1.14, 2.19)	1.77 (1.23, 2.53)	1.76 (1.22, 2.53)	2.03 (1.35, 3.07)
Current	2.61 (1.55, 4.40)	2.68 (1.49, 4.84)	3.42 (1.96, 5.98)	3.80 (1.99, 7.26)
Alcohol use in past year				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes, 1 drink or less per day	0.73 (0.50, 1.08)	0.79 (0.51, 1.22)	0.55 (0.36, 0.85)	0.58 (0.35, 0.96)
Yes, more than 1 drink per day	0.75 (0.53, 1.07)	0.65 (0.43, 0.98)	0.70 (0.48, 1.03)	0.58 (0.37, 0.92)
Leisure time activity compared to others of own age				

	History of hot flashes		Current hot flashes (Hot flashes in last 30 days)	
	Age-adjusted OR (95% CI)	Covariate-adjusted ^d OR (95% CI)	Age-adjusted OR (95% CI)	Covariate-adjusted ^d OR (95% CI)
As much	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
More	0.91 (0.63, 1.33)	0.97 (0.64, 1.48)	0.89 (0.59, 1.35)	0.98 (0.61, 1.59)
Less	1.13 (0.78, 1.64)	1.02 (0.68, 1.55)	1.11 (0.73, 1.68)	1.02 (0.64, 1.64)
Age at menarche				
<10 years	1.64 (0.87, 3.09)	1.22 (0.59, 2.51)	1.86 (0.94, 3.66)	1.28 (0.58, 2.82)
11 or 12 years	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
13 or 14 years	1.16 (0.83, 1.62)	1.07 (0.74, 1.56)	1.10 (0.75, 1.59)	0.95 (0.61, 1.47)
15	0.89 (0.54, 1.45)	0.83 (0.48, 1.43)	0.93 (0.55, 1.60)	0.90 (0.48, 1.70)
Menopausal status				
Premenopausal	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Perimenopausal	5.52 (3.86, 7.88)	5.34 (3.69, 7.73)	6.96 (4.72, 10.28)	6.69 (4.44, 10.08)
History of oral contraceptive use				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	1.55 (1.01, 2.38)	1.89 (1.16, 3.08)	1.31 (0.82, 2.09)	1.62 (0.95, 2.79)
Ever been pregnant				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	1.30 (0.79, 2.14)	1.25 (0.72, 2.17)	1.25 (0.72, 2.18)	1.14 (0.61, 2.13)
Number of pregnancies				
Never been pregnant	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1 or 2	1.19 (0.69, 2.03)	1.22 (0.67, 2.22)	1.13 (0.62, 2.07)	1.10 (0.56, 2.18)
3 or 4	1.38 (0.82, 2.34)	1.35 (0.75, 2.43)	1.30 (0.72, 2.34)	1.24 (0.64, 2.42)
5	1.35 (0.75, 2.43)	1.07 (0.55, 2.07)	1.39 (0.72, 2.66)	0.97 (0.46, 2.07)
Age at first birth				
No live births	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
20 years	1.56 (0.91, 2.70)	1.14 (0.60, 2.19)	1.71 (0.94, 3.12)	1.04 (0.50, 2.19)
21 to 25 years	1.20 (0.75, 1.91)	1.26 (0.74, 2.13)	1.27 (0.75, 2.14)	1.22 (0.67, 2.22)
26 to 30 years	1.24 (0.78, 1.97)	1.33 (0.80, 2.22)	1.23 (0.73, 2.06)	1.35 (0.75, 2.43)
30 years	1.03 (0.66, 1.62)	1.23 (0.74, 2.02)	0.99 (0.59, 1.64)	1.20 (0.68, 2.13)
Depressive symptoms				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)

	History of hot flashes		Current hot flashes (Hot flashes in last 30 days)	
	Age-adjusted OR (95% CI)	Covariate-adjusted ^a OR (95% CI)	Age-adjusted OR (95% CI)	Covariate-adjusted ^a OR (95% CI)
Yes	2.03 (1.38, 2.97)	1.62 (1.06, 2.48)	2.34 (1.55, 3.53)	1.84 (1.15, 2.95)
Diabetes medication				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	2.08 (0.97, 4.46)	1.62 (0.69, 3.81)	2.68 (1.20, 5.99)	1.85 (0.74, 4.60)
Anti-hypertensive medication				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	1.52 (1.00, 2.32)	1.39 (0.85, 2.27)	1.80 (1.14, 2.84)	1.55 (0.90, 2.67)
Depression medication				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	1.27 (0.79, 2.02)	1.10 (0.65, 1.87)	1.24 (0.74, 2.09)	1.03 (0.57, 1.89)
Estradiol, pg/mL (continuous)	0.44 (0.34, 0.57)	0.63 (0.48, 0.83)	0.39 (0.29, 0.51)	0.59 (0.43, 0.81)
Testosterone, ng/mL (continuous)	0.88 (0.70, 1.11)	0.89 (0.69, 1.15)	0.92 (0.71, 1.18)	1.00 (0.75, 1.33)
Progesterone, ng/mL (continuous)	0.64 (0.56, 0.72)	0.79 (0.68, 0.92)	0.59 (0.52, 0.68)	0.77 (0.65, 0.91)
Ovarian volume, cm ³ (continuous)	0.72 (0.56, 0.93)	0.92 (0.70, 1.22)	0.69 (0.52, 0.91)	0.88 (0.64, 1.20)

95% CI = 95% confidence interval; OR = odds ratio

^a covariates included in all multivariable models are: participant age, race, education, body mass index, smoking, alcohol consumption, and menopausal status

Table 4

Age- and covariate-adjusted odds ratios (ORs) and 95% confidence intervals (CI) for the associations between demographic characteristics, health habits, reproductive factors, and hormones, with more severe hot flashes or more frequent hot flashes

	Moderate or severe hot flashes		Weekly or daily hot flashes	
	Age-adjusted OR (95% CI)	Covariate-adjusted ^a OR (95% CI)	Age-adjusted OR (95% CI)	Covariate-adjusted ^a OR (95% CI)
Age, years				
45 to 49	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
50 to 54	3.07 (2.16, 4.36)	1.81 (1.19, 2.76)	3.62 (2.47, 5.30)	1.61 (0.99, 2.62)
Education				
Some college or tech school or less	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Graduated college or more	0.55 (0.38, 0.78)	0.73 (0.48, 1.12)	0.54 (0.37, 0.81)	0.75 (0.46, 1.24)
Race				
White	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Black	1.41 (0.97, 2.06)	0.94 (0.58, 1.53)	1.49 (0.99, 2.26)	0.90 (0.51, 1.61)
Other	1.28 (0.55, 2.99)	1.39 (0.55, 3.55)	1.10 (0.42, 2.88)	1.58 (0.52, 4.82)
Employed				
Yes	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
No	0.83 (0.55, 1.25)	1.27 (0.78, 2.09)	0.79 (0.51, 1.25)	1.30 (0.74, 2.30)
Body mass index (kg/m ²)				
<25	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
25 to <30	1.07 (0.69, 1.64)	0.77 (0.47, 1.27)	1.24 (0.78, 1.98)	0.89 (0.50, 1.59)
30	1.39 (0.93, 2.09)	0.95 (0.58, 1.55)	1.20 (0.76, 1.90)	0.84 (0.47, 1.52)
Cigarette smoking				
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Former	1.91 (1.32, 2.78)	2.12 (1.39, 3.22)	1.51 (1.00, 2.29)	1.78 (1.08, 2.92)
Current	3.59 (2.03, 6.34)	3.51 (1.82, 6.76)	3.19 (1.72, 5.93)	3.44 (1.60, 7.43)
Alcohol use in past year				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes, 1 drink or less per day	0.67 (0.43, 1.05)	0.73 (0.44, 1.21)	0.72 (0.44, 1.17)	0.75 (0.41, 1.37)
Yes, more than 1 drink per day	0.71 (0.47, 1.06)	0.58 (0.37, 0.94)	0.80 (0.51, 1.24)	0.66 (0.38, 1.15)
Leisure time activity compared to others of own age				

	Moderate or severe hot flashes		Weekly or daily hot flashes	
	Age-adjusted OR (95% CI)	Covariate-adjusted ^d OR (95% CI)	Age-adjusted OR (95% CI)	Covariate-adjusted ^d OR (95% CI)
As much	0.95 (0.62, 1.45)	0.98 (0.60, 1.60)	0.68 (0.43, 1.09)	0.67 (0.37, 1.19)
More	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Less	1.24 (0.81, 1.90)	1.10 (0.69, 1.78)	0.92 (0.58, 1.46)	0.83 (0.48, 1.43)
Age at menarche				
<10 years	1.69 (0.83, 3.44)	1.08 (0.47, 2.51)	1.60 (0.71, 3.61)	0.92 (0.34, 2.49)
11 or 12 years	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
13 or 14 years	1.12 (0.76, 1.64)	1.01 (0.56, 1.57)	1.04 (0.68, 1.60)	0.89 (0.53, 1.50)
15	0.82 (0.47, 1.46)	0.91 (0.48, 1.74)	1.07 (0.59, 1.92)	1.03 (0.60, 2.14)
Menopausal status				
Premenopausal	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Perimenopausal	6.27 (4.21, 9.35)	5.78 (3.80, 8.78)	12.54 (7.90, 19.93)	12.42 (7.64, 20.19)
History of oral contraceptive use				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	1.47 (0.90, 2.41)	1.74 (0.99, 3.07)	1.32 (0.77, 2.27)	1.73 (0.90, 3.29)
Ever been pregnant				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	1.16 (0.66, 2.02)	1.01 (0.54, 1.88)	1.32 (0.69, 2.51)	1.19 (0.56, 2.55)
Number of pregnancies				
Never been pregnant	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1 or 2	0.95 (0.52, 1.76)	0.89 (0.45, 1.77)	1.08 (0.54, 2.20)	1.15 (0.50, 2.63)
3 or 4	1.41 (0.77, 2.54)	1.27 (0.66, 2.46)	1.40 (0.71, 2.77)	1.31 (0.59, 2.95)
5	0.99 (0.50, 1.95)	0.62 (0.28, 1.37)	1.59 (0.76, 3.34)	1.03 (0.42, 2.51)
Age at first birth				
No live births	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
20 years	1.86 (1.01, 3.41)	1.25 (0.60, 2.63)	2.03 (1.04, 3.99)	1.25 (0.51, 3.06)
21 to 25 years	1.29 (0.76, 2.20)	1.27 (0.70, 2.32)	1.27 (0.69, 2.32)	1.35 (0.65, 2.81)
26 to 30 years	1.18 (0.69, 2.01)	1.23 (0.68, 2.24)	1.37 (0.75, 2.47)	1.46 (0.72, 2.93)
30 years	0.85 (0.50, 1.45)	1.06 (0.59, 1.92)	1.01 (0.56, 1.83)	1.25 (0.63, 2.50)
Depressive symptoms				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)

	Moderate or severe hot flashes		Weekly or daily hot flashes	
	Age-adjusted OR (95% CI)	Covariate-adjusted ^a OR (95% CI)	Age-adjusted OR (95% CI)	Covariate-adjusted ^a OR (95% CI)
Yes	2.39 (1.57, 3.64)	1.78 (1.11, 2.86)	2.34 (1.41, 3.54)	1.82 (1.04, 3.17)
Diabetes medication				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	2.56 (1.13, 5.79)	1.69 (0.66, 4.36)	1.78 (0.66, 4.78)	0.91 (0.28, 3.00)
Anti-hypertensive medication				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	1.75 (1.10, 2.79)	1.47 (0.84, 2.55)	1.49 (0.88, 2.52)	1.36 (0.70, 2.67)
Depression medication				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	1.44 (0.86, 2.40)	1.19 (0.66, 2.17)	1.28 (0.72, 2.29)	1.06 (0.52, 2.15)
Estradiol, pg/mL (continuous)	0.41 (0.31, 0.55)	0.63 (0.46, 0.87)	0.35 (0.25, 0.78)	0.62 (0.43, 0.89)
Testosterone, ng/mL (continuous)	0.93 (0.72, 1.20)	0.98 (0.73, 1.32)	0.87 (0.66, 1.16)	0.93 (0.66, 1.32)
Progesterone, ng/mL (continuous)	0.61 (0.53, 0.70)	0.78 (0.66, 0.92)	0.51 (0.43, 0.60)	0.69 (0.57, 0.84)
Ovarian volume, cm ³ (continuous)	0.73 (0.55, 0.97)	0.98 (0.72, 1.35)	0.66 (0.47, 0.90)	0.95 (0.66, 1.37)

95% CI = 95% confidence interval; OR = odds ratio

^a covariates included in all multivariable models are: participant age, race, education, body mass index, smoking, alcohol consumption, and menopausal status