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RISK OF LONG TERM HOT FLASHES AFTER NATURAL MENOPAUSE: EVIDENCE FROM THE PENN OVARIAN AGING COHORT

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Abstract

Objectives—To estimate the risk of hot flashes relative to natural menopause and evaluate associations of hormone levels, behavioral and demographic variables with the risk of hot flashes following menopause.

Methods—Annual assessments of 255 women who were premenopausal at baseline and reached natural menopause during 16 years of follow-up.

Results—The prevalence of moderate/severe hot flashes increased in each premenopausal year, reaching a peak of 46% in the first two years after the final menstrual period (FMP). Hot flashes decreased slowly following menopause and did not return to premenopausal levels until 9 years after FMP. The mean duration of moderate/severe hot flashes after FMP was 4.6 (SD2.9) years (4.9, SD3.1 years for any hot flashes). One-third of women at 10 or more years following menopause continued to experience moderate/severe hot flashes. African American women (obese and non-obese) and obese white women had significantly greater risk of hot flashes compared to non-obese white women (interaction P=0.01). In multivariable analysis, increasing FSH levels before FMP (P<0.001), decreasing estradiol (OR 0.87, 95% CI: 0.78–0.96, P=0.008), and increasing anxiety (OR 1.05, 95% CI: 1.03–1.06, P<0.001) were significant risk factors for hot flashes, while higher education levels were protective (OR 0.66, 95% CI: 0.47–0.91, P=0.011).

Conclusions—Moderate/severe hot flashes continued on average for nearly 5 years following menopause; more than one- third of women observed for 10 or more years following menopause had moderate/severe hot flashes. Continuation of hot flashes for more than 5 years following

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menopause underscores the importance of determining individual risk/benefit when selecting hormone or non-hormonal therapy for menopausal symptoms.

Keywords

menopause; hot flashes; vasomotor symptoms; race; obesity; hormone therapy

INTRODUCTION

Hot flashes are widely accepted as the cardinal and most troublesome symptom of menopause and are experienced to some degree by most women as their reproductive years end.[1,2] Hormone therapy continues to be the primary treatment in the medical management of hot flashes, but its risks, which were identified in the Women's Health Initiative trials,[3] now limit its use for menopausal symptoms to "the shortest period of time" …"not to exceed 3–5 years" in the guidelines of the North American Menopause Society.[4]

Empirical evidence to support the 3 to 5 year recommendation for hormone therapy administered for hot flashes is lacking. This study was motivated by previous studies that suggested hot flashes continued more than 5 years for some women but did not consistently identify the prevalence of moderate/severe hot flashes following the final menstrual period (FMP) or identify risks for hot flashes that extended beyond 5 years after the FMP. In a meta-analysis of primarily cross-sectional studies, nearly half the women reported hot flashes 4 years after the final menstrual period (FMP) and 10% reported symptoms 10 years after the FMP.[5] In a study of Australian women, the mean duration of hot flashes from symptom onset to study endpoint was 5.2 years,[6] but the duration following menopause, which is a key marker for medical management, was not identified. A survey of over 8,000 Latin American women indicated that more than 60% reported vasomotor symptoms 12 years after menopause.[7] We previously reported that the *total* median duration of hot flashes was 10.2 years when estimated from symptom onset in the late reproductive years through the menopause transition.[8] In that study, the prospective identification of hot flashes in the early menopause transition contributed strongly to their long duration. However, many participants had not progressed beyond menopause, and the duration of hot flashes after the FMP, which is the most common period for medical management, was not well characterized.

The data are now available to examine the prevalence and risks of hot flashes in the postmenopausal years. This study estimated the prevalence of hot flashes in relation to the FMP and evaluated risk factors for hot flashes that continued more than 5 years following the FMP. We also explored whether these risk factors predicted a short or long continuation of hot flashes (i.e., more than 3–5 years) following the FMP. The cut points for time following the FMP were guided by the data and provided empirical support for the recent revisions in the early and late stages postmenopause that were presented in STRAW+10 staging of reproductive aging.[9]

METHODS

Study participants

The study evaluated 255 women in the Penn Ovarian Aging Study (POAS) who reached natural menopause during a 16-year follow-up period (1996–2012). Only participants who reached natural menopause were included in order to address the primary aim of estimating the risk of hot flashes in relation to the FMP. Comparisons of the study variables at baseline between the sample and the remainder of the cohort that was not observed to reach natural menopause during the study (N=181) showed no significant differences with exception of age, which was older in the study group at baseline (42.2 versus 40.4 years, P<0.001).

The full cohort of 436 women was randomly identified by telephone digit dialing in Philadelphia County, PA, using stratified sampling to obtain equal numbers of African American and white women as previously described.[10] At enrollment, all women were premenopausal with regular menstrual cycles of 22–35 days for the previous three cycles, ages 35–48 years, had an intact uterus and at least one ovary. Exclusion criteria at cohort enrollment included current use of any hormonal or psychotropic medications, alcohol or drug abuse, major psychiatric disorder in the past year, pregnancy or breast feeding, uncontrolled hypertension, and serious health problems known to compromise ovarian function. The Institutional Review Board of the University of Pennsylvania approved the study, and all participants provided written informed consent.

Study design

Following cohort enrollment, follow-up assessments were conducted for 16 years at intervals of approximately 9 months in the first five years and then annually, with a two-year gap between assessments 10 and 11. Study data were collected at two in-home visits, which were timed to the early follicular phase of the menstrual cycle (days 2–6) in two consecutive menstrual cycles, or approximately one month apart in non-cycling women for 14 assessment periods. Assessments 15–16 were conducted by telephone interview. The study was described to participants as a general women's health study. Trained research interviewers obtained menstrual dates, structured interview data on overall health, blood samples for hormone assays, and anthropometric measures. Participants completed a set of validated self-report measures to assess health and other behavioral measures of the study at each assessment period.

Study variables

The primary outcome variable of moderate or severe hot flashes was reported by the participants at each follow-up period using a validated menopausal symptom list embedded in the structured interview questionnaire.[11] At each follow-up, the interviewer asked whether hot flashes or night sweats occurred in the past month, whether they occurred in the past year, and the severity, rated as 0 (none), 1 (mild), 2 (moderate), 3 (severe). Time in years was evaluated in relation to the FMP. The FMP was identified after 12 or more months of no menstrual bleeding and designated as time 0 for each subject to allow longitudinal evaluation of hot flashes each year before FMP (up to but not including time 0) and from the FMP onward. The cessation of moderate or severe hot flashes was defined as no moderate or

severe hot flashes reported for at least one year. Any hot flashes (mild, moderate, severe) were evaluated in the same manner as a secondary outcome.

Estradiol and follicle stimulating hormone (FSH) were measured by radioimmunoassay in the Clinical and Translational Research Center of the University of Pennsylvania using Coat-A-Count commercial kits (Siemens). The blood samples were collected at each study visit (providing a possible maximum of 28 samples per woman), centrifuged and frozen in aliquots at −80C. Assays were conducted in batches that included four visits per participant to reduce the within-woman variability resulting from assay conditions. All assays were performed in duplicate and repeated if values differed by greater than 15%. Inter-assay and intra-assay coefficients of variation were less than 5%.

Other covariate selections were based on previously determined associations with hot flashes and the aims of this study: current age, age at FMP, race (self-reported African American or white), body mass index (kg/m^2, >=30, <30); alcohol use >=1/week (yes, no), current smoking (yes, no), currently employed, (yes, no), education (>HS, <=HS), history of depression as assessed by medical history at enrollment in the cohort. Validated self-report questionnaires included the Zung Anxiety Index,[12] the Center for Epidemiologic Studies Depression Scale (CES-D),[13] the Perceived Stress Scale (PSS),[14] and physical health as rated on the SF-12 Health Survey.[15] Each scale provided continuous scores for analysis. Higher scores indicated more symptoms with exception of the SF-12 where higher scores indicated better health.

Statistical analysis

Longitudinal evaluations of the 255 participants in each study year provided 3,856 outcome reports for analysis. Forty percent of the sample had more than 6 years of observations after the FMP and 11% had more than 10 years of observations after the FMP. All available data were included in analysis. Generalized linear mixed effects regression models for repeated measures were used to estimate the bivariable and multivariable associations of the study variables with moderate/severe hot flashes. Variance estimates for the statistical tests on the regression coefficients were adjusted for repeated observations from each participant using generalized estimating equations.[16] All models were adjusted for time, which was defined in three segments relative to the FMP: 1) premenopause: each year before FMP (up to but not including time 0); 2) early postmenopause: FMP (time 0) to <6 years post FMP; 3) late postmenopause: >=6 years post FMP. (See cut point definitions below). This 3-level categorical variable was included in each model. The total duration of hot flashes was calculated for each participant from her first report of moderate or severe hot flashes to her last observed report of moderate/severe hot flashes in follow-up. Observations of hot flushes at the last available assessment were considered censored. Hot flushes were also censored at times of reported hormone use, pregnancy or breast feeding in all models. The present sample included no observations of hysterectomy or bilateral oophorectomy inasmuch as only women who reached natural menopause were included as described above. The models were repeated to evaluate a secondary cut point at <=3 years postmenopause and had nearly identical results.

All covariates were defined a priori. Each was added singly to the basic model with time and interaction with time. All potentially time-varying covariates were treated as such in modeling. Covariates that were associated with hot flashes at P<=0.20 were included in multivariable models to determine the independent contribution of the covariates to the outcome of hot flashes. Inclusion in final multivariable models was guided by whether each variable remained statistically significant at P<=0.05 or modified other significant associations by more than 15%. Hypothesized interactions with time were examined for BMI, race and hormones. No 3-way interactions met criteria for inclusion.

The cut points for early and late postmenopause were identified from estimates of hot flashes at each postmenopausal year relative to the FMP (depicted in Figure 1). The cut point at year 6 after the FMP had the largest symptom decrease from the FMP with reliable sample size and was consistent with the cut point between early and late postmenopause suggested in the revised STRAW-10 staging.[9] The secondary cut point at year 3 after the FMP had the first (but smaller) decrease from the peak hot flash estimates and was consistent with the cut point in early postmenopause suggested in STRAW-10.

Hormone levels were modeled using natural log transformations to reduce the influence of large values. The subject mean of the two hormone measures obtained at each assessment period was used in analysis. Hormones were entered separately in multivariable models due to their high correlation. In the exploratory model, the rate of change for each hormone (slope) *prior to the FMP* was used to predict hot flash duration after the FMP. The rate of change was calculated for each woman as the linear regression line for all points in the observed linear range prior to the FMP, as previously described.[17] Odds ratios for the hormones are presented per 1 unit (standard deviation) change in log hormone.

An exploratory analysis of short versus long continuation of hot flashes after the FMP included 158 participants who had moderate/severe hot flashes for at least one year after the FMP. The short-continuation group included participants whose moderate/severe hot flashes were observed to end within the 3-year follow-up interval. Participants whose follow-up ended prior to 3 years and reported moderate/severe hot flashes at their last observation were excluded because it was not possible to define the cessation of moderate/severe hot flashes within the 3-year interval for these women. Also, participants who had insufficient follow-up after the FMP to accurately determine the cessation of hot flashes within the first three years after the FMP were excluded. Participants who had moderate/severe hot flashes for more than 3 years after the FMP comprised the long-continuation group.

Statistical power calculations were computed using STATA version 12 (College Station, TX). Assumptions were based on data in the cohort and included a 35% risk of hot flashes for the unexposed group (mild or no hot flashes), at least 8 repeated measures per woman, type I alpha error of 5%, and within woman correlation of 0.4 for 80% power to detect an odds ratio of 1.93 for risk factors with a low prevalence of 20%. The detectible odds ratio is 1.76 for risk factors with prevalence of 30% and even lower for risk factors with prevalence greater than 30%. For the exploratory aim of identifying predictors of short versus long continuation of moderate/severe hot flashes, approximately 35% of the 158 women were classified in the short continuation subgroup, as defined by moderate/severe hot flashes that

ended within 3 years after the FMP. We examined which subject level risk factors with prevalence of 20% to 50% were associated with short continuation compared to long continuation following menopause. We assumed 25% with short continuation of hot flashes in the unexposed group with similar assumptions as above. Based on available data, there is 80% to detect odds ratios of 3.6 to – 2.77, respectively, in the exploratory analysis. Power is greater for continuous risk factors.

All analyses were conducted using the SAS 9.3 statistical package (SAS, Inc., Cary, NC). Statistical tests were two-sided, with P<=0.05 considered significant.

RESULTS

Sample description

Two hundred fifty-five participants were followed for 16 years with a mean of 15.1 outcome reports per participant and 1,336 person years of follow-up after the LMP. During the follow-up, 203 women (80%) reported moderate or severe hot flashes; 44 women (17%) had only mild hot flashes and 8 women (3%) reported no hot flashes. The mean age was 42.16 (SD 3.38) years at baseline and 51.47 (SD 3.32) years at FMP; 49% were African American and 51% were white (Table 1).

Prevalence of hot flashes in relation to the FMP

The peak prevalence of moderate or severe hot flashes was 46% and occurred in the first two years after the FMP (Figure 1). Ten years before the FMP, the prevalence was 16% and increased to 32% in the year before the FMP. The prevalence of moderate/severe hot flashes decreased slowly after the peak years. Return to a premenopausal level did not occur until approximately 10 years post-FMP, when the prevalence of 32% was the same prevalence as in the year before FMP.

The peak prevalence of *any* hot flashes (mild, moderate or severe) was approximately 74% and likewise occurred in the first two years post-FMP. Ten years before the FMP, the prevalence was 32% and increased to 58% in the year before the FMP. Return to a premenopausal level did not occur until 5–9 years post-FMP, when the prevalence of any hot flashes was approximately 58%, the same prevalence as in the year before FMP.

Hot flash duration after the FMP

In the subgroup of 182 women who reported moderate or severe hot flashes *after* the FMP, the mean duration of hot flashes a*fter the FMP* was 4.6 (SD 2.9) years. The mean duration of *any* hot flashes (mild, moderate or severe, n=230) after the FMP was only slightly longer (4.9 [SD 3.1]) years. Ten percent (25/255) of the participants had no hot flashes after the FMP. The *total* mean duration of moderate/severe hot flashes from initial onset to observed endpoint was nearly two times longer at 8.8 (SD 4.4) years. The total mean duration of any hot flashes was 10.2 (SD4.2) years (Table 2).

Associations with time and hormone levels

Table 3 shows associations of the a priori covariates with moderate/severe hot flashes in time-adjusted analysis. The prevalence of moderate or severe hot flashes was significantly associated with time in all models. Compared to early postmenopause (FMP +5 years), the risk of hot flashes was 66% lower before the FMP and but only 29% lower in late postmenopause (6+ years after FMP), a further indication of the slow decline in risk of hot flashes (OR 0.34, 95% CI: 0.28–0.41, P<0.001 and OR 0.71, 95% CI: 0.52–0.97, P=0.003, respectively).

FSH had a strong interaction with time in relation to hot flashes (P<0.001) that indicated the risk of hot flashes increased 63% with each 1 standard deviation increase in log FSH *before the FMP* (OR 1.63, 95% CI: 1.45–1.83, P<0.001) in multivariable analysis (Table 4). The association of FSH with hot flashes was not significant after the FMP (i.e., the early postmenopause stage and late postmenopause stage at 6+ years), when further FSH increases were moderate and then stabilized at postmenopausal levels (shown in Figure 2). Estradiol was evaluated separately in the multivariable model and had no significant interaction with time. Each unit (SD) decrease in log estradiol over the study interval resulted in 14% increase in the risk of hot flashes (OR 0.86, 95% CI: 0.77–0.96, P=0.008).

A significant interaction between BMI and race (P=0.01) in relation to hot flashes indicated that African American women (both obese and non-obese) and obese white women had the greatest risk of moderate/severe hot flashes over the study interval, while non-obese white women had the lowest risk (Table 4 and Figure 3). Among the 4 subgroups, there was no significant difference in age at FMP or duration of hot flashes *after the FMP* (Table 2). However, African American women had a longer total duration of hot flashes (9.5, SD 4.3 years versus 8.1, SD 4.4 years for white women, P=0.03), suggesting that the racial difference in risk of hot flashes occurred before the FMP.

Anxiety remained a significant risk factor for hot flashes in multivariable analysis, with an increased risk of 5% for each point increase in the anxiety score) over the study time period. Higher education levels were protective, with 34% lower risk of hot flashes among women with education beyond high school (Table 4). Age at FMP was included in all multivariable models but was not significant and added no additional information to the variable of time. Depressed mood (CES-D), history of depression, perceived stress, and poorer physical health were significantly associated with hot flashes in unadjusted analysis (Table 3), but not in multivariable analysis, due in part to their high correlations with anxiety. Current smoking, alcohol use, and employment had no significant association with moderate/severe hot flashes over time relative to the FMP.

The analyses were repeated to estimate associations with moderate/severe hot flashes using the earlier cut-point of >=3 years post-FMP; results were nearly identical to those shown in Tables 3 and 4. The analyses were also repeated to estimate associations with *any* hot flashes (mild, moderate, severe); results were consistent with those shown in Tables 3 and 4.

Predictors of short versus long continuation of hot flashes after FMP

We explored whether risk factors measured *before* the FMP predicted a short or long continuation of hot flashes *after the FMP*. The cut-point was at 3 years following FMP, as defined above. Only race remained a significant predictor after adjusting for all other variables in the model in this subgroup analysis. African American women were more than twice as likely as white women to be in the long-term group (OR 2.17, 95% CI 0.99–4.78, P=0.05). Contrary to our expectation, the duration of hot flashes before the FMP did not predict a short or long continuation of hot flashes after the FMP (OR=1.05, 95% CI: 0.93–1.17, P=0.38).

DISCUSSION

The mean duration of moderate/severe hot flashes *after the FMP* was more than 4½ years in this population-based sample that was followed for 16 years. The prevalence of hot flashes peaked in the year following FMP, but the mean prevalence of moderate/severe hot flashes did not return to its level *before* the FMP until approximately 10 years later. When the total duration of hot flashes was considered, including time before the FMP, the mean duration of moderate/severe hot flashes was nearly 9 years. These findings are consistent with other recent reports of the duration of hot flashes[5–8,18] and add further evidence that many women may experience hot flashes considerably longer than several years following menopause.

Hormone levels were significantly associated with hot flashes over the study interval. It is noteworthy that increasing FSH levels were strongly associated with hot flashes *before the FMP* but not in the early or late postmenopausal stages. We speculate that the strong interaction between FSH and hot flashes was due to the large increase in FSH levels that occurred before the FMP (i.e., the first time interval in the study), when FSH levels approximately doubled (as shown in Figure 2), while there was much less increase in FSH levels after the FMP as FSH gradually stabilized at postmenopausal levels.” Estradiol over the study interval had a weaker association with hot flashes, but the pattern of estradiol over time appeared notably similar to its pattern in the detailed hormone studies of Berger et al.[19] and Randolph et al.[20] We observed that the largest decrease in estradiol levels occurred approximately between year −2 to year +3 around the FMP, which Randolph et al identified as a significant decrease. These findings add support to the researchers’ conclusion that the hormone patterns around the FMP were a relatively consistent process in ovarian aging and were not associated with age at FMP. Further studies might determine whether the remission of hot flashes occurs following this observed decrease in estradiol levels as estradiol levels stabilize at postmenopausal levels.

The association of race with hot flashes was consistent with previous studies that found African American women were more likely to report hot flashes.[21–25] These findings added that African American women had a longer *total* duration of hot flashes compared to white women, but that neither age at FMP nor duration of hot flashes after the FMP differed between the two racial groups. Taken together, the findings suggested that racial differences in hot flashes occurred *before* menopause, which was consistent with our previous studies where African American women had an earlier onset of hot flashes and lower estradiol levels in the premenopausal stage compared to white women.[26] We know of no

demonstrated explanation for lower estradiol levels in premenopausal African American women, but speculate that differences in body composition and lean body mass contribute to lower estradiol levels and earlier onset of hot flashes.

In this study, body mass index (BMI) significantly modified the racial association with hot flashes, but the association was complex. Obese African American women, obese white women but also non-obese African American women had a greater risk of hot flashes. Again, we speculate that the increased risk of hot flashes in obese women was associated with their lower estradiol levels premenopause (and an earlier onset of hot flashes) as previously identified,[26, 27] but finding that non-obese African American women also had a greater risk of hot flashes remains unexplained. A report from the SWAN studies indicated that African American women were more likely to report hot flashes and also had greater symptom sensitivity, which supported postulates that cultural differences affect hot flash reporting, but further evidence is needed.[21]

Anxiety symptoms have been identified as a strong risk factor for hot flashes,[8, 10, 21, 28–30] but it is not known whether anxiety amplifies or is primarily a predictor of hot flashes.[31] It has also been suggested that the association between anxiety symptoms and hot flashes is due to an overlap of somatic symptoms of both disorders rather than to the psychological condition of anxiety.[30] Both anxiety and hot flashes have physiologic and psychological components that are difficult to disentangle, and whether anxiety is associated with responses to hot flash treatments is also not known. Increased understanding of the role of anxiety in hot flashes might lead to treatments that reduce both anxiety and hot flashes, but further studies that evaluate these issues are needed.

The finding that smoking was not associated with risk of long term hot flashes was consistent with other studies that found no relationship between smoking and hot flash duration.[5,8] Previous findings in our cohort indicated that smokers were more likely to experience hot flashes,[32] had an increased risk of entry into the menopause transition,[33] and that genetic susceptibility played a role in smoking associations with hot flashes.[34] The cohort has a high proportion of current smokers (40% versus 18% for adult women in the U. S.[35]), and smoking has been clearly associated with an earlier menopause, possibly due to its antiestrogenic effects,[34, 36] but it appears that smoking was not a factor in the risk of hot flashes after the FMP.

A limitation of the study is that current users of hormone therapy and women with surgical menopause were not included, and other studies to identify associations between these conditions and hot flash duration are needed. Our evaluation of risk factors for a short or long continuation of hot flashes following the FMP was conducted in a smaller subgroup with limited power and results should be interpreted with caution. A number of women continued to report hot flashes at study endpoint, and it is possible that longer follow-up would increase the prevalence and risks of hot flashes following the FMP. While we evaluated multiple risk factors known to be associated with hot flashes, other variables may be important. Our findings are based on a population-based cohort of African American and white urban women who were in general good health with no current hormone use and may not be generalizeable to all perimenopausal women.

The primary strengths of this report are the evaluation of hot flashes in relation to time before and after the FMP over a 16-year period. All participants were premenopausal at baseline and reached menopause during the study, which provided clear identification of menopause with minimal recall bias. The population-based sample was randomly identified and stratified to have similar numbers of African American and white women for analysis of racial associations. The repeated measures of hot flash reports and hormones were concomitant, and the multiple samples for hormone assays were collected in the early follicular phase in menstruating women for consistent assessments.

CONCLUSION

This study shows that women can expect hot flashes to continue on average for 4–5 years *after the FMP*, and that some women will experience moderate/severe hot flashes for more than 10 years after the FMP. The risk of hot flashes was modified by clinically evaluable risk factors that included race, obesity, anxiety and education levels. When the natural duration of hot flashes could exceed the 3–5 years recommended for HT, it is not surprising that women may experience a return of hot flashes after discontinuing HT, although this requires further studies. The findings point to the importance of individualized treatment by considering the potential duration of hot flashes together with the increasing evidence of effective treatment options[4, 37] when managing the postmenopausal woman.

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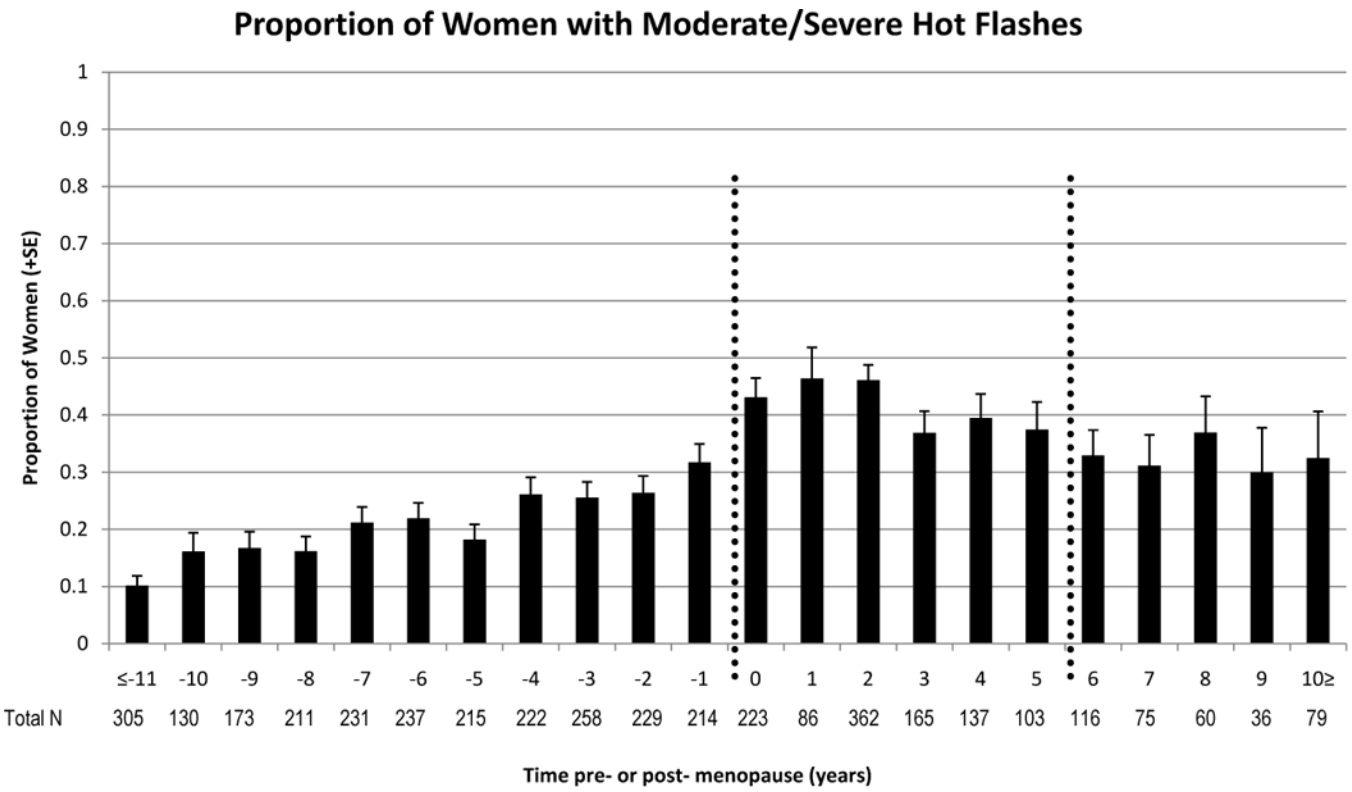

Figure 1.

Proportion of women with hot flashes at each year before and after the final menstrual period (Time 0). Dotted lines indicate time categories used in analysis: Premenopause: each year before FMP up to but not including time 0; early postmenopause: time 0 – 5.9 years; late postmenopause: ≥6 years.

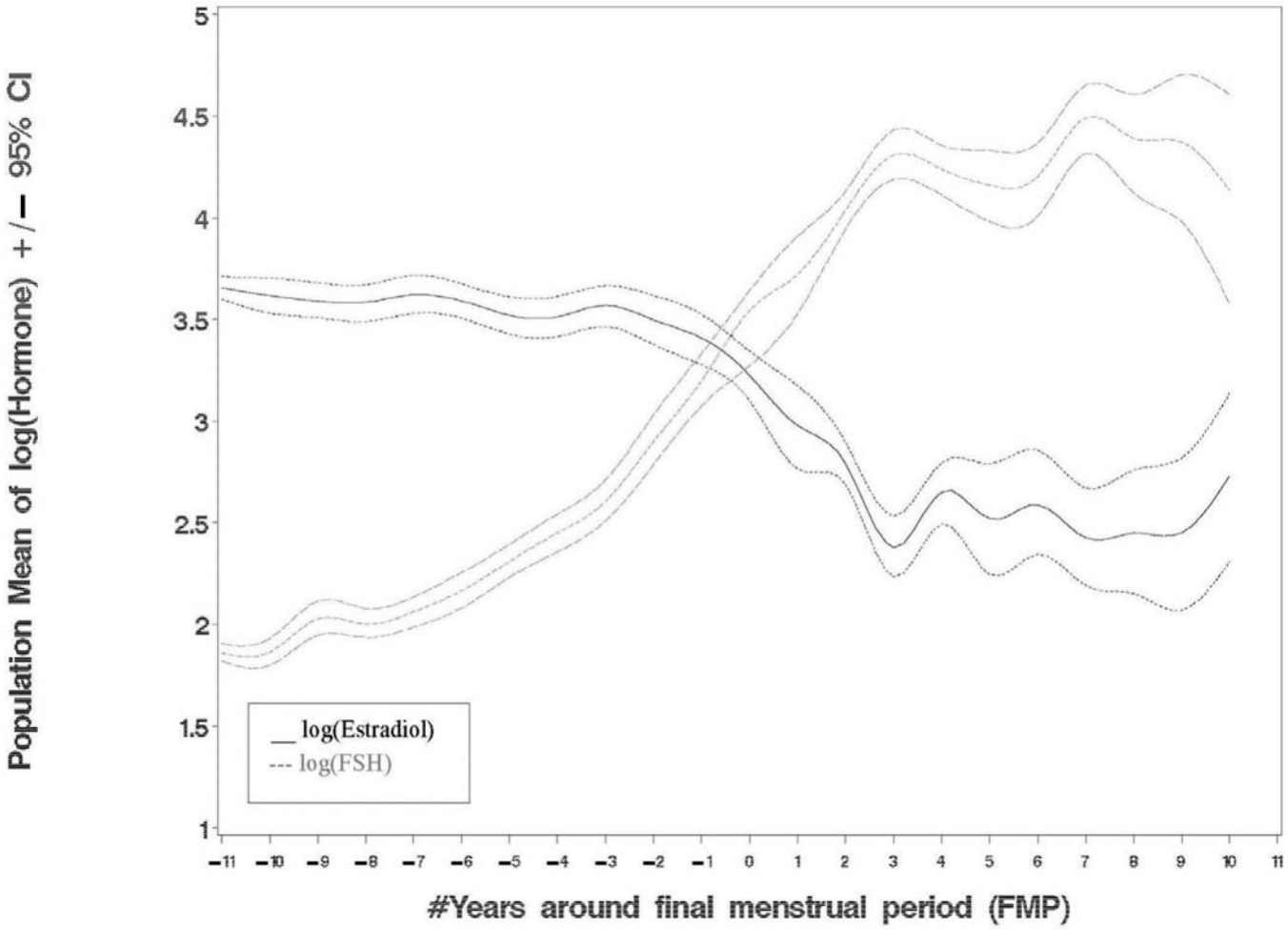

Figure 2.

Adjusted means (95% CI) in the years around the final menstrual period (Time 0) for natural logarithm-transformed estradiol (pg/mL) (solid line) and FSH (IU/L) (dotted line), N=255.

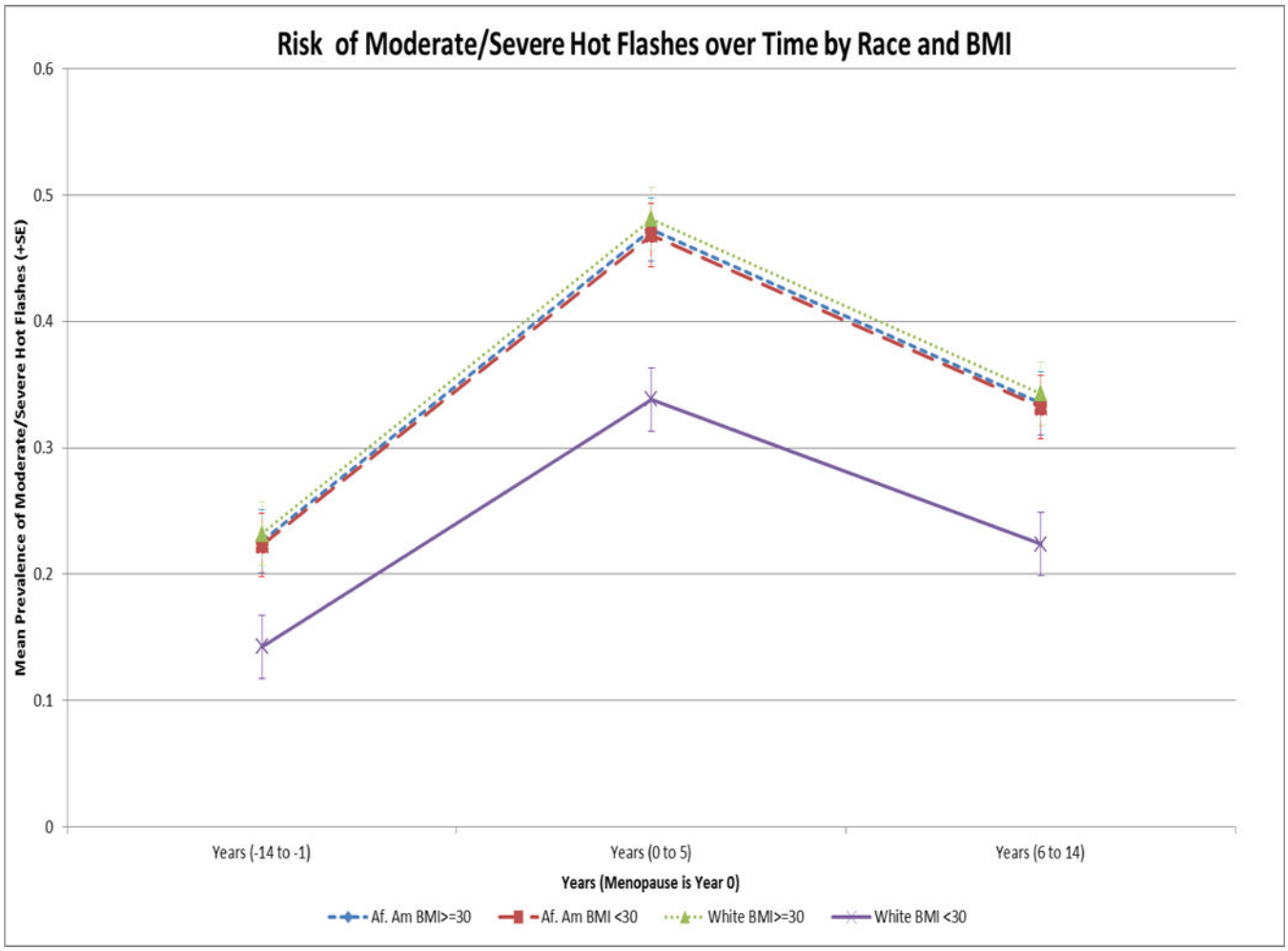

Figure 3.

Mean prevalence of moderate/severe hot flashes over time for race by BMI (interaction P=0.01), N=255. Data shown in Table 4.

Table 1

Characteristics of the Sample at Baseline

Variable	Baseline, N=255
	Mean(SD)
Age, y	42.16(3.38)
Age at FMP, y	51.47(3.32)
BMI, kg/m	29.21(7.75)
Anxiety (Zung), mean(SD)[a]	34.59(7.70)
Perceived stress (PSS) [b]	21.00(7.76)
Depression (CES-D) [c]	14.76(10.66)
Physical health (SF12)	50.11(8.34)
Estradiol, pg/mL	43.67(30.61)
FSH, mIU/mL	8.08(3.74)
	N(%)
CES-D ≥16	100(39.2)
History of depression	115(45.1)
Alcohol ≥1/wk	26(10.2)
Current smoker	102(40.0)
Employed	215(84.3)
Education >HS	144(56.5)
≤HS	111(43.5)
Race	
African American	124(48.6)
White	131(51.4)

[a] Score categories by Zung are 20–35 (normal), 36–47 (moderate), 48–60 (high).

[b] Mean score for community-based adult females is 25.6 (SD 8.2).

[c] The standard cut point for high depressive symptoms is ≥ 16.

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Table 2

Duration of Hot Flashes in 16 Year Follow-up

			Duration after FMP (yrs)			Total Duration (yrs)		
Hot Flashes	**N**	**Age at FMP, mean (SD)**	**Mean (SD)**	**Median**	**Range, yrs**	**Mean (SD)**	**Median**	**Observed Range, yrs**
Moderate-Severe	182[a]	51.3 (3.3)	4.6 (2.9)	4.0	12.9	8.8 (4.4)	9.4	14.7
Race × BMI[b]								
African American, <30	43	50.6 (3.5)	4.9 (3.5)	5.4	12.9	9.9 (4.1)	10.6	14.7
African American, ≥ 30	49	51.8 (3.5)	4.7 (2.6)	4.5	10.9	9.1 (4.5)	11.1	14.7
White, < 30	62	51.6 (3.2)	4.4 (3.0)	3.6	11.8	7.8 (4.6)	6.9	14.6
White, ≥ 30	28	50.7 (2.2)	4.3 (1.9)	4.0	7.9	8.8 (3.8)	9.1	11.2
Any	230[a]	51.4 (3.3)	4.9 (3.1)	4.5	14.7	10.2 (4.2)	12.0	15.0

[a] Number of participants who reported hot flashes after the FMP.

[b] Interaction of race × BMI, P=0.018.

Table 3

Odds Ratios for Risk Factors for Hot Flashes Adjusted for Time [a], N=255

Variable	Odds Ratio	95% CI	P Value
Time			<0.001
11–1 yrs before FMP	0.34	0.28 – 0.41	<0.001
FMP + 5 yrs	Reference	—	—
≥ 6 yrs after FMP	0.71	0.52 –0.97	0.003
FSH [b,c]			<0.001[d]
1–11 yrs before FMP	1.50	1.34 – 1.67	<0.001
FMP + 5 yrs	1.07	0.91 – 1.25	0.400
≥ 6 yrs after FMP	0.77	0.54 – 1.10	0.150
Estradiol	0.87	0.78 – 0.96	0.008
Race			0.003
African American	1.64	1.18 – 2.27	
White	0.61	0.44 – 0.85	
BMI			0.006
≥ 30	1.39	1.10 – 1.76	
< 30	0.72	0.57 – 0.91	
Anxiety (Zung)[e]	1.04	1.02 – 1.05	<0.001
Education			0.003
≤ HS	1.64	1.18 – 2.28	
> HS	0.61	0.44 – 0.85	
Age at FMP	0.99	0.98 – 1.01	0.439
Employed [b]			0.019 [d]
Employed premenopause	0.55	0.35 – 0.88	0.012
Employed in 0–5 yrs	1.14	0.66 – 1.97	0.626
Employed in 6+ yrs	0.84	0.30 – 2.38	0.742
Depression (CES-D)			
≥ 16	1.48	1.23 – 1.78	<0.001
< 16	0.68	0.56 – 0.81	
History of depression			<0.001
Yes	1.91	1.37 – 2.66	
No	0.52	0.38 – 0.73	
Stress (PSS)	1.02	1.01 – 1.03	0.002
Physical Health (SF12)	0.98	0.95 – 0.99	0.013

[a] Time in 3 categories (−11 to –1 years before FMP; 0–5.9 years after FMP; ≥ 6 years after FMP). Time was included and significant in all models.

[b] Odds ratios are for the interaction with time.

[c] Odds ratio indicates the likelihood of hot flashes for each 1 SD(0.84) increase in log FSH.

[d] P Value for interaction with time.

[e] Odds ratio is for each 1point increase in anxiety scale.

Table 4

Final Multivariable Model for Risk Factors of Hot Flashes Around FMP [a], N=255

Variable	Odds Ratio	95% CI	P Value
Time			<0.001
11-1 yrs before FMP	0.12	0.05 – 0.29	<0.001
FMP + 5 yrs	Reference	—	—
≥ 6 yrs after FMP	3.12	0.46 – 21.4	0.246
FSH[b]			<0.001
1–11 yrs before FMP	1.63	1.45 – 1.83	<0.001
FMP + 5 yrs	1.10	0.94 – 1.29	0.222
≥ 6 yrs after FMP	0.79	0.53 – 1.17	0.232
Estradiol[c]	0.86	0.77 – 0.96	0.008
BMI × race[d]			0.011
African American BMI <30 v white BMI <30	1.81	1.20 – 2.72	0.005
African American high BMI v white low BMI	1.73	1.19 – 2.52	0.004
White high BMI v white low BMI	1.80	1.24 – 2.61	0.002
Anxiety score[e]	1.05	1.03 – 1.06	<0.001
Education			
>HS vs ≤HS	0.66	0.47 – 0.91	0.011
Age at FMP	1.01	0.99 – 1.03	0.306

[a] Time in 3 categories (each year before FMP up to but not including time 0; time 0 – 5.9 years after FMP; ≥ 6 years after FMP). Time was included and significant in all models.

[b] Odds ratio indicates the likelihood of hot flashes for each 1 SD (0.84) increase in log FSH.

[c] Estradiol entered without FSH due to high correlations. Other model estimates remained similar. Estradiol × time, P=0.26.

[d] Contrasts depicted in Figure 3.

[e] Odds ratio is for each 1 point increase in anxiety scale.