Published in final edited form as:
Menopause. 2009 ; 16(4): 728–734. doi:10.1097/gme.0b013e3181967e16.

TEMPORAL ASSOCIATIONS OF HOT FLASHES AND DEPRESSION IN THE TRANSITION TO MENOPAUSE

Ellen W. Freeman, PhD[1],[2], **Mary D Sammel, ScD**[3], and **Hui Lin, MS**[4]

[1]Department of Obstetrics/Gynecology, University of Pennsylvania School of Medicine, Philadelphia, PA.

[2]Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA.

[3]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, PA.

[4]Center for Research in Reproduction and Women's Health, University of Pennsylvania School of Medicine, Philadelphia, PA.

Abstract

Objective—Evaluate associations between hot flashes and depressed mood in the menopausal transition and associations of these symptoms with reproductive hormone changes.

Design—10-year follow-up in a population-based cohort of the women who had no experience of hot flashes or depressed mood at baseline.

Results—The incidence of hot flashes significantly increased compared to the incidence of depressed mood in the 10-year follow-up (P<0.001). Sixty-seven percent of the women reported hot flashes, 50% reported depressed mood, and 41% reported both symptoms during the study interval. Reporting both hot flashes and depressed mood was greater than expected if the processes operated independently (P<0.001). Of the women who experienced both symptoms, depressed mood was more likely to precede hot flashes (RR=2.1, 95% CI: 1.5, 2.9). Within-woman increases in FSH levels were associated with the onset of depressed mood in unadjusted analysis (P=0.05). Increased FSH levels, decreased Inhibin b levels and the variability of estradiol were significantly associated with hot flashes. FSH and Inhibin b remained significantly associated with hot flashes in the final multivariable models (P<0.001).

Conclusions—Both hot flashes and depressive symptoms occur early in the menopausal transition in women with no previous experience of these symptoms. Depressive symptoms are more likely to precede hot flashes in women who report both symptoms. The findings support the concept that the changing hormonal milieu of the menopausal transition is one of multiple factors associated with the onset of symptoms.

INTRODUCTION

Hot flashes, variously termed hot flushes or vasomotor symptoms, are the predominant symptom associated with menopause. Over 70% of women may experience hot flashes,

Correspondence: Dr. Ellen W. Freeman, Department of Obstetrics/Gynecology, 3701 Market Street, Suite 820 (Mudd), Philadelphia, PA 19104-5509. <freemane@mail.med.upenn.edu> TEL: 215-662-3329; FAX 215-349-5521. .

although other menopausal symptoms such as depressed mood and poor sleep are both common and distressing.[1-4] The temporal associations of menopausal symptoms with hot flashes and associations of these symptoms with changes in reproductive hormones are poorly understood. While some believe that depressed mood in perimenopausal women is an end result of hot flashes or night sweats that lead to poor sleep, which in turn leads to depression, data that demonstrate these associations are lacking.

The prevalence of hot flashes peaks around menopause when over 70% of women report experiencing this symptom.[1,5] Although hot flashes are associated with changes in reproductive hormones such as estradiol, FSH and Inhibin b, the etiology remains poorly understood. A leading hypothesis is that hot flashes are triggered centrally by noradrenergic activation in association with changes in estrogen, which is known to influence thermoregulatory functioning.[6]

The risk of depression also appears to increase in the menopausal transition, although data are not consistent and whether depression is related to the changes in reproductive hormones is controversial.[1, 7-12] We previously found that new onsets of depressive symptoms and diagnosed depressive disorders in our population-based cohort of generally healthy mid-life women were more likely to occur when a women was in the menopausal transition compared to when she was premenopausal.[7,8] Changes in reproductive hormones, including a greater variability of estradiol and cycle-to-cycle fluctuations of estradiol levels in the early menopausal transition were significantly associated with these depressive symptoms.[8] In another study of associations of hormones with the severity of menopausal symptoms, we found that a greater variability of estradiol was significantly associated with women's reports of hot flashes.[1] The results of these separate studies supported the possibility that destabilizing effects of the fluctuations or changes of reproductive hormones of estradiol are important factors for both depressive symptoms and hot flashes.[8]

The objectives of the present study were to evaluate associations *between* depression and hot flashes and how they relate to each other. We first identified the incidence and timing of hot flashes and depressed mood in the menopausal transition and determined the likelihood that they co-occur. We then identified which symptom occurred first – hot flashes or depressed mood – among the women who had neither symptom at baseline and experienced both symptoms in the study interval. Finally, we examined the hormone measures and other risk factors at the onset of each symptom to determine their individual and combined effects on the occurrence of hot flashes and depressed mood.

METHODS

Cohort Participants

All women in the Penn Ovarian Aging cohort who had *no* reports of hot flashes, no history of depression, scores below 16 on the Center for Epidemiologic Studies Depression Scale (CES-D) and no current DSM-IV diagnosis as assessed by the Prime-MD at enrollment in the cohort were selected for this study (N=170). These women were enrolled in a population-based cohort of 436 women identified by random-digit dialing to households in Philadelphia County, Pennsylvania as described in previous reports.[8, 13]

At enrollment in the cohort, the participants were ages 35 to 47 years (mean 41.9 years +/− 3.4 SD), with regular menstrual cycles in normal range (22-35 days) for the previous three cycles, had an intact uterus and at least one ovary. Exclusion criteria included current use of psychotropic or hormonal medications, including hormonal contraception and hormone therapies (any subsequent hormone use was censored in the analysis); pregnancy or breast feeding; serious health problems known to compromise ovarian function (e.g., diabetes

mellitus, liver disease, and breast or endometrial cancer); and alcohol or drug abuse within the past year. The sampling was stratified to obtain equal numbers of African American and Caucasian women. The Institutional Review Board of the University of Pennsylvania approved the study, and written informed consent was obtained from all enrolled women.

Study Design

The subjects in this study were followed for 10 years with 11 assessment periods. Periods 2-6 were at 9-month intervals, periods 7-10 were at annual intervals, and period 11 was approximately two years after period 10. Each assessment period had two visits, scheduled in the first 6 days of the two consecutive menstrual cycles or one month apart in non-cycling women, to obtain blood samples for the hormone assessments (yielding a possible maximum of 22 hormone samples per participant).

Trained research interviewers obtained the blood samples and all other study data in individual in-person interviews at the participants' homes. The study was explained to the participants as a general women's health study. At each assessment period, a structured interview questionnaire focused on overall health, and subjects completed a set of validated self-report measures to assess health and the symptom variables of the study.

Study Variables

Hot flashes—Hot flashes were included in a validated symptom list that was embedded in 6 the structured interview at each assessment.[14] The participants were asked whether hot flashes occurred in the past month, the frequency of their occurrence and the severity rated on a 4-point scale from 0 (none) to 4 (severe). The presence or absence of hot flashes at each assessment in the 10-year interval was used in this study.

Depression—Current depressive symptoms were assessed by the CES-D, a 20-item selfreport questionnaire.[15] The standard CES-D cutoff score of 16 or greater was used to define high depressive symptoms or depressed mood.

Hormones—Over 98% of the samples from women with identifiable menstrual cycles were collected between days 1 and 6 of the cycles, when these hormones are at low levels in cycling women. Assays of estradiol and follicle stimulating hormone (FSH) were conducted in the Translational Clinical Research Center of the University of Pennsylvania. All assays were performed in duplicate, with the means of the duplicates used in analysis. Estradiol and FSH were measured by radioimmunoassay using Coat-A-Count commercial kits (Diagnostic Products, Los Angeles, CA). The inter and intra assay coefficients of variation were less than 5%. Dimeric Inhibin b was measured in serum by Patrick Sluss, PhD, Massachusetts General Hospital, Boston, using a sensitive, 2-site nonisotopic immunoassay (Serotec, Oxford, England). The intra-assay and interassay coefficients of variation were less than 5% and 8.5%, respectively (range, 15-500 pg/mL). Values below the sensitivity threshold (15 pg/mL) were given the threshold value.

The two hormone values obtained in each study period were averaged for each subject. The subject's mean value at each study period and her deviation from the average of the two hormone measurements (SD) were used in the analyses. In cases where two hormone values were not obtained in an assessment period, the single value was used for the mean, and the standard deviation was set at missing for that period. This approach was used to provide a measure of the woman's hormone fluctuations separate from the hormone levels, and to avoid over-estimation of the hormone values that would occur by relating two hormones measures at each assessment to the single measures of other risk factors. Log-transformed

values were used in all analyses; hormone levels are expressed as geometric means with 95% confidence intervals.

Other risk factors—Other potential risk factors were assessed at each assessment period. Their selection was based on their significance in previous studies and the goals of this study: age, race (African American or Caucasian), current smoking (yes, no), body mass index (BMI), education (>high school, <= high school) and perceived stress (PSS) as assessed by the validated questionnaire of Cohen et al. [16] A higher total score of the PSS indicates greater stress.

Statistical analysis

The frequencies of depressive symptoms (CES-D scores) and hot flashes, the relative risk of the onset of these symptoms, and the time to onset of each symptom were identified. Chi square tests and t statistics were used in tests of descriptive data.

The associations of within-woman changes in risk factors for each symptom were estimated using a conditional (fixed effects) logistic regression model.[17] The conditional regression considers each women as her own control and having her own personal risk for reporting the symptom outcome (e.g., depressed mood or hot flashes). Each women contributed all data from cohort enrollment through the first assessment in which she reported the symptoms of interest.

An increment in risk associated with a change in each risk factor was estimated for each woman by comparing the average level of the covariate when the woman had the first onset of the symptom with the previous average covariate level when she did not have the symptom. The individual estimates were then averaged for the study group. The interpretation of the estimated association is the ratio of the average odds of reporting the risk factor at the outcome (e.g., onset of the symptom) compared with the average odds of reporting the risk factor when depressive symptoms were not present. An OR greater than 1 indicates an increase in the risk factor variable at the time of the measured onset compared with the average risk factor value preceding the event. An OR less than 1 indicates a decrease in the risk factor at the time of onset compared with the value before the onset.

The unadjusted associations of the potential risk factors with each symptom were estimated, and all risk factors were then estimated in the multivariable model to identify their independent contributions after adjusting for the presence of all other variables. Because the conditional model estimates within-woman changes, only potentially changing risk factors were considered. We used a backward elimination strategy to determine whether any of the variables include in the model modified the estimates of other significant associations by 15% or more. [18] All analyses were performed using the SAS statistical software package (version 9.1; SAS Institute, Cary, NC). Statistical tests were 2-tailed, with P<=0.05 considered significant.

RESULTS

Participants

At baseline, all participants were premenopausal with a mean age of 41.9 (SD 3.4) years. Table 1 shows the study variables and demographic characteristics compared at baseline between the 170 study participants and the remaining cohort. The hormone measures and BMI at baseline did not significantly differ between the study group and the remaining cohort. Although the participants were slightly older, the difference did not appear to be clinically meaningful. The study participants (who were symptom-free at baseline) reported

less stress (P<0.001), were less likely to smoke (P<0.001), and more likely to be Caucasian (more African American women reported hot flashes and/or depressive symptoms at baseline and consequently were not included in this study).

Incidence of hot flashes and depressed mood

Of the 170 women who had neither hot flashes nor depressed mood at the start of the study, 114 (67%) reported hot flashes and 85 (50%) reported depressed mood (CES-D>=16) during the subsequent 10-year study period. The incidence of hot flashes significantly increased compared to the incidence of depressed mood (chi-square test of homogeneity = 14.3, df =1, P=0.0002), indicating that many more women experienced hot flashes than depressed mood in the study interval.

Forty-one percent (70/170) of the women experienced both hot flashes and depressed mood, either sequentially or concurrently in the 10-year interval (Figure 1). The experience of having both hot flashes and depressed mood was greater than would be expected if these processes operated independently (chi-square = 18.5; df=3; P=0.0007).

In this group of women who were symptom free at baseline, 24% (40/170) experienced depressed mood first, prior to reporting hot flashes. This was 2 times higher than would be expected if these two symptoms operated independently (RR=2.1, 95% CI: 1.5, 2.9; data shown in Appendix 1). In contrast, only 8% (13/170) of the women reported hot flashes prior to reporting depressed mood, 31% *fewer* women than would be expected if these two symptoms operated independently (RR=0.68, 95% CI: 0.40, 1.18). The time to reports of depressed mood was 2.2 years (SD 2.2) into the study on average. Hot flashes occurred 1 ½ years after the reports of depressed mood on average (time between a subject's first report of depressed mood and her first report of hot flashes: 1.53 years, SD 3.25, P=0.0002).

Hormone Levels

We examined the change in the woman's own levels of the measured hormones at the first report of depressed mood or hot flashes compared to the woman's mean levels of the hormone before the symptom report (Table 2). In unadjusted analysis, the change in the woman's FSH level was nearly 3 times greater at the onset of high CES-D scores compared to the woman's mean levels before the onset of the depressive symptoms (OR=2.79; 95% CI:1.15-6.75; P=0.023). This association between FSH and CES-D scores was no longer significant after adjusting for all other variables in the final model (Table 3).

The change in the woman's own levels of FSH and Inhibin b were significantly associated with the onset of hot flashes in unadjusted analysis. The within-subject variability of estradiol and FSH were also significantly associated with the outcome of hot flashes in unadjusted analysis (OR=1.94; 95% CI:1.03, 3.63; P=0.040 and OR=2.29; 95% CI:0.99, 5.25; P=0.052, respectively). The associations between FSH and Inhibin b with hot flashes remained significant in the final adjusted models (Tables 2 and 4).

Other Risk Factors

The unadjusted associations of BMI and perceived stress were significantly associated with high CES-D scores and remained significant in the multivariable model (Table 3). The unadjusted association of BMI was also significantly associated with hot flashes (OR=1.23; 95% CI:1.06, 1.41; P=0.005), although the association did not remain significant in the multivariable model. Again noting that the conditional model examines within-woman *change* in variables at the time of symptom onset compared to their mean values prior to the symptom onset, there were no significant within-woman changes in perceived stress or smoking associated with the onset of hot flashes.

Adjusted associations of risk factors for depressive symptoms and hot flashes

CES-D model—Using a conditional logistic regression model, the repeated observations for each woman were compared to identify which risk factor changes were associated with the woman's first report of a high CES-D score. Within this modeling framework, women on average were 1.40 times more likely to have an increase in BMI (P=0.03) and 1.08 times more likely to have an increase in stress scores (P=0.04) at the onset of depressive symptoms. The small subgroup of women who reported hot flashes either before (8%) or concurrently with depressed mood (10%), had 8 times the odds of having depressed mood compared to the odds of having depressed mood prior to reporting hot flashes after adjusting for all other variables in the model (OR=8.88; 95% CI: 2.57, 30.68; P<0.001). (Table 3).

Hot flash model—Compared with the woman's own status before the onset of hot flashes, the women on average were more likely to have an increase in FSH levels (P<0.001) and a decrease in Inhibin b levels (P<0.001) at the first report of hot flashes (shown in Table 2). For a woman who had depressed mood (high CES-D scores) before hot flashes, and after adjusting for all other risk factors in the model, the odds of having hot flashes at a subsequent assessment was 3 times greater compared to not having depressed mood (OR=3.06; 95% CI: 1.43, 6.58; P=0.004) (Table 4). The inclusion of CES-D scores in the multivariable model did not influence the associations of the other risk factors with hot flashes, indicating that depressive symptoms did not confound the associations between other risk factors and hot flashes but were an independent risk factor for some women.

DISCUSSION

This study was conducted in a population-based cohort of mid-life women who reported no hot flashes, no depressed mood and no history of depression at baseline. Of these women who were symptom-free at the outset, 67% reported hot flashes and 50% reported depressed mood (high CES-D scores) in the next 10 years of follow-up. Forty-one percent of the study group reported both hot flashes and depression. Only 24% of the women reported neither hot flashes nor depressed mood in the 10-year interval.

Many studies confirm the high prevalence of menopausal hot flashes. Vasomotor symptoms were reported by nearly 60% of women in the Study of Women's Health across the Nation (SWAN).[19,20] In our cohort, 30-40% of premenopausal and late premenopausal women reported hot flashes, increasing to over 70% of women in the late transition and postmenopausal stages.[1] In contrast, the prevalence of depressed mood in the menopausal transition is lower and is also less clear, due in part to the episodic nature of depression, considerable differences in study populations, definitions of menopausal status, and the methods of assessing depressive symptoms that range from self- reported complaints to clinical diagnoses of major depression. Recent studies that have identified depressed mood in the menopausal transition include the community-based Harvard Study of Moods and Cycles,[9, 10] where a 2-fold increase in depressive symptoms was observed among perimenopausal women who had no previous depression. In an 8-year follow-up of our cohort, women with no previous depression were over 4 times more likely to experience depressed mood (high CES-D scores) and 2 ½ times more likely to have a diagnosis of MDD compared to when they were premenopausal.[8] In a 5-year follow-up of the SWAN study, late perimenopausal women were nearly 2 times more likely to report high CES-D scores compared to premenopausal women.[21] In a clinical study, there was a 14-fold increased risk of depression in the 2 years around menopause compared to the premenopausal years of women who were monitored for both menopausal status and the occurrence of major depressive disorder.[10]

The number of subjects who reported having both hot flashes and depressed mood was significantly greater than would be expected if the two symptoms functioned independently. These findings are consistent with the clinical observations that menopausal symptoms frequently co-occur and support the concept that the menopausal transition is a "window of vulnerability" where changes in the balance of ovarian hormones are associated with physical and psychological symptoms. While the findings indicate that changes in reproductive hormone levels are associated with these symptoms, further studies are needed to elucidate the mechanisms that underlie the onset of symptoms in this transition period.

We found that depressed mood was more likely to occur *before* hot flashes at a rate that was 2.1 times higher than would be expected if these two symptoms operated independently. There was also a significant time interval of about 1 ½ years on average between reports of depressed mood and reports of hot flashes. Notably, the inclusion of hot flashes in the multivariable model for depressed mood did not influence the associations of the other risk factors with depressed mood, indicating that hot flashes did not confound the associations between other risk factors of depressed mood but were an independent risk factor for some women. These findings taken together suggest that there may be different mechanisms as well as common mechanisms underlying the development of menopausal symptoms.

Both depressed mood and hot flashes occurred in the early stages of the menopausal transition and both symptoms were associated with early hormone changes. When women first reported depressed mood, we observed a within-woman increase in FSH levels compared to the woman's previous FSH levels, while the onset of hot flashes was independently associated with increased FSH levels and decreased Inhibin b levels. An unadjusted association of hot flashes with the variability of estradiol was also observed but did not remain significant in the multivariable models. These hormone changes are among the earliest markers of ovarian aging in the transition to menopause[22,23] and appear to be associated with the rise of both somatic and dysphoric mood symptoms in this time period. Higher FSH concentrations were significantly associated with the frequency of hot flashes and with the odds of reporting more frequent symptoms in the SWAN study.[24] We believe that the within-woman hormone changes were more observable for hot flashes than for depressive symptoms, because overall, hot flashes were reported later in the menopausal transition when hormone changes were more detectable. These observed hormone associations are consistent with our previous studies, where mean levels of FSH, Inhibin b and the variability of estradiol contributed to depressive symptoms and hot flashes in the menopausal transition.[1,8]

Of the risk factors in this study that examined within-woman changes, only hormone changes and high CES-D scores contributed independently to the onset of hot flashes. Women with high CES-D scores were 3 times more likely to report hot flashes. However, several other risk factors contributed independently to depressive symptoms, which have been linked to both social and biological factors in previous studies of perimenopausal women.[9, 25, 26] Greater stress and high BMI were significantly associated with depressive symptoms after adjusting for all other variables in the model. In a small subgroup of women who experienced hot flashes first, hot flashes were a strong predictor of depressive symptoms. Inasmuch as the reverse was more frequently observed, i.e., depressive symptoms preceded hot flashes, it suggests that endocrine events are a shared component but not the only factor in the development of these co-occurring symptoms.

Limitations of the study should be considered. If women who reported hot flashes or depression at baseline were included or if the study were started at later or earlier points in the menopausal transition, other results might be obtained. Use of oral contraceptives and menopausal hormone therapies were excluded, and the study cannot address the extent to

which hormone use modulates symptoms. Considering that symptoms may be episodic (particularly depressed mood), the fixed intervals of the follow-up assessments (approximately 9-12 months) may lack precision that would be obtained with more frequent assessments. It is also possible that some women who were included in the study had an undetected history of depression or experienced hot flashes that were not identified in the initial interviews. However, the analysis compares the women to their own baselines, and undetected symptoms would bias the results to the null hypothesis. The study examined within-woman changes and did not address point-in-time differences between groups. Within-woman differences in the cycle day of the hormone measures could potentially increase the variability of the hormones, although we have previously shown that the hormone measures are non-differential with respect to cycle day (over 98% were on days 1-6 of the menstrual cycle) and believe the results are conservative and biased toward the null hypothesis. There are likely other important risk factors that were not included in the study, and the results cannot be generalized to women who were not represented in this cohort without further investigation.

This study uniquely focused on the question of whether depressed mood occurs before or after the onset of hot flashes in women with no history of these symptoms. Major strengths include the longitudinal assessment of depressive symptoms, hot flashes and reproductive hormones for a 10-year period in women who were premenopausal at baseline and had no previous experience of these symptoms. The results indicate that both hot flashes and depressive symptoms occurred early in the menopausal transition and that the depressive symptoms are more likely to precede hot flashes in women with no previous experience of either symptom. The findings support the concept that the changing hormonal milieu is one of multiple factors associated with both physical and psychological symptoms that occur in the menopausal transition.

Summary sentences

Associations between hot flashes and depressed mood were examined in a 10-year follow-up of the Penn Ovarian Aging cohort. Among women who had no previous experience of either symptom, 41% reported both hot flashes and depressive symptoms. Depressed mood was more likely to precede hot flashes by an interval of 1 ½ years on average. Early changes in FSH and Inhibin b levels and variability of estradiol were associated with these symptoms.

Acknowledgments

Funding: This study was supported by a grant from the National Institutes of Health, Bethesda, MD, #RO1 AG12745 (Dr. Freeman) and RR024134 (Clinical and Translational Research Center).

Appendix 1

Data showing the observed and expected frequencies and the relative risks for depressed mood and hot flashes.

Symptom order	Observed		Expected		Observed/Expected
	Frequency	Proportion	Proportion*	Frequency	Relative Risk
d,h	41	.2412	.1645	28	1.47 (1.078, 1.989)
H,d	15	.0882	.1645	28	0.54 (0.323, 0.889)
D,h	44	.2588	.3355	57	0.77 (0.574, 1.037)

Symptom order	Observed		Expected		Observed/Expected
	Frequency	Proportion	Proportion*	Frequency	Relative Risk
D,H	40	.2353	.1118	19	2.10 (1.544, 2.870)
H,D	13	.0765	.1118	19	0.68 (0.397, 1.178)
H∩D	17	.1000	.1118	19	0.89 (0.556, 1.439)
Total	170	1	1	170	

D= depression observed; H=hot flashes observed d=depression not observed; h=hot flashes not observed H∩D=co-occuring symptoms

* expected proportions were computed assuming independent bernoulli events with P(H)=0.67 and P(D)=0.5.

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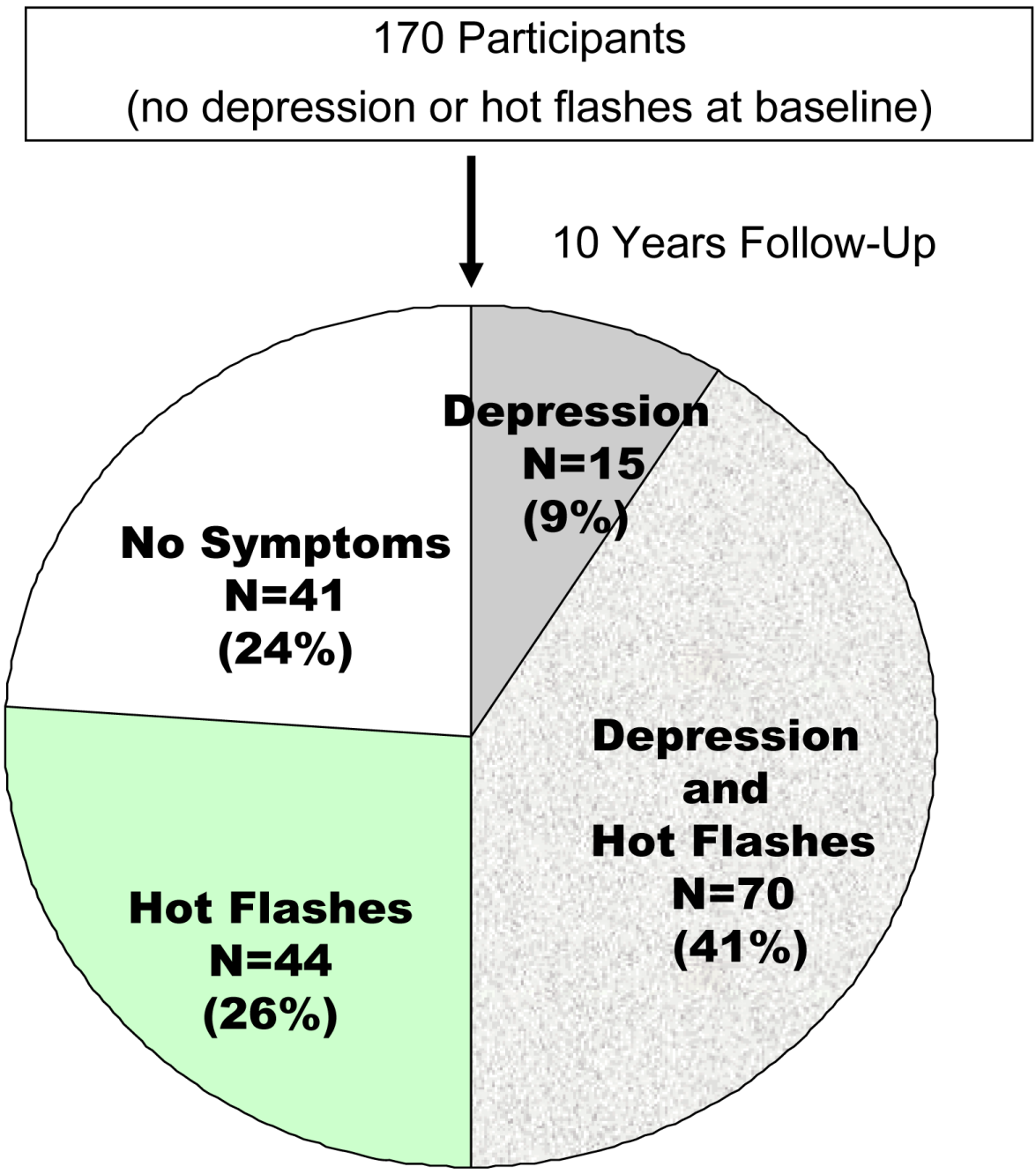

Figure 1.
Prevalence of Depression and Hot Flashes During 10-Year Follow-Up

Table 1

Study Variable at Baseline Compared Between the Study Group and the Remaining Cohort

	Study Group N=170		Remaining Cohort N=260		P Value
Age (years)	41.91	(3.43)	41.13	(3.45)	0.021
BMI (kg/m^2)	28.95	(6.80)	29.43	(8.52)	0.523
Stress (PSS Score)	18.05	7.38)	23.29	(7.49)	<0.001
Estradiol					
Mean (pg/ml)	33.78	(30.37, 37.57)	33.34	(30.83, 36.06)	0.844
FSH					
Mean (ng/mL)	7.15	(6.73, 7.60)	7.22	(6.83, 7.63)	0.838
Inhibin b					
Mean (ng/mL)	60.83	(54.90, 67.39)	63.66	(58.79, 68.92)	0.487
Smoking (yes)	47	(28)	119	(45)	<0.001
Education (> HS)	118	(69)	126	(47)	<0.001
Race					0.001
African American	69	(41)	150	(56)	
Caucasian	101	(59)	116	(44)	

Data are given as mean with standard deviation (SD), geometric mean with 95% confidence interval, or number with percentage of participants as appropriate for the variable.

Table 2

Odds Ratios of Hormones from the Final Multivariable Model for Onset of Hot Flashes And Depressive Symptoms (CES-D ≥16)

Hormone	Hot Flashes				Depressive Symptoms			
	OR				OR			
	Unadjusted	Adjusted*	95% CI	P Value	Unadjusted	Adjusted*	95% CI	P Value
Estradiol								
Mean	0.90	0.87	0.53, 1.45	0.603	1.35	1.77	0.86, 3.63	0.121
SD	1.94‡	1.70	0.89, 3.27	0.110	1.01	0.86	0.24, 3.11	0.816
FSH								
Mean	4.44⊥⊥	4.37	2.25, 8.49	<0.001	2.79 ‡	1.69	0.63, 4.52	0.299
SD	2.29 ‡	2.23	0.92, 5.40	0.076	2.13	2.08	0.42, 10.41	0.373
Inhibin b								
Mean	0.23⊥⊥	0.22	0.12, 0.43	<0.001	0.75	0.80	0.32, 1.99	0.627
SD	1.61	1.40	0.64, 3.07	0.397	1.99	2.50	0.83, 7.56	0.105

*The final multivariable models are shown in Tables 3 and 4.

‡P<0.05

⊥⊥P<0.001 in unadjusted analysis

Table 3

Odds Ratios (ORs) of Study Variables From the Final Multivariable Model for 85 Participants with 1st Onset of Depressive Symptoms (CES-D ≥16)

	OR *			
Variable	**Unadjusted**	**Adjusted**	**95% CI**	**P Value**
Estradiol				
Mean	1.35	1.77	0.86, 3.63	0.121
SD□	1.01	0.86	0.24, 3.11	0.816
BMI	1.22 ǂ	1.40	1.03, 1.90	0.030
Stress (PSS)	1.01 ⊥⊥	1.08	1.01, 1.16	0.035
Smoking, yes	3.94	1.54	0.16, 14.85	0.711
Hot flashes, yes	9.48 ⊥⊥	8.88	2.57, 30.68	<0.001

* In this within subject analysis, an OR greater than 1 indicates that a woman is more likely to report the presence of the risk factor at the time of reporting hot flashes; an OR less than 1 indicates a woman is less likely to report the risk factor at the time of hot flashes.

□ Refers to odds per 1 unit change in the SD of the hormone. The SD is the deviation of the hormone measures around the participant's mean, calculated for each participant at each assessment period.

ǂ $P < 0.05$

⊥⊥ $P<0.001$ in unadjusted analysis.

Table 4

Odds Ratios (ORs) of Study Variables From the Final Multivariable Model for 114 Participants with 1st Onset of Hot Flashes

	OR[a]			
Variable	**Unadjusted**	**Adjusted**	**95% CI**	**P Value**
FSH				
Mean	4.44[c]	4.37	2.25, 8.49	<0.001
SD[b]	2.29[d]	2.23	0.92, 5.40	0.076
BMI	1.22[c]	1.16	0.97, 1.40	0.105
Stress (PSS)	1.02	1.00	0.95, 1.06	0.909
Smoking, yes	3.46	1.38	0.30, 6.29	0.678
CES-D ∃16	2.36[d]	3.06	1.43, 6.58	0.004

[a] In this within-woman analysis, an OR > 1 indicates that a woman is more likely to report the presence of the risk factor at the time of reporting hot flashes; an OR < 1 indicates a woman is less likely to report the risk factor at the time of hot flashes.

[b] Refers to odds per 1 unit change in the SD of the hormone. The SD is the deviation of the hormone measures around the participant's mean, calculated for each participant at each assessment period.

[c] $P < 0.005$ in unadjusted analysis.

[d] $P < 0.05$