ORIGINAL ARTICLE

Hormones and Menopausal Status as Predictors of Depression in Women in Transition to Menopause

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Background: Associations between depressed mood and hormonal changes during transition to menopause are controversial. To our knowledge, there has been no prospective study of these associations in women commencing when they are premenopausal.

Objective: To longitudinally study the associations among reproductive hormones, menopausal status, and other predictors of depressed mood in midlife women.

Design: Cohort study with 6 assessment periods during a 4-year interval. Blood samples were collected 12 times during the follicular phase (days 2-6).

Setting: Philadelphia County, Pennsylvania.

Participants: A randomly identified, population-based, stratified sample of African American (n=218) and white (n=218) women aged 35 to 47 years with regular menstrual cycles, no hormonal or psychotropic medication use, and no serious physical or mental health problems at enrollment.

Main Outcome Measures: Center for Epidemiologic Studies Depression Scale score and history of depression via the Primary Care Evaluation of Mental Disorders.

Results: There was an increased likelihood of depressive symptoms during transition to menopause and a decreased likelihood after menopause after adjustment for other predictors of depression, including history of depression, severe premenstrual syndrome, poor sleep, age, race, and employment status ($P=.03$). The likelihood of depressive symptoms decreased for individuals with a rapidly increasing follicle-stimulating hormone profile ($P\leq.001$) and also decreased with age compared with premenopausal women ($P=.02$). Participant aggregate profiles with increasing estradiol levels were significantly associated with depressive symptoms in bivariate analysis ($P=.053$).

Conclusions: Depressive symptoms as assessed herein increased during transition to menopause and decreased in postmenopausal women. Hormone associations provided corroborating evidence that the changing hormonal milieu contributes to dysphoric mood during transition to menopause.

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WHETHER DEPRESSIVE symptoms are associated with changes in reproductive hormone levels such as those that occur during transition to menopause is a controversial issue in women's health. The low estrogen levels of postmenopausal women were long believed to be associated with involutional melancholia, and the low estrogen theory was supported by the results of estrogen administration, which reduced depressive symptoms in some studies,[1-3] although others found no greater effect than with placebo use.[4] A recent study[5] indicated that estrogen deficiency may play a role in depression in premenopausal women, although other researchers[6] suggested that the destabilizing effect of repeated fluctuations during menstrual cycles rather than low levels of estrogen may be the important factor in dysphoric mood in cycling women.

Epidemiologic data[7] indicate that the risks of depression are greatest in the reproductive years, when hormone levels fluctuate during the menstrual cycle. Several studies[8-10] reported that irritability, nervousness, and dysphoria increased in the transition to menopause, observations that are consistent with the possibility that fluctuations or rates of change of estradiol are associated with depressive symptoms in vulnerable women. Suppression of these hormonal fluctuations in premenopausal women eliminated menstrually related dysphoric symptoms; after pharmacologic

suppression of ovarian function, the administration of physiologic doses of estrogen induced dysphoric symptoms in women with premenstrual syndrome (PMS) but not in controls.[11] However, in perimenopausal women with major depression, estrogen treatment effectively reduced the depression.[12-14] These diverse studies not only indicate that the association between estrogen and depression is complex and varies with context[15] but also suggest that estrogen has a role in depressive symptoms in the menopausal transition.

This study examines depressive symptoms and reproductive hormones during a 4-year interval in the Penn Ovarian Aging Study, an ongoing longitudinal study of ovarian aging in a population-based cohort. The objectives are (1) to identify the prevalence of depressive symptoms during this interval; (2) to determine associations among measures of depressed mood, menopausal status, reproductive hormones, and other predictors of depressive symptoms reported in the literature; and (3) to conduct a secondary analysis of these associations for the subgroup of women with a diagnosis of major depressive disorder (MDD) during the study. We hypothesize that the strongest predictor of depressed mood in midlife women is a history of depression and that fluctuations or changes in hormone levels are associated with depressed mood during transition to menopause.

METHODS

STUDY COHORT

The population-based cohort was identified by random digit dialing to households in Philadelphia County as previously described[16] and stratified to enroll equal numbers of African American and white women. Eligibility criteria for enrollment into the cohort included 35 to 47 years of age, menstrual cycles in the reference range (22-35 days) for the previous 3 months, and at least 1 ovary and uterus. Exclusion criteria were current use of psychotropic or hormonal medications, including hormonal contraception and replacement therapies; pregnant or breastfeeding; serious health problems known to compromise ovarian function (eg, diabetes mellitus, liver disease, and breast or endometrial cancer); alcohol or other drug abuse within the past year; and non-English speaking. The study was approved by the University of Pennsylvania institutional review board, and written informed consent was obtained from participants.

A total of 436 women (75% of those eligible) were enrolled in the cohort (218 were African American and 218 were white). At the sixth assessment period, approximately 4 years later, data were obtained from 353 participants (81% of the cohort). Comparisons of baseline data between the study group and the 83 individuals who discontinued participation showed no significant differences in demographic background variables or in measures of depressive symptoms, diagnosis of MDD, menopausal status, or hormone levels.

ASSESSMENT PERIODS

Data were collected during 6 assessment periods at approximately 8-month intervals. Each assessment period had 2 visits, scheduled between days 2 and 6 of 2 consecutive menstrual cycles, to obtain blood samples for hormone assays. This narrow visit window was selected to provide an accurate assessment of basal follicle-stimulating hormone (FSH) levels in the early follicular phase, when changes associated with ovarian aging were expected to be most pronounced.[17] Repeated measures of the other study hormones (estradiol, dehydroepiandrosterone sulfate, luteinizing hormone, and testosterone) are also believed to be most reliable in the follicular phase.[18]

ASSESSMENTS OF STUDY VARIABLES

Trained research interviewers administered a structured questionnaire, measured height and weight to determine body mass index, and collected blood samples for hormone assays. The structured interview focused on overall health and included demographic background information, menstrual cycle dates, reproductive history, general health status and behaviors (including medications, smoking, alcohol and caffeine consumption, and history of depressive disorders), and common menopausal symptoms. Current age was determined by subtracting the birth date from each interview date, and the standard categories of population studies and census data were used (ie, 35-39, 40-44, 45-49, and 50-54 years).

OUTCOME VARIABLES

The primary outcome measure was the Center for Epidemiologic Studies Depression Scale (CES-D),[19] a 20-item self-report inventory for assessing current depressive symptoms. The standard CES-D cutoff score of 16 or greater was used to define high depressive symptoms; a higher CES-D cutoff score of greater than 24 was also examined as a closer approximation of a clinical diagnosis of depression. The diagnosis of *DSM-IV* MDD was obtained during each assessment period by trained research interviewers administering the Primary Care Evaluation of Mental Disorders,[20] which is a standardized and validated diagnostic assessment procedure designed for primary care research and practice that yields *DSM-IV* diagnoses for mood, anxiety, alcohol, and eating disorders.

Blood samples were collected between days 2 and 6 of the menstrual cycle or 1 month apart in nonmenstruating women. The samples were centrifuged and frozen in aliquots at –70°C. Assays were conducted at the General Clinical Research Center, University of Pennsylvania Medical Center, in batches that included 4 visits per participant to reduce the within-subject variability due to assay conditions. Estradiol, FSH, luteinizing hormone, dehydroepiandrosterone sulfate, and testosterone levels were measured by radioimmunoassay using commercial kits (Coat-A-Count; Diagnostic Products Corp, Los Angeles, Calif). Assays were performed in duplicate for all hormones, and they were repeated if the values differed by more than 15%. The interassay and intra-assay coefficients of variation were calculated from the assays conducted for the 6 assessment periods, with all coefficients being less than 5%.

MENOPAUSAL STATUS

Menopausal status was determined from the data on menstrual bleeding, which included menstrual dates recorded in the individual's daily symptom diaries, the menstrual dates at each study interview, the dates of the 2 previous menstrual periods, the number of menstrual periods between assessments, and cycle length. The definitions for the menopausal status groups were based on the Staging System for Reproductive Aging in Women, a consensus group statement sponsored by the National Institutes of Health, the North American Menopause Society, and the American Society for Reproductive Medicine.[21] At every assessment period, each participant was assigned to one of the following categories based on bleeding patterns:

- Premenopausal: regular menstrual cycles in the 22- to 35-day range

- Early transition: change in cycle length of 7 days or longer in either direction from the participant's own baseline for at least 2 cycles
- Late transition: 3 to 11 months of amenorrhea
- Postmenopausal: 12 months or more of amenorrhea without hysterectomy.

We required 2 cycles of change for the early transition and at least 3 cycles of amenorrhea for the late transition phase because we considered fewer cycles to be too unreliable.

HORMONES

The hormone variables were constructed to provide a summary profile of the hormone values for each participant during the study. An aggregate profile for each hormone for each participant was calculated by fitting a regression model using the participant's hormone values during the study and age as the time axis. To capture the shape of the profile over time, a polynomial of 2 (3 for estradiol) was used. A mathematical transformation of the model design space (age matrix) using orthogonal polynomials was conducted to construct independent tests on the shape (linear trend, quadratic trend, or cubic) of the hormone profile during the study.[22,23] These regression coefficients summarized (1) the trajectory (direction) of the hormone levels during the study (ie, the linear, quadratic, and cubic terms), (2) the estimated mean square error term that summarized the participant-specific fluctuations in the hormone level (residual heterogeneity), and (3) the number of hormone measures for each participant (maximum of 12), and they were used in the analyses of this study.

PREDICTORS

The selection of predictor variables was based on their significance in previous studies[24-29] and the goals of this project and included race (white or African American), current age, history of depression (reported in the baseline structured interview or a Primary Care Evaluation of Mental Disorders diagnosis of depressive disorder at baseline), menopausal status (defined in the "Menopausal Status" subsection), poor sleep as reported at each assessment period on the validated St Mary's Sleep Questionnaire[30] (categorical responses of badly, fairly badly, or very badly for the item "How well did you sleep last night?"), hot flashes (yes or no), current smoking, severe PMS (yes or no; the "yes" group included only those who also rated severe interference with functioning as a 4 on a 4-point scale), history of postpartum depression, currently employed, education (high school or less vs more than high school), marital status (married, living with partner vs all other), and living children (yes or no). Current use of antidepressant medication was an exclusion criterion at enrollment but was queried at each follow-up and examined for its association with the outcomes in multivariate analyses.

STATISTICAL ANALYSIS

The frequencies and distributions of the CES-D scores and the diagnosis of MDD were examined at each assessment period. Multivariate logistic regression for repeated measures was used to estimate the effects of the covariates on depressive symptoms as assessed by CES-D scores ($\geq$16 vs $<$16). All available data for each participant were included in the repeated-measures models. Variance estimates for the Wald statistics of the true logistic coefficients were adjusted for the repeated observations from each participant using generalized estimates equations.[31] In multivariate modeling, the model began with race, age, history of depression, and menopausal status. The hormone variables (described in the "Hormones" subsection) were initially examined in models adjusted for race, age, and history of depression. All other potential predictors with $P \leq .20$ in the preliminary bivariate analyses were then added sequentially to the models. Hypothesized interactions were examined. The final selection of covariates was guided by whether the variable remained statistically significant at $P \leq .05$ and whether its inclusion modified other significant associations in the model by 15% or more.[32] Secondary analyses using the same procedures were conducted for the outcomes of CES-D score greater than or equal to 25 and for a diagnosis of MDD (yes or no).

A secondary analysis was conducted for the "new cases" of CES-D scores of 16 or greater during the 4-year study using a conditional (fixed-effects) logistic model.[33] A second subanalysis was conducted for the new cases of an MDD diagnosis during the study. Only factors that changed over time in the primary analyses (ie, menopausal status, poor sleep, severe PMS, hot flashes, and FSH levels) were included to identify which factors affected within-subject changes in CES-D scores or MDD diagnosis. The log of the mean FSH level ($\geq$20 vs $<$20 mIU/mL) for each participant at each assessment period was examined. The hormone profiles were not used in this analysis because the profiles, which represented participant aggregate summaries over time, were inappropriate for the conditional model.

All analyses were performed using a statistical software package (SAS version 8.0; SAS Institute Inc, Cary, NC). Statistical tests were 2-tailed, with $P \leq .05$ considered significant.

RESULTS

PARTICIPANTS

Of the 353 participants at the sixth assessment period, 21 did not have usable blood samples, leaving 332 participants for this study. Another 36 observations from participants who were using hormone therapy or oral contraceptives, who were pregnant or breastfeeding, or who had a hysterectomy or an ovariectomy were not included in the analyses. The mean (SD) age of the cohort at the end point was 44.6 (3.5) years (range, 38-52 years). Half of the cohort was African American (n = 165) and half was white (n = 167); 59% had an education beyond high school, and 82% were employed.

MENOPAUSAL STATUS

All participants were premenopausal at enrollment. Menopausal status at each assessment period is given in **Table 1**. After 4 years, 73% of participants remained premenopausal, 21% were in early transition ($\geq$7-day change in either direction in cycle length compared with baseline for at least 2 cycles), 3% were in late transition (3-11 months with no menses), and 3% were postmenopausal (no menses for $\geq$12 months). Participant ages ranged from 38 to 51 years in the premenopausal group and from 44 to 51 years in the postmenopausal group.

DEPRESSIVE SYMPTOMS AND MDD

In Table 1, CES-D scores of 16 or higher increased during transition to menopause and were lower after menopause ($P = .047$). A *DSM-IV* diagnosis of MDD ranged from 10% to 13% in premenopausal women and was less fre-

Table 1. Center for Epidemiologic Studies Depression Scale Scores by Menopausal Status at Each Assessment Period During the 4-Year Study*

	Assessment Period					
Menopausal Status	1 (n = 332)	2 (n = 323)	3 (n = 302)	4 (n = 309)	5 (n = 302)	6 (n = 312)
Premenopausal	15.1 ± 10.8 (332)	14.9 ± 9.6 (279)	14.8 ± 10.1 (256)	15.3 ± 10.8 (249)	13.2 ± 11.0 (230)	12.7 ± 10.8 (227)
Early transition	NA	16.1 ± 10.0 (40)	17.8 ± 10.3 (40)	16.9 ± 11.1 (45)	13.6 ± 9.3 (55)	14.6 ± 9.8 (64)
Late transition	NA	18.3 ± 13.8 (4)	16.0 ± 9.3 (4)	17.1 ± 7.9 (11)	14.4 ± 7.8 (8)	13.1 ± 7.1 (10)
Postmenopausal	NA	NA	1.0 ± 1.4 (2)	6.0 ± 4.3 (4)	13.8 ± 10.1 (9)	10.6 ± 10.4 (11)

Abbreviation: NA, not applicable.
*Data are given as mean ± SD score (number of participants). Wald $\chi^2_3 = 7.95$; $P = .047$.

Table 2. Major Depressive Disorder by Menopausal Status at Each Assessment Period During the 4-Year Study*

	Assessment Period					
Menopausal Status	1 (n = 332)	2 (n = 323)	3 (n = 302)	4 (n = 309)	5 (n = 302)	6 (n = 312)
Premenopausal	34 (10)	41 (13)	29 (10)	28 (9)	39 (13)	33 (11)
Early transition	0	7 (2)	1 (<1)	6 (2)	7 (2)	14 (4)
Late transition	0	1 (<1)	0	0	1 (<1)	0
Postmenopausal	0	0	0	0	0	1 (<1)
Total	**34** (10)	**49** (15)	**30** (10)	**34** (11)	**47** (16)	**48** (15)

*Data are given as number (percentage). Wald $\chi^2_2 = 2.56$; $P = .28$.

Table 3. Depression Measures During the 4-Year Study by History of Depression in 332 Women*

	Ever During 4-Year Study†					
	CES-D Score ≥16		CES-D Score ≥25		MDD	
History of Depression	Yes	No	Yes	No	Yes	No
Yes	69 (28)	0	54 (35)	15 (8)	54 (43)	15 (7)
No	174 (72)	89 (100)	99 (65)	164 (92)	72 (57)	191 (93)
Total	**243**	**89**	**153**	**179**	**126**	**206**

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; MDD, major depressive disorder.
*Data are given as number (percentage). $P<.001$, by χ^2 test for each measure.
†There were 6 assessments at approximately 8-month intervals.

quent (≤4%) in women in the transition phases, although the numbers in the transition phases were too small for analysis (**Table 2**). A history of depression at baseline was 21%. As expected, participants with a history of depression were statistically significantly more likely to report high CES-D scores and to have an MDD diagnosis during the study than were those with no history of depression (**Table 3**).

PREDICTORS OF DEPRESSIVE SYMPTOMS

The bivariate associations of the study variables with CES-D scores and with MDD diagnosis during the 4-year study are given in **Table 4**. Menopausal status was significantly associated with CES-D scores ($P = .047$), with an increased likelihood of scores of 16 or higher in the transition phases and a lower likelihood after menopause compared with premenopausal women. All but 3 of the other 14 study variables were statistically significantly associated with CES-D scores. The odds ratios (ORs) for the associations with MDD were generally similar to those for the associations with CES-D scores. The associations of menopausal status and age did not reach statistical significance because of the much smaller numbers with MDD (10%-15% of the cohort) and because there were only 3 participants with MDD in the late transition and postmenopausal phases (Table 4).

HORMONES AND DEPRESSIVE SYMPTOMS

There was a significant inverse association between FSH levels and CES-D scores adjusted for age, race, and history of depression (**Table 5**), indicating that the likelihood of depressive symptoms decreased in participants with rapidly increasing FSH levels (quadratic profile, $P = .002$). The associations between the participant aggregate FSH profiles and menopausal status are de-

Table 4. Bivariate Association Between the Study Variables and CES-D Scores and MDD During the 4-Year Study of 332 Women

Variable	CES-D Score ≥16		MDD	
	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Race				
African American (n = 165)	1.99 (1.44-2.74)	<.001	2.02 (1.34-3.00)	<.001
Caucasian (n = 167)	1.00	NA	1.00	NA
Current age, y		<.001*		.16*
35-39	1.00	NA	1.00	NA
40-44	0.59 (0.11-1.08)	<.07	0.65 (0.42-1.01)	.06
45-49	0.49 (0.34-0.72)	<.001	0.70 (0.43-1.14)	.15
50-54	0.34 (0.11-1.08)	<.001	0.31 (0.07-1.38)	.12
Menopausal status†		.047*		.28*
Premenopausal	1.00	NA	1.00	NA
Early transition	1.33 (0.95-1.86)	.10	1.12 (0.75-1.67)	.58
Late transition	1.79 (0.90-3.56)	.10	0.33‡ (0.08-1.44)	.14
Postmenopausal	0.36 (0.09-1.39)	.14	NA	NA
History of depression (n = 69)	3.65 (2.58-5.18)	<.001	6.22 (4.25-9.10)	<.001
Hot flashes (n = 142)	2.01 (1.53-2.64)	<.001	1.99 (1.45-2.75)	<.001
Poor sleep (n = 61)	3.47 (2.47-4.89)	<.001	3.12 (2.17-4.56)	<.001
PMS (n = 62)	5.77 (4.30-7.75)	<.001	5.40 (3.85-7.59)	<.001
Education more than high school (n = 196)	0.50 (0.36-0.69)	<.001	0.64 (0.43-0.95)	.03
Not employed (n = 61)	2.83 (1.90-4.23)	<.001	2.40 (1.54-3.75)	<.001
Current smoker (n = 120)	1.75 (1.26-2.43)	<.001	1.63 (1.09-2.42)	.02
History of postpartum depression (n = 127)	1.59 (1.15-2.21)	.005	1.87 (1.26-2.78)	.002
Marital status				
Married, living together (n = 197)	1.00	NA	1.00	NA
Other (n = 135)	1.54 (1.12-2.13)	.008	1.54 (1.04-2.29)	.03
Living children				
Any (n = 279)	1.00	NA	1.00	NA
None (n = 53)	1.41 (0.91-2.19)	.13	1.24 (0.69-2.25)	.47
Age at menarche (mean [SD], 12.6 [1.7] y)	1.08 (0.98-1.20)	.13	1.06 (1.01-1.25)	.04
BMI (mean [SD], 29.3 [8.2] kg/m^2)	1.01 (0.99-1.03)	.17	1.04 (1.02-1.06)	<.001

Abbreviations: BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; MDD, major depressive disorder; NA, not applicable; PMS, premenstrual syndrome.
**P* value for overall significance of the risk factor.
†Number of participants at each assessment period is given in Table 1.
‡Late transition and postmenopausal were combined because there is only 1 postmenopausal participant with MDD.

picted in the **Figure**, which shows that FSH levels (summarized during the 4-year study) were low in the premenopausal group and increased in the transition groups.

Women who experienced increased estradiol levels during the study were more likely to report high CES-D scores (quadratic profile, $P=.05$), although the overall association of estradiol did not reach statistical significance (Table 5). This pattern of higher estradiol levels observed in early transition to menopause[34] is believed to result from an increased ovarian follicular response to increased FSH levels.[35] An association between decreasing estradiol levels and CES-D scores was also observed (cubic profile, $P=.07$), but it was limited by the small number of participants who reached menopause during the study. The hormone profiles of luteinizing hormone, dehydroepiandrosterone sulfate, and testosterone were not significantly associated with CES-D scores. Only 3 women with MDD reached the late transition or postmenopausal phase in this study, an insufficient number for determining associations between the hormone profiles and the MDD diagnosis.

ASSOCIATIONS WITH SIGNIFICANT PREDICTORS

Table 6 gives the final multivariate model of independent predictors of depressive symptoms controlled for all other variables in the model. Women in early transition to menopause were 55% more likely to report high CES-D scores, and women in late transition to menopause were nearly 3 times more likely to report these depressive symptoms compared with premenopausal women (OR, 2.89; 95% confidence interval [CI], 1.29-6.45; $P=.01$). Depressive symptoms decreased with age, with the 50- to 54-year age group being 66% less likely to experience depressive symptoms compared with the 35- to 39-year age group (OR, 0.34; 95% CI, 0.11-1.03; $P=.06$). The likelihood of depressive symptoms decreased for participants with a rapidly increasing FSH profile during the study ($P\leq001$). Women with a history of depression were more than twice as likely to report depressive symptoms (OR, 2.45; 95% CI, 1.61-3.72; $P<.001$). African American women remained nearly twice as likely to report depressive symptoms as white women (OR, 1.89;

95% CI, 1.35-2.63; $P<.001$). Other significant predictors of depressive symptoms included severe PMS, poor sleep, and lack of employment (Table 6).

The same set of variables was examined in a secondary analysis of the subgroup with a diagnosis of MDD (assessed at each of the 6 study periods). The major predictor of MDD was a history of depression, with women who had a history of depression being nearly 5 times more likely to have an MDD diagnosis during the 4-year study (OR, 4.75; 95% CI, 3.17-7.13; $P<.001$). Other significant predictors of MDD controlled for all other variables in the model were severe PMS, poor sleep, and hot flashes. Adjustment for antidepressant medications, which were more likely to be used in the MDD group, did not alter the results. Menopausal status and age were not significant predictors of MDD, but the number of women in the MDD group who reached the late transition or postmenopausal phase was too small for meaningful analysis. Similarly, the lack of association with FSH profiles was likely to be because only 8 women with a diagnosis of MDD reached an FSH level greater than 20 mIU/mL during the study.

The results of a secondary analysis of CES-D scores using a cutoff score greater than 24 (to provide a closer approximation to clinical depression) were similar to those given for MDD in Table 6 (data not shown).

We conducted a secondary analysis of the subgroup of women who were new cases of high CES-D scores during the study (n=152) to determine which factors measured at each assessment period (menopausal status, poor sleep, PMS, hot flashes, and FSH levels) were associated with these new cases with no previous history of depression. The new cases were nearly twice as likely to occur in the early transition phase compared with the premenopausal phase (OR, 1.94; 95% CI, 1.01-3.74; $P=.048$), and age was inversely associated with high CES-D score (OR, 0.81; 95% CI, 0.69-0.96; $P=.01$) (**Table 7**). Although higher FSH levels were nearly twice as likely to be associated with high CES-D scores, the association was not statistically significant in this small subgroup. The same analysis was conducted for the new cases of MDD (n=53). Although the OR for new cases of MDD increased in the early transition phase, the number of participants was too small for reliable analysis (Table 7).

Table 5. Hormonal Associations With Depressive Symptoms (CES-D) Adjusted for Race, Age, and History of Depression in 332 Women

Hormone and Estimate	CES-D Score ≥16	
	Odds Ratio (95% CI)	*P* Value
Follicle-stimulating hormone		**.009***
Intercept	1.02 (0.88-1.19)	.76
Linear	1.12 (0.80-1.55)	.51
Quadratic	0.56 (0.39-0.82)	**.002**
Residual heterogeneity	2.01 (0.85-4.73)	.11
No. of measures	1.07 (0.96-1.18)	.21
Estradiol		.13*
Intercept	0.93 (0.84-1.03)	.17
Linear	1.03 (0.84-1.26)	.78
Quadratic	1.27 (1.00-1.60)	**.05**
Cubic	1.30 (0.98-1.73)	.07
Residual heterogeneity	1.56 (0.82-2.98)	.18
No. of measures	1.07 (0.97-1.19)	.17

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval.

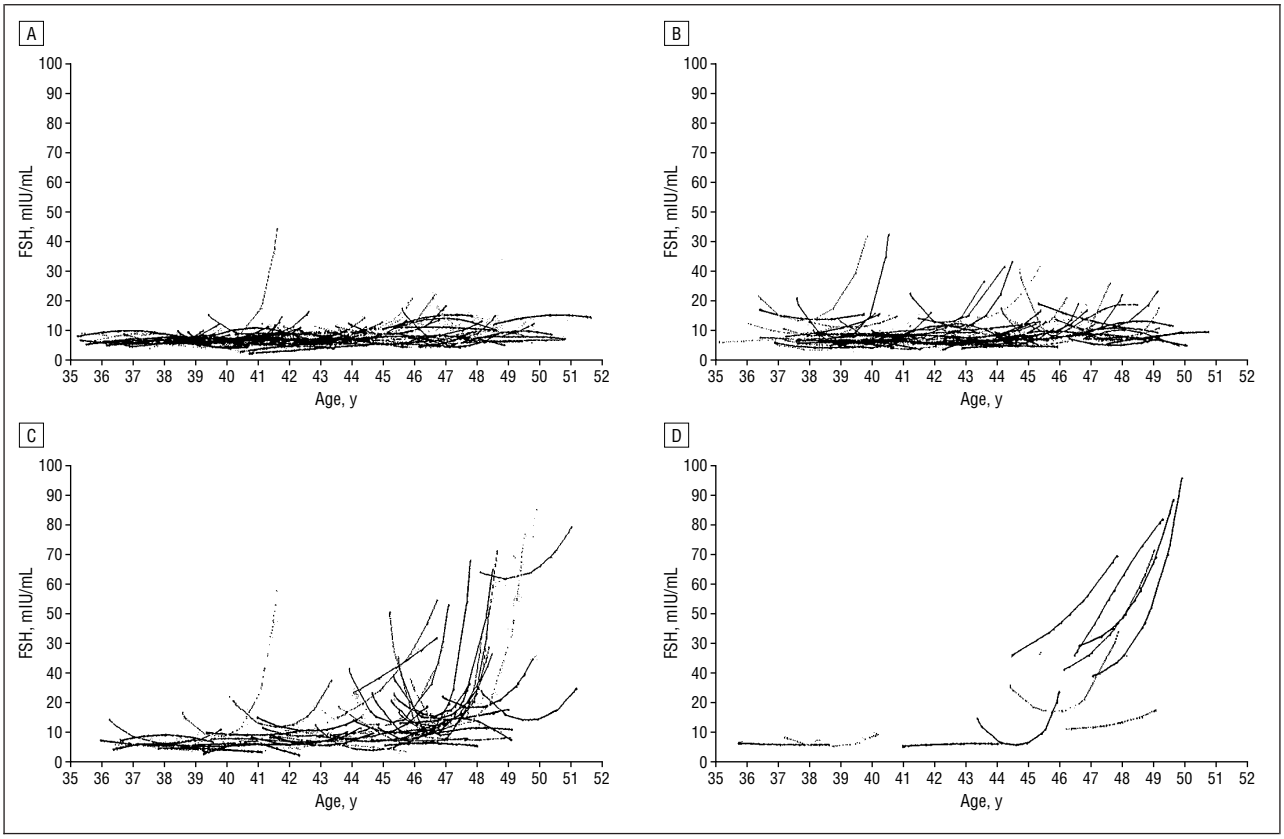
*P value for overall significance of the risk factor. Overall significance for luteinizing hormone, $P=.23$; dehydroepiandrosterone sulfate, $P=.43$; and testosterone, $P=.51$ (data not shown).

COMMENT

In this longitudinal, population-based cohort study, depressive symptoms as measured by the CES-D significantly increased during transition to menopause and decreased after menopause after controlling for other important variables, including history of depression, age, PMS, poor sleep, hot flashes, race, and employment status. Consistent with the association of menopausal phase, depressive symptoms also decreased with age, with the oldest women (50-54 years) being 66% less likely to report depressive symptoms. When we examined new cases of depressive symptoms in women who had no history of depression before enrolling in the cohort, we found that depressive symptoms were nearly twice as likely to occur in the early transition phase. New cases of MDD diagnoses were also more likely to occur in the early transition phase, although the small numbers in the MDD group were insufficient for statistical significance. These findings add support to another recent community-based study[36] of more than 2000 women that used the Edinburgh Depression Scale and identified increased depressive symptoms in the transition from premenopause to perimenopause. The Study of Women's Health Across the Nation[37] also reported that rates of "psychologic distress" were highest in early perimenopausal women. In the Massachusetts Women's Health Study,[38] the percentage of women with depressive symptoms (as assessed by the CES-D) also was highest in the perimenopausal group compared with premenopausal and naturally postmenopausal women.

The hypothesis that fluctuations in estradiol levels were associated with depressive symptoms was supported by the evidence that women with increasing estradiol profiles, which occur with ovarian aging in early transition to menopause,[34] reported more depressive symptoms. Decreasing estradiol levels, which occur closer to menopause, were marginally associated with more depressive symptoms, although less than 5% of the cohort reached menopause during the study, providing little power for this analysis. It will be important to further investigate the associations between fluctuations in estradiol levels and depressive symptoms as larger numbers of women in this cohort reach menopause.

Less expected was the statistically significant inverse association between depressive symptoms and FSH profiles, indicating that the likelihood of depressive symptoms decreased in the presence of rapidly increasing FSH levels during the 4-year study. It is unlikely that FSH contributes directly to depressive symptoms, but, as a marker of ovarian aging, these results provide corroborating hor-



Predicted follicle-stimulating hormone (FSH) profiles by menopause status: premenopausal (A), early transition (B), late transition (C), and postmenopausal (D).

monal evidence that menopausal status is associated with the dysphoric mood observed in menopausal transition.

In secondary analyses, a history of depression was the strongest predictor of MDD in this cohort. Women who had a history of depression were nearly 5 times more likely to have an MDD diagnosis during the study. Severe PMS, poor sleep, and hot flashes also independently predicted MDD. The vasomotor findings support previous results, which indicated that perimenopausal women with vasomotor symptoms were more than 4 times more likely to be depressed.[39] However, the present results also showed that hot flashes were not statistically significantly associated with the subclinical levels of depressive symptoms as assessed by the CES-D, a difference that warrants further study of the relationship between vasomotor and depressive symptoms. Inasmuch as only 3 individuals with MDD reached the late transition or postmenopausal phase, the data were insufficient for determining associations of menopausal phase and hormone measures in the secondary analysis of MDD. Nonetheless, the findings indicate the importance of further study of the associations between hormonal changes and major depressive episodes in larger numbers of women with a diagnosis of MDD.

African American women remained nearly twice as likely as white women to report depressive symptoms after adjustment for the other study variables, including employment, menopausal status, history of depression, PMS, poor sleep, hot flashes, and FSH level. Racial differences may have occurred because of unassessed variables that were beyond the focus of the project such as life events or other psychosocial factors that differentially affect race. Another possibility is a differential response bias in the self-reported CES-D score, although the racial difference was also found with the MDD diagnosis, which was obtained by interview. Similar findings of an increased prevalence of depressive symptoms in African Caribbeans compared with European white respondents in a community-based study[40] in Britain suggest that the racial difference is not simply an artifact of study measures but is an important factor for further study and treatment of depressive disorders.

There are several limitations to this study. The study was not designed to address questions about postmenopausal status, and few women reached menopause in the 4-year study (<5% of the cohort). The hormone measures were in the follicular phase and do not address other questions that require luteal phase measures, determination of the midcycle peak, or 24-hour blood sampling. The effect of measurement error, which results in bias toward the null hypothesis and which can potentially be increased if several variables such as hormones and symptoms are measured with error, cannot be excluded. Only a subgroup of women in the randomly identified, population-based cohort had a diagnosis of MDD during the study (10%-15%, which is consistent with population estimates[7]), and further study of MDD to confirm the present results is needed. Participant reports of severe PMS (which was a strong predictor of depressive symptoms and MDD) were not confirmed by prospective daily symptom ratings, although the prevalence of 14% for women with severe PMS at baseline is well within

Table 6. Predictors of CES-D Score and MDD in Multivariate Analysis

Variable	CES-D Score		MDD	
	Odds Ratio (95% CI)*	*P* Value	Odds Ratio (95% CI)*	*P* Value
Race				
White	1.00	NA	1.00	NA
African American	1.89 (1.35-2.63)	<.001	1.52 (1.03-2.24)	.04
Current age, y		.02†		.85†
35-39	1.00	NA	1.00	NA
40-44	0.61 (0.42-0.90)	.01	0.95 (0.60-1.51)	.83
45-49	0.56 (0.36-0.86)	.008	1.16 (0.71-1.89)	.56
50-54	0.34 (0.11-1.03)	.06	1.03 (0.12-8.89)	.98
History of depression	2.45 (1.61-3.72)	<.001	4.75 (3.17-7.13)	<.001
Menopausal status		.03†		.40†
Premenopausal	1.00	NA	NA	NA
Early transition	1.55 (1.04-2.32)	.03	1.11 (0.61-2.03)	.72
Late transition	2.89 (1.29-6.45)	.01	0.24 (0.03-2.21)‡	.21
Postmenopausal	0.78 (0.10-6.17)	.82	NA	NA
Severe PMS	3.80 (2.55-5.67)	<.001	2.98 (1.99-4.46)	<.001
Poor sleep	2.95 (2.08-4.19)	<.001	1.99 (1.30-3.04)	.002
Not employed	1.97 (1.29-3.01)	.002	1.46 (0.95-2.23)	.08
Hot flashes	1.27 (0.93-1.74)	.13	1.57 (1.10-2.25)	.01
Follicle-stimulating hormone		.004†		.48†
Intercept	0.99 (0.86-1.13)	.84	0.87 (0.74-1.04)	.12
Linear	1.22 (0.88-1.69)	.23	1.17 (0.82-1.68)	.39
Quadratic	0.50 (0.34-0.73)	<.001	1.08 (0.68-1.72)	.73
No of measures	1.09 (0.98-1.20)	.11	0.95 (0.82-1.09)	.43
Antidepressant medications	NA	NA	4.83 (2.17-10.76)	<.001

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; MDD, major depressive disorder; NA, not applicable; PMS, premenstrual syndrome.
*Odds ratios are adjusted for all other variables listed in the table.
†*P* value for overall significance of the risk factor.
‡Late transition and postmenopausal were combined because there is only one postmenopausal participant with MDD group.

Table 7. Predictors of Depressive Symptoms During the 4-Year Study in 152 Women With No History of Depression at Baseline*

Variable	CES-D Score ≥16*		MDD (n = 53)†	
	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Current age	0.81 (0.69-0.96)	.01	1.34 (0.99-1.81)	.06
Menopausal status				
Premenopausal	1.00	NA	1.00	NA
Early transition	1.94 (1.01-3.74)	.048	1.61 (1.57-4.54)	.37
Late transition, postmenopausal	0.84 (0.17-4.03)	.82	0.00‡	NA
Sleep	1.84 (1.02-3.33)	.04	1.24 (0.44-3.50)	.68
Hot flashes	1.24 (0.74-2.05)	.42	1.51 (0.62-3.68)	.37
Follicle-stimulating hormone ≥20 mIU/mL (log)	1.77 (0.73-4.31)	.21	1.80 (0.41-7.81)	.44

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; MDD, major depressive disorder; NA, not applicable.
*Participants with no previous history or diagnosis of depression at visit 1 and a CES-D score of 16 or higher during the 4-year study.
†Participants with no previous history or diagnosis of depression at visit 1 and MDD during the 4-year study.
‡Only 3 "new cases" of MDD in the late transition and postmenopausal groups.

the range identified in epidemiologic studies.[41] Finally, the participants represented a population-based sample of African American and white women, and the results cannot be generalized to women in nonurban areas or to other racial groups.

A major strength of this study is the unique focus on hormones and symptoms in early transition to menopause, a period which has had little systematic examination to date. The cohort was premenopausal at enrollment and was followed at 8-month intervals for 4 years to assess symptoms and hormones in conjunction with the ovarian decline that leads to menopause. The response rates in this long-term prospective study remained high, and the multiple observations during the study were sufficient for the main aims and conclusions of this study.

In summary, depressive symptoms increased during transition to menopause as identified by menstrual bleeding patterns. A significant inverse association of participant aggregate profiles of FSH with depressive symptoms provided strong corroborating evidence that the changing hormonal milieu contributes to dysphoric mood in this transition period.

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