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Higher DHEA-S (Dehydroepiandrosterone Sulfate) Levels are Associated with Depressive Symptoms during the Menopausal Transition: Results from the PENN Ovarian Aging Study

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Abstract

Background—The influence of sex hormones on mood during menopause has been the subject of ongoing investigation. Because dehydroepiandrosterone sulfate (DHEA-S) levels have been associated with several indicators of health outcomes associated with healthy aging, this PENN Ovarian Aging study (POAS) investigation was undertaken to determine the relationship between DHEA-S levels and both depressive symptoms and major depression during the transition through menopause. The original report revealed an unexpected positive correlation between DHEA sulfate (DHEA-S) levels and depressive symptoms in the cohort at baseline. To determine whether the positive association of DHEA-S levels and depression persists in a longitudinal analysis, the cohort was studied over 11 years.

Methods—Longitudinal cohort study with 11 assessments during an 11 year interval in Philadelphia, Pennsylvania. *Participants:* A randomly identified, population-based sample of 436 African American and Caucasian premenopausal women aged 35 to 47 years at enrollment. *Outcome Measures:* Center for Epidemiologic Studies Depression Scale score and standardized diagnosis of major depression.

Results—In a multivariable model, DHEA-S levels were positively associated with depressive symptoms, when adjusted for age, menopausal stage, race, smoking status and body mass index. There was no relationship between DHEA-S levels and a diagnosis of major depression.

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Conclusions—DHEA-S levels were positively associated with depressive symptoms and not with major depression during the menopausal transition.

Keywords

menopausal transition; dehydroepiandrosterone sulfate; depressive symptoms; major depression; longitudinal cohort

Introduction

Physicians have been fascinated with the symptoms and biological underpinnings associated with the menopausal transition since the word “menopause” was coined in 1813. (Stolberg, 2007) However, systematic investigations of hormonal variations and their relationships to menopausal symptoms did not occur until several longitudinal studies, including the PENN Ovarian Aging study, were initiated approximately 15 years ago. Elevated depressive symptoms have been noted during the menopausal transition. The adrenal androgens, dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) are the most abundant steroid hormones in the body and have been positively associated with several indicators of wellness, including a broad range of health outcomes associated with successful aging. (Goldman & Glei, 2007) DHEA and DHEA-S appear to be important in the regulation of mood. (Dubrovsky, 2006; Maninger, Wolkowitz, Reus, Epel, & Mellon, 2009; Tichomirowa et al., 2005; Wolkowitz et al., 1997) Thus, we performed a cross sectional analysis of the women in the PENN Ovarian Aging (POAS) cohort at baseline and found a positive association between DHEA-S levels and depressive symptoms, which was unexpected. (Morrison, Ten Have, Freeman, Sammel, & Grisso, 2001) The current follow-up longitudinal study was undertaken to determine whether the positive relationship of DHEA-S levels and depression persists in a longitudinal analysis over 11 years.

During the overall lifespan, circulating levels of DHEA-S decline approximately 2% per year with aging. Data from SWAN study has demonstrated that during the menopausal transition, a gender specific change in DHEA-S levels has been observed with > 84% of women experiencing an increase in DHEA-S levels from premenopause/early perimenopause to late perimenopause/early postmenopause. (Crawford et al., 2009) Included among the functions of dehydroepiandrosterone (DHEA), the desulfated form of DHEA-S, is that it serves as a substrate for the synthesis of androgens and estrogens in women. (von Muhlen, Laughlin, Kritz-Silverstein, Bergstrom, & Bettencourt, 2008), so the gender specific increase in DHEA-S during the menopausal transition is particularly interesting for both mental and physical health.

In women over the lifespan, conclusions in the literature about the relationship between DHEA-S levels and depressive symptoms have been mixed.(Haren et al., 2007; Morsink et al., 2007; Yaffe et al., 1998) Two studies during the menopausal transition have produced longitudinal data over ~8 years. Both studies have had negative results. (Bromberger et al., 2010; Dennerstein, Randolph, Taffe, Dudley, & Burger, 2002) The first was a study of 226 Australian (Caucasian only) women aged 45–55, who had menstrual periods within the past 3 months and were assessed annually for 8 years during their menopausal transition. Serum DHEA-S levels and mood were unrelated in this study. (Dennerstein et al., 2002) The SWAN (Study of Women’s Health Across the Nation) study, a community based sample of 3302 premenopausal and perimenopausal multiethnic women from the United States, aged 42–52 years, were studied over 8 years.(Bromberger et al., 2010) No relationship was found between DHEA-S levels and elevated depressive symptoms, as assessed by the Center for Epidemiologic Studies Depression Scale. However, a longitudinal association of higher

testosterone levels with elevated depressive symptoms during the menopausal transition was found in the SWAN cohort. Neither study reported major depression.

In a post-hoc analysis, using a method of statistical centering on age, lower levels of DHEA-S were associated with depressive symptoms among the older women in the POAS cohort and high DHEA-S levels were associated with depressive symptoms in the younger half of the cohort (Morrison et al., 2001). The current PENN Ovarian Aging Study includes longitudinal data encompassing 11 assessment periods over 11 years. Thus, this study was undertaken to confirm prospectively the relationship between DHEA-S levels and both depressive symptoms and major depression in women during the transition through menopause. Based on the cross sectional findings of a differing relationship of DHEA-S levels and depressive symptoms by age discovered in a post-hoc cross-sectional analysis of the POAS cohort at baseline, we also planned to investigate the interaction of DHEA-S levels and depressive symptoms by age group at baseline.

Methods

Cohort

The population-based cohort was identified by random digit dialing to households in Philadelphia County as previously described and enrolled equal numbers of African American and Caucasian women (Freeman, Sammel, Lin, & Nelson, 2006). Eligibility criteria for enrollment included: 35 to 47 years of age, menstrual cycles in the reference range (22–35 days) during the previous 3 months, and at least 1 ovary plus intact uterus. Exclusion criteria included: current use of psychotropic or hormonal medications, pregnancy or breast-feeding, serious health problems known to compromise ovarian function, alcohol or drug abuse within the previous year, and non-English speaking. The study was approved by the University of Pennsylvania Institutional Review Board and written informed consent was obtained from the participants.

Study Design

Data were collected in 11 assessment periods over 11 years. The first 6 periods were at 8–9 month intervals, and periods 7–10 were at annual intervals, with a 2-year gap between period 10 and 11. Each assessment period had two visits, scheduled at home or work, between days 1 and 6 of two consecutive menstrual cycles (or a one month interval in non-cycling women) in order to obtain blood samples for the hormone assays (maximum of 22 samples per participant). The full cohort (N= 436) was included in this report. At the 11th assessment period, 131 women had withdrawn for the following reasons: withdrew consent (n=21), lost to follow up (n=40), time constraints (n=10), medical or personal problems (n=9), moved from area (n=9), no reason given (n=31) and deceased (n=11). All available data for each participant was included in the repeated measures models. Observations during pregnancy, breast-feeding, hormone use, current psychotropic use and use of medications associated with altered DHEA-S levels were censored at the times of their occurrence. Hormone measurements taken after a participant reported hysterectomy, oophorectomy or cancer were set to missing from occurrence onward. Comparison of baseline data between participants who continued throughout the study and dropouts revealed no significant differences in age, history of depression, DHEA-S level, race, smoking history, body mass index, hot flashes, educational level, and income level. *Study Measures*. All data were obtained by trained research interviewers in individual in-person interviews. The structured interview, which was repeated at each assessment, focused on overall health and included demographic information, menstrual cycle dates, reproductive history, general health status, and behaviors (including smoking, alcohol, medications used). During assessment periods 1–6, the diagnosis of Major Depression (MDD) was ascertained by the Primary Care

Evaluation of Mental Disorders (PRIME-MD)(Spitzer et al., 1994). The Patient Health Questionnaire, a self-administered diagnostic instrument which was derived from the clinician administered PRIME-MD by the team that created the PRIME-MD, was used to make the diagnosis of major depression during periods 7–11(Spitzer, Kroenke, & Williams, 1999). Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977).

Age was dichotomized into two age groups based on the mean age at the baseline visit, since the post-hoc analysis at baseline by age group had suggested a different relationship of DHEA-S and depressive symptoms in the younger and older women in the POAS cohort. (Morrison et al., 2001) The PENN-5 definitions of menopausal stage (Gracia et al., 2005) were adapted from the consensus statement on a Staging System for Reproductive Aging Women (STRAW). (Soules et al., 2001) At each assessment, the participant was assigned to one of the following 5 categories, based on the bleeding patterns at that assessment: *1) premenopausal*, regular menstrual cycles in the 22–35 day range, with no change in cycle length*; 2) late premenopausal*, 1 cycle change of ≥7 days; 3) *early transition*, changes in cycle length of ≥7 days in either direction from the participant's personal baseline at enrollment in the cohort, observed for at least two consecutive cycles in the study or 60 days of amenorrhea; *late transition*, 90 days to 11 months of amenorrhea during the study; *postmenopausal*, ≥ 12 months of amenorrhea.

In addition to age and menopausal stage, variables with previous reports of association with DHEA-S levels and studied in the cohort at baseline were included in the multivariable model. Race (lower DHEA-S levels in African American women compared with Caucasians) (Girgis et al., 2000; Morrison et al., 2001), body mass index (BMI)(Lasley et al., 2002; Mazza et al., 1999) and smoking (Lasley et al., 2002; Khaw, Tazuke, & Barrett-Connor, 1988) were selected for study as covariates. Variables noted to influence DHEA-S levels after the publication of the baseline study, such as alcohol use (Randolph et al., 2003; Rinaldi et al., 2006), were then tested to determine whether their addition influenced the model. Testosterone levels and estradiol levels were added separately to the final model to investigate whether the relationship between DHEA-S and mood was influenced by these metabolites of DHEA-S.

Non-fasting blood samples for the hormone assays were collected between days 1 and 6 of the menstrual cycle in 2 consecutive cycles at each of the 11 assessment periods. Blood samples were taken between 10 AM and 7 PM.

Assays of serum levels of DHEA-S and other hormones (testosterone, estradiol, follicle stimulating hormone (FSH), luteinizing hormone (LH) were conducted in the General Clinical Research Center using commercial kits (Coat-a Count; Diagnostic Products, Los Angeles, CA) .Additional technical information has been previously reported. (Manson, Sammel, Freeman, & Grisso, 2001) DHEA levels were not measured. Inter-assay and intra-assay coefficients from the General Clinical Research Center at PENN were 7.8% and 7.7% respectively. Hormone levels obtained during the study were averaged for each subject at each assessment period. Assays were conducted in batched samples of ~20 women, including 2–4 samples per woman from consecutive time points.

Statistical analysis

Data from all observed assessment periods were included in all analyses, with the exceptions described above. Covariate values assessed concurrently with the response variable were also utilized. A natural logarithm transformation of hormone levels was used in all analyses to accommodate modeling assumptions and reduce the influence of skewed data. The distribution of continuous CES-D was examined at each assessment period to assure that

normality assumptions were met. For this outcome, a general linear mixed regression model for repeated measures was used to estimate the unadjusted and adjusted associations of each study variable with the CES-D score. Results were summarized using means and standard errors for categorical variables, and regression coefficients (slopes) and standard errors for continuous measures. The dichotomous outcome, MDD, was fit to a generalized linear mixed model. This model is an extension of logistic regression to accommodate repeated observations per subject. For each type of model, we assumed that the repeated outcomes for each woman's measures were equicorrelated, and statistical tests for covariate associations were adjusted using generalized estimating equation (GEE) methodology. (Zeger, Liang, & Albert, 1988) This specialized statistical technique is similar to analysis of variance for repeated measures in that the point-in-time associations between the covariates of interest (DHEA-S levels, menopausal status, age, race, etc.) and outcome (depression status) are averaged over time, i.e., combine cross-sectional (between women) and longitudinal (within woman) estimates of association and correct statistical tests for the correlation due to multiple measures within women. This method is more flexible than the repeated measures ANOVA, because it does not require each woman to have the same number of repeated measurements or measurements taken at fixed time points, as long as missing information can be assumed missing-at-random, i.e., missing data do not depend upon the unobserved outcome measures. Reproductive hormone levels and all other covariates associated with depression status in the unadjusted analyses at $p < 0.20$ were included in the model selection process for the multivariable models. The final selection of covariates was guided by whether each variable remained statistically significant at $p \leq 0.05$ or whether its inclusion modified other significant associations in the model by 15% or more. (Maldonado & Greenland, 1993) Post-hoc calculations determined that this study had 80% power to detect a difference in natural log DHEA-S (ln[DHEA-S]) between subjects with MDD compared to those without MDD for a 1 standard deviation (0.7) difference between these groups. This amount represents a change in DHEA-S levels of 16% or more. The SAS statistical software package, version 9.1, was used for all analyses. Statistical tests were two-tailed, with P-values ≤ 0.05 considered significant.

Results

Table 1 shows study variables at baseline and at the 11 year endpoint. At endpoint, the mean (SD) age was 50.6 (3.5) years; 47.3% were African American and 52.7% were Caucasian. At baseline, all participants were premenopausal; at endpoint, approximately 33% of the cohort was postmenopausal, ~59% were in the menopausal transition. Two percent of the participants were still premenopausal and ~6% had a hysterectomy and/or oophorectomy. Mean DHEA-S levels of the remaining study participants had decreased from baseline levels on average ~13% by the 11 year time point.

DHEA-S Levels and Depression

DHEA-S levels were positively associated with depressive symptoms (CES-D scores) in the longitudinal analysis, in both the unadjusted (Estimate = 1.21, $p = 0.007$) and adjusted analyses (Estimate = 1.07, $p = 0.013$) as shown in Table 2. No change in direction of the relationship of DHEA-S levels and depressive symptoms was found in the cohort, by age group at baseline. Both age groups had a positive association of DHEA-S levels and depressive symptoms. DHEA-S levels were not associated with MDD, as shown in Table 3.

Interactions. No two-way interactions were found between DHEA-S level and age group or DHEA-S levels and race in the final model for depressive symptoms and the final model for MDD.

Influence of Testosterone, Estradiol on Final Model

The individual addition of either testosterone levels or estradiol levels to the final model did not affect the observed relationship between DHEA-S and CES-D scores (Table 2). Both testosterone and estradiol are metabolites of DHEA. With univariate analysis, testosterone levels were inversely related to CES-D scores (Estimate=−0.40, p=0.02) and estradiol levels were unrelated to CES-D scores. The diagnosis of MDD was unrelated to levels of testosterone or estradiol on univariate analysis. When levels of testosterone and estradiol were added to the multivariable model separately, neither were significantly related to CES-D scores, nor did they affect the observed association between DHEA-S levels and depression (data not shown).

Menopausal Stage and Depression

Perimenopause and postmenopause were associated with lower depressive symptom scores when compared with premenopause. Both stages of perimenopause (early p=0.004, late p=0.016) as well as the postmenopausal stage (p<0.0001) were inversely associated with CES-D scores in the both the adjusted and unadjusted models as shown in Table 2. For the diagnosis of MDD, women in the late perimenopausal transition (OR=0.27, p= 0.006) were significantly less likely to have MDD, when compared with premenopausal women. Women during the early perimenopause (OR=0.70, p=0.07) and postmenopause (OR=0.39, p=0.053) also appeared to have a trend towards a decreased risk of MDD when compared with premenopausal women, though these findings did not meet criteria for statistical significance (Table 3, adjusted model).

Other Covariates

Body mass index is known to have a relationship with DHEA-S levels (Burger, Dudley, Cui, Dennerstein, & Hopper, 2000), but the SWAN study suggests that there are ethnic/racial variations in both the direction and intensity of the relationship. (Lasley et al., 2002) The unadjusted estimate of the relationship of DHEA-S levels and depressive symptoms was 1.21, and the adjusted relationship was 1.07 (Table 2). The adjusted relationship between DHEA-S levels and depressive symptoms without BMI in the model was 0.83 suggesting that ~20% of the relationship between DHEA-S levels and depression seen in the unadjusted analysis was explained by BMI. The use of alcohol, which has been associated with DHEA-S levels (Randolph et al., 2003), was not significantly associated with CES-D scores in the multivariable model, nor did it affect the relationship between DHEA-S levels and depressive symptoms (Estimate=1.08, p=0.01).

Discussion

DHEA-S is an abundant hormone of the hypothalamic-pituitary-adrenal axis that has been purported to be associated with successful aging and mental function.(Morsink et al., 2007) When adjusted for both age group and menopausal status, as well as race, smoking and BMI, plasma DHEA-S levels and depressive symptoms are positively associated during the menopausal transition. The PENN Ovarian Aging cohort is the only cohort of reproductive aging in women in which all members start in the premenopause. The present finding, confirms the positive association of DHEA-S levels and depressive symptoms found in our baseline cross-sectional analysis published in 2001. Thus, the association of DHEA-S and depressive symptoms has been confirmed longitudinally. The positive association between DHEA-S levels and depressive symptoms has been demonstrated in the only community based cohort studied during the menopausal transition in which all participants start in the premenopausal stage.

Two other longitudinal studies followed women for 8 years through the menopausal transition and found no relationship between depressive symptoms and DHEA-S levels. (Dennerstein et al., 2002)(Bromberger et al., 2010) The study of Australian women employed a non-standard measure of depressive symptoms (negative affect scale) until recently, and studied slightly older women. Some of the women were perimenopausal, not premenopausal, at baseline, so the difference in results might be due to methodological differences. (Dennerstein et al., 2002) The Australian investigators are planning an updated report of DHEA-S levels and depressive symptoms in their cohort. (Ryan et al., 2009) In the SWAN cohort, a substantial proportion (44%) also began the study in early perimenopause, not premenopause. (Bromberger et al., 2010) Thus, an association of DHEA-S levels and depressive symptoms may be obscured by a substantial proportion of the cohort beginning in perimenopause. Though no relationship of depressive symptoms and DHEA-S was found in the SWAN cohort, a positive association between high depressive symptoms and both total and free testosterone levels was shown. (Bromberger et al., 2010) We did not find the association of DHEA-S levels and depressive symptoms mediated by testosterone levels in our cohort. When testosterone levels were added into the multivariable model, the association of DHEA-S and depressive symptoms did not change.

Some cross-sectional, community-based studies in African American middle aged (Haren et al., 2007) and geriatric (Barrett-Connor E. von Mühlen D. Laughlin GA. Kripke A, 1999; Morsink et al., 2007) women have suggested either no relationship or an inverse relationship between DHEA-S levels and depressive symptoms. Cross-sectional studies may fail to detect an existing correlation because the wide variability of DHEA-S levels among different subjects cannot be accounted for by repeated measures in the same person, as they are in longitudinal studies. Another explanation for the differences in findings between the cross-sectional studies mentioned and the present longitudinal study are due to physiological differences in the population studied, since the cross-sectional studies did not investigate women during the menopausal transition. The present results confirm the overall findings of our own baseline cross-sectional study, which reported a positive association between DHEA-S levels and depressive symptoms during the menopausal transition, though it did not confirm our post-hoc analysis, by age group.

In studies with clinical populations with major depression (MDD), an association between major depression and elevated DHEA-S levels has been noted. (Takebayashi et al., 1998;Assies et al., 2004). Moreover, successful treatment of depression was followed by reductions in both DHEA-S levels (Takebayashi et al., 1998;Fabian et al., 2001) and DHEA levels (Fabian et al., 2001) In the last (11^{th}) assessment of our cohort, there was a 5.3% prevalence of MDD (16/300), typical of a healthy community based cohort. However, there may not have been adequate power to detect a weak relationship between DHEA-S levels and MDD. Post-hoc power calculations determined that this study had 80% power to detect a difference in DHEA-S levels of 16% or more.

Depressive Symptoms and Menopausal Transition Stage

The relationship of menopausal stage and depression is not the focus of this report. Therefore, we will comment on this briefly. In our cohort overall, depressive symptoms decrease during the menopausal transition. The prevalence of major depression was also decreased in the late menopausal transition compared with premenopausal women. An interaction of history of major depression and menopausal stage was found in this study. The interaction suggests a more complicated relationship between major depression and menopausal stage during the menopausal transition and will be the focus of a subsequent report. In an earlier analysis of the subset of women with no history of depression in the PENN Ovarian Aging cohort (N=231), we found that women with no history of depression had an increased odds of having MDD during the perimenopausal transition (OR=2.5) and

an increased odds for risk of elevated depressive symptoms (OR=4.29) during the perimenopausal transition (Freeman et al., 2006). In the current study, using a test for interactions when major depression was the outcome , the interaction of the variables "history of depression" and "menopausal status" was significant, p=0.003. Because of the interaction of the history of major depression and menopausal stage discussed, it is possible that women with no history of major depression are at increased risk of depression during the menopausal transition and women with a previous history of depression are not. This finding will be investigated in a separate, focused study.

In the SWAN study, perimenopausal and postmenopausal women had significantly increased risk of having elevated depressive symptoms compared with premenopausal women. (Bromberger et al., 2010) Major depression was not reported. The populations of the two studies are somewhat different. Women using hormones and psychotropic medications were included in the SWAN report, whereas women using hormones and psychotropics were not included in the POAS cohort. Both cohorts have similar findings in terms of the relationship of depressive symptoms and age, with an inverse association of depressive symptoms with increasing age during the menopausal transition. The relationship of menopausal stage and depressive symptoms and major depression requires further study in our cohort because of the interaction discussed above.

Mechanism of DHEA-S Association with Depression

The association of DHEA-S and depressive symptoms is unlikely to be mediated by levels of its metabolites, testosterone and estradiol. When each was added to the multivariable model separately, they did not affect the observed association between DHEA-S levels and depression as discussed above. Whether the association of DHEA-S levels and depressive symptoms represents increased adrenal activity with an associated increase in cortisol production could not be determined from the current study, as cortisol was not measured

Limitations

In the present study, only women during the transition to menopause were evaluated and only two racial/ethnic groups were represented. Women taking antidepressants and other psychotropics were excluded from this cohort. Thus, the POAS cohort is a healthier population when compared to other studies of midlife such as SWAN and the Seattle midlife cohort. In addition, the association between DHEA-S levels and depressive symptoms may not hold for women at other times of life, or in women of different ethnic/racial groups, or in men.

While the direction of the association of DHEA-S and depressive symptoms is positive and statistically significant in the multivariable model, the association is somewhat weak. In the present study, DHEA-S levels were obtained throughout the day (between 10 AM and 7PM), and DHEA-S levels obtained late in the day may be lower than those obtained earlier (Assies et al., 2004; Carlström K. Karlsson R. Von Schoultz B, 2002). However, these diurnal fluctuations in DHEA-S levels are minor, probably related to serum albumin levels (Carlström K. Karlsson R. Von Schoultz B, 2002), and are probably clinically insignificant. Finally, the PENN-5 criteria for menopausal status are not the same as the STRAW criteria and both of these criteria continue to be validated.

Summary

The present study demonstrated a positive association between levels of DHEA-S, an abundant adrenal hormone, and depressive symptoms in healthy women living in the community during the transition through menopause, when adjusted for both age and menopausal group in the multivariable model. This confirms the association of DHEA-S

levels and depressive symptoms found during our baseline analysis of the cohort at premenopause. Our study represents the first longitudinal report of a positive association of DHEA-S levels and depressive symptoms in a community based population during the menopausal transition.

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Table 1

Study Variables at Baseline and 11 year Endpoint (11TH Assessment)

	Baseline Assessment N=436 N (%) or Mean value (SD)	**11th Assessment 11 year endpoint N=300[1] Mean value (SD) or N (%)**
Age	41.4(3.5)	50.6 (3.5)
Race		
Caucasian	217 (49.8)	158(52.7)
African American	219 (50.2)	142(47.3)
Menopausal Stages		
Premenopausal	436(100)	6 (2.0%)
Late Premenopause	0	9(3.0%)
Early Transition	0	106(35.3%)
Late Transition	0	62(20.7%)
Postmenopause	0	100 (33.3%)
Hysterectomy or oophorectomy	0	17 (5.7%)
CES-D	15.2(10.8)	11.6 (9.6)
Current Major Depression	36/425[2] (8.5%)	16/298[3] (5.4%)
DHEA-S levels μg/dL	106.4(56.6) N=408	92.3 (56.5) N=294
Current Smoking	166(38.1)	95(31.7)
BMI	29.2 (7.9) N=428	31.4(8.7) N=284

[1] 5 subjects were missing at Period 11

[2] 11 subjects did not have the assessment performed at baseline

[3] 2 subjects did not have the assessment performed at endpoint

Table 2

Estimated associations with depressive symptoms (CES-D) from the univariate and final multivariable model

Variables	Unadjusted Estimate	Adjusted Estimate	95% Confidence Limits	P value
Natural Log of Mean DHEA-S level	1.21**	1.07	0.22, 1.91	0.013*
Menopausal Status	Unadjusted p≤****0.0001			Adjusted p≤****0.0001
Premenopause	Reference	Reference	Reference	
Late Premenopause	−0.94*	−0.42	−1.26, 0.43	0.33
Early Transition Perimenopause	−2.30****	−1.18	−1.98, −0.38	0.004**
Late Transition Perimenopause	−2.35****	−1.48	−2.68, −0.27	0.016*
Postmenopause	−4.41****	−3.32	−4.71 , −1.92	<0.0001****
Age >41	−3.64****	−2.78	−3.86, −1.71	<0.0001****
Race group African American	2.65***	2.95	1.41, 4.48	0.0002***
Smoker	2.58****	1.66	0.56, 2.77	0.003**
Body Mass Index	−0.08 p=0.059	−0.04	−0.12, 0.03	0.26
Natural Log of Mean Testosterone Levels[1]	−0.40*	−0.17	−0.55, 0.20	0.37
Natural Log of Mean Estradiol Levels[1]	0.20	−0.06	−0.47, 0.34	0.76

P values for analyses

* ≤0.05

** ≤0.01

*** ≤0.001

**** ≤0.0001

[1] Not included in baseline multivariable model, only included to measure metabolite effect

Table 3

Odds ratios for associations with diagnosis of Major Depression from the univariate and final multivariable model

Variables	Unadjusted Odds Ratio	Adjusted Odds Ratio	95% Confidence Limits	P value
Natural Log of Mean DHEA-S level	0.99	0.95	0.72, 1.26	0.72
Menopausal Status	Unadjusted p **** ≤0.0001			Adjusted p =0.0002 ***
Premenopause	Reference	Reference	Reference	
Late Premenopause	1.23	1.20	0.84, 1.70	0.32
Early Transition Perimenopause	0.63 **	0.70	0.47, 1.04	0.07
Late Transition Perimenopause	0.28 ***	0.27	0.15, 0.64	0.006 **
Postmenopause	0.35 **	0.39	0.15, 1.01	0.053
Age >41	0.52 ****	0.67	0.47, 0.96	0.029*
Race group African American	2.50 ****	2.14	1.37, 3.36	0.0009 ***
Smoker	1.98 ***	1.78	1.23, 2.61	0.002 **
Body Mass Index	1.02 *	1.03	1.01, 1.05	0.01 **
Natural Log of Mean Testosterone Levels [1]	1.01	1.05	0.88, 1.24	0.61
Natural Log of Mean Estradiol Levels [1]	1.05	1.06	0.85, 1.32	0.60

P values for analyses

* ≤0.05

** ≤0.01

*** ≤0.001

**** ≤0.0001

[1] Not included in baseline multivariable model, only included to measure metabolite effect