Published in final edited form as:

Menopause. 2012 August ; 19(8): 877–885. doi:10.1097/gme.0b013e3182432de6.

Association of Sex Hormones and SHBG with Depressive Symptoms in Post-menopausal Women: the Multi-Ethnic Study of Atherosclerosis

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Abstract

Objective—Sex hormones are thought to play an important role in the pathophysiology of depressive disorders in women. This study assessed the associations of total testosterone (T), bioavailable T, estradiol (E2), dehydroepiandrosterone (DHEA) and sex hormone binding globulin (SHBG) with depressive symptoms stratified on postmenopausal stage to determine whether associations were strongest for early postmenopausal women.

Methods—Women (N=1824) free of depressive symptoms at baseline (2000–2002) in the Multi-Ethnic Study of Atherosclerosis were categorized into tertiles of years postmenopause: T1, 0–10 years; T2, 11–20 years; and T3, 21–58 years. Multivariable-adjusted relative risks (RR) and 95% confidence intervals were computed for the incidence of depressive symptoms, as defined by a score of 16 or higher on the Center for Epidemiologic Studies Depression scale at examination 3 (2004–2005).

Results—In analysis including all sex hormones, the RRs for incident depressive symptoms associated with 1 unit higher log(total T) was 0.57 (p=0.13), log(E2) was 0.78 (p=0.04), log(SHBG) was 1.84 (p=0.003) and log(DHEA) was 1.45 (p=0.08) in T1. Without adjustment for SHBG, the RR for log(bioavailable T) was 0.16 (p=0.04). However, in T2 and T3, there were no meaningful associations of hormone or SHBG levels with incident depressive symptoms. When stratified by HT use, results were consistent for HT users but attenuated for HT non-users.

Conclusions—In women early postmenopause, sex hormones were associated with incident depressive symptoms.

Keywords

sex hormones; CES-D; depression; testosterone; estradiol; SHBG

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Conflict of interest statement: None of the authors have any conflicts of interest to disclose.

INTRODUCTION

Gender differences in the prevalence of depressive disorders from puberty through the perimenopause are well established,^{1,2} with female:male ratios ranging from 1.3 to 2.1 across studies.¹ Sex hormones are thought to play a significant role in the pathophysiology of depressive disorders, and therefore might contribute to this gender difference. Recent research is targeting how changes in sex hormones during the premenstrual period, during pregnancy, following pregnancy, and during the perimenopause and menopause, may contribute to the onset of depressive disorders.^{3–8} At least four studies support the hypothesis that unpredictable fluctuations in endogenous ovarian hormones are associated with increased risk for depressive symptoms or disorders during the perimenopause.^{6,9–11} Also, exogenous estrogens appear to relieve depressive symptoms during the perimenopause,¹² but not during the postmenopausal period.^{13–14} Few studies have examined associations of endogenous female sex hormones with depressive symptoms in exclusively postmenopausal women,^{15–16} and those studies had no more than 138 participants.

There are even fewer studies of the associations of androgens with depressive symptoms or depressive disorders than those for estrogens and progestins. One epidemiologic study conducted in pre- and peri-menopausal women reported a significant, inverse association between testosterone (T) and depressive symptoms after adjustment for potential confounding factors.¹⁷ Another study examined associations of total T and free T with depressive symptoms in women aged 70–79 years.¹⁸ In that study, free T, but not total T, was inversely associated with depressive symptoms. Recently, Deecher et al.¹⁹ proposed that “neurophysiological processes responsible for the maintenance of emotional homeostasis are impacted by (ovarian) hormonal regulation” and “brain adaptation in the postmenopausal stage results in a physiology that is less dependent on and/or vulnerable to modulation by ovarian hormones.” If this hypothesis is true, then sex hormones could impact depressive symptoms in the early postmenopausal period before such an adaptation occurs. Indeed, studies showing no relationships of endogenous sex hormones¹⁵ or exogenous hormones with postmenopausal depression¹³ included women with mean age of 70 years¹⁵ or who were on average 17.1 years postmenopause.¹³ Only one prospective study examined associations of sex hormones with depressive symptoms in a sample of younger postmenopausal women,¹⁶ but, as noted, that study had limited statistical power. More research is needed to better understand the relationship of sex hormones with depressive symptoms among women with broad age range and postmenopausal stage range. The Multi-Ethnic Study of Atherosclerosis (MESA), which includes White, Black, Hispanic and Chinese post-menopausal women in the age range of 45 to 84 years, provides an opportunity to study the association of sex hormones with depressive symptoms in women who are recently or long-term postmenopausal. We hypothesize that sex hormones measured at baseline (2000–2002), in particular low levels of T and estradiol, will be associated with incidence of high depressive symptoms (i.e., Center for Epidemiologic Studies Depression Scale (CES-D) score of 16 or higher) at exam 3 (2004–2005) in women early in postmenopause. The associations will be weaker or absent in women who are later postmenopause.

METHODS

Study population

MESA is a population-based study initiated in 2000 to investigate the prevalence and progression of subclinical cardiovascular disease in a sample of 6814 non-Hispanic white, African-American, Chinese-American and Hispanic men and women, aged 45–84 years, who were free of clinical cardiovascular disease at baseline. Participants were recruited from

six US communities: Baltimore City and County, MD; Chicago, IL; Forsyth County, NC; New York, NY; Los Angeles County, CA; and St. Paul, MN. Details on the design, recruitment, and cohort examination procedures²⁰ and methods for blood collection and measurement of sex hormones²¹ were published elsewhere. All participants gave informed consent, and the MESA protocol was approved by the Institutional Review Board at each participating site.

From the 3601 women in the MESA cohort, we excluded 592 without sex hormone levels, 3 missing menopausal status, 47 who were not menopausal, 62 missing age at menopause, 15 missing CES-D score at baseline, 403 who did not return to the third examination or who were missing CES-D score at exam 3, 31 who were missing information on hormone therapy, 95 who were missing covariate data, and 529 who had clinically significant depression at baseline defined as CES-D ≥ 16 and/or taking antidepressant medication at baseline. Included in the analytic cohort were 1824 women.

Blood collection and assessment of endogenous sex hormones

Blood specimens from fasting participants were collected between 7:30 am and 10:30 am, processed within 30 minutes of phlebotomy, and stored at -70°C using a standardized protocol and shipped to two central laboratories. Using stored blood collected from the baseline MESA exam, serum sex hormone and binding protein concentrations were measured at the University of Massachusetts Medical Center in Worcester, MA. Total T and dehydroepiandrosterone (DHEA) were measured directly using RIA kits, and sex hormone binding globulin (SHBG) was measured by chemiluminescent enzyme immunoassay using Immulite kits obtained from Diagnostic Products Corporation (Los Angeles, CA). Bioavailable T was calculated using total T and SHBG concentrations according to the method of Södergard et al.²² Estradiol (E2) was measured using an ultra-sensitive radioimmunoassay kit from Diagnostic System Laboratories (Webster, TX). Assay variability was monitored by including $\sim 10\%$ blind, quality control samples in each batch. The intra- and inter-assay technical errors were 8.13 and 9.31%, respectively, for total T; 5.22 and 6.39%, respectively, for SHBG; 8.75 and 5.86%, respectively, for E2; and 7.45 and 8.49% for DHEA.

Menopausal status

Women were classified as postmenopausal if (a) they responded ‘yes’ to the question, ‘Have you gone through menopause (change of life)?’, or (b) had a prior hysterectomy and bilateral oophorectomy. Years postmenopause was computed as baseline age minus self reported age at menopause, unless the woman had a hysterectomy and a bilateral oophorectomy, in which case years postmenopause was taken to be years from age at hysterectomy.

Outcome variable assessment

Depressive symptoms were measured at the baseline (2000–02) and the third examinations (2004–05) using the 20-item CES-D scale,²³ which has a maximum score of 60. The CES-D, which was administered in English, Spanish, Cantonese, and Mandarin, asks participants to indicate how often they experienced each symptom in the past week (“rarely or none of the time (less than 1 day),” “some or a little of the time (1–2 days),” “a moderate amount of the time (3–4 days),” or “most of the time (5–7 days).” Scores for the four possible responses range from 0 to 3 points. Examples of symptoms included in the scale are poor appetite, trouble concentrating, restless sleep, feelings of depressed mood, crying spells, feeling disliked, talking less than usual, and inability to “get going.” A cutoff score of ≥ 16 is suggested in epidemiologic studies to indicate a high level of depressive symptoms.^{23–24}

Other Participant Characteristics

Information on participant demographic and lifestyle characteristics, medical history, and medication use was collected with standardized questionnaires: height and weight were measured and body mass index (BMI) was calculated as weight (kilograms)/height (meters squared). Age, race/ethnicity, years of education, cigarette smoking history, alcohol intake, medication intake including hormone therapy (HT) and annual income were self-reported. Women were asked to bring in all medications they were taking to each examination, but they were not specifically asked if they were taking a medication for depression. Physical activity measured by a total intentional exercise variable was categorized into four levels: 0 MET-min/week, greater than 0 but less than or equal to 720 MET-min/week, greater than 720 but less than or equal to 1800 MET-min/week, and greater than 1800 MET-min/week. Cutpoints for the three higher categories were selected to approximate tertiles among participants with greater than 0 MET-min/week. Income, which was categorized into 13 levels, was initially modeled using dummy variables, and was treated in final analysis as an ordinal variable with range 1 to 13.

Statistical Analysis

Statistical analyses were conducted using SAS for Windows, release 9.2 (SAS Institute Inc., Cary, NC). Years postmenopause at the baseline exam, which ranged from 0 to 58 years, was categorized into tertiles based on sample size and the associations of sex hormones with depressive symptoms at exam 3 were assessed separately for each tertile. Because some participants were taking antidepressant medication at the time the CES-D was measured, two approaches were used for analyzing the outcome depressive symptoms.²⁵ First, CES-D score at examination 3 was analyzed as a binary trait. A treated participant was assumed to have an untreated CES-D score at least as high as 16. Thus we classified a participant as having a high level of depressive symptoms if her CES-D score was greater than or equal to 16 or if she was taking an antidepressant medication. Multivariable modified Poisson regression,²⁶ implemented through SAS PROC GENMOD with a REPEATED statement to obtain robust error variances, was used to assess the associations of sex hormones with this binary outcome and compute relative risks (RRs). Tests for interactions between tertiles of years postmenopause and hormones were obtained by specifying the TYPE 3 option in the MODEL statement of PROC GENMOD. The interaction terms were used to obtain tertile specific RRs for the sex hormones. For the second approach we treated CES-D score as a continuous variable with right censoring on the observed scores for participants treated with antidepressants. That is, we assumed the observed score for a treated participant would be a lower bound for the untreated score of that individual. The censored normal regression model was used to analyze CES-D scores as a continuous outcome.

Sex hormone levels were modeled as quartiles as well as log transformed continuous variables (with 1 added prior to transforming for total T and bioavailable T due to 0 values) with each sex hormone in a separate model. Analyses were conducted for all women and adjusted for HT use, and then for strata of HT non-users and HT users. In addition to the separate models for each hormone, the analyses for all women, HT non-users and HT users were assessed with log total T, log SHBG, log E2, and log DHEA entered simultaneously into the model. Log bioavailable T was evaluated together with log E2 and log DHEA, but not log SHBG in the model.

Four sensitivity analyses were done. Because menopausal status was self-reported, the combined hormones models (i.e. with log total T, log SHBG, log E2 and log DHEA) for all women were examined excluding women who were 0 years postmenopause. To address the concern of reverse causality and because we did not have information on history of depression, we excluded from analysis an additional 535 women who had a baseline CES-D

score between 8 and 15 as this range has been identified as probable “subthreshold depression”.^{27–29} We also evaluated the combined hormones models excluding the women who had hysterectomy and bilateral oophorectomy because they might differ from women who had natural menopause. Finally, we evaluated the associations after excluding participants who were taking anti-depressant medication at exam 3.

RESULTS

Baseline characteristics are shown in Table 1 stratified by tertile of years postmenopause and status of depressive symptoms at examination 3. The highest tertile (T3) had the lowest proportion of women with depressive symptoms at examination 3 (11.7%) compared to the middle (T2) and lowest (T1) tertiles. In each tertile, women with depressive symptoms were slightly younger and more likely to be smokers. In T1 and T3, women with depressive symptoms had lower physical activity and in T2 and T3 they had lower median income. Of the 596 women taking HT, 247 (41.4%) were taking estrogen with progestin, 314 (52.7%) were taking estrogen alone, 5 (0.8%) were taking a progestin alone, and 30 (5.0%) were not classified. In general, compared to those not taking HT, women taking HT were younger, fewer years postmenopause, had lower BMI, exercised more, more likely to be white, more likely to have had hysterectomy with bilateral oophorectomy, more likely to be a college graduate and have higher income, and more likely to be a current drinker.

Among women without clinically significant depression at baseline (n=1824), the associations of each hormone level with the incidence of clinical depression at examination 3 for women stratified by tertiles of years postmenopause are presented in Table 2. Total T was inversely associated with risk of depressive symptoms in models with adjustment for HT in T3. Bioavailable T was inversely associated and SHBG was positively associated with risk of depressive symptoms in models with adjustment for HT in both T1 and T3. No consistent patterns of associations between E2 and risk of depressive symptoms were observed. There was a borderline inverse association of DHEA with risk of depressive symptoms with adjustment for HT in T3. The statistical significance of the associations when stratifying by use of HT was in general, although with a few exceptions, attenuated as compared to the models based on all women. Tests for interactions between tertiles of years postmenopause and log transformed sex hormones were marginally statistically significant for bioavailable T ($p=0.16$), but not SHBG or any other hormone.

For the censored normal regression model in which CES-D score was modeled as a continuous variable and assumes that the observed score for a medication treated individual is a lower bound for her untreated score, no meaningful associations between hormone levels and CES-D score were observed (data not shown).

Correlations among the sex hormones and SHBG were present. However, among total T, E2, SHBG, and DHEA, none of the intercorrelations exceeded 0.36 and among bioavailable T, E2, and DHEA, none exceeded 0.33.

In analyses with mutual adjustment for hormone concentrations (Table 3), in T1, SHBG was positively and E2 was inversely and statistically significantly associated with risk ($p=0.003$ and $p=0.04$, respectively) in all women. Similarly, after adjustment for E2 and DHEA, bioavailable T was strongly and inversely associated with the risk of depressive symptoms in T1. After mutual adjustment, there were no meaningful associations of sex hormones or SHBG in either T2 or T3. When the combined hormone models were stratified by HT use (Table 3), results for HT users were consistent with those in all women. For HT non-users, the directions of the associations were maintained although the significance attenuated.

In the censored normal regression analysis, whereas none of the beta coefficients for any sex hormone were statistically significant in T1 in the previous analysis, when mutually adjusted, only log SHBG and log E2 were meaningfully associated, and in opposite directions, with CES-D score ($p=0.04$ and 0.03 , respectively).

The sensitivity analyses evaluating the four hormones simultaneously but excluding: (1) women who were 0 years postmenopause; (2) women with “subthreshold” depressive symptoms; (3) women who had hysterectomy and bilateral oophorectomy; and (4) women taking anti-depressants at exam 3, yielded findings similar to those above (data not shown). Of note, after excluding women who were potentially still perimenopausal, the RRs for log SHBG and log E2 in T1 of years postmenopause maintained similar direction, magnitude, and significance. The associations for log SHBG after excluding women with baseline CES-D ≥ 8 were robust as well (RR=1.70 and $p=0.07$ for T1 and RR=2.27 and $p=0.003$ for T3), although the RR for log E2 in T1 was somewhat attenuated (RR=0.84, $p=0.37$). In the analysis excluding women on anti-depressants, the RRs for total T, SHBG, E2, DHEA, and bioavailable T all became slightly stronger than those seen in Table 3.

DISCUSSION

In a large, multi-ethnic cohort of postmenopausal women who were free of clinically significant depressive symptoms at baseline, we examined associations of sex hormones and SHBG with the incidence of depressive symptoms based on a CES-D score ≥ 16 among three groups of women stratified according to time since menopause. In multivariable analysis of hormones separately, for women who were furthest from menopause (group T3) associations with incident depressive symptoms were inverse for total and bioavailable T and DHEA and positive for SHBG.

More importantly, in multivariable analysis controlling for other hormone levels, results showed statistically significant inverse associations of bioavailable T and E2, and positive associations of SHBG with risk of depressive symptoms measured four years later only in the group of women with the fewest years postmenopause (i.e., 0–10 years). There were no meaningful associations of sex hormones or SHBG in the two groups of women with a greater number of years postmenopause. When the multiple hormone models were stratified by HT users and nonusers, the findings suggested the associations were stronger in users of HT as compared to nonusers. A potential two-fold higher prevalence of depression among women than men is frequently used as one basis for the hypothesis that sex hormones may be causally related to depression.³⁰ In this study the combination of nearness to menopause and mutual adjustment of hormones yielded significant hormone associations and stratification by HT usage suggested the hormone associations are augmented by exogenous estrogen. In contrast to our study, most other studies of sex hormones and the risk of depression/depressive symptoms in postmenopausal women, did not account for time since menopause and/or did not adjust hormone levels for each other,^{18,31–32} and primarily focused on non HT users. For example, Barrett-Connor et al.,³⁰ studied cross sectional associations of endogenous total and bioavailable E2 and T, estrone, DHEA, DHEAS, androstenedione, cortisol, and SHBG with depressed mood and depression, determined by the Beck Depression Inventory, in 699 non HT using postmenopausal women aged 50 to 89 years. Only DHEAS levels were significantly inversely associated with depressed mood and with clinical depression in this study which had an age range similar to the present study, but did not consider time since menopause and did not adjust for multiple hormones. In a cross-sectional study, Breuer et al.³² studied an age group of frail, elderly women whose mean age was 87.8 years, which is most comparable to tertile 3 in the present study; in that study which conducted separate analyses of hormones, neither total T nor DHEA were correlated with depression score measured by the Cornell Depression Scale.³² In the Health ABC

Study,¹⁸ inverse associations of free T, but not total T with depressive symptoms were observed in cross sectional analyses of 1449 women aged 70–79 years. In the Health ABC Study, 21.7% of women were oral estrogen users and estrogen use was adjusted for in statistical analyses. The Melbourne Women's Midlife Project (MWMP)¹⁶ included postmenopausal non HT users aged 55.9 to 66.8 years, who are most comparable to the earliest menopause group in the present study. The MWMP found no associations between depressive symptoms measured by the 10 item CES-D and total or bioavailable T or E2, which were examined separately; however, a 2-year decline in E2 levels was associated with risk of depressive symptoms in women who were no more than 11 years post final menstrual period.

The Study of Women's Health Across the Nation (SWAN),³³ which included 3302 women still menstruating and aged 42 to 52 years at the baseline exam, excluded from the analyses data collected during HT use. At the eighth annual exam, 66% of the attending women were postmenopausal and would be comparable to the earliest menopause group in the current study. Interestingly, no associations with depressive symptoms for concurrent E2 levels or change from baseline in E2 levels were found. In contrast to the inverse associations for total T found in the present study, the SWAN found positive associations between concurrent log-transformed T levels and increase from baseline in log-transformed T levels with CES-D scores over the eight annual study visits. It should be noted that the SWAN did not present models in which total T, E2 and/or SHBG were mutually adjusted for each other. In our study, we observed negative confounding after mutually adjusting for multiple sex hormones and SHBG in the group of women nearest to menopause. In summary, the studies reviewed here (i.e. MWMP and SWAN) seem to suggest hormone-depression associations occur more often in women closer to menopause.

The hypothesis that time since menopause may be important was spawned by a review¹⁹ of clinical and epidemiologic studies and animal models that support the concept that in women, the serotonergic and noradrenergic neurotransmitter systems are affected by changes in ovarian hormonal status, and this may lead to perimenopausal depression. Deecher et al.¹⁹ included in their concept that after menopause, the female brain adapts to the cessation of the ovarian hormone fluctuations. Hence, we examined hormone-depressive symptom associations over a range of the postmenopausal years.

The roles of exogenous androgens and estrogens on risk of postmenopausal depression are unclear. There have been few randomized controlled trials (RCT) of exogenous T in women.^{34–35} While the studies reviewed by a clinical practice guideline³⁴ and a subsequent review³⁵ do not support a recommendation for exogenous androgens for depressed mood, they do recommend additional study of androgen action on several physiological targets, which include mood.^{34–35} The Endocrine Society also recently issued a Scientific Statement regarding the benefits and risks of menopausal HT, where the focus was on estrogens and estrogens with progestogens³⁶ as opposed to androgens.³⁴ After evaluating meta-analyses, RCTs (including flawed RCTs), and observational studies pertinent to mood symptoms or depression, the Scientific Statement reported no level A evidence (i.e., consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies) to support the use of menopausal HT (i.e. estrogens) for symptoms of depression. Before RCTs are conducted for either exogenous androgens or estrogens, other observational studies focusing on better understanding changes in endogenous sex hormones in relation to the onset of menopause and their interplay with depressive symptoms are needed. Indeed, only two cohorts^{37–40} provide significant insight into patterns of change in endogenous sex hormones in a window of up to 10 years surrounding the final menstrual period. Changes in sex hormones well beyond 10 years should be of interest as well. Although the SWAN³³ extended the work of previous studies^{37–40} and examined the

interplay of change in hormones with depressive symptoms, their findings require replication.

Until only recently, under the premise of the “free hormone hypothesis” SHBG was not considered to be a risk factor for any chronic diseases.⁴¹ Increasingly, however, the view is being taken that SHBG may not be merely a transport glycoprotein, but it may have independent biological effects.^{41–44} Caldwell and colleagues identified SHBG in the human hypothalamus⁴⁵ and indicate that SHBG is internalized into brain cells.⁴⁶ To the best of our knowledge, this is the first study to find SHBG positively associated with risk for elevated depressive symptoms in women. This finding was strongest among women who were most recently postmenopausal. In the only two other studies reported, no associations were observed.^{16,30} In one study, SHBG levels in relation to Beck Depression Inventory (BDI) scores in 699 postmenopausal women³⁰ were examined, whereas a smaller study¹⁶ limited the analysis of SHBG to comparing mean SHBG levels between 103 and 35 women classified by the 10-item CES-D as not depressed and with depression, respectively. It is not clear whether differences in characterizing depressive symptoms among these studies, or whether potential differences in postmenopausal duration, as noted in our study, explain differences across studies. Future epidemiologic studies are needed to confirm our findings for SHBG and more research is needed to extend the neuroendocrine work of Caldwell and colleagues.

There is considerable laboratory evidence supporting causal associations of endogenous T and E2 levels, although to a much lesser extent SHBG, with depressive symptoms. Preclinical studies and animal models show that T and E2 have actions in the serotonergic, dopaminergic, and noradrenergic systems.^{19,35,47} Estrogens and androgens also modulate hippocampal neurogenesis,^{35,48} which has a role in depression.⁴⁹ Intriguingly, age might modify the effects of E2 on hippocampal neurogenesis in the female rat.⁴⁸ While the effects of androgens on hippocampal neurogenesis in the rat are less studied than those of estrogens,⁴⁸ this observed interaction of E2 with age on neurogenesis raises the question of whether an interaction with age may be seen with T in the female rodent. It might be speculated that the property of hippocampal neurogenesis is one mechanism behind our observation of T -- depressive symptoms association in the group closest to menopause.

In our study, we observed a positive association of depression with DHEA levels. Although the literature on endogenous DHEA and depression is inconsistent,⁵⁰ several mechanisms may underlie a putative association.⁵⁰ However, data from clinical trials suggest a beneficial effect of exogenous DHEA supplementation on depression.⁵⁰

The strengths of the current study include the large sample size, which permitted us to examine associations according to different postmenopausal age groups, the prospective nature of data collection, and the availability of baseline measure of the CES-D score so that prevalent cases of high depressive symptoms could be excluded from the analysis. One limitation was a single measurement of sex hormones was used to characterize a woman's hormonal status, and this may result in some misclassification, particularly for E2. Another limitation was the inability to relate change in hormone levels determined from repeated measures to depressive symptoms at exam 3. Besides assessing absolute levels of hormones, which may be too simplistic, patterns of changes in sex hormone levels and other parameters that characterize change must be considered in relation to depression or depressive symptoms in women. In addition, we did not distinguish women with surgical menopause from those with natural menopause, and classifying participants as having depressive symptoms based on anti-depressant usage is another potential source of misclassification if the participant was taking the medication for a condition other than depression. Finally, we relied on the CES-D to classify participants as having depressive symptoms as opposed to

using a structured clinical interview and we had insufficient numbers of women to explore race/ethnic differences in associations.

CONCLUSION

In conclusion, our findings suggest bioavailable T and E2 are inversely associated with depressive symptoms in women who are early postmenopause and SHBG is positively associated. These findings are more pronounced in users of HT. The positive association for SHBG to our knowledge has not been reported before, and requires further study. The possibility that changes in sex hormone levels might also be important cannot be excluded. Future longitudinal studies that have the ability to adjust for important confounders and include a broad range of postmenopausal women might focus on replicating our findings for SHBG, bioavailable T, and E2.

Acknowledgments

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full listing of participating MESA investigators and institutions can be found at <http://www.mesa-nhlbi.org>.

This work was supported by R01 HL074406, R01 HL074338 and contracts N01-HC-95159 through N01-HC-95165 and N01-HC-95169 from the National Heart, Lung, and Blood Institute.

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SUMMARY

In women who were within 10 years of menopause, bioavailable testosterone and sex hormone binding globulin were inversely associated with incident depressive symptoms and estradiol was positively associated. In women who were more than 10 years postmenopause, these associations were not apparent.

Table 1

Baseline characteristics of participants for each tertile of years postmenopause according to their depressive symptoms status at examination 3 of the MESA study.

Variable	No clinically significant depressive symptoms at Exam 3	Clinically significant depressive symptoms at Exam 3
Tertile 1: 0–10 years	N=546	N=87
Age, mean (SD), y	56.3 (5.3)	55.2 (5.0)
Age at menopause, mean (SD), y	50.8 (4.6)	49.9 (4.7)
Non-Hispanic white	37.0%	48.3%
Chinese American	15.0%	12.6%
African American	28.6%	17.2%
Hispanic	19.4%	21.8%
Body mass index, mean (SD), kg/m ²	28.9 (6.2)	27.9 (5.8)
Smoker	12.6%	20.7%
Current drinker	53.8%	55.2%
Physical activity, median	750	420
Educ, HS or some college	50.5%	50.6%
BS or more	37.9%	37.9%
Income, median range	\$40,000–49,999	\$50,000–74,999
Current HT	37.7%	47.1%
Hysterectomy and bilateral oophorectomy	13.2%	11.5%
Tertile 2: 11–20 years	N=497	N=80
Age, mean (SD), y	64.8 (5.3)	63.7 (6.4)
Age at menopause, mean (SD), y	49.4 (4.8)	48.2 (5.8)
Non-Hispanic white	40.6%	36.3%
Chinese American	13.5%	6.3%
African American	26.8%	25.0%
Hispanic	19.1%	32.5%
Body mass index, mean (SD), kg/m ²	28.0 (5.6)	29.3 (5.4)
Smoker	7.4%	16.3%
Current drinker	51.3%	43.8%

Variable	No clinically significant depressive symptoms at Exam 3	Clinically significant depressive symptoms at Exam 3
Physical activity, median	810	814
Educ, HS or some college	49.7%	48.8%
BS or more	32.2%	18.8%
Income, median range	\$35,000–39,999	\$25,000–29,999
Current HT	30.6%	35.0%
Hysterectomy and bilateral oophorectomy	16.1%	16.3%
Tertile 3: 21–58 years		
	N=542	N=72
Age, mean (SD), y	72.4 (6.4)	72.2 (7.4)
Age at menopause, mean (SD), y	43.9 (6.8)	43.6 (8.3)
Non-Hispanic white	40.0%	41.7%
Chinese American	12.2%	8.3%
African American	29.3%	25.0%
Hispanic	18.5%	25.0%
Body mass index, mean (SD), kg/m ²	27.7 (5.5)	28.1 (5.7)
Smoker	6.5%	8.3%
Current drinker	45.0%	47.2%
Physical activity, median	735	645
Educ, HS or some college	53.0%	55.6%
BS or more	25.8%	19.4%
Income, median range	\$25,000–29,999	\$20,000–24,999
Current HT	26.4%	36.1%
Hysterectomy and bilateral oophorectomy	27.3%	25.0%

Table 2

Multivariable adjusted relative risks (95% confidence intervals) for incident depressive symptoms at examination 3 (2004–2005) according to quartiles of sex hormones for women free of clinically significant depressive symptoms at baseline (2000–2002) in the Multi-Ethnic Study of Atherosclerosis.

	Q1	Q2	Q3	Q4	p-value ^a
Total T (nmol/l)	0–0.56	0.59–0.90	0.94–1.32	1.35–22.80	RR (95% CI) per 1 unit increase in logHormone
Years Post T1: 0–10					
All women ^b	1	1.38 (0.82, 2.33)	1.19 (0.69, 2.06)	0.63 (0.32, 1.26)	0.69 (0.38, 1.27)
HT non-users ^c	1	1.14 (0.54, 2.40)	1.00 (0.49, 2.03)	0.64 (0.27, 1.51)	0.78 (0.33, 1.85)
HT users ^d	1	1.81 (0.87, 3.79)	1.68 (0.78, 3.64)	0.66 (0.22, 1.99)	0.71 (0.32, 1.55)
Years Post T2: 11–20					
All women	1	0.78 (0.42, 1.46)	1.11 (0.63, 1.95)	1.15 (0.65, 2.02)	1.15 (0.61, 2.15)
HT non-users	1	0.66 (0.30, 1.45)	1.01 (0.50, 2.02)	1.05 (0.52, 2.10)	1.19 (0.52, 2.71)
HT users	1	1.07 (0.40, 2.87)	1.28 (0.51, 3.21)	1.41 (0.55, 3.64)	1.18 (0.46, 3.03)
Years Post T3: 21–58					
All women	1	1.09 (0.64, 1.83)	0.79 (0.41, 1.52)	0.56 (0.28, 1.12)	0.50 (0.25, 1.00)
HT non-users	1	1.65 (0.79, 3.48)	1.11 (0.45, 2.70)	0.70 (0.28, 1.79)	0.49 (0.21, 1.16)
HT users	1	0.56 (0.23, 1.36)	0.52 (0.18, 1.50)	0.49 (0.16, 1.57)	0.53 (0.17, 1.72)
Bio T (nmol/l)	0–0.10	0.14–0.21	0.22–0.35	0.38–5.10	
Years Post T1: 0–10					
All women	1	0.74 (0.44, 1.25)	0.73 (0.42, 1.25)	0.59 (0.33, 1.07)	0.28 (0.07, 1.14)
HT non-users	1	0.66 (0.30, 1.45)	0.58 (0.26, 1.28)	0.60 (0.27, 1.30)	0.43 (0.08, 2.48)
HT users	1	0.74 (0.36, 1.50)	1.13 (0.53, 2.38)	0.36 (0.10, 1.32)	0.14 (0.02, 1.17)
Years Post T2: 11–20					
All women	1	0.83 (0.47, 1.48)	1.00 (0.56, 1.79)	0.93 (0.52, 1.66)	1.11 (0.35, 3.49)
HT non-users	1	0.76 (0.33, 1.75)	0.99 (0.45, 2.16)	0.94 (0.43, 2.03)	1.32 (0.33, 5.22)
HT users	1	0.99 (0.44, 2.26)	1.04 (0.37, 2.92)	1.05 (0.35, 3.16)	1.06 (0.15, 7.26)
Years Post T3: 21–58					
All women	1	1.18 (0.70, 1.99)	0.98 (0.54, 1.78)	0.40 (0.16, 0.96)	0.17 (0.03, 0.89)
HT non-users	1	1.47 (0.69, 3.13)	1.26 (0.56, 2.86)	0.36 (0.11, 1.14)	0.14 (0.02, 1.02)
HT users	1	0.86 (0.36, 2.05)	0.63 (0.19, 2.04)	1.03 (0.26, 4.10)	0.32 (0.02, 4.93)
SHBG (nmol/l)	11.5–40.5	40.6–59.5	59.6–94.9	95.0–439.0	
Years Post T1: 0–10					
All women	1	1.12 (0.63, 1.99)	0.99 (0.54, 1.84)	1.62 (0.91, 2.86)	1.47 (1.04, 2.08)
HT non-users	1	1.25 (0.64, 2.41)	1.11 (0.50, 2.44)	2.19 (0.87, 5.53)	1.56 (0.82, 2.96)
HT users	1	0.87 (0.27, 2.87)	0.78 (0.28, 2.16)	1.29 (0.54, 3.11)	1.49 (0.90, 2.46)
Years Post T2: 11–20					
All women	1	0.89 (0.50, 1.57)	1.07 (0.60, 1.92)	1.12 (0.61, 2.06)	1.15 (0.78, 1.68)

	Q1	Q2	Q3	Q4	p-value ^a
Total T (nmol/l)	0–0.56	0.59–0.90	0.94–1.32	1.35–22.80	RR (95% CI) per 1 unit increase in logHormone
HT non-users	1	0.91 (0.50, 1.67)	1.15 (0.60, 2.22)	0.90 (0.29, 2.80)	1.10 (0.58, 2.09)
HT users	1	0.45 (0.08, 2.58)	0.69 (0.18, 2.66)	0.82 (0.24, 2.84)	1.04 (0.56, 1.94)
Years Post T3: 21–58					
All women	1	2.26 (0.98, 5.24)	2.19 (0.96, 5.00)	2.14 (0.92, 4.99)	1.45 (1.00, 2.11)
HT non-users	1	2.43 (0.98, 6.00)	2.35 (0.96, 5.77)	1.33 (0.40, 4.40)	1.18 (0.69, 2.02)
HT users	1	1.14 (0.11, 11.58)	1.35 (0.16, 11.17)	1.93 (0.26, 14.15)	1.81 (0.93, 3.52)
E2 (pmol/l)	9.18–44.05	47.72–73.42	77.09–165.20	168.87–2756.92	
Years Post T1: 0–10					
All women	1	0.91 (0.51, 1.63)	0.74 (0.41, 1.34)	0.82 (0.45, 1.48)	0.86 (0.68, 1.08)
HT non-users	1	0.98 (0.52, 1.82)	0.56 (0.26, 1.21)	0.71 (0.17, 2.94)	0.68 (0.46, 1.02)
HT users	1	NA			0.87 (0.65, 1.17)
Years Post T2: 11–20					
All women	1	0.74 (0.41, 1.32)	0.95 (0.54, 1.66)	0.83 (0.44, 1.55)	0.89 (0.69, 1.14)
HT non-users	1	0.86 (0.47, 1.58)	1.02 (0.54, 1.92)	0.66 (0.12, 3.69)	0.79 (0.53, 1.18)
HT users		NA			0.93 (0.60, 1.45)
Years Post T3: 21–58					
All women	1	0.98 (0.51, 1.88)	1.24 (0.65, 2.34)	1.36 (0.71, 2.63)	1.05 (0.81, 1.36)
HT non-users	1	0.97 (0.49, 1.90)	1.31 (0.65, 2.61)	1.83 (0.59, 5.65)	1.08 (0.68, 1.73)
HT users		NA			1.20 (0.79, 1.83)
DHEA (nmol/l)	0.59–6.97	7.01–10.20	10.24–14.40	14.44–57.26	
Years Post T1: 0–10					
All women	1	1.40 (0.71, 2.77)	1.18 (0.60, 2.29)	1.45 (0.75, 2.78)	1.07 (0.76, 1.52)
HT non-users	1	0.87 (0.30, 2.48)	1.27 (0.51, 3.18)	0.93 (0.37, 2.36)	0.87 (0.55, 1.37)
HT users	1	1.93 (0.80, 4.70)	0.87 (0.31, 2.42)	2.47 (1.03, 5.92)	1.41 (0.84, 2.37)
Years Post T2: 11–20					
All women	1	0.72 (0.42, 1.22)	0.56 (0.31, 1.03)	0.69 (0.40, 1.17)	0.78 (0.54, 1.13)
HT non-users	1	0.70 (0.34, 1.44)	0.67 (0.33, 1.37)	0.75 (0.39, 1.46)	0.87 (0.55, 1.39)
HT users	1	0.76 (0.34, 1.68)	0.29 (0.07, 1.21)	0.61 (0.24, 1.57)	0.66 (0.38, 1.14)
Years Post T3: 21–58					
All women	1	1.26 (0.75, 2.11)	0.78 (0.42, 1.46)	0.73 (0.35, 1.53)	0.72 (0.49, 1.04)
HT non-users	1	1.75 (0.84, 3.63)	1.23 (0.55, 2.75)	0.95 (0.38, 2.42)	0.92 (0.55, 1.52)
HT users	1	0.78 (0.34, 1.78)	0.29 (0.08, 1.09)	0.53 (0.13, 2.12)	0.56 (0.38, 0.82)

^afor trend in log transformed hormone

^bAll women: Adjusted for age, BMI, current smoker, ethnicity, exercise categories, education, income, current drinker, and HT

^cHT non-users: Adjusted for age, BMI, current smoker, ethnicity, exercise categories, education, income, and current drinker

^dHT users: Restricted to HT users and adjusted for age, BMI, current smoker, ethnicity, exercise categories, education, income, and current drinker

NA: Not available due to computational problem

Multivariable-adjusted relative risks for incident depressive symptoms (CES-D 16) with hormones adjusted for each other in all participants, HT non-users, and HT users.

Table 3

		All Women (N= 1824)			HT Non-users (N=1228)			HT Users (N=596)		
		RR ^a	(95% CI)	p-value	RR ^a	(95% CI)	p-value	RR ^a	(95% CI)	p-value
Total T ^b (nmol/l)	Tertile 1	0.57	(0.27, 1.19)	0.13	0.94	(0.36, 2.48)	0.91	0.30	(0.10, 0.93)	0.04
	Tertile 2	1.26	(0.68, 2.30)	0.46	1.28	(0.56, 2.89)	0.56	1.50	(0.58, 3.87)	0.40
	Tertile 3	0.58	(0.30, 1.15)	0.12	0.47	(0.20, 1.09)	0.08	0.76	(0.27, 2.10)	0.59
SHBG ^b (nmol/l)	Tertile 1	1.84	(1.23, 2.74)	0.003	1.47	(0.75, 2.87)	0.26	2.24	(1.24, 4.05)	0.007
	Tertile 2	1.11	(0.74, 1.67)	0.62	1.01	(0.49, 2.07)	0.98	1.00	(0.52, 1.92)	0.99
	Tertile 3	1.30	(0.87, 1.94)	0.21	1.23	(0.73, 2.08)	0.43	1.64	(0.77, 3.49)	0.20
E2 (pmol/l) ^b	Tertile 1	0.78	(0.61, 0.99)	0.04	0.71	(0.45, 1.09)	0.12	0.70	(0.47, 1.03)	0.07
	Tertile 2	0.93	(0.71, 1.21)	0.59	0.78	(0.47, 1.29)	0.33	0.94	(0.62, 1.42)	0.76
	Tertile 3	1.01	(0.79, 1.30)	0.92	1.12	(0.74, 1.70)	0.60	0.94	(0.61, 1.44)	0.76
DHEA ^b (nmol/l)	Tertile 1	1.45	(0.96, 2.21)	0.08	1.03	(0.61, 1.74)	0.91	2.56	(1.21, 5.42)	0.01
	Tertile 2	0.77	(0.52, 1.14)	0.19	0.94	(0.55, 1.60)	0.81	0.60	(0.32, 1.15)	0.13
	Tertile 3	0.82	(0.54, 1.25)	0.36	0.99	(0.59, 1.68)	0.98	0.62	(0.40, 0.96)	0.03
Bio T ^c (nmol/l)	Tertile 1	0.16	(0.03, 0.92)	0.04	0.63	(0.10, 4.07)	0.63	0.01	(0.001, 0.33)	0.008
	Tertile 2	1.36	(0.46, 4.03)	0.58	1.64	(0.43, 6.29)	0.47	1.55	(0.26, 9.27)	0.63
	Tertile 3	0.27	(0.06, 1.26)	0.10	0.12	(0.01, 0.92)	0.04	0.64	(0.08, 4.96)	0.67

^aRR per 1 unit increment in log Hormone

^bRegression models included variables for age, BMI, current smoker, ethnicity, exercise categories, education, income, current drinker, total testosterone, SHBG, E2, DHEA, and for the model with all women, HT.

^cRegression models included variables for age, BMI, current smoker, ethnicity, exercise categories, education, income, current drinker, bioavailable testosterone, E2, DHEA, and for the model with all women, HT.