Published in final edited form as:

Maturitas. 2008 February 20; 59(2): 114–127.

Endogenous hormones, participant characteristics, and symptoms among midlife women

Lisa Gallicchio, Ph.D.^{1,2}, Chrissy Schilling, Ph.D.³, William A. Romani, Ph.D.⁴, Susan Miller, Sc.D.⁵, Howard Zacur, M.D., Ph.D.⁵, and Jodi A. Flaws, Ph.D.⁶

¹The Prevention and Research Center, Weinberg Center for Women's Health and Medicine, Mercy Medical Center, Baltimore, Maryland 21202

²Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland 21205

³Department of Biochemistry and Molecular Biology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205

⁴Department of Physical Therapy and Rehabilitation Science, University of Maryland School of Medicine, Baltimore, Maryland 21201

⁵Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

⁶Department of Veterinary Biosciences, University of Illinois, Urbana, Illinois 61802

Abstract

Objectives—The primary aim of this study was to examine the associations between endogenous hormone levels and symptoms other than hot flashes in a sample of midlife women.

Methods—Data from a community-based sample of 603 women aged 45 to 54 years who had never used hormone therapy were analyzed. Each participant completed a questionnaire to obtain data on demographic and lifestyle characteristics as well as symptoms, including headache, insomnia, vision problems, vaginal discharge and dryness, irritability, and incontinence. In addition, each participant provided a blood sample that was used to measure estrogen, androgen, and sex hormone binding globulin (SHBG) concentrations by enzyme-linked immunosorbent assay.

Results—Prevalence rates of symptoms ranged from 51.4% (irritability) to 18.6% (vision problems). In adjusted analyses, the free estradiol index (FEI) was significantly and positively associated with the reporting of insomnia (odds ratio (OR) 1.28; 95% confidence interval (CI) 1.01, 1.61). Further, higher SHBG levels were significantly associated with lower odds of reporting vision problems (OR 0.44; 95% CI 0.23, 0.81).

Conclusions—This study provides evidence that hormones are associated with insomnia and visual problems during midlife. However, some of these results conflict with previous findings. Given the overall paucity of literature on these issues, more investigation is warranted.

Corresponding Author: Jodi A. Flaws, Ph.D., University of Illinois, Department of Veterinary Biosciences, 2001 S. Lincoln Ave., Room 3223, Urbana, IL 61802, Telephone (217) 333-7933, Fax (217) 244-1652, Email jflaws@uiuc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

androgens; estrogens; incontinence; insomnia; menopausal transition; midlife; sleep; symptoms

Introduction

During the menopausal transition, women can experience a number of physical and psychological symptoms, including hot flashes, vaginal dryness, sleep disruption, and irritability [1,2]. Many of these symptoms are experienced by a high percentage of women during this time period; for example, hot flashes have been documented to occur in up to 70% of midlife women [3–6]. These symptoms can affect a woman's quality of life [1]. In some cases, these symptoms can be so severe that women seek medical attention [7].

In general, women and clinicians attribute symptoms during the menopausal transition to the hormonal changes that occur during this time period, and, in fact, a number of studies have provided consistent evidence that an association between hot flashes and estrogen levels exists [8–13]. Less information is available, however, on the associations between endogenous hormone levels and symptoms other than hot flashes. Further, those studies that have published results on associations between hormones and symptoms other than hot flashes have provided inconsistent findings. For example, several recently published studies have examined the role of hormones in sleep disruption among midlife women. In a population-based sample of 436 women in Philadelphia County, Pennsylvania, Hollander et al [14] showed that poor sleep, defined using the question "How well did you sleep last night?" was associated with low estradiol levels in women aged 45 to 49 years. In contrast, Kravitz et al [15] found a small, non-significant, positive association between estrogen metabolites and trouble sleeping in an analysis of data from 630 women aged 43 to 53 years in the Study of Women's Health Across the Nation (SWAN). In the SWAN study, a significantly higher concentration of follicle-stimulating hormone (FSH) was associated with trouble sleeping among pre-menopausal women; a significantly higher concentration of a progesterone metabolite (i.e. pregnanediol glucuronide) was associated with trouble sleeping among peri-menopausal women.

The lack of consistency with regards to the published findings and the paucity of studies on this subject make treatment decisions difficult. Therefore, additional studies are needed to understand the role of endogenous hormones in the development of symptoms other than hot flashes during midlife. To address this issue, we examined the associations between endogenous hormone levels and symptoms (other than hot flashes) in a large population-based study of women aged 45 to 54 years in the Baltimore metropolitan area in Maryland. This area includes Baltimore city and several surrounding counties (Anne Arundel, Baltimore (the county of Baltimore does not contain the city of Baltimore), Carroll, Harford, and Howard). Symptoms chosen were those that had been observed to increase in prevalence during the menopausal transition and, therefore, have been hypothesized to be the result of changes in hormone concentrations. As a secondary aim, we also examined the associations between demographic characteristics and lifestyle habits and the experiencing of these symptoms.

Methods

Study sample

A cross-sectional population-based study of midlife women aged 45 to 54 years was conducted in the Baltimore metropolitan area to examine the associations among demographic characteristics, health and lifestyle behaviors, hormone levels, and the reporting of hot flashes (primary outcome) and other symptoms (secondary outcomes). The methods of this study have been described in detail elsewhere as have the results pertaining to hot flashes [8,16]. Briefly,

women aged 45 to 54 years were recruited from the general population by mass mailing an invitation to participate to area households in the Baltimore metropolitan region. Women who were interested in participating were screened by telephone and an appointment was scheduled for a clinic visit if they were eligible. Women were eligible if they were 45 to 54 years old, had at least 3 menstrual periods in the past 12 months, were not on hormone therapy, were not pregnant, had an intact uterus and at least one ovary, and did not have a history of ovarian, endometrial, or breast cancer.

In total, the study office received 2299 calls resulting from the mass mailing. From these calls, the study staff determined that 639 women were eligible (27.8%) and willing to participate. The majority of women who called the office were ineligible because they were either clearly pre-menopausal (590 women) or post-menopausal (426 women). Some women who called the clinic (494 women) were ineligible to participate because they were currently using hormone therapy or herbal agents, were taking oral contraceptives, had cancer, or were not in the correct age range. A small number of women declined to participate in the study because they were not interested after it was described in detail to them (96 women), they did not think the study compensation was adequate (26 women), they did not have the time (16 women), or they did not want to travel to the clinic (12 women).

Clinic visits were scheduled in the morning to minimize diurnal fluctuations in hormone levels. [17,18] Participants had their blood drawn for hormone assays, were weighed, had their height, waist and hip circumference measured, and had their blood pressure recorded. They were then asked to complete a 26-page survey that obtained information on demographics, reproductive history, menstrual cycle characteristics, hormonal contraceptive use, symptoms, hormone therapy (HT) use, medical history, and health behaviors (smoking, alcohol use, vitamin use, eating habits) [16]. A total of 639 women completed the questionnaire and provided blood for hormone analyses. All women gave written informed consent according to procedures approved by the University of Illinois, University of Maryland School of Medicine, and Johns Hopkins University Institutional Review Boards.

Study variables

Data on headache, weakness, insomnia (difficulty sleeping), visual problems, vaginal discharge, vaginal dryness, irritability, and incontinence (problems with controlling urine flow) were collected using the question “Did/do you experience any of the following symptoms on a regular basis (once a week or more) anytime during a month?” Response choices for this question for each symptom were: yes, no, and don’t know. Race information was obtained by asking participants to self-define their race as Caucasian, African-American, Hispanic, Asian, or other. Marital status and education level were self-reported by the participant; marital status was categorized as ‘single,’ ‘married/living with partner,’ or ‘other’ (widowed or divorced/separated), and, based on the distribution of participant responses, education was categorized as ‘high school or less,’ ‘some college,’ ‘college graduate,’ and ‘graduate courses.’ Body mass index (BMI) was calculated using the National Institutes of Health on-line BMI calculator and categorized as ≤ 24.9 kg/m², 25.0–29.9 kg/m², and ≥ 30.0 kg/m². Only two participants had a BMI of <18.5 kg/m², considered “underweight” by the National Institutes of Health (<http://www.nhlbisupport.com/bmi/>), and, therefore, these participants were included in the ≤ 24.9 kg/m² category. Smoking was categorized as current, former, or never. Current alcohol use was categorized as yes or no based on the answer to the question “Have you had at least 12 alcoholic drinks in the past year?”

Usual physical activity was categorized as inactive/light and moderate/heavy using participant responses to questions regarding usual physical activity performed at work, home, and leisure during the last 12 months. For each area (work, home, and leisure), a participant was asked to think about the things she usually did during the last 12 months and to describe the kind of

physical activity she performed. Possible responses were: inactive, light, moderate, and heavy. Detailed definitions of these responses were provided for the participant on the questionnaire (for example, heavy physical activity was defined as performing vigorous activity on a regular basis, including jogging, singles tennis, paddleball, high intensity aerobics; or engaging in heavy activities such as carrying weights, strenuous farm work or gardening). A score was assigned to each response such that inactive equaled 1 and heavy equaled 4. For women who were employed, home, leisure, and work physical activity scores were added; for women who were not employed, the total score equaled the home score plus the leisure score plus the average of the home and leisure score. A woman who had a physical activity score of 7 or less was categorized as inactive or having light overall physical activity; a woman who had a physical activity score of 8 or greater was categorized as having moderate/heavy overall physical activity. No data were collected on the frequency of physical activity.

Menopausal status was categorized as pre- or peri-menopausal based on definitions used in previously published studies [19,20]. Pre-menopausal women were those who reported experiencing their last menstrual period within the past 3 months and experiencing 11 or more periods within the past year. Peri-menopausal women were those who reported experiencing: 1) their last menstrual period within the past year but not within the past 3 months or 2) their last menstrual period within the past 3 months and experiencing 10 or fewer periods within the past year. Data on days since last menstrual period were also collected and based on self-report.

Measurement of Hormone Levels

Serum concentrations of sex hormone binding globulin (SHBG), total estradiol, estrone, testosterone, androstenedione, progesterone, and dehydroepiandrosterone sulfate (DHEA-S) were measured using enzyme-linked immunosorbent assays (ELISA). ELISA kits for estradiol, testosterone, androstenedione, and DHEA-S were obtained from Diagnostic Systems Laboratories, Inc. (Webster, TX). ELISA kits for estrone, progesterone, and SHBG were obtained from American Laboratory Products Company (Windham, NH). The assays were run using the manufacturers' instructions. All assays were conducted in the same laboratory by a single investigator. All samples were run in duplicate and mean values for each participant were used in the analysis. The laboratory personnel were blinded with respect to any information concerning study participants. For quality control purposes, positive controls containing known amounts of estradiol, estrone, testosterone, androstenedione, progesterone, DHEA-S, or SHBG were included in each batch. Further, some samples were run in multiple assays to ensure that the assay values did not dramatically shift over time. In addition, only assay kits were used that had been determined to be reliable and precise, to have minimal cross-reactivity with other hormones, and that have been validated against a gold standard assay (radioimmunoassay) by the manufacturer.

The minimum detection limits for the estradiol, estrone, testosterone, androstenedione, progesterone, DHEA-S, and SHBG assays were 7pg/ml, 10pg/ml, 0.04ng/ml, 0.03ng/ml, 0.1ng/ml, 15ng/ml, and 0.1nmol/L respectively. No estradiol, estrone, testosterone, androstenedione, DHEA-S, or SHBG measurements were below the limit of detection. For progesterone measurements that were below the limit of detection ($n = 66$), the value was set at the limit of detection (0.1 ng/ml). The average intra-assay co-efficient of variation was $3.3 \pm 0.17\%$ for estradiol, $4.8 \pm 0.25\%$ for estrone, $2.2 \pm 0.56\%$ for testosterone, $2.5 \pm 0.60\%$ for androstenedione, $2.1 \pm 0.65\%$ for progesterone, $1.9 \pm 0.63\%$ for DHEA-S, and $2.4 \pm 0.67\%$ for SHBG. The average inter-assay co-efficient of variation for all assays was less than 5%.

To calculate the amount of estradiol unbound by SHBG (free estradiol index, FEI), a ratio of total estradiol to SHBG was calculated using a conversion factor to change pg/ml of estradiol to nmol/L: $100 \times (\text{total estradiol} \times 0.003671) / \text{SHBG}$. The free testosterone index (FTI) was also calculated using a conversion factor to change ng/ml of testosterone to nmol/L: $100 \times (\text{total}$

testosterone $\times 3.467$) / SHBG [21]. We also investigated the ratio of estrogens to progesterone by examining estradiol/progesterone and (estradiol + estrone)/progesterone.

Statistical analysis

Because the use of hormone therapy may affect or be affected by symptoms, women in the study sample who reported past use of hormone therapy were excluded from the analysis ($n = 36$). All hormone values were log-transformed because none were normally distributed. Generalized linear models were conducted to examine the associations between each symptom (yes/no variable) and the plasma hormone levels adjusted for days since last menstrual period. Chisquare analyses were conducted to assess the distribution of categorical demographic factors and health and lifestyle characteristics between women experiencing each symptom and women not experiencing the symptom. Odds ratios (ORs) and 95% confidence intervals (95% CI) were generated using multiple logistic regression to examine the associations of symptoms with the demographic characteristics, lifestyle habits, and hormones adjusted for the other variables. All demographic factors and health and lifestyle characteristics were examined in each model to determine their adjusted association with each symptom. Only those hormones significantly associated with the symptoms in the generalized linear model analyses were analyzed as part of the multiple logistic regression analyses. To avoid multicollinearity among hormones in a single regression model, hormones with a Pearson correlation coefficient of > 0.9 were inserted separately into the model and the hormone that was associated with the best fit model, as determined using the $-2 \log$ likelihood ratio, was retained. All analyses were stratified by menopausal status; however, the results did not differ and therefore, results for the entire sample are reported.

To address the issue of multiple testing for the hormones and the symptoms in this study, p -values for the associations between the hormone variables and the symptoms were adjusted for the false discovery rate using the method proposed by Benjamini and Hochberg [22] in the software package R 2.0.1.

A two sided p -value of less than or equal to 0.05 was considered statistically significant. Unless otherwise specified, all analyses were performed using SAS Version 9.1 (Cary, NC).

Results

Study characteristics

The mean age and BMI of the participants were 48.5 years (standard deviation (SD) 2.4) and 27.9 kg/m² (SD 6.9), respectively. Most participants were Caucasian (83.7%), were married or living with a partner (67.2%), had at least some college education (84.5%), and were perimenopausal (59.4%; Table 1). Approximately 23% were nulliparous; 8.9% were smokers at the time of enrollment into the study and 38.1% were former smokers.

The prevalence rates of symptoms in the study sample were: headache, 39.6%; insomnia, 44.3%; vision problems, 18.6%; vaginal dryness, 20.9%; vaginal discharge, 26.2%; irritability, 51.4%; and incontinence, 21.7% (Table 2). Statistically significant differences were observed in the prevalence of irritability by menopausal status (pre-menopausal: 47.4%, perimenopausal: 55.7%; $p = 0.05$) and by age group (45 to 49: 56.1%; 50 to 54: 44.5%; $p = 0.0075$). In contrast, statistically significant differences by menopausal status and age group were not observed for the other symptoms.

Endogenous hormones and symptoms

The mean estradiol concentration was significantly lower among women reporting vaginal dryness compared to women reporting no vaginal dryness; in contrast, the mean estradiol

concentration was significantly higher among women reporting insomnia compared to those who reported no insomnia (Table 2). Compared to their counterparts, the mean FEI was significantly higher among women reporting insomnia or incontinence. Further, incontinence and vision problems were each associated with higher FTI (Table 3). No significant associations were observed between the seven symptoms and estrone, testosterone, androstenedione and DHEAS.

SHBG was significantly associated with insomnia, vision problems, and incontinence (Table 4). Specifically, participants reporting insomnia, vision problems, or incontinence had significantly lower mean SHBG concentrations than those participants not experiencing these symptoms. Further, vaginal dryness was significantly associated with lower mean progesterone levels. In addition, compared to their counterparts, women reporting insomnia had significantly higher mean estradiol to progesterone and estradiol + estrone to progesterone ratios. Headache, vaginal discharge and irritability were not significantly associated with SHBG, progesterone, or the ratios of estrogens to progesterone.

After adjustment for multiple testing, only the associations between incontinence with the FTI and SHBG remained statistically significant ($p = 0.02$ for both comparisons).

Demographic and lifestyle characteristics and symptoms

After adjustment for other covariates, age was significantly associated with irritability (Table 5); specifically, women who were older (aged 50 to 54 years) were less likely to report irritability (OR 0.61; 95% CI 0.42, 0.89) than women who were younger (aged 45 to 49 years). Further, compared to Caucasian women, African-American women were significantly more likely to report vision problems (OR 2.26; 95% CI 1.21, 4.20). Being married/living with a partner was associated with higher odds of experiencing headaches compared to being single (OR 1.85; 95% CI 1.04, 3.31), while being more educated was associated with lower odds of experiencing headaches compared to being less educated (OR 0.35; 95% CI 0.21, 0.61 for graduate school compared to high school degree or less).

Menopausal status was significantly associated with irritability in the adjusted analyses; perimenopausal women were approximately 50% more likely to report irritability than premenopausal women (Table 5). In addition, women who reported having 3 or more children had lower odds of insomnia compared to nulliparous women (OR 0.43; 95% CI 0.25, 0.74). Current smoking was associated with increased odds of irritability (OR 2.84; 95% CI 1.43, 5.64) compared to never smokers. Further, BMI was significantly and positively associated with incontinence ($>30\text{kg/m}^2$ versus $<25\text{kg/m}^2$: OR 2.79; 95% CI 1.51, 5.14) (Table 6). Current alcohol use and physical activity were not associated with any of the symptoms examined.

After adjustment for other covariates, several of the associations between the hormone levels and the symptoms that were statistically significant in the unadjusted analyses remained significant. Specifically, FEI was significantly and positively associated with the reporting of insomnia independent of demographic characteristics, lifestyle habits, and the ratio of estrogens to progesterone (Table 5). Further, higher SHBG levels were significantly associated with lower odds of reporting vision problems (OR 0.44; 95% CI 0.23, 0.81).

Discussion

The present cross-sectional study is one of the largest to examine the associations between hormones and symptoms experienced by women during the menopausal transition. In a separate publication, we showed that hot flashes are associated with low estradiol and estrone levels [8], a finding that has been replicated by the majority of previously published

investigations [9–13,23,24], although several recent longitudinal studies suggest that follicle-stimulating hormone (FSH) concentrations may be a more important predictor of vasomotor symptoms than estrogen concentrations [5,25]. In the present analyses, we addressed a gap in the literature by examining the associations between endogenous hormone levels and symptoms other than hot flashes, including incontinence and visual problems, among midlife women who had never used hormone therapy.

In this study, insomnia was significantly associated with a higher mean FEI independent of other hormones, demographic characteristics, and lifestyle habits. Estrogen has been shown to be related to cortical stimulation [26,27], and this stimulation, in turn, may result in difficulties in falling asleep. Despite the biological plausibility of our finding, our results are only somewhat consistent with the published literature. Similar to our results, a study conducted in the Daily Hormone Study component of SWAN observed a positive association, although not statistically significant, between urinary estrone levels and trouble sleeping among 630 women aged 43 to 53 years [15]. In contrast, in a population-based sample of 436 women in Philadelphia County, Pennsylvania, Hollander et al [14] showed that poor sleep was associated with low estradiol levels in women aged 45 to 49 years. Further, Ford et al [28] showed using data from the Michigan Bone Health Study that higher estradiol levels were associated with lower odds of being in the highest quartile of bothersome sleep/fatigue compared to the lower quartile (OR 0.7; 95% CI 0.6, 0.9). Recent publications from the Penn Ovarian Aging Study and the Seattle Midlife Women's Health Study reported no association between estradiol and poor sleep or sleep problems [5,24]. A separate publication from the Daily Hormone Study component of SWAN found no difference in sleep problems among older reproductive-age women who were experiencing 1) an estrogen increase and a luteinizing hormone (LH) surge, 2) an estrogen increase only, or 3) neither an estrogen nor a LH increase [29].

Several reasons could be postulated for the conflicting results of studies examining the association between estrogen concentrations and insomnia or sleep problems. First, there are large differences in the characteristics of the populations under study; for example, Ford et al [28] enrolled women at a younger age than our study and did not exclude hormone therapy users, as we did. Another potential explanation for the conflicting results is that data and blood collection in our study was not timed to a particular day or phase of the menstrual cycle. Hence, if the association between FEI and sleep problems differs by menstrual cycle phase, important differences in the association, some of which may be more consistent with previous publications, would have been masked. Finally, unlike our study, other published studies have reported results solely on total estrogen concentrations and not on the unbound fraction of estrogen levels [30]. This is important because it is the unbound estrogen that is biologically active and may result in clinical outcomes.

In this study, we also found that vision problems were negatively associated with SHBG concentrations. It is unknown what the biological plausibility of this finding is, although low SHBG could be a marker of higher circulating concentrations of other hormones, such as estradiol and testosterone. To our knowledge, this is the first study that has examined the associations between visual problems and hormones during the menopausal transition, although one study was identified in the published literature that assessed the relationship between hormones and cataract among post-menopausal women. In that study, conducted among 1,451 women aged over 60 years in the Pathologies Oculaires Liees a l'Age (POLA) Study in France, Defay et al [31] showed that a cataract diagnosis was not significantly associated with estradiol (OR 0.94; 95% CI 0.72, 1.22), testosterone (OR 1.02; 95% CI 0.85, 1.22), or SHBG levels (OR 1.04; 95% CI 0.87, 1.26). However, higher DHEAS levels were associated with lower odds of cataract (OR 0.81; 95% CI 0.66, 0.99); this association remained significant after adjustment for other cataract risk factors. Other studies of post-menopausal women have shown that women who reported ever using HT, current use of HT, or use of HT

for a longer period of time had a reduced risk of cataracts [30,32–37]. In contrast, it should be noted that studies by Eisner et al [38] have shown no changes in the optic cups of users of anastrozole, an aromatase inhibitor that blocks estrogen production, compared to a control group, suggesting no association between estrogen and visual changes. Although understudied, ophthalmic problems may be a prevalent symptom experienced by women during the menopausal transition [39], and the etiology of this symptom should be given increased attention.

In addition to examining the associations between hormone levels and symptoms, we investigated the associations between the symptoms and demographic and lifestyle characteristics adjusting for other covariates (including hormones). In these analyses, we confirmed findings from previous studies, such as the strong, positive, independent association between body mass and incontinence [28,40,41]. The association between body mass and incontinence, as well as the association between smoking and irritability, provide additional data to support what is already known about the adverse effects of smoking and high body mass on health among midlife women and those who are aging. Physicians and public health educators should continue to emphasize the need for cigarette smoking cessation as well as the importance of healthy behaviors such physical activity.

Several limitations of this study should be considered. First, the data on symptoms were based on self-report and questions that were not validated, and the severity of symptoms was not considered. Thus, some misclassification may have occurred and resulted in the masking of associations between hormone levels and severe symptoms. Second, this study was cross-sectional, and, therefore, we are unable to determine whether the symptom was one that was newly experienced during the menopausal transition when the hormone concentrations may have been changing. In addition, we cannot make a statement as to the temporal relationship between the statistically significant correlates in this study and the symptoms. Third, as with most survey-based studies, there may be a significant amount of selection bias, as those who participated in the study may differ from those who did not. Those participating may be more likely to have experienced symptoms than the general population and, therefore, the prevalence of symptoms reported in this manuscript may be overestimated. Further, the results reported in this manuscript may not be generalizable to the entire population of midlife women.

Additionally, only one blood sample was taken and, further, the blood draw was not conducted on the same phase in the menstrual cycle for all women. Therefore, hormone levels likely represent an average hormone value over the cycle, as hormones fluctuate within individual women depending the day of the menstrual cycle [42]. Other studies such as the Seattle Midlife Women's Health Study, SWAN, and the Melbourne Women's Midlife Health Project have collected timed blood samples, which have been and will be useful in elucidating the associations between hormones and symptoms during specific menstrual cycle phases. Finally, a large number of comparisons between hormone concentrations and symptoms were performed, and, therefore, the significant associations observed may have been due to chance. As stated in the results section, an adjustment for multiple testing was performed and only the associations between incontinence with FTI and SHBG remained statistically significant.

It should also be noted that we did not categorize menopausal status according to the Stages of Reproductive Aging Workshop (STRAW) criteria [43]; this was because these criteria were developed after this study was funded and in the process of being conducted. In this study, it is likely that the peri-menopausal group encompassed two or three of the reproductive transition stages suggested in the STRAW staging system. Therefore, it is possible that events (symptoms) occurring in one stage may be obscured by the total menopausal transition or that associations between the hormones and symptoms in a particular stage may have been obscured.

While the number of studies on hormones, risk factors and hot flashes during midlife has increased substantially in the past 5 years, the role of demographic characteristics, lifestyle factors, and hormonal changes during the menopausal transition in the experiencing of other symptoms is less well studied. This study provides evidence that hormones are involved in the occurrence of insomnia and visual problems during midlife. However, some of these results conflict with previous findings. Given the overall paucity of literature on these issues, more investigation in this area is warranted. Analyses of longitudinal studies such as the Penn Ovarian Aging Study that aim to track hormone levels and symptoms across the menopausal transition are needed to accurately characterize these relationships. Findings from this type of study will help aid in the development of treatments that will perhaps alleviate the symptoms that reduce the quality of life in midlife.

Acknowledgements

This study was supported by NIH grant AG18400.

References

1. Bankowski BJ, Gallicchio LM, Whiteman MK, Lewis LM, Zacur HA, Flaws JA. The association between menopausal symptoms and quality of life in midlife women. *Fertil Steril* 2006;86:1006–1008. [PubMed: 16962115]
2. Woods NF, Mitchell ES. Symptoms during the perimenopause: prevalence, severity, trajectory, and significance in women's lives. *Am J Med* 2005;118:14S–24S.
3. Schwingl PJ, Hulka BS, Harlow SD. Risk factors for menopausal hot flashes. *Obstet Gynecol* 1994;84:29–34. [PubMed: 8008318]
4. Dennerstein L, Dudley EC, Hopper JL, Guthrie JR, Burger HG. A prospective population-based study of menopausal symptoms. *Obstet Gynecol* 2000;93:351–358. [PubMed: 10960625]
5. Freeman EW, Sammel MD, Lin H, et al. Symptoms associated with menopausal transition and reproductive hormones in midlife women. *Obstet Gynecol* 2007;110:230–240. [PubMed: 17666595]
6. Freeman EW, Sammel MD, Lin H, Gracia CR, Kapoor S, Ferdousi T. The role of anxiety and hormonal changes in menopausal hot flashes. *Menopause* 2005;12:258–266. [PubMed: 15879914]
7. Guthrie JR, Dennerstein L, Taffe JR, Donnelly V. Health care-seeking for menopausal problems. *Climacteric* 2003;6:112–117. [PubMed: 12841881]
8. Visvanathan K, Gallicchio L, Schilling C, et al. Cytochrome gene polymorphisms, serum estrogens, and hot flushes in midlife women. *Obstet Gynecol* 2005;106:1372–1381. [PubMed: 16319265]
9. Erlik Y, Meldrum DR, Judd HL. Estrogen levels in postmenopausal women with hot flashes. *Obstet Gynecol* 1982;59:403–407. [PubMed: 7078891]
10. McCoy N, Culter W, Davidson JM. Relationships among sexual behavior, hot flashes, and hormone levels in perimenopausal women. *Arch Sex Behav* 1985;14:385–394. [PubMed: 4062536]
11. Guthrie JR, Dennerstein L, Hopper JL, Burger HG. Hot flushes, menstrual status, and hormone levels in a population-based sample of midlife women. *Obstet Gynecol* 1996;88:437–442. [PubMed: 8752255]
12. Wilbur J, Miller AM, Montgomery A, Chandler P. Sociodemographic characteristics, biological factors, and symptom reporting in midlife women. *Menopause* 1998;5:43–51. [PubMed: 9689194]
13. Overlie I, Moen MH, Holte A, Finset A. Androgens and estrogens in relation to hot flushes during the menopausal transition. *Maturitas* 2002;41:69–77. [PubMed: 11809345]
14. Hollander LE, Freeman EW, Sammel MD, Berlin JA, Grisso JA, Battistini M. Sleep quality, estradiol levels, and behavioral factors in late reproductive age women. *Obstet Gynecol* 2001;98:391–397. [PubMed: 11530118]
15. Kravitz HM, Janssen I, Santoro N, et al. Relationship of day-to-day reproductive hormone levels to sleep in midlife women. *Arch Intern Med* 2005;165:2370–2376. [PubMed: 16287766]
16. Gallicchio L, Miller SR, Visvanathan K, et al. Cigarette smoking, estrogen levels, and hot flashes in midlife women. *Maturitas* 2006;53:133–143. [PubMed: 16368467]

17. Bao AM, Liu RY, Van Someren EJ, Hofman MA, Cao YX, Zhou JN. Diurnal rhythm of free estradiol during the menstrual cycle. *Eur J Endocrinol* 2003;148:227–232. [PubMed: 12590642]
18. Vermeulen A. The hormonal activity of the postmenopausal ovary. *J Clin Endocrinol Metab* 1976;42:247–253. [PubMed: 177438]
19. Whiteman MK, Staropoli CA, Langenberg P, McCarter RJ, Kjerulff KH, Flaws JA. Smoking, body mass, and hot flashes in midlife women. *Obstet Gynecol* 2003;101:264–272. [PubMed: 12576249]
20. Gallicchio L, Visvanathan K, Miller SR, et al. Body mass, estrogen levels, and hot flashes in midlife women. *Am J Obstet Gynecol* 2005;193:1353–1360. [PubMed: 16202725]
21. Sowers MR, Finkelstein JS, Ettinger B, et al. The association of endogenous hormone concentrations and bone mineral density measures in pre- and perimenopausal women of four ethnic groups: SWAN. *Osteoporos Int* 2003;14:44–52. [PubMed: 12577184]
22. Benyamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc B* 1995;57:289–300.
23. Dennerstein L, Leher P, Burger HG, Guthrie JR. New findings from non-linear longitudinal modelling of menopausal hormone changes. *Hum Reprod Update* 2007;13:551–557. [PubMed: 17616552]
24. Woods NF, Smith-Dijulio K, Percival DB, Tao EY, Taylor HJ, Mitchell ES. Symptoms during the menopausal transition and early postmenopause and their relation to endocrine levels over time: observations from the Seattle Midlife Women's Health Study. *J Womens Health (Larchmt)* 2007;16:667–677. [PubMed: 17627402]
25. Randolph JF Jr, Sowers M, Bondarenko I, et al. The relationship of longitudinal change in reproductive hormones and vasomotor symptoms during the menopausal transition. *J Clin Endocrinol Metab* 2005;90:6106–6112. [PubMed: 16144949]
26. Smith MJ, Adams LF, Schmidt PJ, Rubinow DR, Wassermann EM. Effects of ovarian hormones on human cortical excitability. *Ann Neurol* 2002;51:599–603. [PubMed: 12112106]
27. Inghilleri M, Conte A, Curra A, Frasca V, Lorenzano C, Berardelli A. Ovarian hormones and cortical excitability. An rTMS study in humans. *Clin Neurophysiol* 2004;115:1063–1068. [PubMed: 15066531]
28. Ford K, Sowers M, Crutchfield M, Wilson A, Jannausch M. A longitudinal study of the predictors of prevalence and severity of symptoms commonly associated with menopause. *Menopause* 2005;12:308–317. [PubMed: 15879920]
29. Weiss G, Skurnick JH, Goldsmith LT, Santoro NF, Park SJ. Menopause and hypothalamic-pituitary sensitivity to estrogen. *JAMA* 2004;292:2991–2996. [PubMed: 15613667]
30. Freeman EE, Munoz B, Schein OD, West SK. Hormone replacement therapy and lens opacities: the Salisbury Eye Evaluation project. *Arch Ophthalmol* 2001;119:1687–1692. [PubMed: 11709021]
31. Defay R, Pinchinat S, Lumbrosos S, et al. Relationship between hormonal status and cataract in French postmenopausal women: The POLA Study. *Ann Epidemiol* 2003;13:634–644.
32. Klein BE, Klein R, Ritter LL. Is there evidence of an estrogen effect on age-related lens opacities? The Beaver Dam Eye Study. *Arch Ophthalmol* 1994;112:85–91. [PubMed: 8285900]
33. Klein BE, Klein R, Lee KE. Reproductive exposures, incident age-related cataracts, and age-related maculopathy in women: the beaver dam eye study. *Am J Ophthalmol* 2000;130:322–326. [PubMed: 11020411]
34. Cumming RG, Mitchell P. Hormone replacement therapy, reproductive factors, and cataract. The Blue Mountains Eye Study. *Am J Epidemiol* 1997;145:242–249. [PubMed: 9012597]
35. Benitez del Castillo JM, del RT, Garcia-Sanchez J. Effects of estrogen use on lens transmittance in postmenopausal women. *Ophthalmology* 1997;104:970–973. [PubMed: 9186438]
36. Younan C, Mitchell P, Cumming RG, Panchapakesan J, Rochtchina E, Hales AM. Hormone replacement therapy, reproductive factors, and the incidence of cataract and cataract surgery: the Blue Mountains Eye Study. *Am J Epidemiol* 2002;155:997–1006. [PubMed: 12034578]
37. Wozzala K, Hiller R, Sperduto RD, et al. Postmenopausal estrogen use, type of menopause, and lens opacities: the Framingham studies. *Arch Intern Med* 2001;161:1448–1454. [PubMed: 11386895]
38. Eisner A, Toomey MD, Falardeau J, Samples JR, Vetto JT. Differential effects of tamoxifen and anastrozole on optic cup size in breast cancer survivors. *Breast Cancer Res Treat* 2007;106:161–170. [PubMed: 17260092]

39. Metka M, Enzelsberger H, Knogler W, Schurz B, Aichmair H. Ophthalmic complaints as a climacteric symptom. *Maturitas* 1991;14:3–8. [PubMed: 1791770]
40. Holtedahl K, Hunskaar S. Prevalence, 1-year incidence and factors associated with urinary incontinence: a population based study of women 50–74 years of age in primary care. *Maturitas* 1998;28:205–211. [PubMed: 9571595]
41. Dallosso HM, McGrother CW, Matthews RJ, Donaldson MM. The association of diet and other lifestyle factors with overactive bladder and stress incontinence: a longitudinal study in women. *BJU Int* 2003;92:69–77. [PubMed: 12823386]
42. Garcia-Closas M, Herbstman J, Schiffman M, Glass A, Dorgan JF. Relationship between serum hormone concentrations, reproductive history, alcohol consumption and genetic polymorphisms in pre-menopausal women. *Int J Cancer* 2002;102:172–178. [PubMed: 12385014]
43. Soules MR, Sherman S, Parrott E, et al. Stages of Reproductive Aging Workshop (STRAW). *J Womens Health Gend Based Med* 2001;10:843–848. [PubMed: 11747678]

Table 1

Selected characteristics of study sample (n = 603)

	n	%
Age (years)		
45 to 49	399	66.2
50 to 54	204	33.8
Race		
White	505	83.7
Black	86	14.3
Other	10	1.7
Marital Status		
Single	78	12.9
Married/living with partner	405	67.2
Other ^a	119	19.7
Education		
High school or less	93	15.4
Some college	163	27.0
College graduate	149	24.7
Graduate courses	198	32.8
Menopausal status		
Pre-	235	39.0
Peri-	358	59.4
Parity		
0	139	23.1
1	107	17.7
2	219	36.3
3 or more	138	22.9
Smoking status		
Current	54	8.9
Former	230	38.1
Never	318	52.7
Body mass index (kg/m ²)		
<25	259	42.9
25 to 29	161	26.7
≥30	182	30.2
Current alcohol drinker		
Yes	397	65.8
No	206	34.2
Physical activity		
None/light	359	59.5
Moderate/heavy	244	40.5

Note: Percentages for some characteristics do not add up to 100% due to missing data

^a widowed or divorced/separated

Table 2
Unadjusted associations between endogenous estrogens and menopausal symptoms

	n	%	Estradiol, pg/ml		Free Estradiol Index (FEI)		Estrone (pg/ml)	
			Geometric Mean (95% CL)	p-value	Geometric Mean (95% CL)	p-value	Geometric Mean (95% CL)	p-value
Headache								
Yes	239	39.6	94.8 (85.4, 105.2)	0.3	0.636 (0.562, 0.720)	0.8	132.0 (120.5, 143.8)	0.8
No	364	60.4	101.2 (93.0, 110.1)		0.622 (0.563, 0.688)		133.9 (124.6, 143.8)	
Insomnia								
Yes	267	44.3	106.1 (96.1, 117.1)	0.04	0.714 (0.635, 0.802)	0.003	133.1 (122.3, 144.8)	0.9
No	329	54.6	92.6 (84.8, 101.2)		0.565 (0.509, 0.627)		132.1 (122.6, 142.5)	
Vision problems								
Yes	112	18.6	93.7 (80.3, 109.2)	0.5	0.707 (0.590, 0.847)	0.1	130.4 (114.5, 148.6)	0.8
No	482	79.9	99.4 (92.4, 107.0)		0.606 (0.556, 0.661)		132.8 (124.8, 141.3)	
Vaginal discharge								
Yes	126	20.9	100.3 (88.2, 114.0)	0.6	0.644 (0.554, 0.750)	0.7	138.6 (124.3, 154.5)	0.4
No	468	77.6	98.0 (90.8, 105.9)		0.622 (0.568, 0.682)		131.3 (123.0, 140.2)	
Vaginal dryness								
Yes	158	26.2	86.1 (74.5, 99.6)	0.04	0.567 (0.477, 0.673)	0.2	128.6 (113.7, 145.6)	0.6
No	440	73.0	102.0 (94.7, 109.9)		0.638 (0.584, 0.697)		134.2 (125.9, 142.9)	
Irritability								
Yes	310	51.4	93.8 (85.7, 102.7)	0.1	0.612 (0.550, 0.681)	0.6	126.7 (117.3, 136.9)	0.1
No	284	47.1	104.1 (94.6, 114.5)		0.639 (0.571, 0.716)		139.4 (128.5, 151.2)	
Incontinence								
Yes	131	21.7	100.7 (87.5, 116.0)	0.7	0.751 (0.636, 0.886)	0.01	147.0 (130.5, 165.5)	0.1
No	460	76.3	98.0 (90.9, 105.7)		0.593 (0.543, 0.648)		129.9 (121.9, 138.5)	

Table 3
Unadjusted associations between endogenous androgens and menopausal symptoms

	Testosterone, ng/ml		Free Testosterone Index (FTI)		Androstenedione, ng/ml		DHEA-S, ng/ml	
	Geometric Mean (95% CL)	p-value	Geometric Mean (95% CL)	p-value	Geometric Mean (95% CL)	p-value	Geometric Mean (95% CL)	p-value
Headache								
Yes	0.452 (0.417, 0.489)	0.3	2.86 (2.54, 3.22)	0.7	2.01 (1.88, 2.14)	0.8	362.5 (337.1, 389.9)	0.2
No	0.477 (0.447, 0.508)		2.77 (2.51, 3.04)		2.03 (1.92, 2.13)		384.8 (362.9, 408.1)	
Insomnia								
Yes	0.467 (0.433, 0.503)	1.0	2.96 (2.65, 3.32)	0.2	1.97 (1.86, 2.09)	0.9	361.1 (337.0, 386.8)	0.1
No	0.466 (0.436, 0.499)		2.69 (2.43, 2.97)		2.01 (1.89, 2.14)		388.1 (365.0, 412.8)	
Vision problems								
Yes	0.472 (0.421, 0.530)	0.7	3.37 (2.83, 4.01)	0.02	2.02 (1.84, 2.23)	0.9	379.9 (341.6, 422.6)	0.7
No	0.461 (0.436, 0.487)		2.66 (2.44, 2.89)		2.00 (1.92, 2.10)		372.0 (353.5, 391.4)	
Vaginal discharge								
Yes	0.465 (0.422, 0.513)	0.9	2.82 (2.44, 3.27)	0.9	2.02 (1.87, 2.19)	1.0	380.3 (347.9, 415.9)	0.8
No	0.468 (0.441, 0.496)		2.80 (2.57, 3.06)		2.02 (1.93, 2.12)		374.5 (355.0, 395.2)	
Vaginal dryness								
Yes	0.449 (0.402, 0.501)	0.5	2.79 (2.36, 3.29)	1.0	2.01 (1.83, 2.19)	0.9	391.4 (353.5, 433.2)	0.4
No	0.470 (0.444, 0.497)		2.77 (2.55, 3.02)		2.02 (1.93, 2.12)		373.6 (354.6, 393.6)	
Irritability								
Yes	0.481 (0.449, 0.515)	0.2	2.96 (2.67, 3.29)	0.1	2.08 (1.96, 2.20)	0.1	381.1 (357.8, 406.0)	0.4
No	0.448 (0.416, 0.481)		2.60 (2.33, 2.89)		1.95 (1.84, 2.07)		367.7 (344.0, 393.0)	
Incontinence								
Yes	0.505 (0.454, 0.561)	0.1	3.56 (3.03, 4.17)	0.0006	2.06 (1.89, 2.24)	0.6	399.2 (362.0, 440.2)	0.2
No	0.453 (0.428, 0.479)		2.59 (2.38, 2.82)		2.00 (1.91, 2.10)		368.6 (349.8, 388.4)	

Table 4

Unadjusted associations between endogenous SHBG, progesterone, estradiol to progesterone ratio, and estradiol plus estrone to progesterone ratio with menopausal symptoms

	SHBG, nmol/L		Progesterone, ng/ml		Estradiol: Progesterone Ratio		Estradiol + Estrone: Progesterone Ratio	
	Geometric Mean	p-value	Geometric Mean	p-value	Geometric Mean	p-value	Geometric Mean	p-value
Headache								
Yes	54.7 (50.7, 59.0)	0.1	0.717 (0.594, 0.865)	0.1	132.2 (109.0, 160.3)	0.1	335.0 (280.9, 399.5)	0.1
No	59.7 (56.1, 63.5)		0.926 (0.795, 1.077)		109.3 (93.6, 127.8)		270.5 (234.6, 311.8)	
Insomnia								
Yes	54.6 (50.8, 58.7)	0.05	0.750 (0.627, 0.896)	0.1	141.5 (118.0, 169.8)	0.007	341.0 (288.6, 402.8)	0.02
No	60.2 (56.4, 64.2)		0.915 (0.780, 1.073)		101.2 (86.0, 119.1)		260.0 (224.0, 301.7)	
Vision problems								
Yes	48.6 (43.5, 54.4)	0.008	0.691 (0.524, 0.912)	0.1	135.6 (102.0, 180.2)	0.3	347.8 (268.2, 451.1)	0.2
No	60.2 (57.1, 63.5)		0.875 (0.766, 0.999)		113.7 (99.2, 130.2)		281.9 (248.9, 319.2)	
Vaginal discharge								
Yes	57.2 (52.0, 62.8)	0.8	0.859 (0.681, 1.083)	0.8	116.8 (92.1, 148.1)	1.0	301.8 (243.3, 374.5)	0.9
No	57.8 (54.7, 60.2)		0.832 (0.724, 0.957)		117.8 (102.1, 135.8)		293.0 (257.2, 333.9)	
Vaginal dryness								
Yes	55.8 (50.1, 62.0)	0.4	0.636 (0.490, 0.836)	0.02	135.3 (103.5, 176.9)	0.2	358.9 (281.0, 458.4)	0.1
No	58.7 (55.5, 62.0)		0.904 (0.791, 1.033)		112.9 (98.4, 129.4)		277.9 (245.1, 314.9)	
Irritability								
Yes	56.3 (52.6, 60.2)	0.2	0.814 (0.690, 0.960)	0.5	115.3 (97.4, 136.4)	0.8	288.5 (247.3, 336.6)	0.9
No	59.8 (55.7, 64.1)		0.880 (0.740, 1.046)		118.3 (99.1, 141.2)		293.6 (249.7, 345.3)	
Incontinence								
Yes	49.2 (44.5, 54.5)	0.0004	0.815 (0.632, 0.952)	0.5	123.6 (95.3, 160.4)	0.7	324.2 (255.5, 411.3)	0.4
No	60.6 (57.4, 64.1)		0.844 (0.737, 0.967)		116.1 (101.0, 133.5)		286.8 (252.4, 325.8)	

Adjusted odds ratios (ORs) and 95% confidence limits for the associations between participant characteristics, endogenous hormones, and headache, insomnia, vision problems, and irritability

	Headache		Insomnia		Vision problems		Irritability	
	n	OR (95% CL) ^d	n	OR (95% CL) ^d	n	OR (95% CL) ^d	n	OR (95% CL) ^d
Age (years)								
45 to 49	57.9	1.00 (ref)	46.1	1.00 (ref)	19.9	1.00 (ref)	56.1	1.00 (ref)
50 to 54	42.1	0.70 (0.48, 1.02)	42.3	0.90 (0.62, 1.32)	16.9	0.73 (0.44, 1.20)	44.5	0.61 (0.42, 0.89)
Race								
White	39.2	1.00 (ref)	46.0	1.00 (ref)	16.5	1.00 (ref)	52.2	1.00 (ref)
Black	43.0	1.03 (0.60, 1.75)	38.4	0.62 (0.36, 1.06)	30.6	2.26 (1.21, 4.20)	53.5	0.95 (0.56, 1.61)
Other	40.0	0.87 (0.21, 3.65)	30.0	0.66 (0.16, 2.82)	30.0	1.20 (0.22, 6.47)	40.0	0.39 (0.09, 1.68)
Marital Status								
Single	33.3	1.00 (ref)	48.1	1.00 (ref)	19.5	1.00 (ref)	52.0	1.00 (ref)
Married or w/partner	41.7	1.85 (1.04, 3.31)	43.8	0.92 (0.53, 1.62)	17.0	0.79 (0.38, 1.66)	51.9	1.22 (0.70, 2.13)
Other	36.1	1.36 (0.71, 2.61)	45.8	0.92 (0.49, 1.73)	23.9	1.07 (0.48, 2.39)	53.5	1.30 (0.69, 2.45)
Education								
High school or less	55.9	1.00 (ref)	42.4	1.00 (ref)	24.2	1.00 (ref)	54.4	1.00 (ref)
Some college	42.9	0.55 (0.32, 0.94)	50.0	1.28 (0.73, 2.24)	19.8	0.88 (0.44, 1.76)	54.7	0.95 (0.55, 1.65)
College graduate	36.2	0.40 (0.23, 0.70)	46.3	1.20 (0.67, 2.14)	19.2	0.86 (0.42, 1.77)	52.1	0.89 (0.51, 1.56)
Graduate courses	31.8	0.35 (0.21, 0.61)	40.5	1.04 (0.59, 1.82)	15.4	0.88 (0.43, 1.79)	49.2	0.90 (0.52, 1.55)
Menopausal status								
Pre-	40.0	1.00 (ref)	44.0	1.00 (ref)	19.5	1.00 (ref)	47.4	1.00 (ref)
Peri-	38.8	0.98 (0.68, 1.41)	44.9	1.02 (0.71, 1.48)	17.9	0.90 (0.56, 1.44)	55.6	1.46 (1.02, 2.10)
Parity								
0	41.0	1.00 (ref)	49.3	1.00 (ref)	11.6	1.00 (ref)	54.4	1.00 (ref)
1	44.9	1.15 (0.66, 1.99)	52.8	1.08 (0.63, 1.88)	26.7	2.47 (1.17, 5.20)	59.1	1.11 (0.64, 1.94)
2	37.9	0.75 (0.46, 1.20)	46.8	0.81 (0.50, 1.30)	20.9	2.12 (1.07, 4.20)	49.5	0.77 (0.48, 1.23)
3 or more	37.0	0.68 (0.40, 1.16)	30.9	0.43 (0.25, 0.74)	16.9	1.51 (0.70, 3.25)	48.9	0.73 (0.43, 1.22)
Smoking status								
Never	40.6	1.00 (ref)	42.5	1.00 (ref)	14.1	1.00 (ref)	46.7	1.00 (ref)
Former	39.1	0.86 (0.60, 1.26)	44.3	0.95 (0.66, 1.39)	24.2	1.90 (1.16, 3.09)	54.6	1.40 (0.98, 2.02)
Current	37.0	0.69 (0.36, 1.31)	59.3	1.81 (0.95, 3.45)	22.6	1.50 (0.68, 3.29)	73.6	2.84 (1.43, 5.64)
Body mass index (kg/m ²)								
<25	37.1	1.00 (ref)	40.7	1.00 (ref)	15.6	1.00 (ref)	48.4	1.00 (ref)
25 to 29	36.0	0.88 (0.58, 1.36)	42.7	0.98 (0.63, 1.53)	17.2	0.73 (0.40, 1.34)	55.8	1.28 (0.84, 1.94)
≥30	46.7	1.39 (0.89, 2.16)	52.2	1.43 (0.86, 2.37)	24.6	0.91 (0.48, 1.73)	54.7	1.06 (0.68, 1.65)
Current alcohol drinker								
No	40.8	1.00 (ref)	46.1	1.00 (ref)	19.8	1.00 (ref)	52.2	1.00 (ref)
Yes	39.0	1.03 (0.71, 1.51)	44.1	0.88 (0.60, 1.28)	18.4	1.07 (0.65, 1.75)	52.2	1.03 (0.71, 1.50)
Physical activity								
None/light	39.8	1.00 (ref)	45.2	1.00 (ref)	19.3	1.00 (ref)	52.6	1.00 (ref)
Moderate/heavy	39.3	1.00 (0.70, 1.44)	44.2	0.97 (0.68, 1.40)	18.2	0.96 (0.59, 1.55)	51.7	0.98 (0.68, 1.40)
Hormone 1 ^b								
Hormone 2 ^c								
Hormone 3 ^d								

OR = odds ratio; 95% CL = 95% confidence limits; SHBG = sex hormone binding globulin

^aOR adjusted for other listed covariates

b. insomnia: FEI; vision problems: FTI

^c insomnia: SHBG; vision problems: SHBG
^d insomnia: ratio of estradiol+estrone to progesterone

Table 6

Adjusted odds ratios (ORs) and 95% confidence limits for the associations between participant characteristics, endogenous hormones, and incontinence, vaginal dryness, and vaginal discharge

	Incontinence		Vaginal dryness		Vaginal discharge	
	n	OR (95% CI) ^a	n	OR (95% CI) ^a	n	OR (95% CI) ^a
Age (years)						
45 to 49	22.8	1.00 (ref)	19.0	1.00 (ref)	28.3	1.00 (ref)
50 to 54	20.8	0.82 (0.52, 1.31)	25.5	1.47 (0.94, 2.31)	22.8	0.73 (0.48, 1.12)
Race						
White	22.6	1.00 (ref)	20.7	1.00 (ref)	25.6	1.00 (ref)
Black	19.1	0.55 (0.28, 1.07)	23.5	1.25 (0.67, 2.33)	31.4	1.23 (0.70, 2.17)
Other	10.0	0.41 (0.05, 3.54)	20.0	0.63 (0.08, 5.28)	30.0	0.71 (0.14, 3.57)
Marital Status						
Single	19.7	1.00 (ref)	15.4	1.00 (ref)	31.2	1.00 (ref)
Married or w/partner	21.6	0.75 (0.37, 1.51)	23.1	1.64 (0.80, 3.40)	24.8	0.67 (0.37, 1.23)
Other	25.2	0.96 (0.44, 2.11)	19.0	1.06 (0.47, 2.41)	29.0	0.87 (0.44, 1.72)
Education						
High school or less	28.3	1.00 (ref)	24.2	1.00 (ref)	31.5	1.00 (ref)
Some college	22.5	0.79 (0.41, 1.50)	22.2	1.11 (0.58, 2.13)	21.6	0.51 (0.28, 0.93)
College graduate	25.2	1.02 (0.53, 1.98)	19.9	0.92 (0.46, 1.84)	30.6	0.85 (0.47, 1.54)
Graduate courses	16.8	0.73 (0.38, 1.40)	20.0	0.94 (0.49, 1.81)	24.9	0.65 (0.37, 1.17)
Menopausal status						
Pre-	19.5	1.00 (ref)	18.0	1.00 (ref)	26.9	1.00 (ref)
Peri-	24.3	1.25 (0.79, 1.96)	22.9	1.07 (0.68, 1.69)	26.3	1.06 (0.71, 1.57)
Parity						
0	16.6	1.00 (ref)	17.7	1.00 (ref)	24.6	1.00 (ref)
1	23.3	1.52 (0.75, 3.07)	23.1	1.24 (0.63, 2.46)	30.2	1.48 (0.81, 2.72)
2	24.4	1.71 (0.92, 3.17)	22.2	1.18 (0.65, 2.15)	26.9	1.32 (0.77, 2.25)
3 or more	23.5	1.71 (0.87, 3.36)	21.7	1.14 (0.59, 2.18)	24.6	1.12 (0.62, 2.02)
Smoking status						
Never	19.7	1.00 (ref)	20.1	1.00 (ref)	27.9	1.00 (ref)
Former	25.2	1.18 (0.76, 1.84)	21.7	1.05 (0.60, 1.64)	24.6	0.81 (0.54, 1.22)
Current	22.6	0.84 (0.39, 1.82)	24.5	1.33 (0.63, 2.81)	25.9	0.77 (0.38, 1.54)
Body mass index (kg/m ²)						
<25	14.4	1.00 (ref)	22.2	1.00 (ref)	26.2	1.00 (ref)
25 to 29	22.3	1.40 (0.80, 2.45)	17.5	0.67 (0.39, 1.13)	28.1	1.12 (0.71, 1.77)
≥30	33.5	2.79 (1.51, 5.14)	23.3	0.84 (0.49, 1.43)	25.4	0.98 (0.60, 1.60)
Current alcohol drinker						
No	23.4	1.00 (ref)	23.7	1.00 (ref)	25.5	1.00 (ref)
Yes	21.5	0.92 (0.59, 1.44)	20.0	0.86 (0.55, 1.35)	26.9	1.18 (0.78, 1.80)
Physical activity						
None/light	22.4	1.00 (ref)	21.8	1.00 (ref)	25.8	1.00 (ref)
Moderate/heavy	21.9	1.27 (0.82, 1.99)	20.3	0.88 (0.56, 1.37)	27.3	1.06 (0.71, 1.58)
Hormone 1 ^b						
Hormone 2 ^c						
Hormone 3 ^d						
		0.94 (0.53, 1.69)		0.83 (0.64, 1.08)		

OR = odds ratio; 95% CL = 95% confidence limits; SHBG = sex hormone binding globulin; FEI: free estradiol index; FTI: free testosterone index

^aOR adjusted for other listed covariates

^bIncontinence: FEI; vaginal dryness: progesterone

^cIncontinence: FTI; vaginal dryness: estradiol

^dIncontinence: SHBG