MsFLASH Analysis of Diurnal Salivary Cortisol and Palpitations in Peri and Postmenopausal Women

Janet S. Carpenter, PhD, RN, FAAN[1], **James E. Tisdale, PharmD**[2,3], **Joseph C. Larson, MS**[4], **Ying Sheng, PhD, RN**[1], **Chen X. Chen, PhD, RN**[1], **Diane Von Ah, PhD, RN**[1], **Richard Kovacs, MD**[3], **Susan D. Reed, MD, MPH**[5], **Rebecca C. Thurston, PhD**[6], **Katherine A. Guthrie, PhD**[4]

[1]Indiana University School of Nursing, Indianapolis, IN 46202

[2]Purdue University College of Pharmacy, West Lafayette, IN 47907

[3]Indiana University School of Medicine, Indianapolis, IN 46202

[4]Data Coordinating Center, Fred Hutchinson Cancer Research Center, Seattle, WA

[5]University of Washington, Seattle, WA

[6]University of Pittsburgh, Pittsburgh, PA.

Abstract

Objective: To evaluate the relationship between diurnal salivary cortisol patterns and distress from heart palpitations in midlife women.

Methods: We analyzed baseline data from 293 women who were eligible for a 3×2 factorial trial of exercise or yoga vs. routine activity, and omega-3 fish oil vs. placebo for vasomotor symptoms. Women self-collected salivary cortisol using swabs at four time points over two consecutive days and reported distress from heart racing or pounding during the past two weeks using a single item. Sample description and covariate data included demographics, clinical data, vasomotor symptom frequency from daily diaries, medication use, and validated questionnaires on depression, stress, and insomnia (Patient Health Questionnaire-8, Perceived Stress Scale, and Insomnia Severity index). Data were analyzed using descriptive statistics, chi-square and t-tests, and repeated measure linear regression models.

Results: Participants were on average 54.6 (SD=3.6) years old, most were white (67%),, most were postmenopausal (84%), and 26% reported distress related to palpitations. In adjusted models, the morning (wake plus 30-minute) geometric mean daily salivary cortisol concentrations were significantly more blunted in those with distress from palpitations compared to those without distress (p 0.03). When all covariates were controlled, distress from palpitations was the sole significant predictor of wake plus 30-minute cortisol (–0.25 [–0.45 to –0.04], p=0.02).

Conclusions: Palpitations among midlife women may be associated with blunted morning cortisol, and this relationship is not explained by demographics, clinical variables, vasomotor symptoms, medications, depression, stress, or insomnia.

Corresponding author: Janet S. Carpenter, PhD, RN, FAAN, IU School of Nursing, 600 Barnhill Drive NU338, Indianapolis, IN 46260, phone 317-278-6093, fax none, carpentj@iu.edu.

Keywords

Cortisol; menopause; palpitations; hormone; biomarker

INTRODUCTION

Heart palpitations occurring during the menopause transition are poorly understood. Women report palpitations as skipped, irregular, or exaggerated heartbeats or heart pounding.[1, 2] Palpitations are common during the menopause transition. A recently published review concluded that palpitations affect as many as 40% of perimenopausal women and 54% of postmenopausal women.[3] Another recent study found 25% of women reported some distress related to palpitations and that distress was related to lower menopausal quality of life.[4] Greater understanding of palpitations could further symptom assessment and management during the menopause transition.

Identification of biomarkers associated with palpitations may help elucidate biological mechanisms to further treatment efforts. Biomarkers can be used as risk factors in identifying women who may be most in need of interventions to prevent or manage symptoms. Biomarkers can also help identify protective factors that can help prevent symptoms or prevent severe symptoms.[5] There are five types of biomarkers recommended as a minimum dataset for symptom science research: cortisol, inflammatory cytokines, hypothalamic-pituitary-adrenal axis marker, brain derived neurotrophic factor, and genetic polymorphisms.[6] Of these, only genetic markers have been studied in relation to palpitations in women during the menopause transition. Two studies showed no associations between palpitations in peri- or postmenopausal women and CYP1B1 Leu432Val[7, 8] or CYP17A1rs743572[9] genotypes. These genotypes are linked to estrogen/progesterone synthesis or serum concentrations. The only other biomarkers that have been studied in relation to palpitations prevalence during the menopause transition are (1) serum thyroid-stimulating hormone (rho=−0.18, p=0.02) and (2) free thyroxine (rho=0.25, p=0.04).[10] In an ongoing literature review, we have found no other studies of biomarkers of palpitations during the menopause transition.

The data repository from the Menopause Strategies Finding Lasting Answers to Symptoms and Health (MsFLASH) trial 03 provides a unique opportunity to evaluate the potential biomarker, cortisol. Cortisol is recommended as a key biomarker of symptoms[6] and was previously found to be associated with menopausal vasomotor symptoms.[11, 12] In peri- and post-menopausal women, a blunted awakening cortisol response was associated with more frequent[11, 12] and severe[12] daily diary-recorded vasomotor symptom. Excess cortisol may affect the myocardial tissue directly through cardiomyocyte glucocorticoid signaling and indirectly by heightening catecholamine and renin-angiotensin effects.[13] In addition, cortisol may be related to high vasomotor symptom frequency through stress/anxiety/depression, declining serum estrogen concentrations, and/or insomnia.[11] Research shows cortisol directly affects the cardiovascular system[14] and health outcomes.

Using MsFLASH data from three trials (n=759), we previously identified covariates to consider in research on heart palpitations in women at the menopause transition.[4] Smoking

(past, current) was associated with lower odds of reporting distress from palpitations, whereas body mass index, depressive symptoms, perceived stress, and insomnia were all positively associated with distress from palpitations.[4]

The overall purpose of our investigation was to compare daily salivary cortisol patterns between midlife women who did and did not report distress from palpitations in the past two weeks. We anticipated finding a relationship between variations in diurnal cortisol patterns and distress from palpitations, and we compared daily cortisol patterns between women who did and did not report distress from menopausal heart palpitations controlling for stress, depression, insomnia, and other potential covariates.

METHODS

Design and Setting

This was a cross-sectional analysis of baseline data from the MsFLASH trial 03. MsFLASH research sites in Indianapolis, Oakland, and Seattle enrolled participants between 2011 and 2012. Other publications detail trial results.[15–19] Briefly, the trial was a 3×2 factorial design of exercise or yoga vs. routine activity and omega-3 fish oil vs. placebo with outcomes assessed at baseline and 12 weeks.

Sample

All participants met common MsFLASH inclusion criteria, which included age 40–62 years, in good general health, being peri- or postmenopausal based on menses or follicle stimulating hormone (FSH) and estradiol values, and reporting 14 or more episodes of bothersome or severe vasomotor symptoms (hot flashes, night sweats) per week during a 3 week screening period. Common and trial specific exclusion criteria were: use of hormones, hormonal contraceptives, or any treatments for vasomotor symptoms in the past month; regular user of omega-3 products; regular user of exercise, yoga, or related activities; contraindications to the study interventions, or major depressive episode in the past 3 months. In addition, for this analysis, women were excluded if they were missing all 8 cortisol samples, palpitations distress information, or data on covariates (e.g., demographics, clinical data, stress, depressive symptoms, insomnia).

The trial did not exclude women taking selective serotonin reuptake inhibitors, selective serotonin norepinephrine inhibitors, monoamine oxidase inhibitors other medications for anxiety/depression/sleep, St. John's Wort gabapentin, pregabalin, selective estrogen receptor modulators, aromatase inhibitors, or glucocorticoids. To account for the possible impact of these medications on cortisol, we included use of any of these medications in the past 4 weeks (yes, no) in the analysis.

Dataset

The dataset for this analysis consisted of baseline data from questionnaires, data collected during baseline study visits, and salivary cortisol values from self-collected swabs. Distress from heart palpitations was assessed with a single item of experiencing "distress from heart racing or pounding in the past two weeks" with response options of "not at all", "a little

bit", "moderately", "quite a bit", or "extremely". Similar to another paper,[4] responses of "not at all" were coded as "no palpitations distress" and all other responses were coded as "palpitations distress".

Salivary cortisol values were obtained at 4 time points on each of two baseline days: upon awakening (wake), 30 minutes later (wake+30), early afternoon, and bedtime. As detailed in our prior publication, women were given specific instructions about how to complete the self-collection to ensure quality samples were obtained.[11] Women used pre-labeled Salivette swabs (Starstedt AG & Co, Lumbrecht, Rhineland-Palatinate, Germany) and placed them into their home freezer within 4 hours of collection. Within 1–3 weeks of sample collection, women transported the swabs in freezer bags to the clinical sites where the swabs were stored at −70 °C degrees until they were analyzed. Swabs were later shipped to and analyzed by the University of Washington School of Nursing laboratory using high-sensitivity cortisol enzyme immunoassay kits (Salimetrics, State College, PA). The sensitivity is < 0.007 μg and the assay range is 0.012–3.000 μg/dl.

Covariate data included demographics (age, race/ ethnicity, marital status, employment), clinical data [smoking history, menopause status, body mass index (BMI), systolic and diastolic blood pressure,], medication use, vasomotor symptom frequency from daily diaries, and scores from the Perceived Stress Scale,[20] Patient Health Questionnaire,[21, 22] and Insomnia Severity index.[23]

Analysis

The analysis included data from 293 of the 355 women included in the MsFLASH 03 trial. Of the 355 women included in the trial, 46 were excluded for missing baseline cortisol data at all of the 8 collection times, another 2 were excluded for missing palpitations distress data, and another 14 were excluded for missing covariate data.

This analysis followed the analytic strategy used in Reed et al.'s paper on diurnal cortisol and vasomotor symptoms.[11] Demographic, clinical, and symptom data were compared between palpitations distress groups (no, yes) using t-tests and chi-square tests. No adjustments were made for multiple comparisons given the exploratory nature of the analysis. The distributions of cortisol values at all 4 time points were skewed, thus the values were log transformed. Geometric means and their corresponding 95% confidence intervals for salivary cortisol at each time point were graphed. Additional calculated values included estimated daytime cortisol exposure (as the mean daily area under the curve over the two days), To evaluate the associations of cortisol and palpitations distress, data from both days of cortisol collection were included as repeated measures in linear regression models of log transformed cortisol values at each time point as a function of palpitation distress (yes/no) and other factors in three adjusted models. Model 1 adjusted day and clinical center. Model 2 adjusted covariates in model 1, age, race/ethnicity, marital status, full-time employment, smoking, menopause status, body mass index, systolic blood pressure, diastolic blood pressure, and vasomotor symptoms. Model 3 adjusted covariates in model 2, medication use in the past 4 weeks (any use of selective serotonin receptor inhibitor, selective serotonin norepinephrine receptor inhibitor, monoamine oxidase inhibitor, anti-anxiety medication (unspecified), tricyclic antidepressants, St. John's Wort, other medications for anxiety/

depression/sleep, gabapentin, pregabalin, selective estrogen receptor modulators, aromatase inhibitors, glucocorticoids), depression, stress, and insomnia. Anxiety was highly correlated with depressive symptoms and was not included in the models. Robust standard errors were calculated via generalized estimating equations to account for correlation between repeated measures from each participant. Analyses were conducted in SAS for Windows Version 9.4 (Cary, NC).

Results

There were 76 women (26%) who reported any degree of distress from palpitations. Characteristics for the sample of 293 women and for palpitations distress groups are shown in Table 1. Groups did not differ on age, race/ethnicity, marital status, employment, smoking history, menopause status, BMI, or systolic or diastolic blood pressure. The majority of participants were white or Black, never smokers, married or partnered, overweight or obese, postmenopausal, and with normal blood pressure. Women reporting palpitations distress reported significantly higher levels of use of one of the aforementioned medications in the past 4 weeks (35.5% vs. 21.2%, p=0.01), vasomotor symptoms (8.4±4.5 vs. 7.3±3.7, p=0.04), perceived stress (17.1±6.2 vs. 12.6±6.9, p<0.001), depressive symptoms (4.0±4.0 vs. 3.5±3.4, p<0.001), and insomnia severity (13.8±5.5 vs. 10.9±5.0, p<0.001) compared to those reporting no distress.

Figure 1 shows mean daily cortisol values by palpitations distress groups at each time point on each of the two assessment days. Both groups demonstrated the expected diurnal variation in salivary cortisol, with higher morning and lower evening values. However, visually, there appeared to be a flattened cortisol awakening response with slightly blunted Wake and Wake+30 cortisol values in the palpitations distress group compared to the no distress group. Afternoon and bedtime cortisol values appeared similar.

Adjusted models in Table 2 show significantly more blunted Wake+30 cortisol values in the palpitations distress group compared to those without distress (odds ratio [OR] = −0.26 [95% CI, −0.47 to −0.05]; OR = −0.24 [95% CI, −0.45 to −0.02]; OR = −0.25 [95% CI, −0.45 to −0.04]; all p ≤ 0.03). Total area under the curve, wake, afternoon, and bedtime cortisol values were not significantly different between distress groups in the adjusted models.

Details of the significant adjusted model for Wake+30 cortisol values are shown in Table 3. Palpitations distress remained a significant predictor of Wake+30 cortisol (OR = −0.25 [95% CI, −0.45 to −0.04], p = 0.02) after adjusting for day, clinical center, age, race/ethnicity, marital status, employment, smoking, menopause status, BMI, systolic and diastolic blood pressure, vasomotor symptoms, medication use, depressive symptoms, stress, and insomnia. Other cortisol timepoints were not significant.

DISCUSSION

This report details salivary cortisol patterns in relation to menopausal palpitations. Our goal in conducting this analysis was to begin to characterize biomarkers of heart palpitations in menopausal women, which may help unravel the mechanisms or biological pathways

involved and assist in targeting therapies. We had available assayed salivary cortisol swabs and self-reported palpitations distress data along with other carefully collected data on covariates from the MsFLASH network.[24] The available dataset was unique in this regard and suitable for addressing the study purpose.

Psychological stress does not seem to explain study findings. Persons experiencing acute psychological stress also exhibit blunted cortisol awakening responses. [25, 26] However, in our sample, the relationship between blunted Wake+30 cortisol and palpitations distress was not explained by perceived stress, depressive symptoms, or other variables including demographics, vasomotor symptoms, or insomnia severity. In addition, there is no evidence that the distress from palpitations is a severe enough stressor to alter cortisol awakening responses.

Whether palpitations, or palpitations distress and the associated blunted morning cortisol response are associated with ECG abnormalities remains unknown. We have found only two published studies combining self-reported palpitations with electrocardiographic (ECG) findings that included women.[27, 28] Neither reported menopause status. Other studies done in people with Cushing's disease suggest that there could be a physiological relationship between a blunted cortisol awakening response and palpitations. People with Cushing's have blunted cortisol awakening response,[29] also exhibit arterial hypertension, and are at high risk of arrhythmias, including atrial fibrillation.[30, 31] These arrythmias may be experienced as palpitations. Men with Cushing's disease exhibit both blunted cortisol awakening response and low serum testosterone concentrations with resulting QT interval prolongation and potentially higher risk of ventricular arrhythymias.[32] It does not appear that similar studies have been done in women, though low serum progesterone concentrations have also been associated with QT interval prolongation, though there is not yet evidence to support a higher risk of ventricular arrhythmias.

Disrupted diurnal cortisol patterns, even without palpitations, are associated with cardiovascular mortality.[33, 34] In an analysis of 250 patients undergoing coronary artery bypass graft surgery, blunted morning or elevated evening values in salivary cortisol samples taken throughout a single day were related to more major adverse cardiac events and greater mortality at a mean of 2.7 years post-surgery.[34] In the CARDIA study, flattened cortisol slopes across 4 time points (e.g., blunted at all time points) were associated with coronary calcification,[35] a risk factor for adverse cardiac events. In contrast, in a secondary analysis of the London-community-based Whitehall II study, only elevated evening salivary cortisol concentrations (rather than blunted morning cortisol levels) were significantly associated with cardiovascular mortality.[33]

The findings have some potential clinical implications. Findings help unravel the mechanisms or biological pathways that might be involved in development of palpitations during the menopause transition. Greater knowledge in this area could help with early detection and/or early prevention. Knowing that women reporting distress from palpitations have blunted morning cortisol levels, which are a marker of cardiovascular disease, is indicative that fully assessing reported palpitations is important.

There were strengths and limitations to this study. In terms of strengths, this was a relatively large sample of peri- and post-menopausal women with a sufficient number reporting palpitations distress. Salivary cortisol values were collected at four time points over two days. Palpitations data were obtained using a self-report item as is common in other studies (see review[36]). Data on vasomotor symptoms, depressive symptoms, stress, and insomnia severity were obtained using well-validated measurement tools. Body mass index and blood pressure were assessed with standardized procedures during study clinic visits. Limitations were sample exclusion of women without vasomotor symptoms, limited racial and ethnic diversity, and dichotomizing the complex symptom of heart palpitations into a "yes", "no" variable. Real time bother related to palpitations at the time of cortisol collection was not available. Future studies could improve the data collection methods.

CONCLUSION

This study suggests that palpitations distress was associated with blunted morning salivary cortisol, which has in turn been associated with increased cardiovascular mortality in some populations. The longer-term cardiovascular consequences of the relationship between menopausal palpitations and blunted morning cortisol response in women warrants further study.

Sources of Funding:

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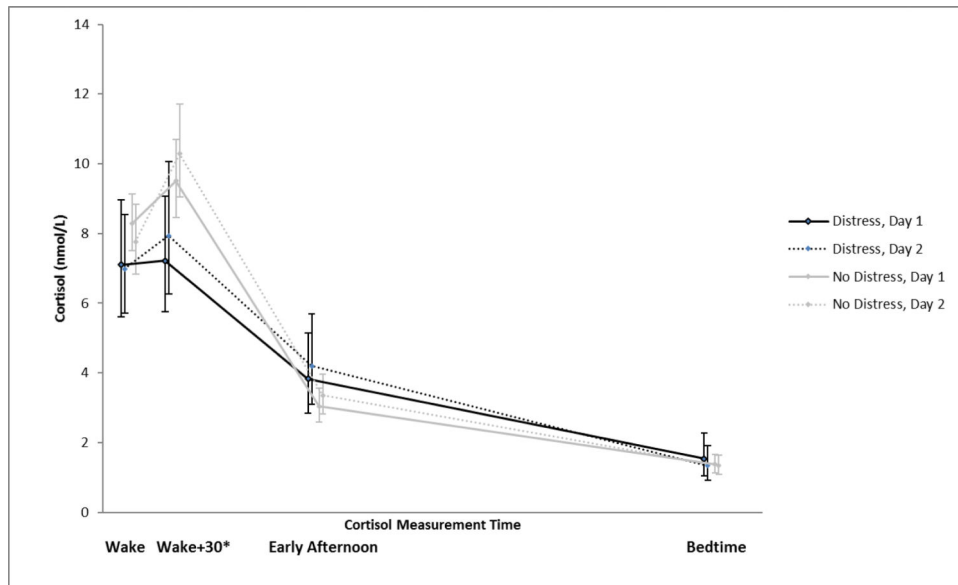
Figure 1.
Geometric Mean Salivary Cortisol Concentrations Over Time by Reported Palpitations Distress

Figure 1 shows mean daily cortisol values by palpitations distress groups at each time point on each of the two assessment days. Both groups showed the expected salivary cortisol diurnal variation (higher morning, lower evening). Compared to the no distress group, the palpitations distress group had significantly lower Wake+30 cortisol values. *p< .05

Table 1.

Frequency Statistics for Demographic and Clinical Characteristics by Reported Distress from Heart Palpitations During the Menopause Transition

	All (n=293)				Distress from palpitations							p [a]
					No (n=217)				Yes (n=76)			
	n	%	M	SD	n	%	M	SD	n	%	M	SD	
Race/Ethnicity													0.17
White	196	66.9			151	69.6			45	59.2			
Black	68	23.2			48	22.1			20	26.3			
Other/Unknown [b]	29	9.9			18	8.3			11	14.5			
Married /partnered	198	67.6			148	68.2			50	65.8			0.70
Employed full-time	178	60.8			135	62.2			43	56.6			0.39
Smoking													0.52
Never	193	65.9			140	64.5			53	69.7			
Past	76	25.9			60	27.6			16	21.1			
Current	24	8.2			17	7.8			7	9.2			
Menopause Status													0.40
Postmenopausal	245	83.6			181	83.4			64	84.2			
Late transition	43	14.7			31	14.3			12	15.8			
Early transition	5	1.7			5	2.3			0	0.0			
BMI (kg/m^2)													0.95
<25	107	36.5			82	37.8			25	32.9			
25 – <30	112	38.2			80	36.9			32	42.1			
30	74	25.3			55	25.3			19	25.0			
Medications [c]	73	24.9			46	21.2			27	35.5			0.01
Age at screening (years)			54.6	(3.6)			54.8	(3.7)			54.1	(3.4)	0.16
Systolic BP (mm Hg)			117.2	(13.6)			116.6	(13.4)			118.8	(14.1)	0.23
Diastolic BP (mm Hg)			72.6	(9.2)			72.4	(9.0)			73.0	(9.7)	0.65
VMS frequency			7.6	(3.9)			7.3	(3.7)			8.4	(4.5)	0.04
PSS Stress			13.8	(7.0)			12.6	(6.9)			17.1	(6.2)	<0.001
PHQ-8 Depression			4.0	(3.7)			3.5	(3.4)			4.0	(4.0)	<0.001

	Distress from palpitations												
	All (n=293)				No (n=217)				Yes (n=76)				p[a]
	n	%	M	SD	n	%	M	SD	n	%	M	SD	
ISI Insomnia			11.6	(5.3)			10.9	(5.0)			13.8	(5.5)	<0.001

[a] p-value comparing participants without distress to those endorsing a little bit, moderately, quite a bit, or extremely distressed from racing or pounding heart in the past two weeks based on Chi-square tests for categorical variables and t-tests for continuous variables.

[b] Other/unknown race/ethnicity in the total sample (n=29) includes 5 Hispanic, 5 American Indian, 12 Asian/Pacific Islander, and 7 unknown race/ethnicity participants. The small numbers of participants in each category precluded a detailed comparison of palpitations by these detailed racial/ethnic group and therefore, participants were combined into one category.

[c] Taking at least one of the following in the past 4 weeks: selective serotonin receptor inhibitor, selective serotonin norepinephrine receptor inhibitor, monoamine oxidase inhibitor, anti-anxiety medication (unspecified), tricyclic antidepressants, St. John's Wort, other medications for anxiety/depression/sleep, gabapentin, pregabalin, selective estrogen receptor modulators, aromatase inhibitors, glucocorticoids.

M=mean; SD=standard deviation; BMI=body mass index; BP=blood pressure; VMS=vasomotor symptoms; PSS=Perceived Stress Scale; PHQ=Patient Health Questionnaire; ISI=Insomnia Severity Index.

Table 2.

Adjusted Models of Cortisol Values by Palpitations Distress

| | | Palpitations Distress | | |
| | | No | Yes | |
	Model	Estimate (95% CI)	Estimate [a] (95% CI)	p [b]
Total AUC[c]	1	1.00 (ref)	−0.13 (−0.35 to 0.09)	0.26
	2	1.00 (ref)	−0.15 (−0.36 to 0.06)	0.17
	3	1.00 (ref)	−0.15 (−0.37 to 0.07)	0.18
Wake	1	1.00 (ref)	−0.11 (−0.31 to 0.08)	0.25
	2	1.00 (ref)	−0.12 (−0.32 to 0.07)	0.21
	3	1.00 (ref)	−0.08 (−0.27 to 0.12)	0.45
Wake + 30	1	1.00 (ref)	−0.26 (−0.47 to −0.05)	0.02
	2	1.00 (ref)	−0.24 (−0.45 to −0.02)	0.03
	3	1.00 (ref)	−0.25 (−0.45 to −0.04)	0.02
Early afternoon	1	1.00 (ref)	0.18 (−0.07 to 0.44)	0.16
	2	1.00 (ref)	0.17 (−0.07 to 0.41)	0.17
	3	1.00 (ref)	0.15 (−0.11 to 0.41)	0.26
Bedtime	1	1.00 (ref)	0.03 (−0.30 to 0.35)	0.88
	2	1.00 (ref)	0.02 (−0.29 to 0.33)	0.91
	3	1.00 (ref)	0.02 (−0.30 to 0.34)	0.90

[a] Estimates, 95% confidence intervals, and

[b] p-values from 15 different repeated measure linear regression models (3 models x 5 outcomes) represent the mean log transformed cortisol difference between participants reporting racing heart distress compared with those not reporting it, after adjustment for other factors as described below.

Model 1: Adjusted for day, clinical center

Model 2: Adjusted for factors in Model 1 + age, race, marital status, full-time employment, smoking, menopause status, body mass index, systolic blood pressure, diastolic blood pressure, vasomotor symptoms

Model 3: Adjusted for factors in Models 1 and 2 + medication use, depression (Patient Health Questionnaire-8), stress (Perceived Stress Scale), and insomnia (Insomnia Severity Index)

[c] Total area under the curve is scaled to the median wake to bedtime, 14 hours

AUC = Area under the salivary cortisol concentration versus time curve; CI = Confidence interval; ref = Reference

Table 3.

Factors Associated with Wake + 30 Cortisol Values Based on Fully Adjusted Model

Variable	Estimate (95% CI)[a]	p-value[a]
Racing heart distress	−0.25 (−0.45 to −0.04)	0.02
Age (5-year increase)	−0.03 (−0.16 to 0.10)	0.67
Race/Ethnicity		0.57
White	1.00 (ref)	
African American	−0.13 (−0.37 to 0.12)	
Other/Unknown[b]	0.02 (−0.22 to 0.26)	
Married / living as married	−0.09 (−0.26 to 0.08)	0.32
Full-time employed	0.02 (−0.16 to 0.19)	0.86
Smoking		0.27
Never	1.00 (ref)	
Past	0.04 (−0.15 to 0.22)	
Current	−0.33 (−0.76 to 0.11)	
Menopause Status		0.13
Early transition	−0.99 (−1.61 to −0.37)	
Late transition	0.03 (−0.19 to 0.25)	
Postmenopausal	1.00 (ref)	
BMI (5 kg/m^2 increase)	0.07 (−0.06 to 0.19)	0.30
Systolic BP (10 mmHg increase)	−0.06 (−0.17 to 0.05)	0.27
Diastolic BP (10 mmHg increase)	0.03 (−0.13 to 0.19)	0.68
VMS/wk (5 event increase)	−0.10 (−0.22 to 0.01)	0.08
Medication use[c]	0.03 (−0.18 to 0.23)	0.79
PHQ-8 Depression (5-point increase)	−0.09 (−0.23 to 0.04)	0.20
PSS Stress (5-point increase	0.05 (−0.03 to 0.12)	0.22
ISI Insomnia (5-point increase)	−0.01 (−0.10 to 0.09)	0.87

[a]Estimates, 95% confidence intervals, and p-values from a repeated measure GEE linear regression model represent the mean log transformed cortisol difference associated with each model variable.

[b]Other/unknown race/ethnicity in the total sample (n=29) includes 5 Hispanic, 5 American Indian, 12 Asian/Pacific Islander, and 7 unknown race/ethnicity participants. The small numbers of participants in each category precluded a detailed comparison of palpitations by these detailed racial/ethnic group and therefore, participants were combined into one category.

[c]Taking at least one of the following in the past 4 weeks: selective serotonin receptor inhibitor, selective serotonin norepinephrine receptor inhibitor, monoamine oxidase inhibitor, anti-anxiety medication (unspecified), tricyclic antidepressants, St. John's Wort, other medications for anxiety/depression/sleep, gabapentin, pregabalin, selective estrogen receptor modulators, aromatase inhibitors, glucocorticoids.

Models are additionally adjusted for day and clinical center.

BMI = Body mass index; BP = Blood pressure; CI = Confidence intervals; ISI = Insomnia Severity Index; PHQ = Patient health Questionnaire; PSS = Perceived Stress Scale; ref = Reference; VMS = Vasomotor symptoms (e.g., hot flashes, night sweats); wk = week. Higher mean values on VMS, PSS, PHQ-8, and ISI indicate greater symptoms.