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Cortisol and Depressive Symptoms in a Population-Based Cohort of Midlife Women

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Abstract

Objective—To determine whether there is a relationship between depressive symptoms and cortisol assessed at first morning awakening, 6PM, and 9PM in a population-based sample of midlife women. If this relationship is not linear, we aim to test whether this relationship is nonlinear, only present in those with more severe depressive symptoms, better accounted for by diurnal slope, or only apparent under uncontaminated conditions.

Methods—We investigated the cross-sectional association between cortisol and depressive symptoms, assessed by the Center for Epidemiological Studies Depression Scale (CES-D) in 408 midlife women (45.7% African-Americans, 54.3% white; mean age = 50.4) participating in the Chicago site of the Study of Women's Health Across the Nation (SWAN).

Results—Diurnal cortisol slope is significantly flatter for women with higher CES-D scores than for less depressed women ($p < .05$ for the interaction). This relationship remains significant even after adjusting for age, smoking status, race, education, income, menopausal status, hormone replacement therapy (HRT), body mass index (BMI), medications, and wake time as well as possibly contaminating factors including physical activity, smoking, eating, or caffeine or alcohol consumption prior to saliva collection. Results using depression assessed categorically (CES-D cutoff ≥ 16) were similar to those using continuous depression in both unadjusted and adjusted analyses ($p = .005$ for the interaction of CES-D by time).

Conclusions—In this population-based sample of midlife women, greater depressive symptoms were associated with a significantly flatter diurnal cortisol slope than those with fewer symptoms, even after adjusting for covariates and possibly contaminating behaviors.

Keywords

diurnal cortisol; depressive symptoms; midlife women; women's health

INTRODUCTION

Hypercortisolism is a well-established correlate of severe depressive states (1-4). Earlier studies noted that patients with severe depressive illness exhibited hypercortisolism, particularly in the late evening or early morning, that was resistant to dexamethasone

suppression (5-7). Significant associations have been demonstrated in samples that compare only those with severe depression to controls (8) as well as those that look only at depressed patients (9,10).

However, the literature examining the relationship between depressive symptoms and cortisol is inconsistent, with some studies demonstrating no significant association at all (11-16). The characterization of hypothalamic-pituitary-adrenal (HPA) axis dysfunction is complicated and affected by a multitude of variables, thus providing an explanation for this observed inconsistency. Moreover, studies that include people with underlying mental health disorders (8,17) tend to find this effect more often than those involving subjects without these issues (12,18).

There are a number of reasons this inconsistency could exist. Alternatively, the relationship between depressive symptoms and cortisol may not be linear. Later life depression has been shown to be associated with both hypo- and hypercortisolemia without the presence of a main effect for depression (11,19).

There are distinct ways to evaluate cortisol levels, including at various time points throughout the day (17), as a response to awakening (12,13,18), expressly at morning or evening times (20), or as the diurnal slope (14). Due to the variation in cortisol levels over the course of the day, assessing it based on its change over time, or slope, may be a more comprehensive approach. Diurnal cortisol fluctuations are being increasingly used as a marker for depressive symptoms (21-23) with recent evidence suggesting altered diurnal secretion of cortisol as a possible endophenotype of depression and indicator of depression susceptibility (24).

Studies evaluating the relationship between depression and cortisol use a wide range of cortisol sampling techniques with inconsistent findings. These techniques include urinary (15,25), salivary (12,16,17) and serum (8,20) samples measured at different times. These varying collection techniques have not yielded a clear consensus about which is most valid. Additionally, collection technique varies between home collection (16) versus the laboratory setting (20) where variables can be more tightly controlled. In the home setting, extraneous factors such as smoking, caffeine, alcohol, food intake, and exercise, if they closely precede salivary sampling, could affect the relationship.

Finally, variations in characteristics of the sample, including such characteristics as physical activity, smoking, age, income, education, race, menopausal status, use of hormone replacement therapy, body mass index (BMI), sleep, and medications affect cortisol levels. Failure to account for these variables as covariates in analyses could affect the consistency of observed associations (26,27).

The purpose of this study was to determine whether there is a relationship between depressive symptoms and cortisol assessed at first morning awakening, 6PM, and 9PM in a population-based sample of midlife women. If this relationship is not linear, we aim to test whether this relationship is nonlinear, only present in those with more severe depressive symptoms, better accounted for by diurnal cortisol slope, or only apparent under uncontaminated conditions.

METHODS

Participants

Participants were 408 women (45.7% African-American; 54.3% White) from the Chicago site of the Study of Women's Health Across the Nation (SWAN) who were participating in

an ancillary study of the impact of menopause on accumulation of visceral adipose tissue (SWAN Fat Patterning Study). SWAN is an ongoing longitudinal study conducted at seven clinical sites of women transitioning through menopause. Eligibility was determined and initial data on socioeconomic, demographic, lifestyle, and health factors were collected via telephone and in-person screening surveys at all sites from November 1995 through October 1997. By design, the Chicago site recruited only non-Hispanic white and black women. A unique feature of the Chicago SWAN site is that it is a population-based design, which drew on a complete community census to recruit a sample of black and white women with a 72% participation rate. These women were recruited in a way that featured comparability on socioeconomic status (SES) within the black and white women, thus minimizing any confound between ethnicity and SES. Details of SWAN recruitment have been reported previously (28,29).

Women were enrolled in the SWAN Fat Patterning Study between August 2002 and December 2005 coincident with their annual SWAN follow-up visits. To be eligible for this ancillary study, women had to have no history of diabetes, chronic liver or renal disease, anorexia nervosa (self-report), hysterectomy and/or bilateral oophorectomy, or alcohol or drug abuse. They were also not currently pregnant or planning to become pregnant. Equipment limitations precluded participation of women with breast implants, hip replacements, or weighing ≥ 299 pounds. Seventy-seven percent of eligible Chicago SWAN participants enrolled in the Fat Patterning Study. Since the menopausal transition was under investigation for the Fat Patterning Study and many of the initial participants were already post-menopausal when the ancillary study began, additional subjects who had yet to complete the menopausal transition were recruited. Thus, 138 women (65% of eligible) who were screened for the original SWAN recruitment but were too young to participate in 1996 were recruited to the Fat Patterning Study. These newly recruited women were younger but did not differ in depressive symptoms, BMI, education, or age-adjusted total fat or visceral adipose tissue from previously recruited women. The final cohort included 435 women (199 African-Americans; 236 Whites). Missing data on depressive symptoms ($n = 22$) and all cortisol levels ($n = 5$), left 408 women (196 African-Americans, 212 Whites) for the current analyses.

Protocol

At entry into SWAN and annually thereafter, all participants completed a standard protocol, with self- and interviewer-administered questionnaires about psychosocial and lifestyle factors, health status, medical history and medication use, menstrual status and symptoms. Full details of the SWAN protocol have been reported previously (29). Covariates of interest for the present analyses were measured during the annual SWAN assessment coincident with recruitment to the Fat Patterning Study. The 138 women recruited specifically for the Fat Patterning Study completed the full SWAN protocol, including all measurements obtained for the annual SWAN visit.

The Rush University Medical Center Institutional Review Boards approved all aspects of the study and all women provided their written informed consent.

Study Measures

Depressive Symptoms—Depressive symptoms were measured continuously according to the Center for Epidemiologic Studies-Depression (CES-D) Scale (30). Subjects were considered to have significant depressive symptoms if they had a CES-D score of 16 or higher and they were considered to have severe depressive symptoms if they had a score of 24 or higher (31). The CES-D value from the closest preceding SWAN core visit to the baseline fat patterning cortisol sample was used. 92% of the CES-D values were collected

no more than 4 months prior to cortisol sampling, and none were collected more than one year prior.

Cortisol Measurements—Participants were instructed to collect home salivary cortisol samples after their SWAN baseline fat patterning visit. They were instructed to collect saliva at 6PM and 9PM that evening and again the following day immediately upon awakening.

All samples were sent to the Kirschbaum laboratory in Germany for quantification. Free cortisol was assayed from saliva centrifuged to obtain a clear specimen of low viscosity. Cortisol levels were then quantified by radioimmunoassay with time-resolved fluometric detection (32). Inter- and intra-assay coefficients of variation were <10% and <8%, respectively.

Covariate Measurements—Covariates were obtained from the SWAN core visit and included age, BMI, education, income, race, menopausal status, use of hormone replacement therapy, medications, and smoking. Education was categorized as having had post-high school training or not. Income was categorized as less than \$20,000, \$20,000-\$50,000, and greater than \$50,000. Menopausal status was divided into four categories for consideration: 1) Premenopausal - regular bleeding, 2) Early perimenopausal - irregular bleeding with bleeding in the last 3 months, 3) Late perimenopausal – bled in the last 3-12 months, and 4) Postmenopausal – no bleeding in the last 12 months.

Subjects maintained a “saliva diary” that included the actual time cortisol samples were taken as well as whether and what time subjects were physically active, drank caffeine or alcohol, smoked, or ate. These variables were analyzed individually with the other covariates as well as packaged together as “contaminating factors” for analysis purposes in order to assess their ability to directly affect the actual cortisol sampling. Wake time was also obtained via the diary but was only used as a covariate, not contaminating factor. All 15 covariates above were used for the adjusted models.

Analyses

Graphical and descriptive statistics confirmed that the cortisol concentrations at all three time points did not follow a normal distribution and were heavily skewed with a long right tail; transformation by natural logarithm normalized the three distributions. All further analyses used these transformed cortisol levels. Univariate statistics were computed for continuous variables and evaluated for consistency with a normal distribution. Means (SD) were used to describe normally distributed variables such as age and body mass index. Median and interquartile range (difference between 75th and the 25th percentiles) were used to characterize variables with highly skewed distributions. Frequencies were determined for categorical variables.

We used t-tests and chi square tests ($p < .05$) to evaluate differences between women with depressive symptoms and those without for population descriptors and potential covariates. To investigate the hypothesis that cortisol levels at any one time point (morning, 6pm, 9pm) vary with increasing depressive symptoms, we used linear regression models of the (log transformed) cortisol levels with continuous depression (CES-D) as the only predictor at each separate time point. To test for a non-linear relationship, quadratic and cubic terms of the continuous depression value were added to the regression models of cortisol at the three collection points. Linear models were adjusted using backward variable selection for age, education, physical activity, smoking status, race, menopausal status, hormone replacement therapy, steroid and antidepressant use. Variables significant with a liberal p-value of $< .15$ were retained. After that set of covariates was identified, use of cigarettes, caffeine, alcohol, exercise and food intake before the cortisol collection that day were adjusted for as a single

indicator variable. To investigate the hypothesis that cortisol levels for women with higher levels of depressive symptoms were greater than those with lower levels, we compared the log transformed cortisol levels at each collection time with a t-test. In addition to the well-established cut-point of 16, we also used a score of 24 as an cut-off for more severe depressive symptoms.

To investigate the difference in diurnal slope associated with different levels of depressive symptoms, we treated the morning collection value as if it was collected on the same day as evening cortisol measures. Time of collection was taken as hours from awakening to collection of cortisol levels. We used a mixed effects regression model with a random intercept and random time variables. This type of model allows for a woman-specific intercept and slope and the assessment of an overall trend. We included a time by CES-D score interaction to investigate the difference in the diurnal slope. We adjusted this model for hours from mean wake time to account for difference in sleep patterns. We used stepwise backward selection to identify significant predictors of the diurnal cortisol slope from a list of variables identified in the literature (education, physical activity, smoking status, race, menopausal status, hormone replacement therapy, steroid and antidepressant/anxiolytic use). Variables significant with a liberal p-value of $<.15$ were retained. Secondary analyses used the dichotomous CES-D as a predictor. These results were very similar to the continuous depression scores. We therefore only present a graphic summary.

RESULTS

Table 1 presents the baseline characteristics of the 408 women participating in the study overall and comparing CES-D ≥ 16 and CES-D < 16 . There were significantly more smokers ($p<.001$), African-Americans ($p=.009$), and lower income people ($p=.005$) in the higher CES-D group. No other differences were detected between the two groups.

Table 2 demonstrates that women with higher levels of depressive symptoms had significantly higher mean levels of cortisol at 6PM ($\beta = .014$, $p<.05$) in the unadjusted linear regression. Depressive symptoms were not found to be predictive of morning or 9PM cortisol levels. This model using depressive symptoms measured continuously was rerun for the 6PM cortisol level using the aforementioned covariates in a backwards stepwise linear regression model. The relationship between cortisol and depression failed to hold after adjustment for smoking and education ($p=.13$ for CES-D, $p<.05$ for smoking). The relationship between cortisol concentrations at the three time points and depressive symptoms, using CES-D as a categorical variable (CES-D ≥ 16 vs CES-D < 16), was examined using a t-test for the unadjusted comparisons and linear regression models for the adjusted models and revealed the same pattern of results.

Quadratic terms were added to the linear models in order to assess a curvilinear relationship between CES-D and cortisol levels at any time point but no curvilinear relationship was detected.

No significant difference at $p=.05$ level was found between those who have severe depressive symptoms (CES-D ≥ 24 , N=19) and those who have less severe depressive symptoms (CES-D < 24). Cortisol levels at the 6PM collection time were marginally lower in the more depressed group ($p<.10$).

Diurnal Cortisol Slope

Table 3 shows the results of the mixed effects regression models to test the hypothesis that the pattern of cortisol over time differs by depressive symptoms as a continuous variable. The basic model on the left shows that in the unadjusted analysis, there is a significant

overall decrease in cortisol from morning to night ($\beta = -0.138$, $p < .001$). With every increase in CES-D by 1 point, the slope flattens, as indicated by the interaction between CES-D and time ($\beta = 0.001$, $p = 0.02$). Figure 1 presents this interaction graphically. Results were very similar in adjusted analyses. Results were also very similar in analyses using the dichotomous CES-D score, as Figure 2 illustrates.

Contamination Factors

The significant continuous (Figure 1) and categorical (Figure 2) relationships between CES-D and diurnal cortisol slope remained significant with the addition of contaminating factors to the model. There was no interaction of contamination and CES-D score ($p = .60$).

DISCUSSION

Due to the inconsistency in the literature regarding the relationship between cortisol and depressive symptoms (11-16), we aimed to understand this association better by studying a large, population-based sample of midlife women. We found that the diurnal slope of salivary cortisol was strongly and independently associated with depressive symptoms in these midlife women. This is a novel finding given that this is a large, generalizable, non-clinical, and community-based epidemiologic sample.

The results of the current study are significant for several reasons. First, they are biologically plausible. Support for this association has been provided by clinical studies aimed at developing hypotheses about the etiology and pathogenesis of depression (33). Of particular relevance is the hypothesis that depression involves changes in the set point of the HPA system, resulting in altered regulation of cortisol secretory activity via changes in corticotropin-releasing hormone (34). The suprachiasmatic nucleus (SCN) is one possible mediator of this diurnal cortisol-depression relationship. The SCN is the hypothalamic clock responsible for the rhythmic changes of the stress system, and it appears to have decreased activity in depression (33). It also has CRH fibers (33), demonstrating an innate hard wiring for a link between depression, corticosteroids, and diurnal variance. Complex systemic dysregulation involving increased CRH and impaired corticosteroid receptor signaling (34) may be clinically manifest as impaired diurnal cortisol variation with depression, as we see with our cohort.

Our study also provides a naturalistic, population-based investigation of cortisol response as opposed to more tightly controlled experimental samples (6,19) or clinical populations (8,17,25). As noted by Breslau, the suspected association between a disease and a characteristic may be most pronounced in, and often comes from, clinical samples, however, the validity of this association frequently comes from its replication in epidemiological studies (35).

Since cortisol is sensitive to, and affected by, a multitude of extraneous influences (36), measuring cortisol reliably in a population-based sample is especially challenging. Our findings indicate that the association with depressive symptoms is not altered by specific behaviors at the time of saliva sampling that may contaminate the cortisol specimen. It is important to identify reliable, rigorous, low cost, and minimal burden physiologic markers of psychosocial stressors for use in large-scale epidemiologic studies (37). We have shown that with only three cortisol samples collected at home over the course of a day we can obtain a slope that demonstrates a valid association with depressive symptoms.

Diurnal cortisol is a reliable marker for depressive symptoms even under the influence of the myriad of variables inevitably present in a population-based sample, including differences in

sociodemographic factors as well as health and lifestyle behaviors. This supports the independence of the relationship from other known predictors.

Interestingly, the flattened diurnal cortisol slope we found possesses different characteristics than some cortisol rhythm disturbances previously demonstrated. Early timing of the nadir of ACTH-cortisol secretion has been demonstrated in major depressive disorder (38) and steeper, more rhythmic cortisol slopes driven by elevated morning cortisol has been shown in depressed women with metastatic breast cancer (23). Our findings, however, illustrate that the dominant effect characterizing flattened cortisol slope seems to be a lower morning cortisol level, which is related in a dose-dependent way to depressive symptoms and does not result in an overall hypercortisolemic state. CES-D scores in this relatively healthy population may reflect less obvious symptomatology than clinical depression, and this blunted or reduced morning rise may be a more subtle, initial sign. In this study of community participants, it appears that a blunting of the diurnal cortisol rhythm is a more sensitive indicator of depression than elevated salivary cortisol levels. Due to the complex and likely bidirectional interaction of cortisol and depressive symptoms, it is difficult to comment on its clinical significance in particular, however, its physiological significance is noteworthy given the disparate findings from previous research.

There may be variation in phenotypes underlying the mechanisms linking psychological processes to health and disease. It has been demonstrated that age, gender, and severity of psychological distress may have varying physiologic manifestations (9). Certain medical comorbidities may also affect this association as flatter diurnal cortisol slope has been found in depressed people with memory problems (21) as well as depressed people with coronary artery disease (22). Understanding these various phenotypes is crucial to targeting populations at risk for adverse health consequences of psychological distress.

Finally, our study population is of clinical importance as midlife women in the late stage of the menopausal transition are particularly vulnerable to depressed mood (39), with suggestive data that estrogen deficiency (40) as well as an increasingly testosterone dominated milieu (41) may contribute to this increased susceptibility. Combined with the loss of protective cardiovascular sex hormones during this time period (42) as well as already lower bone mineral density in premenopausal women with depression (43), this particular population is especially susceptible to adverse physiological effects of depression.

There are several limitations to this study. We had a relatively small number of depressed subjects in this population-based sample. However, given that the diurnal cortisol slope has a strong association with depressive symptoms even with this small number, it does not appear to have affected results. While we have awakening times and information on overall sleep problems, we do not have specific information about sleep from the night preceding morning cortisol measurements. It would be interesting to see whether sleep patterns the night before demonstrate an association with cortisol. Nor do we have overnight cortisol levels that, despite its impracticality, would be interesting to have and see whether depressive symptoms affected very early morning cortisol response. Finally, our CES-D and cortisol assessments were separated in time by as many as a few months, which may not be the traditional nature of how this relationship is usually examined. If this in fact introduced error, the direction of bias would be in the null, however, this is not what we found, lending further strength to the relationship we observed. It is unclear whether a flattened diurnal cortisol slope represents a persistent state characteristic of depression or whether this may be more consistent with a trait characteristic. Further studies investigating the temporal relationship between these variables are needed.

Future research should focus on clarifying its clinical significance and determining whether alteration in diurnal cortisol slope may be associated with adverse health consequences observed in depressed individuals (44). Everson-Rose et al recently showed that increased visceral fat may be one pathway by which depression contributes to excess risk for cardiovascular disease and diabetes (45); it would be meaningful to examine whether diurnal cortisol slope is a mediator in this relationship.

In conclusion, midlife women from a population-based sample with higher CES-D scores have a significantly flatter diurnal cortisol slope than those with lower scores, even after adjusting for covariates and possibly contaminating behaviors. Further research is needed to examine the health implications of this association.

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Abbreviations

HPA	hypothalamic-pituitary-adrenocortical
BMI	body mass index
SWAN	Study of Women's Health Across the Nation
SES	socioeconomic status

CES-D	Center for Epidemiologic Studies-Depression
SCN	Suprachiasmatic Nucleus
CRH	Corticotropin-Releasing Hormone

Figure 1.

Graded association of depression and the diurnal slope of cortisol after adjustment for all covariates. The interaction of CES-D by time is significant ($p<.05$) using the continuous version of the CES-D.

Figure 2.

Average diurnal slope of cortisol for depressed and non-depressed women after adjustment for all covariates. The slope is significantly steeper ($p=.005$ for the interaction of CES-D by time) for women with CES-D<16 than for more depressed women.

Table 1

Baseline Characteristics of the Cohort

	All N = 408	CESD $\geq$ 16 N = 56	CESD < 16 N = 352	p-value *
Age, mean (Std)	50.4 (3.8)	50.4(3.6)	50.4 (3.8)	.94
Smoker, N(%)	82 (20.1)	22 (39.3)	60 (17.0)	<.001
African American, N(%)	196 (45.7)	34 (60.7)	148 (42.0)	.009
Education $\leq$ HS, N(%)	44 (11.1)	7 (13.2)	37 (10.8)	.61
Income, N(%)				.005
< \$20,000	28 (7.0)	8 (15.1)	20 (5.8)	
\$20,000-\$50,000	64 (16.1)	13 (24.5)	51 (14.8)	
>\$50,000	305 (76.8)	32 (60.3)	273 (79.4)	
Menopausal Status, N(%)				.96
Surgical	22 (5.4)	3 (5.4)	19 (5.4)	
Post	147(36.0)	19 (33.9)	128 (36.4)	
Late Peri	33 (8.1)	3 (5.4)	30(8.5)	
Early Peri	136(33.3)	21(37.5)	115(32.7)	
Pre	48 (11.8)	7(12.5)	41(11.7)	
undetermined	22 (5.4)	3(5.4)	19(5.4)	
Uses hormones, N(%)	45 (11.0)	8 (14.3)	37 (10.5)	.40
Corticosteroid Use, N (%)	11 (2.7)	0 (0.0)	11 (3.1)	.18
Antidepressant Use, N(%)	44 (10.8)	12 (21.4)	32 (9.1)	.006
BMI, mean (std)	29.2 (6.4)	29.9 (6.7)	29.0 (6.3)	.32
Ate before 6 pm, N(%)	240 (58.8)	30 (53.6)	210 (59.7)	.39
Ate before 9 pm, N(%)	341 (83.6)	47 (83.9)	294 (83.5)	.94
Exercised before 6 pm, N(%)	28 (6.9)	3 (5.4)	25 (7.1)	.63
Exercised before 9 pm, N(%)	5 (1.2)	1 (1.8)	4 (1.1)	.68
Caffeine before 6 pm, N(%)	100 (25.7)	20 (37)	80 (23.9)	.04
Alcohol before 6 pm, N(%)	70 (17.9)	9 (16.4)	61 (18.1)	.76
Smoking after 5 pm, N(%)	76 (19.4)	21 (38.2)	55 (16.3)	<.001
Wake time	06:53 AM	07:08 AM	06:50 AM	.16

* t-tests was used for normally distributed variables and chi square tests for frequencies

Table 2

Multivariate Correlates of Cortisol at Three Separate Times (Morning, 6PM, and 9PM)

	Morning			6 pm			9 pm		
	Unadjusted β est.	Adjusted β est.	p-value	Unadjusted β est.	Adjusted β est.	p-value	Unadjusted β est.	Adjusted β est.	p-value
CESD ^a	-.010	.156	.44	.014	.009	.13	.004	-.002	.67
Income < \$20,000		-.044	.82		-	-		-	-
Income \$20,000 - \$50,000		-.293	.03		-	-		-	-
African American		-.138	.18		-	-		.419	<.001
Smoker		-	-		.228	.04		.346	.005
Education $\leq$ HS		-	-		.240	.08		-	-
Age		-	-		-	-		.028	.058
Alcohol consumed prior to cortisol sampling that day								-.194	.14
Post Menopausal								-.150	.18

Estimates are beta coefficients from linear models

^a CES-D measured continuously

Table 3

Multivariate Correlates of Cortisol Slope

Variable	Unadjusted		Adjusted**	
	β est.	p-value	β est.	p-value
Intercept	2.644	<.001	2.610	<.001
CES-D ^a	-0.010	0.13	-0.013	0.055
Time	-0.138	<.001	-0.139	<.001
Time* (CES-D)	0.001	0.02	0.001	0.02
Wake time from 7 AM	-	-	0.018	0.42
Smoker	-	-	0.135	0.11
African American	-	-	0.109	0.10
Contaminated	-	-	-0.035	0.59

Estimates are beta coefficients from mixed models

^a CES-D measured continuously

** Adjusted for age, smoking status, race, education, income, menopausal status, HRT, BMI, wake time, medications as well as physical activity, smoking, eating, or caffeine or alcohol consumption prior to saliva collection as indicated by "saliva diary"