ORIGINAL PAPER

International Journal of Occupational Medicine and Environmental Health 2015;28(1):120–129
http://dx.doi.org/10.13075/ijomeh.1896.00208

# NO ALTERATIONS IN DIURNAL CORTISOL PROFILES BEFORE AND DURING THE TREATMENT IN PATIENTS WITH STRESS-RELATED EXHAUSTION

**ANNA SJÖRS[1,2] and INGIBJÖRG H. JONSDOTTIR[1,3]**

[1] The Institute of Stress Medicine, Gothenburg, Sweden
[2] Linköping University, Linköping, Sweden
Department of Medical and Health Sciences, Rehabilitation Medicine
[3] University of Gothenburg, Gothenburg, Sweden
Sahlgrenska Academy, Institute of Neuroscience and Physiology

**Abstract**
**Objectives:** Several theories have emerged in recent years suggesting that neuroendocrinological alterations, mainly changes in cortisol, could be of importance with respect to the link between chronic stress and disease. This study investigated possible deviations in the diurnal cortisol profiles of patients with clinically diagnosed stress-related exhaustion (exhaustion disorder – ED) compared with healthy controls. **Material and Methods:** Salivary cortisol samples taken at home in the morning directly after waking up, 30 min later, and in the evening were compared between ED patients (N = 122; 25% men) and healthy controls (N = 98; 44% men). Follow-up measurements were performed after 6 months (79 patients) and 12 months (68 patients) of the treatment. **Results:** There were no clear differences in diurnal salivary cortisol profiles between the patients and healthy controls. Moreover, salivary cortisol levels and diurnal profiles did not change significantly during the treatment in the patient group. There was some indication of a smaller cortisol awakening response in the male patients compared to the male controls, but the difference appeared to be mainly related to the antidepressant use. **Conclusions:** Diurnal salivary cortisol profiles, at least as measured in this study, give a rather poor reflection of the prolonged stress exposure experienced by patients with ED. Such basal salivary cortisol measurements do not seem suitable as biomarkers for stress-related conditions such as ED or burnout, or as an aid to assess the effects of prolonged stress load in a routine clinical practice.

**Key words:**
**Burnout, Follow-up, Hypothalamus-pitutiary-adrenal axis, Longitudinal study, Salivary cortisol**

## INTRODUCTION

Physiological mechanisms underlying various stress-related conditions are not yet well understood and large efforts are made to find biological markers of stress. The largest focus in this context has been on the hypothalamic-pituitary-adrenal axis (HPA axis), particularly the hormone cortisol. Several theories have emerged suggesting that cortisol is a critical biological intermediary in the link between stress and a disease [1]. An increased level of cortisol due to prolonged stress exposure is thought to cause tissue damage and dysregulation of biological systems. However, models viewing stress-related declines in cortisol level as potentially detrimental have also emerged [2,3].

Although cortisol is a useful marker of acute stress, its applicability as a marker of chronic stress is not as straightforward. As of today, no "gold standard" biological marker

Received: January 30, 2014. Accepted: August 31, 2014.
Corresponding author: A. Sjörs, The Institute of Stress Medicine, Carl Skottsbergs gata 22B, SE-41319 Gothenburg, Sweden (e-mail: anna.sjors@vgregion.se).

of chronic stress has yet been identified. There are currently no laboratory tests available to aid in the diagnosis and evaluation of stress-related conditions such as burnout. Nevertheless, cortisol samples seem to be frequently taken in primary and occupational health care as a rather unspecific measure of 'stress level.'

A recent meta-analysis has found 14 studies on salivary cortisol and burnout, of which 8 were case-control studies and 6 were studies that divided subjects into subgroups based on high or low burnout scores [4]. They have concluded that there was no difference in the cortisol awakening response (CAR) between the patients with burnout and the controls. In an earlier meta-analysis by Chida and Steptoe [5], a negative association has been found between CAR and fatigue, burnout or exhaustion. However, the full diurnal profiles of cortisol secretion have not been addressed in those meta-analyses. There are some indications that cortisol deviations later in the day could be of importance in burnout [6–8].

Danhof-Pont et al. [4] have suggested that future studies should include more well-defined patient groups and take on longitudinal approaches, including measurements before and after the treatment. Two studies have previously investigated the longitudinal development of diurnal cortisol in burnout patients and have found no significant changes in morning cortisol over time [9,10], but have found some indications of decreased daytime cortisol levels after the treatment [9]. Since alterations in HPA-axis activity are still believed to play an important role in the pathophysiology of stress-related conditions such as burnout, further studies on this topic are needed.

The aim of this study was to investigate if there are deviations in the diurnal cortisol profiles of the patients with a clinically diagnosed stress-related condition compared with healthy controls and to follow cortisol levels during the treatment. We recruited patients with Exhaustion Disorder (ED). Exhaustion Disorder, unlike other stress-related conditions such as burnout, has clearly defined diagnostic criteria [11]. There is, however, a considerable overlap between ED and clinical burnout, and practically all patients with ED could be also interpreted as suffering from burnout [12]. Exhaustion Disorder is defined as physical and mental exhaustion experienced for at least 2 weeks, caused by exposure to 1 or more stressors for a minimum of 6 months. Cardinal features are: markedly reduced energy, impaired cognitive functioning and a reduced capacity to meet demands. We have previously reported no differences between ED patients and controls in the cortisol response from awakening to 15 min later [13]. In the present study, the sampling protocol was extended to cover the diurnal cortisol secretion more fully i.e., over 2 consecutive days. Additionally, follow-up measurements were performed after 6 and 12 months of the treatment.

## MATERIAL AND METHODS

### Participants

The patients included in this study were selected from 178 consecutive patients (40 men, 138 women) admitted to the Institute of Stress Medicine, Gothenburg, Sweden between January 2009 and December 2011. All the patients fulfilled the diagnostic criteria for ED as previously described by Jonsdottir and co-workers [14], and had a maximal duration of sick leave of 6 months. Patients with a severe psychiatric disease or a somatic disease that could explain the ED symptoms were not admitted to the clinic.

Symptoms of co-morbid depression and/or anxiety were screened for by using the one-page Primary Care Evaluation of Mental Disorders questionnaire [15], and this was followed up by a physician using a structured interview form conforming with the DSM IV criteria for diagnostic assessment of mood and anxiety disorders. Approximately 6% of the patients did not have a co-morbid condition, whereas 13% of them had anxiety, 8% had depression, and 72% had both anxiety and depression.

The patients received an individually adapted multimodal treatment and follow-up during 18 months at the clinic

as described by Glise et al. [12]. The basics in the treatment program for all the patients were regular visits to a physician with an interval of 4–6 weeks. An important part of these visits was a revision of lifestyle habits such as sleep, meals and physical activity, and these lifestyle topics were repeatedly discussed. All the patients were also offered to enter an 8-week stress reduction group program, as well as a 2-h lecture, teaching the patients the basics concerning stress and the consequences of chronic stress exposure. Cognitive behavioural group therapy for insomnia and/or a recommendation to visit a psychologist for individual psychotherapy were other treatment methods. Antidepressant medication was offered or adjusted when needed.

All the patients that provided analyzable saliva samples for their 1st visit at the clinic were included in this study (N = 122). These patients were representative of all the patients admitted to the clinic regarding age, body mass index (BMI), waist hip ratio (WHR), physical activity level, antidepressant use, co-morbidities, symptom duration, or symptom severity according to the Shirom Melamed Burnout Questionnaire (data not shown).

Ninety-eight healthy controls (55 men, 43 women) were recruited from an ongoing longitudinal cohort study in the Västra Götaland Region, Sweden [16]. Inclusion criteria for controls were, as follows: self-reported good health (i.e., no known somatic or psychiatric disease), age 25–50 years and body mass index (BMI): 18.5–30.

Both the patients and healthy controls underwent a screening examination, including anthropometric measurements and blood samples to assess the following exclusion criteria: current infection, pregnancy, breastfeeding, medication with substances having systemic effects (except for antidepressants for the patients), vitamin B12 deficiency and excessive consumption of alcohol. Physical activity level was assessed with a single choice question developed by Saltin and Grimby [17]. The participants reported the level that best corresponded to their physical activity during the last 3 months: 1) mostly sedentary; 2) light physical activity at least 2 h a week; 3) moderate physical activity at least 2 h a week; 4) intense physical activity at least 5 h a week. In this study, levels 3 and 4 were merged.

The study was approved by the Regional Ethical Review Board in Gothenburg, Sweden, and was conducted in accordance with the Declaration of Helsinki. All the participants included in the study gave their written informed consent.

**Cortisol measurement protocol**

For assessment of the individual diurnal cortisol profile, saliva samples were collected at home on 2 consecutive days. The participants were free to choose 2 typical weekdays, representative of their everyday life. Samples were taken immediately after waking up, 30 min later and at bedtime using Salivette tubes (Sarstedt, Nümbrecht, Germany). The participants were instructed not to brush their teeth, eat or drink anything 30 min before taking a sample. They noted each sampling time in a protocol accompanying the sampling tubes. Samples taken within 15 min from the awakening sample or more than 45 min after the awakening sample were discarded due to non-adherence to the protocol. Female participants were instructed to perform the saliva collection between day 5 and 10 in the menstrual cycle. The same procedure was repeated after 6 and 12 months. The healthy controls collected saliva samples on one day and no follow-up measurements were performed.

Salivette tubes were stored at –20°C until free cortisol levels in saliva were analyzed by the Laboratory for Clinical Chemistry, Sahlgrenska University Hospital using a competitive radioimmunoassay (Spectria Coated Tube Radioimmunoassay, Orion Diagnostica, Espoo, Finland). The limit of detection was 1 nmol/l and the coefficient of variance was below 15%.

Measures of cortisol awakening response (CAR) were obtained by computing the difference between the 2nd and the 1st morning samples. The cortisol decline over

the day (CDD) was calculated as a difference between the 2nd morning sample and the evening sample.

Mean values of the 2 consecutive sampling days were applied in the statistical analyses, for the 3 time points over the day as well as for CAR and CDD.

### Data analyses

Student's t-tests and Chi$^2$ tests were used to compare demographics and questionnaire scores between the patients and controls.

Salivary cortisol concentrations were compared between the patients and controls using the repeated measures analysis of variance (ANOVA). Time of the day (awakening, +30 min and evening) was applied as the repeated factor, in addition to the between-subjects factor group belonging (patient or control) and the time of the day × group interaction effect. Correction of degrees of freedom according to the Greenhouse-Geisser procedure (ε) was performed whenever sphericity was violated. Effect sizes were calculated for significant results by partial eta squared ($\eta^2$), expressing the amount of variance explained in the dependent variable by the respective effect. To elucidate possible changes in salivary cortisol concentrations during the treatment, in the patient group, additional repeated measures ANOVAs were performed with the within-subjects factors time of the day and follow-up (inclusion, 6 months and/or 12 months).

Age, sex, BMI, WHR, physical activity and antidepressant use were considered as potential confounders. These were included as covariates in the analyses if they were related to the outcome measure salivary cortisol, and if they differed between the patients and controls.

Cortisol awakening response and CDD were compared between the patients and controls using the Student's t-tests.

All statistical analyses were performed using SPSS, version 21 (IBM SPSS Inc.). A p value of $< 0.05$ was considered statistically significant. Results are generally presented as mean values and standard deviations (M±SD).

## RESULTS

Figure 1 presents a flow chart of the patients enrollment. Characteristics of the participants are shown in Table 1.

Sex, physical activity and antidepressant use were confounders and, therefore, they were included in the analyses as covariates. Age, BMI and WHR were not related to cortisol and/or group belonging and, therefore, were not considered to be confounders. The results presented below come from both uncorrected and corrected tests.

### Comparison of the patients and controls

Both the patients and controls showed a significant change in cortisol concentrations during the day (Figure 2, time of day effect in Table 2). There was, however, no significant difference between the patient group and the control group in cortisol level (main effect of group) or diurnal profile (time of the day × group interaction effect). Twenty-five patients (20%) and 16 controls (16%) had a negative CAR and excluding these participants did not alter the result.

Time of the day × group interaction effect became statistically significant after controlling for sex, but was not statistically significant after controlling for physical activity and/or antidepressant use (Table 2).

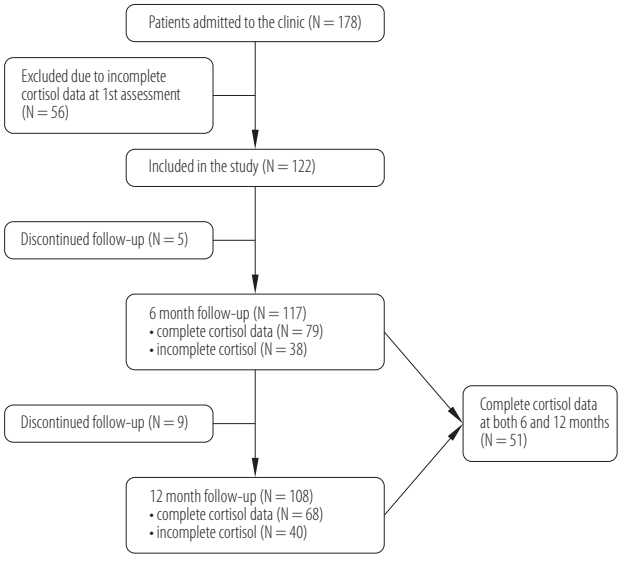


**Fig. 1.** Flow chart of patients

**Table 1.** Demographic factors for the patients and controls

| Variable | Study group | | p |
|---|---|---|---|
| | patients (N = 122) | control (N = 98) | |
| Age (years) (M±SD) | 42±10 | 40±8 | 0.132* |
| BMI (M±SD) | 24.2±3.9 | 23.5±2.4 | 0.100* |
| WHR (M±SD) | 0.86±0.08 | 0.87±0.06 | 0.150* |
| Sex [n (%)] | | | |
| female | 91 (75) | 55 (56) | 0.004** |
| male | 31 (25) | 43 (44) | |
| Burnout [n (%)] | | | |
| SMBQ ≤ 4.4 | 3 (3) | 83 (85) | < 0.001** |
| SMBQ > 4.4 | 103 (97) | 15 (15) | |
| Physical activity [n (%)] | | | |
| sedentary | 38 (32) | 15 (16) | < 0.001** |
| light physical activity | 65 (55) | 37 (40) | |
| regular moderate or intense physical activity | 15 (13) | 40 (44) | |
| Antidepressant use [n (%)] | 43 (35) | 0 (0) | |

M – mean; SD – standard deviation; BMI – body mass index; WHR – waist hip ratio; SMBQ – Shirom Melamed Burnout Questionnaire.
* t-test, ** $Chi^2$ test.

**Table 2.** The repeated measures analysis of variance with time of the day (awakening, +30 min, and evening) as the repeated factor and group belonging (patient or healthy control) as the between-subjects factor

| Variable | F | p | $\eta^2$ |
|---|---|---|---|
| Uncorrected | | | |
| time of day | 414.4 | < 0.001 | 0.66 |
| time of day × group | 3.0 | 0.053 | |
| group | 0.2 | 0.689 | |
| Corrected for sex | | | |
| time of day | 57.6 | < 0.001 | 0.21 |
| time of day × group | 3.5 | 0.034 | 0.02 |
| group | 0.1 | 0.813 | |
| Corrected for physical activity and antidepressant use | | | |
| time of day | 29.5 | < 0.001 | 0.13 |
| time of day × group | 1.1 | 0.326 | |
| group | 0.5 | 0.489 | |

$\eta^2$ – effect size.

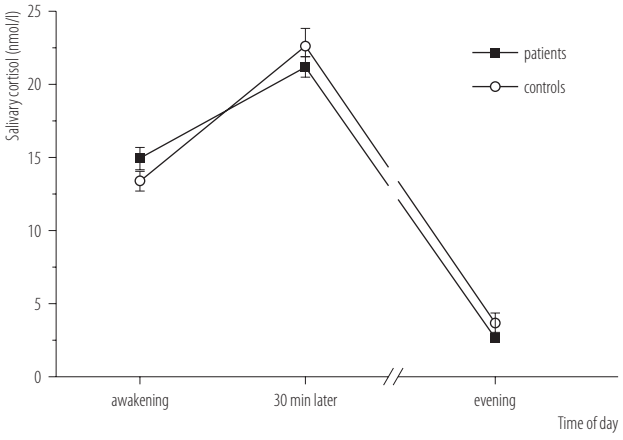


**Fig. 2.** Mean salivary cortisol concentrations (bars represent standard errors) at different times of the day for the patients with stress-related exhaustion (N = 122) and for the healthy controls (N = 98)

Mean CAR in the patient group was 6.3 (±8.5) nmol/l, and in the control group 9.2 (±10.5) nmol/l. According to an independent samples t-test (t = 2.3, p = 0.023), this difference was statistically significant. Analyzing men and women separately revealed that the difference existed only between the male patients and controls (t = 2.8, p = 0.006), however, after controlling for antidepressant use it was no longer significant (F(1,70) = 3.2, p = 0.076). The CDD was not significantly different between the patients and controls (t = 0.2, p = 0.727). Mean values were 18.4 (±8.5) nmol/l in the patient group and 18.9 (±12.7) nmol/l in the control group.

**Follow-up**

The number of patients with complete salivary cortisol data for the 6 and 12 months follow-up can be found in Figure 1. There were no significant differences in baseline cortisol measurements between the 51 patients with complete salivary cortisol data sampled after both 6 months and 12 months and those who participated in both follow-up assessments but did not provide a complete set of saliva samples (N = 57).

The follow-up analysis after 6 months and after 12 months, as well as the combined analysis of the 6 month and 12 month follow-up, all showed a significant time of the day effect (Table 3). There were no significant changes in salivary cortisol from inclusion to 6 months or 12 months (follow-up effect) and no significant time

**Table 3.** The repeated measures analysis of variance with time of the day (awakening, +30 min, and evening) and follow-up (inclusion, 6 months and/or 12 months) as repeated factors

| Variable | Baseline and 6 month follow-up (N = 79) | | | Baseline and 12 month follow-up (N = 68) | | | Baseline, 6 month and 12 month follow-up (N = 51) | | |
|---|---|---|---|---|---|---|---|---|---|
| | F | p | $\eta^2$ | F | p | $\eta^2$ | F | p | $\eta^2$ |
| Uncorrected | | | | | | | | | |
| time of day | 240.3 | < 0.001 | 0.76 | 248.5 | < 0.001 | 0.79 | 223.0 | < 0.001 | 0.82 |
| follow-up | 0.04 | 0.849 | | 0.5 | 0.498 | | 1.9 | 0.155 | |
| time of day × follow-up | 2.2 | 0.118 | | 0.2 | 0.791 | | 1.1 | 0.364 | |
| Corrected for sex, physical activity and antidepressant use | | | | | | | | | |
| time of day | 21.9 | < 0.001 | 0.23 | 22.9 | < 0.001 | 0.27 | 24.1 | < 0.001 | 0.34 |
| follow-up | 2.4 | 0.129 | | 0.02 | 0.886 | | 2.2 | 0.118 | |
| time of day × follow-up | 0.5 | 0.583 | | 1.2 | 0.313 | | 0.5 | 0.720 | |

Abbreviations as in Table 2.

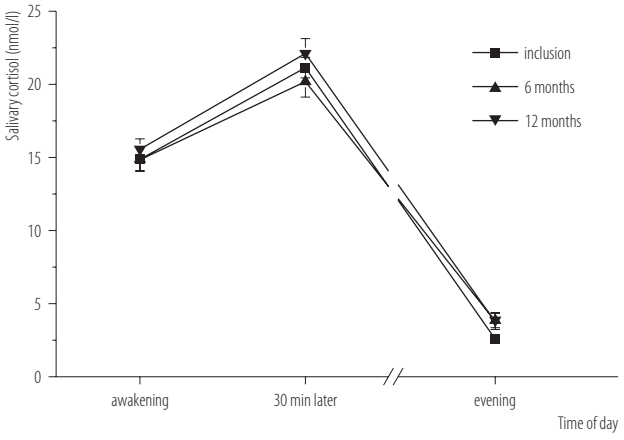


**Fig. 3.** Mean salivary cortisol concentrations (bars represent standard errors) at different times of the day for the patients during inclusion (N = 122), after 6 months of the treatment (N = 79) and after 12 months of the treatment (N = 68)

of day × follow-up interaction effect, indicating that the diurnal profiles were similar at inclusion, after 6 months and after 12 months (Figure 3).

These results remained the same after controlling for sex, physical activity and antidepressant use (Table 3).

## DISCUSSION

The study showed no clear differences in diurnal salivary cortisol between the patients with stress-related exhaustion and the healthy controls. Moreover, salivary cortisol levels and diurnal profiles did not change significantly during the treatment in the patient group. There was some indication of a smaller CAR in the male patients compared with the male controls, but the difference appeared to be mainly related to the antidepressant use.

Previous studies of comparable patient groups have reported no difference in diurnal cortisol [18] or no difference in awakening cortisol, but decreased evening cortisol [6]. Similarly, no relationships have been found between burnout and diurnal cortisol in 2 studies of relatively healthy individuals divided into high and low burnout groups based on self-rated burnout scores [19,20]. However, in the studies of cortisol levels at work, there have been indications of higher daytime cortisol in high burnout groups [7,21]. Others have found that high burnout was related to high cortisol at awakening but have found no relation to group belonging later in the day [22]. These studies of burnout in healthy and/or working populations may not be comparable to the studies of clinically diagnosed patients but still give an indication of the lack of evidence for a relationship between diurnal cortisol and stress-related conditions such as burnout and ED.

Kakiashvili et al. [23] have suggested in a recent review that evaluation of the HPA axis in suspected burnout cases should be brought to the attention of primary care physicians. Our results do not support the idea of using basal salivary cortisol as a diagnostic aid in primary care and, as far as we know, there are no other studies available that clearly support this suggestion.

Furthermore, cortisol levels do not seem to be a valid measure to follow the course of symptoms during the treatment as in this study no changes were observed over time. Salivary cortisol levels are strongly affected by e.g., diurnal fluctuations, acute stress, food intake and medications. Antidepressant medication is fairly common among patients suffering from stress-related conditions. Since we and other authors [9] have shown that CAR is lower in antidepressant users, it is important to take this into consideration in any salivary cortisol measurements. In addition, baseline levels of salivary cortisol vary widely between the studies [4]. There is no standard baseline level to use as a reference, which further complicates the use of salivary cortisol as a diagnostic tool.

Some of the conclusions drawn by Kakiashvili et al. were based on the findings of Juster et al. [24]. However, their study was performed in a healthy working population and we have previously shown that similar approaches do not separate clinically diagnosed patients with stress-related exhaustion from healthy controls [25]. It is, therefore, important not to assume that findings in healthy working

populations can be translated to more severe cases of burnout or ED. Moreover, in the review by Kakiashvili et al., only studies showing an association between hypocortisolism and burnout were referred to, although there is a vast amount of literature showing the opposite or no association at all [e.g., 7,18,21,26,27].

It is, however, important to keep in mind that these results concern basal cortisol measurements. Differences between patients and controls could emerge when the stress system is challenged. Dexamethasone suppression tests in burnout patients have not revealed changes in cortisol suppression compared with controls, indicating sustained negative feedback sensitivity [18,27,28]. Some studies of negative feedback in healthy workers have shown an association between high burnout scores and stronger suppression [19,29]. However, Rydmark et al. [30] have found attenuated HPA-axis responses to the combined dexamethasone and corticotropin-releasing hormone challenge in women on long-term sick-leave with job stress-induced depression, a patient group very similar to, but not identical with, ED patients. Furthermore, the ability to mobilize adequate physiological responses to acute stressors might be impaired in the patients with stress-related conditions.

Measuring cortisol in saliva or in blood poorly reflects chronic levels of cortisol. Recently, hair cortisol measurement has been put forward as a method to provide long-term retrospective measures of cumulative cortisol secretion [31]. Perhaps, such integrated measurements of cortisol secretion can better reflect the HPA-axis activity in individuals that have developed a stress-related illness compared to snapshot measurements like salivary cortisol.

A limitation of this study is the fact that we did not use an untreated group of ED patients as a control group for the longitudinal assessments. We considered it unethical to delay treatment for 12 months in order to obtain ED controls. The patient group was relatively homogenous with regard to co-morbid conditions and the treatment components. Majority of the patients also fulfilled criteria for both anxiety and depression. The patients who only fulfilled the criteria for ED were few, but they did not seem to differ regarding cortisol levels. The basics in the multimodal treatment were the same for all the patients, but some components were adapted with regard to individual needs. The treatment components most likely to influence cortisol were antidepressant medication and physical activity levels, which we controlled for. We had no possibility to control for other treatment components such as cognitive therapy. We also encounter a limitation with regard to daily hassles/life events, which were not reported. We can only cautiously assume that if any major life events had occurred this would have been reflected in larger variations in cortisol levels in these particular patients and this does not seem to be the case. Sleep measures were not registered in this study and it is, therefore, difficult to speculate on the potential influence of e.g., sleep quality on the results. Moreover, adherence to the cortisol sampling protocol was monitored through the participants' own notes of sampling time, which is not as reliable as time-stamped sampling tubes.

## CONCLUSIONS

If measured correctly, salivary cortisol is an excellent indicator of acute stress reactions, whereas its applicability as a marker of chronic stress is highly questionable. Apparently, diurnal salivary cortisol profiles, at least as measured in this study, give a rather poor reflection of the prolonged stress exposure experienced by the patients with ED. Thus, basal salivary cortisol measurements are not suitable to use for diagnostic purposes in a routine clinical practice, i.e., primary care or occupational health services for patients with stress-related conditions such as ED or burnout. Furthermore, basal cortisol levels do not seem to be useful in terms of following the course of stress-related mental illness.

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