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Exhaustion measured by the SF-36 vitality scale is associated with a flattened diurnal cortisol profile

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Summary

The possible association between stress-related exhaustion and reduced activity in the HPA axis is increasingly in focus. The aim of the present study was to examine whether exhaustion measured in a non-patient population is associated with alterations in diurnal cortisol profile. The study population included 78 working individuals. The study group was dichotomised into exhausted and non-exhausted groups by means of the SF-36 vitality scale. Salivary cortisol was measured at three times during one workday: at awakening, 30 minutes after awakening, and in the evening. The results showed that diurnal cortisol variation was significantly reduced in exhausted individuals. The difference in cortisol variation was mainly due to lowered morning cortisol in the exhausted group. Differences in cortisol levels at each sampling time or in mean diurnal output of cortisol were not statistically significant. The results would support the notion that exhaustion is associated with HPA axis hypoactivity as assessed by salivary cortisol. Furthermore, the SF-36 vitality provides a measure of exhaustion that may be useful in epidemiological studies in order to explore long-term health effects of stress-related exhaustion.

Key words: *Chronic stress, exhaustion, HPA activity, low cortisol variability, SF-36 vitality scale*

Introduction

Exhaustion can be described as a condition characterized by fatigue and loss of strength or vitality. The possible association between exhaustion and reduced activity in the hypothalamo-pituitary-adrenal (HPA) axis is increasingly discussed (Nicolson and van Diest, 2000; Raison and Miller, 2003; Fries et al., 2005). This notion is mainly derived from studies concerning different clinically established disorders exhibiting hypocortisolaemic features (e. g., posttraumatic stress disorder, chronic fatigue syndrome, fibromyalgia, atypical depression) in which fatigue constitutes a prominent characteristic (Yehuda et al., 1991; Demitrack and Crofford 1998; Gold and Chrousos 1999). The aetiology of the decreased HPA activity in hypocortisolaemic disorders has been disputed (Cleare, 2004a; 2004b), but since disturbances in the HPA axis are intimately associated with physiological stress response systems, HPA hypoactivity is frequently considered a possible feature of chronic stress (Demitrack and Crofford, 1998; McEwen, 1998; Heim et al., 2000). This view thus contrasts with the more traditional view that stress is characterized by an increased activation of the HPA axis, and it is hypothesized that HPA hyporesponsiveness would constitute a later phase in the chronic stress process, subsequent to an initial period of stress-induced HPA hyperactivity (McEwen, 1998; Fries et al., 2005).

In normal (non-clinical) populations, cortisol patterns indicating hypoactivity in the HPA axis have been observed in association with chronic stress (e. g. Caplan et al., 1979; Goenjian et al., 1996; Adam and Gunnar, 2001; Ranjit et al., 2005). In a study of medically healthy individuals it was shown that cortisol levels that were substantially suppressed due to severe chronic stress returned to normal after termination of the stressful period (Zarkovic et al., 2003). Chronic stress thus seems to exert a “direct” effect on the HPA axis in reducing its activity, i. e. without being mediated by disease. In these studies the potential link between

exhaustion and cortisol was not considered. Most research concerning this relationship has been performed by means of using measures of “burnout” - which include exhaustion as one of several dimensions - but the summarised findings of cortisol in burnout have not yet been conclusive (Mommersteeg et al., 2006). Moreover, the measure of “vital exhaustion”, developed for prediction of myocardial infarction (Appels et al., 1987), has been shown to correlate with attenuated cortisol response and reduced diurnal cortisol variation (Kristenson et al., 1998; Sjögren et al., 2006). It should be noted that the construct of vital exhaustion contains dimensions of both exhaustion and depression (Appels, 1980; Appels et al., 2000; Prescott et al., 2003; McGowan et al., 2004) and cortisol levels associated with vital exhaustion can therefore be regarded as a reflection of a combination of physiological patterns in these two conditions. In a study of particular interest concerning cortisol patterns in exhaustion, the vital exhaustion measurement was used in order to screen for exhaustion after which depressed participants were excluded from the study (Nicolson and van Diest, 2000), thereby ensuring that the reported findings concern exhaustion and not depression. The study was performed on a sample of healthy working males, and a tendency towards overall lower levels of cortisol was found in exhausted individuals compared to controls.

The purpose of the present study was to further explore cortisol patterns in exhaustion as assessed in a non-patient population. For the assessment of exhaustion the SF-36 vitality scale was utilised. Exhaustion measured by this scale has been shown to be differentiable from measures of depression and anxiety (Lindeberg et al., 2006), which would seem valuable considering evidence of increased HPA activity and elevated cortisol levels in depression and anxiety disorders (Gillespie and Nemeroff, 2005; Abelson et al., 2007).

The study objective was to elucidate whether exhaustion measured by the SF-36 vitality scale in a working population was associated with differences in salivary cortisol concentrations and in the diurnal variation of salivary cortisol (cortisol variability). Our primary hypothesis was to find lowered cortisol variability and suppressed concentrations of cortisol (indicating HPA axis hypoactivity) in exhausted individuals compared with non-exhausted.

Methods

Participants and design

The study sample consisted of 78 individuals, 57 females and 21 males, who participated in a follow-up assessment of a cohort study concerning possible predictors of work-related ill-health. The initial cohort ($N = 437$) was identified in the year 2001 and was recruited from five different work-sites including manual and non-manual employees (Hansen et al., 2006). The work-sites were recruited on the basis of possible high workload and were identified in collaboration with the local Labour Inspectorate. The baseline examination, including survey assessment and cortisol sampling, took place at the location of each workplace. The study presented in this paper was cross-sectional, based on the follow-up assessment of employees at four ($N = 265$) of the initial five work-sites (these were the participants who received a questionnaire including the SF-36 vitality scale), and was performed between May 2004 and November 2005. The four work-sites included one pharmaceutical company, one telecommunication company (customer service), one social insurance company, and one wood industry company. After agreement of participation in the follow-up, the study subjects received by post a study questionnaire and a saliva sampling kit, along with a pre-stamped envelope to be used after completion of the survey assessment and the cortisol sampling. 84 individuals (32%) responded to this part of the

follow-up assessment. All participants gave written informed consent to participate in the study. Six individuals were excluded from the study: one who did not obtain any valid cortisol sample, and five who reported medicating with inhaled or nasal corticosteroids.

Questionnaire data

Exhaustion was measured by the SF-36 vitality scale, an instrument assessing fatigue and energy level and forming one of eight subscales in The Medical Outcomes Study Short Form (SF-36) general health survey (Ware and Sherbourne, 1992). The SF-36 was designed for use in clinical practice and research, health policy evaluations, and general population surveys. The SF-36 vitality scale consists of four items: How much of the time during the past 4 weeks (on a scale from 1 – all of the time, to 6 – none of the time) “did you feel full of pep”, did you have a lot of energy”, “did you feel worn out”, and “did you feel tired?” The translation into Swedish was received from the standardised Swedish version of the SF-36 (Sullivan and Karlsson, 1994; Sullivan et al., 1995). In the present study Cronbach’s alpha for the vitality scale was 0.89, indicating high internal scale reliability. After collection of the data, the scorings of the last two items were reversed so that exhaustion was measured in the positive direction (the higher the score the higher the degree of exhaustion), also referred to as inverted SF-36 vitality (Lindeberg et al., 2006). For the purpose of comparison between exhausted and non-exhausted participants, a cut-off score for exhaustion was set at 16 (16-24). This cut-off was chosen in that it would entail an average item score of minimum 4, indicating the experience of exhaustion at least “a good bit of the time” during the past four weeks. Subjects scoring below 16 (4-15) were defined as non-exhausted.

Data on potential confounders such as chronic disease, medication, body mass index (BMI), and daily smoking were obtained through questionnaire. Chronic disease was assessed by asking about current long-term disease or disability (“yes” or “no”; respondents were not asked to specify the disease or disability). Total daily medication represents medication taken on a daily basis (does not include oral contraceptives or estrogens).

Cortisol saliva sampling

The saliva sampling-kit included sampling instructions and three sets of saliva sampling tubes (Salivette®, Sarstedt Ltd., Leicester, UK). The participants were instructed to collect saliva on an ordinary workday (not after or before a day off) at three pre-specified time points: at awakening, 30 minutes after awakening, and at 2100h (all participants worked regular daytime hours). Each participant marked the sampling time at a label attached to the sampling tube. To enhance the quality of saliva samples, the participants were instructed to refrain from brushing their teeth after awakening until they had obtained the second saliva sample, primarily in order to prevent the saliva sampling swabs from contamination of gingival micro-bleeding. The participants were also instructed to refrain from smoking and having a heavy meal one hour prior to saliva sampling. The saliva samples were kept frozen until they were sent to the research department.

Laboratory analysis of cortisol in saliva

For determination of cortisol in saliva, a competitive radioimmunoassay (RIA), the Spectria Cortisol Coated Tube RIA, purchased from Orion Diagnostica, Espoo, Finland, was used. The assay was designed for quantitative *in vitro* measurement of cortisol in serum, plasma, urine, and saliva and the analyses were carried out in accordance with the manufacturer’s

specifications. The method conductance has been validated in inter-laboratory comparison schemes. For detailed information on the laboratory analysis, see Hansen et al. (2003; 2006).

Definition of cortisol variability

Diurnal cortisol variability was defined as the difference between the maximum morning cortisol concentration (the highest measured concentration out of the two morning samples) and the evening cortisol concentration.

Statistical analysis

Descriptive characteristics for the exhausted and non-exhausted groups were calculated.

Due to positively skewed distributions and heteroscedastic variances (proportional to the level of measurements) of cortisol data, the diurnal cortisol variability was ranked and the cortisol concentrations were logarithmically transformed before entering them into statistical analyses. For descriptive purposes, raw medians and 25th and 75th percentiles of cortisol measures were reported.

The correlation between the continuous inverted SF-36 vitality score and diurnal cortisol variability was examined by bivariate correlation (Spearman's rho correlation coefficient).

For exploration of differences in diurnal cortisol variability between exhausted and non-exhausted subjects, univariate analysis of variance (ANOVA) was performed. Categorical predictor was *group* (exhausted or non-exhausted). Gender, age, awakening time (i. e., the

time of the first sample), self-reported chronic disease, BMI, and daily smoking were introduced as covariates in the model in the first step, as well as the two-way interaction *group* by *gender* in order to examine possible differential associations between cortisol variability and exhaustion among males and females. In the second step, total daily medication, use of oral contraceptives or estrogens, thyroid medication, and antidepressants (created as four separate variables) were introduced as covariates one by one. The three latter substances were selected and tested separately since they potentially can influence cortisol levels (Kirschbaum et al., 1999; Adam and Gunnar, 2001; Mason and Pariante, 2006).

Differences in mean diurnal cortisol levels between exhausted and non-exhausted groups were examined in a repeated measures model specified in the general linear MIXED models module. The model was solved using the restricted maximum likelihood (REML) method. Categorical predictors were *group* (exhausted or non-exhausted) and *time of day* (three levels). Interactions and covariates (see above), here including also the two-way interaction *group* by *time of day* in order to examine possible differential cortisol patterns between groups, were introduced in the model (same procedure as previously). A series of first-order autoregressive covariance structures as well as a compound symmetry covariance structure were tested. The Schwarz Bayesian Information Criterion was used to guide the final selection of covariance structure.

In addition, ANOVAs (same procedure as in the ANOVA described above) were performed in order to explore group differences in cortisol concentrations at each of the three sampling times.

The selection of covariates and interactions to be included in the final models was based on a backwards stepwise deletion model, using the factors *group* and *time of day* (in the repeated measures model) as forced-in variables. Initially, all interactions and covariates (except medication) were entered simultaneously into the model. Variables that did not reach a p-value below 0.20 were in the next step eliminated from the model; this higher significance limit is thought to prevent much of the bias that otherwise may arise from this selection method (Greenland, 1989; Mickey and Greenland, 1989; Maldonado and Greenland, 1993).

For all final models and analyses, a p-value below 0.05 was considered statistically significant.

All statistical analyses were performed in SPSS 12.0 (SPSS Inc., 2001).

Results

20 respondents (26 %) scored 16 or above on the inverted SF-36 vitality score and were thereby designated as belonging to the exhausted group. 58 respondents scored below 16 and were thus defined as non-exhausted. Descriptive characteristics of the exhausted and non-exhausted groups are shown in Table 1. Age was slightly lower and body mass index (BMI) was slightly higher in the exhausted group. Daily smoking was fairly evenly distributed between groups, and saliva cortisol was sampled at similar times in the two groups. Chronic disease was reported three times as often in the non-exhausted group as in the exhausted group. None in the exhausted group reported any daily medication, whereas in the non-exhausted group 26 % medicated on a daily basis (including antidepressants, thyroid medication, stomach medicine (anti-acids), painkillers, medication for high blood

pressure, anti-cholesterol medication, and medication for diabetes). Non-exhausted women more frequently reported use of oral contraceptives or estrogens compared with exhausted women (50 % versus 30 %; data not shown in table). Missing data for use of oral contraceptives or estrogens among the women was 26 % (17 % in the exhausted group and 29 % in the non-exhausted group).

Data on cortisol concentrations and cortisol variability in the two groups are shown in Table 2.

There was a statistically significant negative correlation between the inverted SF-36 vitality score and cortisol variability ($r_s = - 0.26$, $p < 0.05$), indicating that the diurnal variation in cortisol decreased with increasing degree of exhaustion.

Further analysis of diurnal cortisol variability in exhausted and non-exhausted groups showed that cortisol variability differed significantly between the groups ($p = 0.038$). Age remained as the only covariate in the final model, and no medication turned out as significant.

The graphically displayed diurnal cortisol profiles demonstrate by visual inspection lower cortisol levels in the exhausted group compared with the non-exhausted group. The observed difference in cortisol variability was derived mainly from the second morning sample and evening cortisol levels did not differ between the groups (Figure 1).

The repeated measures mixed model analysis showed no significant difference in mean diurnal cortisol output between exhausted and non-exhausted groups ($p = 0.33$). Neither were there significant differences in cortisol concentrations at each sampling time ($p > 0.2$).

No interaction analyses were statistically significant.

Discussion

The results of this study showed that exhausted individuals exhibited a flattened diurnal cortisol profile compared with non-exhausted. The flattened profile was due to lowered cortisol levels in the morning whereas evening cortisol did not differ between the groups. Overall cortisol levels thus tended towards being lower in exhausted individuals but these differences were not statistically significant.

A recent meta-analytic review (Miller et al., 2007) revealed that low morning cortisol and high afternoon or evening cortisol, resulting in a flattened diurnal cortisol rhythm as well as a significantly higher daily cortisol output, was the most frequently observed cortisol pattern in chronically stressed individuals compared to controls. Divergent cortisol patterns were e. g. seen in posttraumatic stress disorder in terms of lower daily cortisol output (hypocortisolism). Our results indicated a flattened cortisol rhythm due to lower morning cortisol in exhaustion, whereas no tendency towards higher evening cortisol values was observed. A plausible interpretation of these findings would be that in comparison with most chronic stress states as investigated by Miller et al. (2007), exhaustion is seemingly associated with a cortisol pattern more in line with that seen in hypocortisolaemic fatigue disorders, thus lending further support to the notion of HPA axis hypoactivity in exhaustion.

Some methodological considerations should be addressed. First, contrary to what might be expected, the exhausted group was seemingly healthier than the non-exhausted group (both in

terms of self-reported chronic disease as well as daily medication). It would thus appear that exhaustion was not related to chronic disease in this sample. It may however be argued that chronic disease rendered higher cortisol levels in the non-exhausted group and thereby explained the observed differences in cortisol variability. But since chronic disease and medication were controlled for in the analyses, such a conclusion would seem unlikely. In that self-reported chronic disease has been shown to be an assessment of only moderate validity (Heliövaara et al., 1993), total daily medication was additionally tested in order to further adjust for the potential influence of chronic disease. Second, a proportion (26 %) of the women had missing data for use of oral contraceptives and estrogens, and it may be questioned whether these substances, which might have the potential to lower salivary cortisol levels (Kirschbaum et al., 1999), were satisfactorily controlled for. However, in that the non-exhausted women more frequently reported use of oral contraceptives or estrogens, and the proportion of missing data was larger in the non-exhausted group, it would seem unlikely that these substances explained the results. Third, although statistically significant differences in cortisol variability were found, the relatively small sample size may have resulted in limited statistical power, and statistically non-significant findings should therefore be interpreted with caution. Furthermore, a larger sample would render the possibility to test stricter criteria for the definition of exhaustion (in terms of a higher cut-off score) and thereby perhaps capture more pronounced HPA dysregulation and increased differences in cortisol levels between exhausted and non-exhausted subjects.

In epidemiological stress research, assessments of exhaustion would seem useful. Exhaustion may as such be explored in terms of an outcome of chronic stress, as well as a potential intermediate link between stressor exposure and manifest disease. Previous stress research has to a large extent used measures of depressive symptomatology and anxiety in order to assess

immediate or intervening health effects of chronic stress (Cohen et al., 1995; Zarkovic et al., 2003). Hypothetically, individuals may be prone to different reaction patterns in chronic stress (behaviourally and physiologically), and exhaustion might constitute one such type of response. In turn, the reaction patterns may differ in their potential long-term impact on health. For example, despite the well-established view that depression constitutes a risk-factor for cardiovascular disease (Frasure-Smith and Lespérance, 2006), epidemiological research has reported some evidence that exhaustion is more likely to precede myocardial infarction than is depression (Appels et al., 2000). Interestingly in this regard, Raison and Miller (2003) have proposed a theory that a deficit in, or “not enough”, cortisol in the body (in terms of an insufficient glucocorticoid signalling at the cellular receptor level) might be the crucial pathway for development of disease, whereas an excess glucocorticoid production instead may be a beneficial adaptive mechanism, diminishing stress-related physiological processes.

In contrast, Fries et al. (2005) have proposed that HPA hyporesponsiveness and associated exhaustion may constitute a protective response during chronic stress in terms of dampening the chronic HPA hyperactivity process and promoting recuperation, thereby reducing the assumed damaging effects of an excess glucocorticoid response to chronic stress. Findings that elderly hypocortisolaemic and fatigued subjects had more favourable values on parameters (such as blood-pressure, waist-hip-ratio, and blood parameters) known to constitute risk-factors for cardiovascular disease (Hellhammer et al., 2004) may seem to support this notion. Continued exploration concerning long-term health effects of stress-related exhaustion, also in comparison with other stress-related symptomatology, seems desirable and may contribute to the further understanding of different mechanisms of chronic stress regarding its effects on health and disease.

Tentative stressors related to the observed exhaustion were not explored in this study. Previous research concerning exhaustion has to a large extent focused on work-related exhaustion (Melamed et al., 1992; Pruessner et al., 1999; Maslach et al., 2001). However, circumstances such as early life stress, unemployment, economic hardship, divorce, social isolation, etc., are widely considered to cause or contribute to chronic stress (Rahe, 1990; Lepore, 1995; Dohrenwend, 2006), and the impact on exhaustion of such factors, as well as of work-related factors, should be investigated in further studies. The SF-36 vitality scale can be used as an assessment of exhaustion independently of potential stressors and may thus very well be used in general population studies including both working and non-working populations. Since this study was performed on a working population, it would seem desirable to explore the applicability of these results to other demographic groups.

In summary, the results of the current study provide evidence for that exhausted individuals exhibit physiological features compatible with a hypoactivity in the HPA axis as assessed by salivary cortisol, primarily demonstrated by reduced diurnal cortisol variation. Furthermore, the SF-36 vitality scale appears to provide a useful measure of exhaustion to be utilised in the further exploration concerning the health effects of chronic stress.

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Tables

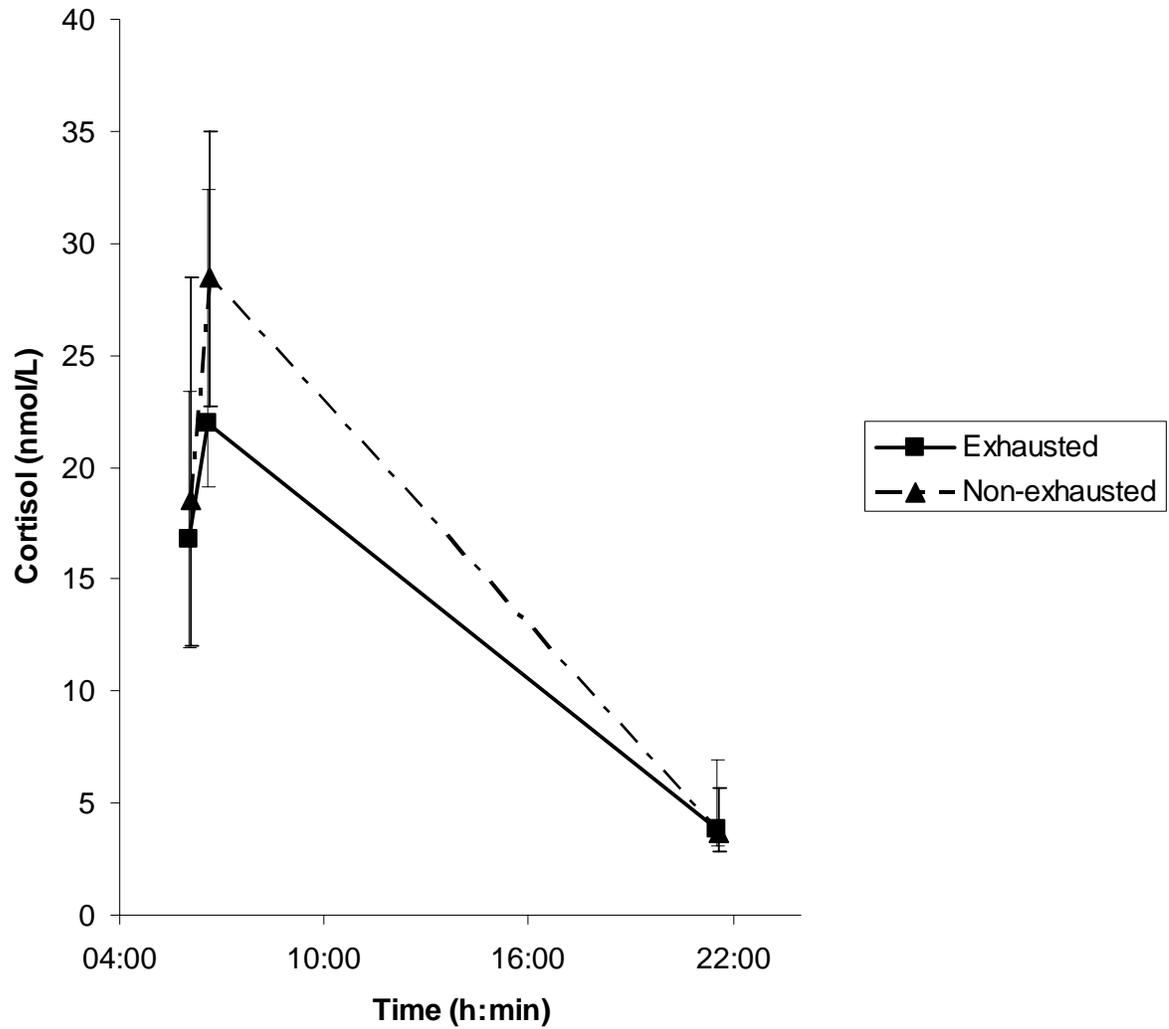
Table 1. Characteristics of exhausted and non-exhausted groups

	Exhausted (<i>n</i> = 20)	Non-exhausted (<i>n</i> = 58)
Inverted vitality score (mean, range)	18 (16-21)	11 (6-15)
Men (<i>n</i> , %)	8 (40 %)	13 (22 %)
Women (<i>n</i> , %)	12 (60 %)	45 (78 %)
Age		
Mean (years, SD)	45 (8)	46 (9)
Range (years)	32 – 56	26 – 63
BMI (mean, SD)	26 (8)	25 (4)
Daily smoking (<i>n</i> , %)	1 (5 %)	4 (7 %)
Self-reported chronic disease	1 (5 %)	9 (16 %)
Daily medication (<i>n</i> , %)		
Total	0	15 (26 %)
Antidepressants	0	1 (2 %)
Thyroid medication	0	4 (7 %)
Cortisol sampling times (mean, SD)		
At awakening	0602h (38min)	0606h (47min)
30 min after awakening	0636h (38min)	0637h (48min)
In the evening	2132h (39min)	2135h (46min)

Table 2. Cortisol concentrations and cortisol variability (nmol/l) in exhausted and non-exhausted groups (medians and 25th and 75th percentiles)

	Exhausted (<i>n</i> = 20)			Non-exhausted (<i>n</i> = 58)		
	MD	25 th perc.	75 th perc.	MD	25 th perc.	75 th perc.
Cortisol variability	19.9	14.9	27.9	26.2	18.1	32.0
Cortisol concentrations						
At awakening	16.8	12.0	23.4	18.5	12.0	28.5
30 min. after awakening	22.0	19.1	32.4	28.5	22.7	35.0
In the evening	3.9	3.1	7.0	3.7	2.8	5.7

Figure



Legend for figure

Figure 1. Diurnal cortisol profiles for exhausted ($n = 20$) and non-exhausted ($n = 58$) groups. Displayed are median cortisol concentrations and 25th and 75th percentiles at awakening, 30 min after awakening, and in the evening (2100h).