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Burnout symptom sub-types and cortisol profiles: What's burning most?

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Summary The current study assessed which specific burnout symptoms were most predictive of distinct diurnal cortisol profiles. Participants included 401 day-shift workers employed in a random sampling of 34 Canadian workplaces. The 16-item Maslach Burnout Inventory was used to extract burnout sub-scales that included emotional exhaustion, cynicism, professional inefficacy, as well as a global burnout average. Consenting workers provided five saliva samples a day (awaking, 30 min after awaking, 1400 h, 1600 h, and bedtime) repeated three times over the course of a week (Saturday, Tuesday, Thursday) to capture workday and non-workday variations. Multilevel regression models were estimated from cortisol measurements at each occasion within a day at level-1, workers at level-2, and workplaces at level-3. Multilevel regression analyses found that emotional exhaustion and a global burnout showed the strongest and consistent negative associations to cortisol in the afternoon and evening. In a separate analysis using regression coefficients, emotional exhaustion and a global burnout average were associated with low cortisol levels 30 min upon awakening. By contrast, professional inefficacy was associated only with lower bedtime cortisol. No associations were detected for cynicism and sex did not emerge as a moderator in secondary analyses. Our findings are discussed in a theoretical framework postulating different pathophysiological stages of burnout development. Specifically, professional inefficacy may be the earliest warning signal culminating with emotional exhaustion that may dampen diurnal cortisol levels.

1. Introduction

Burnout is an enigmatic psychological condition with elusive biological correlates. In accordance, a systematic review of 31 burnout studies incorporating 38 different biomarkers

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suggest that there is no clear-cut biological signature of burnout due to methodological inconsistencies and vast heterogeneity of this ill-defined syndrome (Danhof-Pont et al., 2011). The term ''burn-out'' originated with the personal and professional observations of Freudenberger, a psychoanalyst who described diverse behavioural, emotional, and cognitive debilitations among overcommitted community workers (Freudenberger, 1974). Despite continued debate on the nature of burnout and whether it symptomatically overlaps with other diagnosable psychopathologies like depression or adjustment disorder (Kaschka et al., 2011), growing psychoneuroendocrine evidence suggests that burnout may be associated with distinct alterations in diurnal *hypothalamic-pituitary-adrenal* (HPA) axis production of the stress hormone cortisol.

Cortisol levels normally follow a diurnal rhythm consisting of an acute increase during the first hour after awakening (Pruessner et al., 1997) — known as the *cortisol awakening response* (CAR) — followed thereafter by gradual decreases until attaining the lowest levels around bedtime (Clow et al., 2010a). A meta-analysis of 62 studies recently concluded that while the CAR is positively associated with workplace stress and general life stress, it is negatively associated with symptoms of burnout, fatigue, and exhaustion (Chida and Steptoe, 2009). One of the greatest challenges in deciphering burnout's manifestations, however, is to first identify which specific symptom clusters are most prominently associated with HPA-axis functioning.

Continuing debate centres on whether burnout symptomatologies correspond with hypoactive HPA-axis functioning. Hypocortisolism is a phenomenon that occurs in approximately 20—25% of patients suffering from stress-related diseases like burnout, chronic fatigue syndrome, fibromyalgia, post-traumatic stress disorder, and atypical depression to name a few (for a review, see Fries et al., 2005). Of particular interest are nuances among depression and burnout, two conditions that are qualitatively similar (Tennant, 2001; Iacovides et al., 2003; Nyklicek and Pop, 2005), but suspected to differ substantially in terms of cortisol levels. Studies aiming to delineate distinct cortisol profiles (e.g., awakening concentrations, CAR magnitude, differential afternoon and bedtime concentrations) must first incorporate established operational definitions of burnout.

According to Maslach's seminal formulation and psychometric substantiation, burnout comprises three symptom sub-types: (1) *emotional exhaustion* characterized by one's fatigued inability to occupationally offer oneself affectively; (2) *cynicism* characterized by a distancing attitude or depersonalization away from one's work; and (3) *professional inefficacy* characterized by the inability to perform tasks as adequately as before (Maslach and Jackson, 1981). Of these three popular Maslach burnout sub-types, emotional exhaustion is the most widely reported in the occupational health literature (Maslach et al., 2001). By contrast, there is no consensus on which biomarkers are most consistently associated to Maslach burnout sub-types (Danhof-Pont et al., 2011).

To address this lacuna, the current study assessed whether emotional exhaustion, cynicism, professional inefficacy, and a global burnout average were most predictive of diurnal cortisol concentrations in a representative sample of healthy day-shift workers randomly selected from diverse workplaces and industries. Focus was placed on statistical magnitude in specific Maslach burnout sub-types comparisons with overall HPA-axis activities as well as at precise diurnal time-points. Two approaches were applied: (1) a multilevel regression approach to model cortisol and (2) a cut-off approach based on regression information to help illustrate cortisol patterns according to burnout symptomatologies. Our primary hypothesis was that emotional exhaustion would be most significantly correlated with distinct HPA-axis functioning.

In secondary analyses, we assessed the moderation effect of sex using interaction terms. This was justified because of known inequalities in the distribution of occupations and differential exposure to unique stressors within diverse workplaces that render Canadian women more vulnerable than men to stress-related health problems (Vermeulen and Mustard, 2000; Marchand et al., 2005a, 2005b, 2005c).

2. Methods

2.1. Participants

Data were collected throughout 2009 to 2012 using a sample of 34 Canadian workplaces randomly selected from a list of over 500 companies insured by a large insurance company. For each workplace, a random sample of employees was first selected to answer a questionnaire (N = 1301 workers, average response rate of 66.7%, range 55.3—95.5%). From among these respondents, a sample of 10 to 15 workers per workplace was targeted to participate in the second phase of the research project whereby saliva samples were collected for assessment of cortisol levels in accordance with a previous approach (Marchand et al., 2013).

Overall, 1043 workers were re-invited, of which 401 workers agreed to participate in the current biomarker sub-study (mean of 11.8 workers per workplace, response rate of 39.9%). Women represented 56.1% of workers and the mean age of the entire sample was 41.3 years (SD = 10.81, range 19—69). Participants provided informed consent and were given detailed study instructions. The study protocol for the first and second phase of the research project was approved by the Ethics Committees of the University of Montreal, McGill University, Laval University, Bishops University, and Concordia University.

2.2. Saliva sampling and cortisol determination

Consenting workers were instructed to provide five saliva samples per day at the following occasions as previously done by our group in order to discern diurnal cortisol levels (Juster et al., 2011): (1) awaking, (2) 30 min post-awaking, (3) 1400 h, (4) 1600 h, and (5) bedtime. Because sampling occurred during the workday afternoon and could cause inconvenience, we instructed participants to be as exact as conveniently possible.

Sampling was repeated for 3 days (Saturday, Tuesday, Thursday for the majority of workers) over the course of 1 week to best account for workday and non-workday variability (Kunz-Ebrecht et al., 2004). In total, 94.9% reported that the weekend day (Saturday) was their rest day, while 5.1% reported that a weekday (Tuesday or Thursday) was their rest day which were carefully coded accordingly.

Preliminary analyses ascertained compliance of sampling scheduling and potential confounding effects. For statistical purposes in our main analyses, the baseline was always anchored as the corresponding rest day. This is justified, since it has been shown that cortisol concentrations increase from non-work days to workdays (Steptoe et al., 2004; Maina et al., 2008; Marchand et al., 2013), and this variability should therefore be accounted for to best represent diurnal cortisol rhythmicity over a working week.

Thirty minutes before all saliva sampling (with the exception of the awakening sample), participants were instructed to rinse their mouths and to avoid major meals, cigarettes, caffeinated/sugary beverages, and dairy products. They were furthermore asked to refrain from oral hygiene and strenuous physical activity two hours before sampling. Participants were also instructed to collect the awakening sample immediately after awakening. Compliance was assessed using a logbook whereby participants recorded sampling times thereafter coded to scrutinize adherence effects.

Saliva was collected using empty Salivette tubes (Sarstedt, Ville St-Laurent) using the unstimulated passive-drool method whereby participants use straw to guide saliva flow into a 2 mL tube. Participants stored saliva samples in their home or work freezers until a research assistant retrieved them and stored them at $-20\,^{\circ}C$ until cortisol determinations.

Salivary cortisol concentrations were analyzed at the Centre for Studies on Human Stress (www.humanstress.ca) with a high sensitivity enzyme immune assay kit (Salimetrics® State College, PA, Catalogue No. 1-3102). Frozen samples were brought to room temperature to be centrifuged at 15,000 $\times$ *g* (3000 rpm) for 15 min. The range of detection for this assay is between 0.012 and 3 μg/dl. The intra-assay coefficient of variation ranged between 3.35% and 3.65% and the inter-assay coefficient of variation ranged between 3.75% and 6.41%. All samples were assayed in duplicates and then averaged and then log transformed for some statistical analyses.

2.3. Burnout questionnaire

Burnout symptoms were evaluated on a single occasion before workers began saliva collection regimens. Components and total burnout scores were measured with the Maslach Burnout Inventory 16-items General Survey (Schaufeli et al., 1996). This short form is well suited for evaluating burnout in the general working population. Each item is measured on a 7-point Likert scale for symptom frequencies (0 = Never; 1 = Sporadically. A few times a year or less; 2 = Now and then. Once a month or less; 3 = Regularly. A few times a month; 4 = Often. Once a week; 5 = Very often. A few times a week; 6 = Daily). A principal component analysis on the current sample of the 16 items supports the three expected symptom sub-types (emotional exhaustion: 5-items, cynicism: 5-items, professional inefficacy: 6-items). Internal consistency for burnout symptom sub-types scales was deemed adequate for emotional exhaustion (α = 0.90), cynicism (α = 0.80), professional inefficacy (α = 0.80), as well as a total burnout average of all 16 items (α = 0.89) described below.

In addition to each Maslach burnout sub-type separately, a global burnout average of emotional exhaustion, cynicism, and professional inefficacy (reverse coded from the original professional efficacy sub-scale) was calculated. There is no explicit recommendation for the utility of a global burnout score and there is continued debate on the relative merits of conceptualizing burnout as a uni-dimensional and/or multi-dimensional construct (Brenninkmeijer and VanYperen, 2003). In the interest of minimizing multiple comparisons, our group had previously summarized burnout sub-scales using calculations that combine the three Maslach burnout sub-scales in studies with small sample sizes (Juster et al., 2011, 2013). Despite considerable power in the current sample, this was likewise done to contribute more knowledge to this debate on the utilization of Maslach burnout sub-scales and a global composite vis-à-vis diurnal HPA-axis functioning.

2.4. Covariates

Based on previous reports demonstrating their confounding effects on diurnal cortisol levels, statistical analyses were adjusted for the following covariates: *self-reported time of awakening* (Hucklebridge et al., 2000), *sex* (Larsson et al., 2009), *age* (Van Cauter et al., 1996), *season of sampling* (Persson et al., 2008), *cigarette smoking* (Steptoe and Ussher, 2006), *alcohol consumption* (Badrick et al., 2008), *regular physical activity* (Hansen et al., 2010), *psychotropic drug use* (Granger et al., 2009), *health problems* (Kudielka et al., 2003), and *body mass index* (Bjorntorp and Rosmond, 2000).

Self-reported time of awakening was measured is hours/min. Sex was coded as a binary (0 = men, 1 = women) and age was measured in continuous years. Season of sampling was coded into four categories (1 = Spring, 2 = Summer, 3 = Fall, 4 = Winter). Smoking was recorded continuously as the number of cigarettes smoked per day. For alcohol, respondents indicated the number of alcoholic beverages they had had on each of the 7 days during the week preceding the questionnaire administration. Alcohol intake was quantified by summing the number of drinks consumed daily (standard Canadian drink of 13.6 grams of alcohol equivalents for beer, wine, and spirits). Physical activity over the last 3 months was measured as the frequency of physical activities performed for more than 20 min. Respondents indicated this frequency on a 7 point Likert-type scale (1 = never, 7 = four times and more a week).

Prescribed psychotropic drugs over the last month were dichotomously coded (0 = user and 1 = user) for at least one of the following: tranquilizers (e.g., Valium, Ativan; *n* = 10), antidepressants (e.g., Prozac, Paxil, Effexor; *n* = 20), opiates (e.g., Codeine, Demerol, Morphine; *n* = 6), and sleeping pills (e.g., Imovana, Nytol, Starnoc; *n* = 12). Preliminary analysis revealed that only tranquilizer use was associated with cortisol profiles. Tranquilizer use was therefore included as a covariate in the analyses.

Health status tallied self-reported physical and mental health conditions lasting 6 months and more as diagnosed by a physician using a list of 29 items: food allergies (*n* = 22), seasonal/animal/cosmetic/other allergies (*n* = 98), asthma (*n* = 42), arthritis/rheumatism (*n* = 15), back pain (*n* = 51), hypertension (*n* = 41), migraines (*n* = 40), chronic bronchitis

($n = 5$), emphysema ($n = 0$), chronic pulmonary obstruction ($n = 0$), diabetes ($n = 9$), epilepsy ($n = 1$), cardiac disease ($n = 5$), cancer ($n = 5$), intestinal/stomach ulcer ($n = 6$), cerebrovascular problems ($n = 0$), multiple sclerosis ($n = 1$), urinary incontinence ($n = 7$), intestinal problems ($n = 4$), irritable bowel disorder ($n = 12$), cataract ($n = 3$), glaucoma ($n = 1$), abrasive chemical sensitivities ($n = 3$), thyroid problem ($n = 25$), fibromyalgia ($n = 1$), chronic fatigue syndrome ($n = 2$), schizophrenia ($n = 0$), depression/bipolar disorder ($n = 9$), and anxiety/phobias/obsessive compulsive disorder ($n = 15$). Preliminary analyses revealed that only asthma and back pain were associated with cortisol profiles. Asthma and back pain were therefore included as covariates in the analyses. Finally, body mass index (BMI) was computed as weight (kg) divided by height $(m)^2$.

2.5. Statistical analysis

Preliminary comparison of respondents and non-respondents evaluated possible biases. Main analyses applied multi-level regression models (Goldstein, 1986, 1995; Snijders and Bosker, 1999; Raudenbush and Bryk, 2002) to assess cortisol concentrations in the following levels: (i) cortisol measurements for each Day at level-1, (ii) Workers at level-2, and finally (iii) workplaces at level-3. In this manner, variations within days were embedded within each unit of the second level, followed by variations between participants next embedded within each unit of the third level, and finally the variation between workplaces. This statistical approach allows the full range of data to be taken into account when estimating cortisol variations across each level of the hierarchical data structure.

In addition, the regression models included self-reported time of awakening, four dummy coded variables measuring cortisol concentrations at occasion-2 (30 min after awakening), at occasion-3 (1400 h), at occasion-4 (1600 h), and at occasion-5 (bedtime), as well as two dummy coded variables indexing cortisol concentrations for workday-1 and workday-2 compared to the non-workday. For burnout symptoms, each Maslach sub-scale (exhaustion, cynicism, professional inefficacy, total burnout) was modelled as main effect as well as in interaction with the different sampling occasions.

Statistical analyses were adjusted for awakening time, sex, age, season, smoking, alcohol, physical activities, tranquilizer use, asthma, back pain, and BMI. The model parameters were estimated by the restricted iterative generalized least-squares method (RIGLS) (Goldstein, 1986) using MLwiN Statistical Software version 2.26 (Rasbash et al., 2009). To reduce the asymmetrical distribution and to improve the convergence of the estimation algorithm, cortisol concentrations in μg/dl were multiplied by 100 and log-transformed (natural logarithm). The main effect model was first estimated, followed by a series of interaction tests between burnout measures and sex. The significance of individual regression coefficients was evaluated using a bilateral Z test, and the probability of rejection of the null hypothesis was set strictly at $p < 0.05$. The random coefficients were tested with a halved (divided by 2) p-value (Snijders and Bosker, 1999). The joint contribution of the variables was assessed by means of a likelihood ratio test that followed a χ^2 distribution with the degrees of freedom equal to the number of additional parameters in the model. Interactions were tested using χ^2 with rejection of the null hypothesis set strictly at $p < 0.05$.

Finally in separate analyses of an illustrative nature, lineplots and standard error-bars representing burnout sub-components and salivary cortisol profiles throughout the day were graphed using regression coefficients obtained from the multilevel regression analysis. Scores were then reverted back into original μg/dl units for the sake of comparison. There is no consensus regarding cut-points for burnout; however, using a meaningful cut-point (average score of 4), symptoms were classified according to low symptoms, severe emotional exhaustion, severe cynicism, severe professional inefficacy, and severe total burnout symptoms. The reader will recall that a score of 4 or more represents self-reported burnout symptoms at least once a week.

3. Results

Attrition analysis revealed non-significant differences between respondents ($n = 401$) and non-respondents ($n = 642$) regarding sex, age, burnout, season of sampling, alcohol, physical activities, psychotropic drugs use and health problems. However, respondents smoked less ($p < 0.01$) and had a lower BMI ($p < 0.01$) than non-respondents.

Table 1 reports mean raw cortisol concentrations and the characteristics of the study sample. Some sex differences are identified for cortisol on workday-2, emotional exhaustion, burnout total score, alcohol consumption, psychotropic drug use, health status, and BMI.

In assessing missing data for questionnaires in conjunction to a total of 6150 saliva samples, 5690 samples were analyzable in correspondence with burnout sub-type symptoms and the global burnout average. The sample of workers remaining was therefore $n = 396$.

As previously done (Juster et al., 2011), preliminary analyses ascertained adherence to saliva collection scheduling using a criterion set within a 30 min deviation. Note that this cannot be done for the first awakening and the last bedtime samples. The proportion of compliant participants, that is, those who respected saliva scheduling within 30 min or less, are as follows: +30 min after awakening (98.5%), 1400 h (72.6%), and 1600 h (64.8%). Total adherence was calculated as complete conformity to all three sampling time-points, which was the case for 60.9% of participants. Using total adherence as a covariate in our main multilevel regression analyses did not meaningfully alter the statistical magnitude of our findings and is henceforth not included as a covariate.

Table 2 presents the results of multilevel regression modelling of cortisol concentrations and Maslach burnout symptom sub-types and the global burnout average. In general, results show that cortisol concentrations increase 30 min after awakening indicative of functional CAR in this sample as well as declines for the rest of the day reaching lowest levels at bedtime. The results also show an increase in awakening cortisol levels from the baseline rest day compared to the working days. In terms of burnout sub-types, increased emotional exhaustion was associated with a continuous reduction of cortisol concentrations from occasion-3

Table 1 Sample descriptive statistics.

Variable	Men (n = 176)		Women (n = 225)		Total (N = 401)		
	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Range
Cortisol (μg/dl)							
Rest day	0.147	0.194	0.172	0.246	0.161	0.225	0.012—4.067
Workday-1	0.170	0.215	0.196	0.220	0.186	0.218	0.012—3.336
Workday-2	0.167	0.215	0.198*	0.204	0.185	0.198	0.012—3.000
Burnout							
Emotional exhaustion	1.39	1.13	1.74*	1.35	1.58	1.27	0—6
Cynicism	1.38	1.18	1.28	1.13	1.32	1.15	0—6
Professional inefficacy	1.02	0.85	1.21	1.00	1.13	0.94	0—4.33
Burnout total score	1.25	0.84	1.40*	0.93	1.33	0.90	0—4.37
Covariates							
Gender							
Men					(43.9)		
Women					(56.1)		
Age	41.43	10.33	41.17	11.19	41.28	10.81	19—69
Season							
Spring	(25.0)		(35.5)		(30.8)		
Summer	(12.5)		(26.7)		(20.4)		
Fall	(40.3)		(24.0)		(31.2)		
Winter	(22.2)		(13.8)		(17.6)		
Smoking	1.54	4.67	1.00	3.60	1.23	4.10	0—25
Alcohol	5.48	6.66	3.64*	4.08	4.45	5.44	0—42
Physical activities	4.31	2.02	4.26	2.04	4.28	2.03	1—7
BMI	30.85	6.50	28.70**	6.96	29.65	6.84	17.1—68.2
Tranquilizer use	(1.1)		(3.6)		(2.5)		
Asthma	(7.9)		(12.5)		(10.5)		
Back pain	(14.8)		(11.1)		(12.7)		

Note: sex differences.
* $p < 0.05$.
** $p < 0.01$.

(1400 h) to bedtime. Professional inefficacy was associated with lower bedtime cortisol concentrations, whereas the global burnout average followed the same pattern as the one observed for emotional exhaustion, albeit the statistical magnitude was somewhat reduced. No significant effects were found for cynicism.

Overall findings reveal that cortisol concentrations vary significantly between samples, workers, and workplaces. In terms of covariate effects, smoking was positively associated with cortisol concentrations for emotional exhaustion, professional inefficacy, and total burnout score, but again not for cynicism. Finally, sex was not moderating the associations with emotional exhaustion ($\chi^2 = 1.70$, df = 5, $p = 0.889$), cynicism ($\chi^2 = 1.63$, df = 5, $p = 0.897$), professional efficacy ($\chi^2 = 2.62$, df = 5, $p = 0.759$), and total burnout ($\chi^2 = 2.49$, df = 5, $p = 0.778$).

Subsequent analyses and Fig. 1 illustrate the associations between cortisol concentrations and significant burnout symptom sub-types based on the regression coefficients found in Table 2. Compared to low burnout symptoms, all severe symptoms are associated with higher cortisol concentrations at awakening. Severe emotional exhaustion and severe total burnout were associated with lower cortisol concentrations 30 min after awakening right up until bedtime. This effect is more apparent in the afternoon. With regards to professional inefficacy, a contrasting pattern emerged: severe professional inefficacy has the highest cortisol concentrations at awakening, and then reaches levels of low burnout symptoms 30 min after awakening. Starting from 1400 h onwards, professional inefficacy was then associated with a sharp decline in cortisol concentrations, ending with the comparatively lowest values at bedtime. Overall, the strength of the associations between emotional exhaustion, professional inefficacy, and the global burnout average in relation to cortisol concentrations appear to share similar magnitude.

4. Discussion

The purpose of this study was to assess whether specific Maslach burnout symptom sub-types and a global burnout average were associated with distinct diurnal cortisol profiles among a large sample of Canadian workers. Consistent with existing literature focusing on psychological outcomes (Maslach et al., 2001) and as reported in Table 2, emotional exhaustion was most correlated with cortisol concentrations, particularly afternoon and bedtime levels in our multilevel regression analyses. In comparison, correlations for professional inefficacy were only manifested at bedtime, while those for cynicism were, overall, not significant. Despite this distinction, a global burnout average encompassing all

Table 2 Results of multilevel regression modelling cortisol concentrations in ln[(μg/dl)*100] with the three components and the total scores of the burnout syndrome.

	Emotional exhaustion		Cynicism		Professional inefficacy		Total burnout	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Fixed part								
Constant	3.684**	0.161	3.664**	0.160	3.652**	0.160	3.641**	0.161
Cortisol awakening time	−0.072**	0.008	−0.072**	0.008	−0.072**	0.008	−0.072**	0.008
Occasion-2 (30 min-awakening)	0.327**	0.039	0.323**	0.038	0.252**	0.038	0.312**	0.044
Occasion-3 (1400 h)	−0.337**	0.074	−0.372**	0.073	−0.408**	0.073	−0.338**	0.077
Occasion-4 (1600 h)	−0.548**	0.089	−0.603**	0.089	−0.589**	0.088	−0.547**	0.092
Occasion-5 (bedtime)	-0.632**	0.136	-0.685**	0.136	-0.623**	0.135	-0.605**	0.138
Workday-1	0.042*	0.020	0.042*	0.020	0.042*	0.020	0.040*	0.020
Workday-2	0.050*	0.020	0.050*	0.020	0.050*	0.020	0.048*	0.020
Burnout (awakening)	0.011	0.020	0.025	0.022	0.045	0.027	0.036	0.029
Burnout (30 min-awakening)	−0.035	0.019	−0.039	0.022	0.018	0.026	−0.031	0.027
Burnout (1400 h)	−0.060**	0.020	−0.049*	0.022	−0.023	0.026	−0.072**	0.028
Burnout (1600 h)	−0.057**	0.020	−0.030	0.022	−0.045	0.026	−0.070*	0.028
Burnout (bedtime)	−0.055**	0.020	−0.033	0.022	−0.089**	0.027	−0.091**	0.028
Gender (women)	0.087	0.048	0.079	0.048	0.077	0.048	0.077	0.048
Age	0.000	0.002	0.000	0.002	0.000	0.002	0.000	0.002
Summer	0.052	0.106	0.037	0.105	0.034	0.105	0.046	0.106
Fall	−0.083	0.083	−0.085	0.083	−0.088	0.083	−0.086	0.084
Winter	−0.070	0.102	−0.067	0.102	−0.066	0.101	−0.066*	0.102
Smoking	0.012**	0.005	0.011*	0.005	0.011*	0.005	0.011	0.005
Alcohol	−0.007	0.004	−0.007	0.004	−0.007	0.004	−0.007	0.004
Physical activities	−0.009	0.010	−0.007	0.011	−0.007	0.010	−0.007	0.010
Body mass index	−0.001	0.003	−0.002	0.003	−0.002	0.003	−0.001	0.003
Tranquilizer use	0.321*	0.129	0.312*	0.130	0.310*	0.130	0.313*	0.130
Asthma	−0.136*	0.065	−0.140*	0.066	−0.139*	0.065	−0.137*	0.065
Back pain	−0.120*	0.061	−0.130*	0.061	−0.136*	0.061	−0.127*	0.061
Random part								
σ^2 (workplaces)	0.021**	0.009	0.021**	0.009	0.021**	0.009	0.022**	0.009
σ^2 (workers)	0.124**	0.011	0.130**	0.011	0.125**	0.011	0.125**	0.011
σ^2 (samples)	0.347**	0.007	0.347**	0.007	0.346**	0.007	0.350**	0.007
Fit								
Model χ^2 (df)	5977.7 (23)**		5967.0 (23)**		5981.6 (23)**		5869.0 (23)**	
Interaction burnout-time χ^2 (df)	16.5 (5)**		5.9 (5)		20.5 (5)**		14.5 (5)*	

Note:
* $p < 0.05$,
** $p < 0.01$.

symptom sub-types was likewise characterized by steep declines in PM cortisol concentrations. Importantly in our subsequent analyses using regression coefficients to depict associations in Fig. 1, both severe emotional exhaustion and the severe global burnout average correlated to the lowest cortisol concentrations 30 min upon awakening, consistent with our hypothesis. This therefore provides support for the notion that increased burnout symptomatologies correspond with comparatively lower cortisol levels and perhaps a down-regulation of the CAR or alternatively the CAR initiates earlier. Furthermore, results from the original multilevel regression suggest that emotional exhaustion and global burnout are also associated with the lowest cortisol levels in the afternoon and evening, suggesting an overall flattening of diurnal cortisol in such cases.

In accordance with Chida and Steptoe's (2009) meta-analysis, CAR profiles are thought to be positively associated with depressive symptoms and negatively associated with burnout symptoms. On the other hand, several important studies do not support the notion that burnout is a hypocortisolemic syndrome. One report found that the severity of burnout symptoms appears to be positively associated with morning cortisol levels (Grossi et al., 2005). In another study, burnout patients showed elevated cortisol levels during the first hour after awakening in comparison to healthy control subjects (De Vente et al., 2003). Likewise, chronic burnout was associated with significantly increased cortisol levels, somatic complaints, tension/irritability during and after work, and sleep problems (Melamed et al., 1999).

Increased HPA-axis output throughout the day has also been reported in nurses reporting greater frequency of

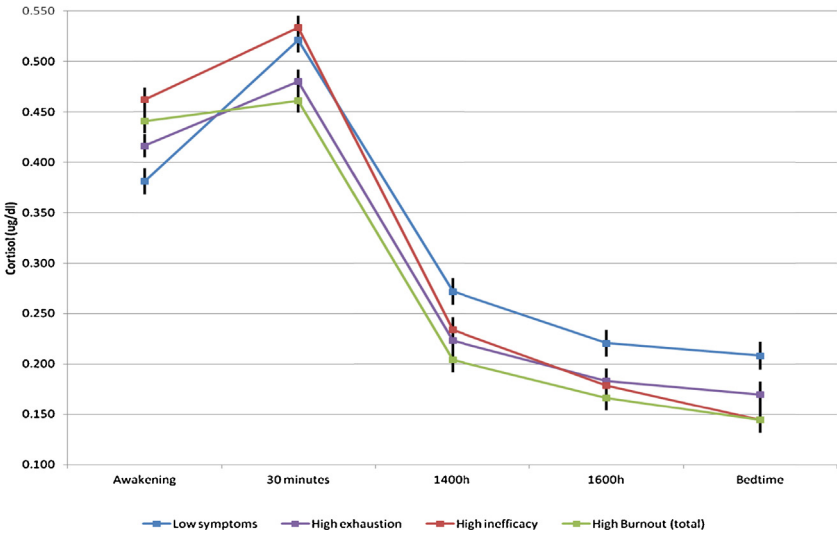

Figure 1 Estimated mean (SE bars) cortisol levels profiled according to low symptoms, severe emotional exhaustion, professional inefficacy, and total burnout symptoms. Note that cynicism is not included since it did not attain statistical significance. Cortisol levels are adjusted for self-reported time of awakening, sex, age, season of sampling, cigarette smoking, alcohol consumption, regular physical activity, tranquilizer use, asthma, back pain, and body mass index.

burnout symptoms but not vital exhaustion (Wingenfeld et al., 2009), a condition that overlaps with burnout in terms of symptoms and cortisol profiles (Kudielka et al., 2006). These mixed findings also occur with other psychopathologies like major depression whereby the CAR is indistinguishable, hyperactive (Pruessner et al., 2003; Chida and Steptoe, 2009; Vreeburg et al., 2009), or hypoactive (Stetler and Miller, 2005; Kuehner et al., 2007). Identifying distinct cortisol profiles requires multiple diurnal time-points, as one study found that low average cortisol levels as well as small differences between morning and evening cortisol levels predicted two-year depression (Grynderup et al., 2013).

Moving beyond differences in CAR, our study reveals that subtle variations in HPA-axis output might further depend on the particular burnout sub-type that may or may not be consistent with morning patterns. As a case in point in analyses illustrated in Fig. 1, the otherwise heightened CAR associated with professional inefficacy was matched with the lowest cortisol levels before bedtime. This underlines the importance of assessing afternoon and evening levels in research on the biological signatures of burnout, since the CAR may be an independent process that does not necessarily correspond with other diurnal time-points (Clow et al., 2010b). In addition to informing the minimal contribution of cynicism in predicting cortisol concentrations and the lack of sex moderation, this study provides evidence that emotional exhaustion may be a key hallmark of biological burnout characterized by a dampened CAR. In light of associations with professional inefficacy showing an opposite pattern, it is possible that the HPA-axis may be recalibrated at distinct symptomatic stages.

An alternative explanation could be that the CAR initiates earlier in cases of severe burnout and emotional exhaustion. It is important to note that both severe emotional exhaustion and severe total burnout symptoms displayed slightly elevated cortisol levels upon awakening in Fig. 1 that was then flattened 30 min thereafter. This may suggest that the CAR initiates earlier for severe forms of burnout for reasons perhaps due to sleep problems, cognitive processes (e.g., worry, anticipation), and/or intertwined health behaviours (e.g., excessive alcohol consumption disrupts beneficial sleep phases). If this were the case, it would not necessarily mean that results are entirely explained by HPA-axis down-regulation, but rather that diurnal events (e.g., CAR, nadir, trough, etc.) have been shifted. While it is not possible to ascertain this in the current study, it does nevertheless highlight the importance of accounting for numerous confounding factors in studies of diurnal cortisol.

Cortisol profiles may moreover exhibit different temporal manifestations depending on the symptom sub-type. Bellingrath et al. (2008) have proposed that high levels of emotional exhaustion in burnout may induce chronic elevation in cortisol levels that up-regulates the sensitivity of glucocorticoid receptors, leading to an especially enhanced negative feedback that can be assessed with pharmacological manipulation of the HPA-axis. For example, teachers reporting increased burnout symptoms displayed blunted CAR and increased dexamethasone suppression of cortisol levels (Pruessner et al., 1999). Conversely, a comprehensive study failed to detect differences in CAR, diurnal-curves, nor dexamethasone suppression differences in burnout patients compared to controls, highlighting the fact that much more research is needed (Mommersteeg et al., 2006a). It is interesting that after 14 sessions of psychotherapy, burnout patients with initially low morning cortisol levels showed increases in cortisol and reductions in symptoms in a separate study (Mommersteeg et al., 2006b). Taken together, it is possible that burnout might originate with hypercortisolemic profiles (e.g., amplified CAR and professional inefficacy) that might change over time into hypocortisolemic profiles (e.g., dampened CAR and emotional exhaustion) that culminate with disability.

In our current investigation of normal diurnal HPA-axis functioning among healthy workers who have not yet burnt

out, we speculate that specific Maslach burnout symptoms might correspond as early-stage warning signals (professional inefficacy) and late-stage warning signals (emotional exhaustion) of impending disability when assessed using triangulated methods that includes cortisol collection. Specifically, if severe emotional exhaustion is indeed a clinical hallmark of burnout and that it is associated with a comparatively low CAR (cortisol +30 min after awakening set as a baseline) as depicted in Fig. 1, it follows that professional inefficacy may be an earlier symptomatic manifestation associated with a comparatively high CAR followed by low cortisol at bedtime. Because our study design is not longitudinal, we can only speculate about this temporality; however, this postulation is parsimonious with existing literature showing that cortisol functioning can become fatigued and recalibrated towards hypocortisolism in order to safeguard against damaging HPA-axis ''overshooting'' and negative feedback ''backfiring''.

Our cross-sectional findings based on a large representative sample of workers have potential clinical implications in the early detection of individuals at risk of succumbing to burnout and potentially other related psychiatric conditions if burnout one day becomes a recognized psychiatric diagnosis. Burnout is currently only included as a residual category within the International Classification of Diseases (ICD-10) nomenclature as ''burnout: state of vital exhaustion'' (Z73.0). Moreover, the American Psychiatric Association did not include it in their recently updated Diagnostic and Statistical Manual of Mental Disorders (DSM-V). If burnout is indeed associated with low levels of cortisol, this has important implications in detection strategies as well as treatment approaches that might optimally up-regulate the HPA-axis rather than down-regulate it with pharmacology (e.g., antidepressants that indirectly dampen cortisol levels via increased serotonin saturation; Juster et al., 2011). Furthermore, if burnout does manifest itself with different symptom clusters and cortisol profiles over time, then there will be different windows of opportunity to tailor treatments appropriately and hopefully develop preventative interventions.

4.1. Limitations

Our first major limitation is the cross-sectional nature of our survey design that measured burnout symptoms only briefly before cortisol sampling. Despite our respectable sample size and only modest differences between responders and non-responders in terms of smoking and anthropometry, the relatively low response rate may have contributed to a selection bias. On the other hand, it could be argued that the random sampling of workers from diverse workplaces safeguards against misrepresentation.

By the same logic, it must be noted that our sample was deliberately heterogeneous with regards to various factors that can affect cortisol levels such as medication and health conditions. While it is well argued that strict exclusionary criteria should be used when investigating biological mechanisms, we felt that this would have limited the generalizability of our findings that were nevertheless well controlled for with our extensive array of covariates that did not diminish statistically meaningful findings. Moreover, we believe that inconsistencies in studies assessing CAR or other time-points might be due in part to the fact that workers are often homogenous to one profession (e.g., nurses, teachers) who experience unique workplace stressors. In accordance, we found that workplace emerged as a significant source of variation in cortisol concentrations in our multilevel regression models that will need to be explored further in future studies.

In terms of the burnout construct vis-à-vis cortisol profiles, we demonstrated that emotional exhaustion and total symptoms were most strongly correlated to cortisol concentrations; however, there is considerable overlap among all the different components that may not be physiologically distinct. For instance, participants provided scores on each one of the sub-types and the arguably redundant global burnout average, which were correlated to each other as well as to cortisol concentrations. Therefore, cortisol concentrations cannot be totally physiologically distinct since subjects experienced, to some degree, each burnout subtype. In addition to Maslach's popular measure of burnout, other instruments (e.g., Shirom-Melamed Burnout Measure (Melamed et al., 1992), Copenhagen Burn-Out Inventory (Kristensen et al., 2005), etc.) could be used to contrast symptomatic constructs (e.g., emotional exhaustion versus physical fatigue, cognitive weariness versus professional inefficacy) in association to distinct biological signatures in future studies.

In terms of cortisol measurement, it would have been ideal to monitor compliance using expensive electronic monitoring and helpful reminder technologies. Even though participants completed logbooks of saliva collection times, research using electronic monitoring technologies reveals that participants are not as compliant as they should be when using ambulatory methods (Kudielka et al., 2003). This may have caused some variations in the collection time points of saliva samples due to participants forgetting to sample or delays due to other reasons such as work demands. Variations due to lack of compliance thus engender measurement error that are difficult to evaluate; however, these errors are quite common in field studies even when strict protocols are maintained. Moreover, our preliminary analyses ascertaining adherence revealed that this did not significantly confound our findings despite substantial non-compliance.

Prospective studies that measure changes in burnout components in relation to recalibrations of HPA-axis functioning and various other biomarkers will yield further insights into which burnout components burn strongest and are most predictive of psychiatry disability. Our study has some noteworthy methodological consistencies that complement existing literature. For instance, the finding that the CAR is amplified on a working day relative to a rest day corroborates reports of an increased CAR on weekdays but not on weekends (Schlotz et al., 2004).

In addition to the advantages of repeated cortisol measurement in saliva, future research might consider assessing cortisol from hair samples to study associations between burnout and cumulative cortisol excretion and allow greater insight into temporal features of burnout symptomatologies. As a retrospective calendar, hair samples are believed to represent long-term cortisol excretion and not short-term concentrations as assessed from saliva samples (van Holland et al., 2011). In addition to stress biomarkers, future studies should address sleep that influences burnout recovery (Sonnenschein et al., 2007) and day-to-day variations in cortisol (Dahlgren et al., 2009).

4.2. Conclusions

In summary, this study demonstrates that emotional exhaustion appears to be the most significant component of Maslach's formulation in association with HPA-axis dysregulations followed by a global burnout average of all sub-scales. In analyses the incorporated multilevel regression coefficients to graph associations separately, both emotional exhaustion and the global burnout average corresponded with low levels of cortisol upon awakening, consistent with the notion that burnout may be manifested by a blunted CAR and therefore perhaps a hypocortisolemic syndrome or alternatively that the CAR starts earlier in severe form of burnout. In light of interesting opposite associations with severe professional inefficacy characterized by a heightened CAR and the lowest bedtime cortisol concentration, future prospective studies must delineate plausible changes in burnout sub-types with increasing levels of distress in relation to subtle recalibrations in HPA-axis functioning.

Most importantly, the notions of "blunted", "flattened", and "hypo" functioning of the HPA-axis in burnout and all psychological conditions can only truly be qualified as such with the development of clinical references for salivary cortisol based on normative data representing diverse working populations. Person-centred approaches can be facilitated by combining, for instance, psychometrics and biometrics to arrive at a greater understanding of specific profiles predictive of disorders and the eventual establishment of standards that are not impossible for cortisol researchers to implement in the near future. Given both professional and personal suffering, researchers must endeavour to establish such norms and further identify biopsychosocial characteristics of burnout in order to refine detection and prevention of this complex syndrome.

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Conflict of interest statement

None declared.

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