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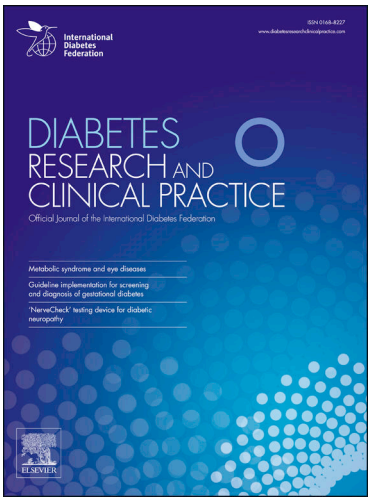

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Diabetes-related distress and daily cortisol output in people with Type 2 diabetes

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Abstract

Aims: Diabetes-related distress is common in Type 2 Diabetes and is linked with poor diabetes control. However, mechanisms underlying this association are unclear. One pathway that could be involved is neuroendocrine dysfunction, as Type 2 Diabetes is associated with altered diurnal cortisol output. This study investigated the link between diabetes-related distress and diurnal cortisol output.

Methods: 134 people with Type 2 Diabetes provided 5 cortisol samples over the course of a day. Multivariate linear regression models were used to assess whether overall and sub-domains of diabetes-related distress measured by the Diabetes Distress Scale, predicted cortisol parameters (waking cortisol, cortisol awakening response, cortisol slope and evening cortisol).

Results: Physician-related distress was associated with greater waking (B = 2.747, p = .015) and evening cortisol (B = 1.375, p = .014), and a blunted cortisol awakening response (B = -3.472, p = .038) adjusting for age, sex, income, body mass index, smoking and time of awakening. No associations were detected for overall distress, emotional, interpersonal or regimen distress.

Conclusion: Physician-related distress was associated with alterations in daily cortisol output. Longitudinal research is required to understand how physician-related distress is associated with diurnal cortisol patterning over time.

Keywords: Type 2 Diabetes; Diabetes-related distress; Cortisol

1. Introduction

Diabetes-related distress refers to the unique emotional burden of living with diabetes [1,2]. The concept goes beyond generalized psychological stress, capturing distress related to self-management, regimen adherence and the risk of future complications [1,2]. Diabetes-related distress is highly prevalent. Results from a study of almost 9000 participants from 17 countries suggest that 44.6% of those with diabetes report considerable diabetes-related distress [3].

Diabetes-related distress has been linked with sub-optimal glycemic control in several studies [1,4,5]. In a study of 506 participants with Type 2 diabetes, individuals who reported greater diabetes-related distress had higher glycated hemoglobin (HbA1c) levels both cross-sectionally and prospectively [1]. Some studies have investigated the sub-domains of diabetes-related distress (emotional burden, interpersonal distress, physician-related distress and regimen-related distress) [6] in relation to glycemic control [7]. One small Canadian study found no association between overall distress and glycemic control, but reported that those with greater regimen-related distress and emotional burden had higher HbA1c levels [7]. These findings emphasize the importance of assessing overall distress, as well as the sub-components of diabetes-related distress.

Considering the links between diabetes-related distress and sub-optimal glycemic control, there is interest in understanding the mechanisms underlying this association [4]. In the wider literature on stress and diabetes, there has been a focus on stress-related biological factors as a potential pathway linking negative psychosocial factors with Type 2 diabetes risk and diabetes complications [8]. One biological mechanism of interest in this regard is neuroendocrine dysfunction. Cortisol (the end product of the hypothalamic pituitary adrenal axis) plays a role in processes relevant to Type 2 diabetes. There is evidence that cortisol responses to acute laboratory stress are altered in people with Type 2 diabetes, in comparison to matched healthy controls [9]. Outside of the laboratory environment, diabetes has been linked with alterations in daily cortisol output. As measured using saliva sampling, cortisol has a distinctive diurnal pattern, characterized by high concentrations on waking, reaching a peak 30-45 minutes after waking (referred to as the cortisol awakening response) then declining over the day [10]. In a study of over 3000

adults, participants with type 2 diabetes had a flatter decline (slope) in cortisol across the day, along with raised evening cortisol levels, than those without diabetes [11]. These components of the diurnal cortisol curve have also been linked with an increased risk of pre-diabetes and diabetes over 9 year follow-up [12] as well as cardiovascular death [13], the leading cause of mortality in people with Type 2 diabetes [14].

Previous work has linked alterations in daily cortisol output with negative psychosocial stress factors including depression [15]. However, no work to date has investigated the link between diabetes-related distress and alterations in daily cortisol output. Depression (from depressive symptoms to clinical depression) is common in Type 2 diabetes and is the most well-research psychosocial factor in this population [16]. However, diabetes-related distress may be a better prognostic factor for glycemic control [1] as the emotional distress is disease specific [17].

To address the lack of literature linking diabetes-related distress and diurnal cortisol, the current study set out to investigate potential associations in adults with Type 2 diabetes. A secondary aim was to assess whether associations between diabetes-related distress and cortisol were independent of depressive symptomology.

2. Subjects, Materials and Methods

2.1 Design

This analysis used data from a larger cross-sectional study examining biological responses to laboratory stress and cortisol in everyday life in people with and without Type 2 diabetes [9]. The overall aim of the study was to investigate associations between stress-related biology and cardiovascular risk [9]. Secondary goals included assessing the impact of demographic characteristics [18], health behaviours [19,20] and psychosocial factors [21–24] on stress-related biology in people with Type 2 diabetes. The participants without diabetes were recruited as a sub-sample of the Whitehall II cohort in 2006-2008 [25]. The participants with Type 2 diabetes were recruited as a comparison sample in 2011-2012. Eligible participants were recruited through diabetes outpatient clinics and primary care practices in London. Those with a history of coronary heart disease were excluded as the primary aim of the larger study was to investigate

cardiovascular risk. Those with inflammatory disease or mood disorders were not included, as these factors influence biological stress responsivity. The number of participants who met the inclusion criteria at the outpatient diabetes clinics was low (<10%), and as a result the majority of participants were recruited from primary care. Eighteen primary care practices agreed to take part in the research out of 36 practices approached. Of the 18 practices that agreed to take part, 16 of these provided participants. It was not possible to calculate a study response rate for primary care recruitment as the practices differed in their requirements surrounding the confidentiality of patient data and the sending of recruitment letters. A total of 140 participants aged 50-75 years with established Type 2 diabetes provided data for the larger study [9] and of those 134 (95.71%) provided data on diabetes-related distress. The National Research Ethics Service (97/0356) granted ethical approval for the study. All participants provided informed consent.

2.2 Psychological measures

Diabetes-related distress was measured using the Diabetes Distress Scale [6]. Participants responded to 17 items on a scale from 1 (not a problem) to 6 (a very serious problem), rating the extent to which each statement distressed them during the past month. The items were totaled and averaged to create an overall diabetes distress score (range 1-6). A mean score >3 is considered clinically meaningful [26]. The scale had good internal consistency (Cronbach's α =0.94) in our study. The Diabetes Distress Scale also has four sub-domains. Emotional burden was assessed with five items (e.g. "*feeling that diabetes controls my life"*). Physician-related distress was assessed with four items (e.g. "*feeling that my doctor doesn't take my concerns seriously enough*"). Regimen-related distress was assessed with five items (e.g. "*not feeling motivated to keep up my diabetes self-management"*), whilst interpersonal distress was assessed with three items (e.g. *"feeling that friends or family don't give me the emotional support that I would like"*). Scores for each of the sub-domains were totaled and averaged and all had good internal consistency (α's >0.85).

The 20 item Centre for Epidemiologic Studies Depression Scale was used to assess depressive symptoms over the previous week [27]. Participants responded to statements such as "*I felt depressed*" and "*I thought my life had been a failure*". Response options ranged from 0 (Rarely or None of the Time) to 3

(Most or Almost All the Time). The overall score could range from 0-60, with higher scores indicating greater depressive symptomology. The scale had good internal consistency (α =0.86).

2.3 Cortisol

Participants provided five salivary cortisol samples over the course of a typical day using Salivettes (Sarstedt). Samples were obtained upon waking (time 1), thirty minutes after waking (time 2), at 10:00-10:30 (time 3), 16:00-16:30 (time 4) and 20:00-20:30 (time 5). Participants were instructed to avoid caffeinated beverages, eating and smoking for thirty minutes prior to sample collection. The samples were stored at -20 degrees before analysis and were assayed at the University of Dresden using a time resolved immunoassay with fluorescence detection. Intra- and interassay coefficient of variations were <8%.

We were interested in waking cortisol, the cortisol awakening response, the slope over the day and evening cortisol as key aspects of the diurnal cortisol rhythm [10]. To calculate the cortisol awakening response the time 1 measurement was subtracted from time 2 measurement. The cortisol slope was calculated by regressing cortisol values at samples 1, 3, 4 and 5 on time after awakening as described previously [11].

2.4 Other measures

Participant age, sex (men/women), ethnicity (white/non-white), smoking status (yes/no) were obtained by self-report. Yearly household income was measured in sterling and categorized in bands of <£20,000, £20,000-£40,000, £40,000-£60,000 or >£60,000. As part of the larger study [9], participants provided a blood sample for the assessment of HbA1c, anthropometric measures were obtained and body mass index was calculated (kg/m^2). Participants self-reported their diabetes medication (oral medication/insulin). Medication adherence was obtained using the Medication Adherence Rating Scale [28]. Participants rated 5 items such as *"I stop taking my diabetes medicine for a while"* on a scale from 1 (always) to 5 (never). The items were totalled with higher scores indicating better medication adherence. The scale had acceptable internal consistency (α= 0.70). These variables were measured as both diabetes-related distress and cortisol

responses vary according to individual characteristics such as age, sex [29,30], ethnicity [31,32] and household income [32,33]. Cortisol responses differ depending on smoking [34] and BMI [35]. HbA1c, medication usage and medication adherence were assessed as these factors are linked with diabetes management [1].

2.5 Statistical Analysis

Cortisol over the day was analyzed using a repeated-measures Analysis of Variance. Pearson's *r* correlations were used to assess associations between diabetes-related distress and the cortisol measures. Significant findings from the correlational analyses were tested using multivariate linear regression, with diabetes-related distress as a continuous score as the predictor variable. Separate models were conducted with waking cortisol (time 1), the cortisol awakening response, cortisol slope or evening cortisol (time 5) as the dependent variable. Age, sex, household income, smoking status, body mass index and time of awakening were included as covariates in all models. These covariates were selected a priori as they may influence cortisol output. In preliminary analyses, we investigated interactions between diabetes-related distress and ethnicity, HbA1c, medication usage and medication adherence respectively on cortisol measures. No significant interactions were detected so these terms were not included in the final models. Regression results are presented as unstandardized regression coefficients *(B)* and 95% confidence intervals (CI). For graphical purposes only, significant results from the regression analyses are illustrated by comparing high and low diabetes-related distress groups defined with the established cut point of 2 [2] using analysis of variance. Analyses were conducted using SPSS V.25.

2.6 Sensitivity analysis

In preliminary analyses, depressive symptomology was positively correlated with overall diabetes-related distress and the sub-domains of distress (*p's* <.01). We conducted a sensitivity analysis to determine whether associations between diabetes-related distress and cortisol were independent of depressive symptomology.

3. Results

3.1 Participant Characteristics

The sample included 134 individuals with Type 2 diabetes with a mean age of 63.58 years (Table 1). The majority of the participants were male, of white ethnicity, with a low household income. The average BMI was 30.84 kg/m^2, with 51.5% of the sample having a body mass index in the obese range. The mean overall diabetes-related distress score was 1.84 and 32.8% of the sample reported high levels (>2) of distress. The average HbA1c was 7.3% (53 mmol/mol), with a range between 5.40-13.10% (36-120 mmol/mol). The majority of participants were taking oral diabetes medication (78.4%). Cortisol varied across the day (F (2.813, 329.149) = 50.269, p <.001). In line with diurnal rhythms, cortisol levels were high on waking, increasing in concentration thirty minutes after waking and followed by a decline over the day. There was a small amount of missing data for some of the cortisol measures due to assaying issues when the data were sent for processing.

3.2 Correlations between diabetes-related distress and cortisol measures

Waking cortisol was significantly correlated with overall distress (r = .198, p = .028) and physician-related distress (r = .258, p = .003), while the cortisol awakening response was correlated with physician-related distress alone (r = -.304, p =.002). Overall distress (r = .178, p =.044) and physician-related distress (r = .205, p =.020) were correlated with the slope. Evening cortisol was associated with physician-related distress (r = .185, p =.037). No significant correlations were found for emotional burden, interpersonal distress or regimen-related distress.

3.3 Regression models with overall diabetes-related distress and physician-related distress

In unadjusted models, diabetes-related distress was a significant predictor of waking cortisol (B = 2.523, p = .028) and the cortisol slope (B = .004, p = .044). However, these associations were attenuated to the null in adjusted models (Table 2). Physician-related distress was significantly associated with waking cortisol

(B = 2.747, p = .015), independent of age, sex, income, body mass index, smoking and time of awakening (Table 3). These results suggest that those with higher physician-related distress had raised waking cortisol concentrations. Participants with higher physician-related distress had a lower cortisol awakening response (B = -3.472, p = .038) and raised evening cortisol concentrations (B = 1.375, p = .014) when controlling for covariates. However, the association between physician-related distress and the cortisol slope was not robust to adjustment (B = 0.003, p =.142). The pattern of cortisol output across the day in those with high and low physician-related distress can be found in Figure 1.

3.4 Sensitivity Analysis

Further analysis was conducted to explore whether the findings changed when depressive symptomology was taken into account. No significant interactions between depression and overall diabetes-related distress or physician-related distress were detected. Associations between physician-related distress and waking cortisol (B = 2.491, CI = .228 to 4.754, p = .031), the cortisol awakening response (B = -4.059, CI = -7.468 to -.650, p = .020) and evening cortisol (B = 1.251, CI = .118 to 2.385, p = .031) remained when depressive symptomology was added as an additional covariate.

4. Discussion

This study investigated the association between diabetes-related distress and diurnal cortisol output in people with Type 2 diabetes. We found that physician-related distress was associated with higher levels of waking and evening cortisol, along with a blunted cortisol awakening response. The findings remained when depressive symptomology was taken into account. No significant associations were established for overall distress, emotional burden, regimen-related distress or interpersonal distress.

Our findings are novel as the link between diabetes-related distress and diurnal cortisol output has not been previously explored. We found that individuals who reported physician-related distress had raised evening cortisol concentrations. Previous research indicates that evening cortisol levels are heightened in people with Type 2 diabetes in comparison with controls [11] and are prospectively associated with

cardiovascular death [13], the leading cause of mortality in people with Type 2 diabetes [14]. It is possible that physician-related distress in people with Type 2 diabetes could exacerbate the link between raised evening cortisol concentrations and later cardiac risk, but further research is required to test this hypothesis.

Physician-related distress was also associated with heightened waking cortisol concentrations and a lower cortisol awakening response in adjusted models. The evidence linking Type 2 diabetes and the cortisol awakening response is mixed with some studies reporting a blunted response [36,37] and others finding no association [11,38]. Both blunted and heightened awakening responses have been associated with psychosocial stress and negative health outcomes [10], perhaps indicating that psychosocial stressors cause a departure from normal morning cortisol output, reflected through a dampening or exaggeration of concentrations. More work is needed to understand the significance of a blunted cortisol awakening response in people with Type 2 diabetes reporting physician-related distress.

On average in our sample, distress scores were highest in the emotional burden and regimen-related distress sub-domains. However, these components of diabetes-related distress were not linked with cortisol. Similarly, no associations were observed for interpersonal distress. It is unclear why physician-related distress in particular would be linked with disturbances in daily cortisol output, even when depressive symptomology was taken into account. One plausible explanation could be related to the concept of perceived control. Physician-related distress relates to the perceived support of doctors and other healthcare professionals in providing diabetes care [6] and as such is an external cause of distress that an individual may not be able to control or change. For other sub-domains, such as regimen-related distress, it may be that although individuals cannot control whether they need medication, they may feel able to control their distress through acquiring appropriate self-management skills and developing strategies to aid medication adherence. There is evidence that perceived control of a situation and trait-like differences in perceptions of control (locus of control) may be linked with cortisol, whereby feeling that a situation is controlled by powerful others (external locus of control) has been related with increased cortisol responsivity to stress [39]. Other literature suggests that perceived control mediates the link between diabetes-related distress and

treatment outcomes [5], contributing to poorer medication adherence and glycemic control. Further research is needed to confirm whether this pathway mediates the relationships observed in the current study.

Another explanation could be poor communication between the individual with diabetes and their healthcare professional. A review of evidence suggests that perceived poor communication from those providing diabetes care is associated with diabetes-related distress and serves to negatively impact self-management and treatment adherence [40]. Efforts are underway to highlight the importance of healthcare professional communication in diabetes care. The 2018 "*Language Matters*" position statement for England highlights the importance of communication for diabetes education and treatment and offers healthcare professionals insight into how to acknowledge the presence of diabetes-related distress [41]. However, it remains difficult to assess how healthcare professionals are implementing these suggestions in diabetes clinics, and whether this has an impact on physician-related distress. Moderate effects have been established when educating and assessing healthcare professionals on communication [42]. As such, a way to improve reports of physician-related distress could be to provide educational training for communication, as opposed to guidance alone. Directly, targeting distress itself through psychological interventions could also be advantageous, as review evidence from 30 randomized controlled trials suggests that diabetes-related distress is amenable to intervention, with benefits for HbA1c at 6-12 month follow-up [43].

Our findings lend support to the notion that diabetes-related distress and depression are separate constructs [1], as our results linking physician-related distress and cortisol were independent of depressive symptomology. Diabetes-related distress may better capture the emotional impact of living with diabetes when compared with measures of depression [17]. There is some evidence that standardized depression scales might overlap or be capturing symptoms of diabetes (e.g. tiredness associated with hyperglycemia) rather than emotional distress [44]. This may account for the lack of interaction between diabetes-distress and depression in the current study. Previous work suggests that diabetes-related distress is cross-sectionally and prospectively associated with HbA1c [1] and there is some evidence that improvements in glycemic control following a diabetes education intervention are associated with changes in diabetes-related distress rather than depressive symptoms [45]. Our results are in keeping with the notion that the influence

of diabetes-related distress on health relevant biological markers in this population may be independent of depression [1], though further research is required to test this assertion.

In the present study we assessed cortisol across the day in a well-characterized sample of participants with Type 2 diabetes and we were able to adjust for a number of potentially confounding factors in our analysis. However, our findings should be assessed in light of various limitations. The sample consisted of people with Type 2 diabetes without history of cardiovascular disease and the majority of participants were of white, European origin. Thus, these results may not readily apply to other groups. Furthermore, the study was cross-sectional and cortisol was only assessed over one day, meaning our results may reflect episodic rather than long-term associations with physician-related distress [46]. Further research is required to understand how diabetes- physician-related distress is associated with diurnal cortisol patterning over time. The range of scores of the physician-related distress scale was modest, with the majority of participants reporting low levels of physician-related distress. The relationships tested in the current study need to be replicated in a larger sample with a greater range of distress scores. We relied on self-report for the timing of sample collection. However, we controlled for awakening time in our analyses and evidence suggests that participants are generally accurate in their recording of this information [47]. Although, we adjusted for a number of covariates in our analyses, but we did not have information on diabetes duration, and it is possible that the impact of physician-related distress on cortisol could differ depending on this. The majority of our sample had well controlled diabetes (based on HbA1c) and were taking oral medication to control Type 2 Diabetes. Diabetes-related distress or physician-related distress did not interact with HbA1c, medication adherence or medication usage in this study (data not shown), which makes it unlikely that diabetes severity impacted the relationships presented in this paper. However, this possibility cannot be completely excluded based on the information available.

Despite, these considerations our results suggest that physician-related distress is associated with higher levels of waking and evening cortisol, along with a blunted cortisol awakening response, independent of depressive symptomology. Increased physician-related distress and corresponding changes

in daily cortisol output could increase the risk of complications in this population. However, further research is required to confirm this assertion.

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Author Contributions

RAH and HB conceived and designed the study conducted the statistical analysis and drafted the manuscript. All authors provided critical revisions and approved the final submitted version.

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Table 1. Participant characteristics (*n* =134)

Variable	N	Mean (standard deviation) or number (%)
Age (years)	134	63.58 (6.89)
Sex (% men)	134	85 (63.4%)
Ethnicity (% white)	134	108 (80.6%)
Body mass index (kg/m^2)	132	30.84 (5.59)
Household Income (£)[b]	129	
<£20,000		54 (40.3%)
£20,000-£40,000		37 (27.6%)
£40,000- £60,000		11 (8.5%)
>£60,000		27 (20.9%)
Smoker (% yes)	134	19 (14.2%)
Overall diabetes distress	134	1.84 (0.88)
Emotional Burden	134	1.92 (1.10)
Physician-related	134	1.57 (1.01)
Regimen-related	134	2.07 (1.04)
Interpersonal	134	1.66 (0.95)
Waking cortisol[c] (nmol/L)	128	19.57 (11.57)
Cortisol awakening response[d] (nmol/L)	102	9.42 (15.20)
Cortisol slope[e](nmol/L per hour)	129	0.02 (0.02)
Bedtime cortisol[f] (nmol/L)	127	5.66 (5.60)
Depressive symptoms[a]	132	11.72 (8.89)
Oral diabetes medication (% yes)[g]	131	105 (78.4%)
HbA1c (mmol/mol and %)[c]	128	56 (16) and 7.3 (1.5)

HbA1C = glycated hemoglobin

Table 2. Overall diabetes-related distress and daily cortisol output

	Unadjusted				Adjusted[a]			
	n	*B*	*p*	*95% CI*	*n*	*B*	*p*	*95% CI*
Waking cortisol (nmol/l)	128	2.523	**.028**	0.28; 4.67	120	2.465	.067	-0.18; 5.11
Cortisol awakening response (nmol/l)	102	-3.228	.058	-6.57; 0.12	95	-1.699	.403	-5.72; 2.32
Slope across the day (nmol/l per h)	129	0.004	**.044**	0.00; 0.01	121	0.003	.167	-0.00; 0.01
Evening cortisol (nmol/l)	127	0.582	.311	-0.55; 1.71	119	0.782	.243	-0.54; 2.10

[a] Adjusted for age, sex, income, body mass index, smoking and time of awakening.

Table 3. Physician-related distress and daily cortisol output

	Unadjusted				Adjusted[a]			
	n	*B*	*p*	*95% CI*	*n*	*B*	*p*	*95% CI*
Waking cortisol (nmol/l)	128	2.910	**.003**	0.99; 4.83	120	2.747	**.015**	0.54; 4.95
Cortisol awakening response (nmol/l)	102	-4.516	**.002**	-7.32; -1.71	95	-3.472	**.038**	-6.75; -0.20
Slope across the day (nmol/l per h)	129	0.004	**.020**	0.00; 0.01	121	0.003	.142	-0.00; 0.07
Evening cortisol (nmol/l)	127	1.039	**.037**	0.06; 2.01	119	1.375	**.014**	0.28; 2.47

[a] Adjusted for age, sex, income, body mass index, smoking and time of awakening.

Figures

Figure 1

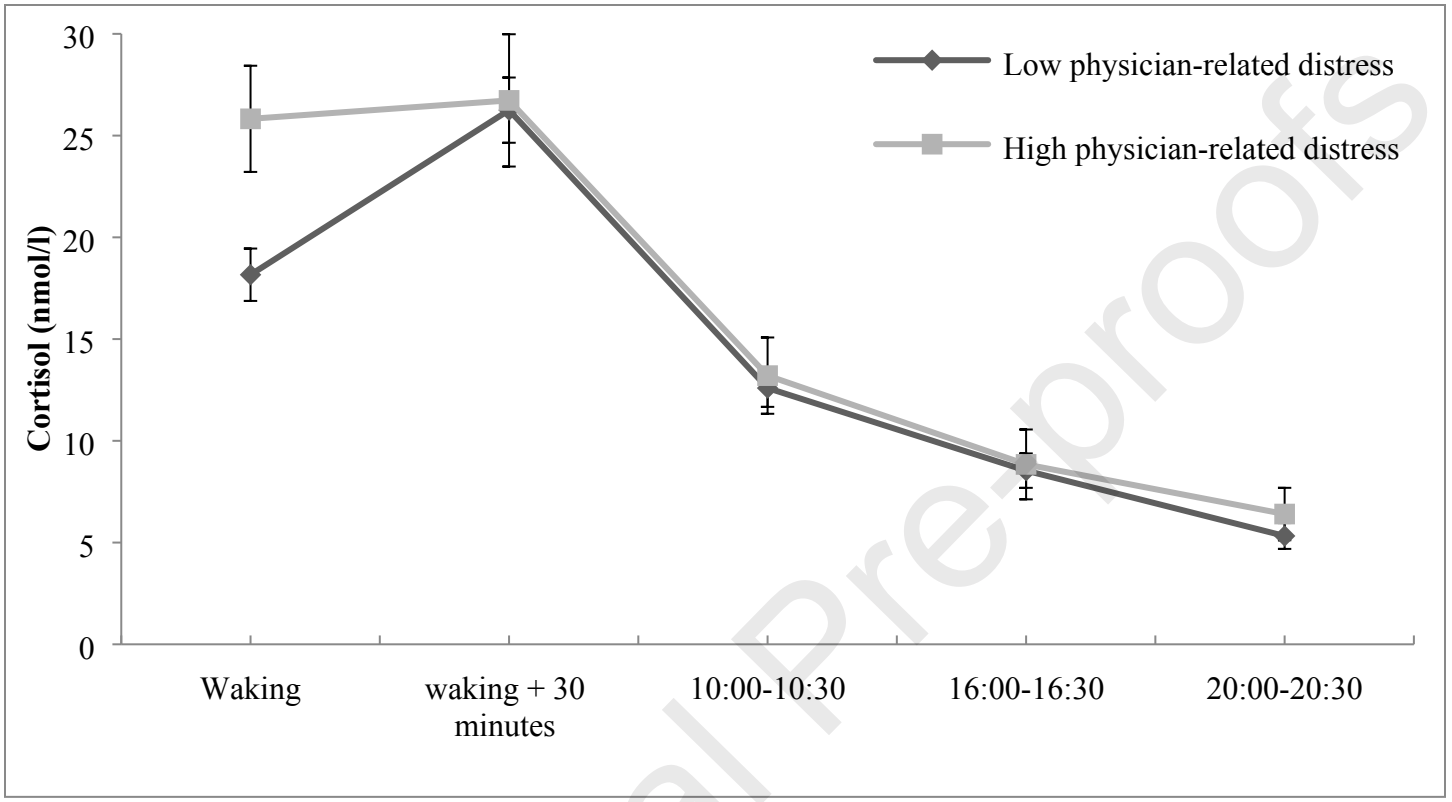

Figure 1 caption: Diurnal cortisol output in the low physician-related distress (<2) and high physician-related distress (>2) groups. Values are adjusted for age, sex, income, body mass index, smoking and time of awakening. Error bars are standard error of mean.