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Salivary cortisol, serum lipids, and adiposity in patients with depressive and anxiety disorders

Gerthe Veen[a,*], Erik J. Giltay[a], Roel H. DeRijk[b], Irene M. van Vliet[a], Johannes van Pelt[c], Frans G. Zitman[a]

[a]*Department of Psychiatry, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands*
[b]*Department of Medical Pharmacology, Leiden/Amsterdam Center for Drug Research and Leiden University Medical Center, Leiden, PO Box 9600, 2300 RC Leiden, The Netherlands*
[c]*Department of Clinical Chemistry, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands*

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Abstract

Depressive and anxiety disorders are associated with an increased risk of cardiovascular disease. Chronic stress induces hypothalamus-pituitary-adrenal (HPA)–axis perturbations, which might subsequently induce atherogenic lipoprotein profiles and adiposity. The aim of the present study was to investigate the relationship between basal saliva cortisol levels and serum lipids and adiposity in psychiatric patients. Eight salivary cortisol samples (awakening; 30, 45, and 60 minutes after awakening; 11:00 AM, 3:00 PM, 7:00 PM, and 11:00 PM) on 2 consecutive days in medication-free outpatients with depressive and/or anxiety disorders (n = 72) and in healthy controls (n = 42) were used to derive 2 measures of HPA-axis function: basal cortisol concentrations (ie, area under the curve [$AUC_{cortisol}$]) and circadian cortisol variability ($variability_{cortisol}$). Index *z* scores were calculated for dyslipidemia (from serum triglycerides, inverse high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol) and adiposity (from body mass index and waist-to-hip ratio). Regression analyses were conducted to determine the contribution of $AUC_{cortisol}$ and $variability_{cortisol}$ in explaining the variance of, respectively, the lipid and adiposity index. Patients showed a higher mean $AUC_{cortisol}$ compared with healthy controls (t = 2.7, P = .01). Both cortisol parameters were independently associated with dyslipidemia in patients after adjustment for age, alcohol use, and smoking habits (β = .31, P = .02 and β = −.29, P = .02, respectively), but not in controls. Cortisol measures were not associated with adiposity in either group. We conclude that elevated basal cortisol concentrations and lower circadian cortisol variability were independently associated with a less favorable lipoprotein profile in patients with depressive and/or anxiety disorders. These data lend support to the hypothesis that the relationship between affective disorders and cardiovascular disease is partly mediated by HPA-axis perturbations.

1. Introduction

Several studies have shown that depression is associated with an increased morbidity and mortality from cardiovascular disease (CVD) [1-3]. There is growing evidence that the same holds for anxiety disorders [4-6]. In a part of patients with depressive and anxiety disorders, dysfunctions of the hypothalamic-pituitary-adrenal (HPA) axis are observed. The most frequently reported finding is hypercortisolemia under basal conditions [7,8]. Another dysfunction that has been found repeatedly is a lower circadian cortisol variability compared with healthy controls [9,10]. As cortisol influences many metabolic processes, these HPA-axis dysfunctions are plausible mediators of the association between depressive and anxiety disorders on the one side and CVD on the other [11].

Cortisol is a stress hormone that has effects not only on blood pressure, glucose metabolism, and the immune system, but also on lipoprotein metabolism and body composition. It stimulates lipolysis and decreases the activity of lipoprotein lipase, partly through its effects on insulin sensitivity. As a consequence of hypercortisolism, serum levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides increase; and serum levels of high-density lipoprotein (HDL) cholesterol decrease. In the long term, this dyslipidemia due to a cortisol excess leads to

* Corresponding author. Tel.: +31 71 5263785; fax: +31 71 5248156.
E-mail address: g.veen@lumc.nl (G. Veen).

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an increase in central adiposity [12-14], an elevated body mass index (BMI), and a higher waist-to-hip ratio (WHR) [15-18]. These metabolic effects of cortisol are clearly shown in studies on the effects of synthetic glucocorticoids during anti-inflammatory and immunosuppressive therapy [19] and on Cushing disease [17,18]. In addition, in healthy participants, a lower circadian cortisol variability was associated with detrimental metabolic effects, that is, high triglycerides, high LDL cholesterol, low HDL cholesterol, high BMI, and high WHR [20-23].

Studies on HPA-axis dysfunctions in patients with depressive disorders are scarce and show contradictory results. In a large cross-sectional survey of elderly depressed patients, high 24-hour urinary cortisol levels were associated with the metabolic syndrome, including high triglycerides and low HDL cholesterol [11]. However, in another study, higher salivary cortisol levels (measured at 3 time points during the day) were associated with lower LDL cholesterol levels in 41 overweight depressed patients (BMI >25 kg/m^2), but not in 37 patients of normal weight [24]. Anxiety disorders were associated with dyslipidemia [25,26]; but to the best of our knowledge, no studies were done on the associations between lipids and cortisol levels in anxiety disorders.

We studied 2 aspects of the HPA-axis function (ie, basal cortisol release over the day and circadian cortisol variability as an indicator of the responsivity of the stress system). Both HPA-axis functions are known to be disturbed in patients with depressive and/or anxiety disorders and are hypothesized to be related to a detrimental lipid metabolism and adiposity. As far as we know, no previous study focused on both aspects of HPA-axis function and their relationship with parameters of dyslipidemia and adiposity in patients with depressive and anxiety disorders. As psychotropic medication is a potential confounder that may affect body weight, serum lipids, and lipoproteins levels [27,28] as well as cortisol levels, we included only patients free of such medication.

2. Methods

2.1. Participants

Seventy-two patients with a depressive and/or anxiety disorder were recruited from the outpatient department of the mental health center Rivierduinen in Leiden, the Netherlands. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnoses were confirmed by trained interviewers using the Dutch version of the Mini International Neuropsychiatric Interview Plus 5.0.0-R [29,30]. Patients with any other Axis I disorder were excluded. Axis I psychopathology was also ruled out by the Mini International Neuropsychiatric Interview Plus 5.0.0-R in 42 healthy controls recruited by advertisement. Exclusion criteria were a history of neurologic or endocrine diseases or other serious medical conditions. Furthermore, participants with substance or alcohol abuse, as well as pregnant or breast-feeding women and premenopausal women with ovariectomy, were excluded. Participants using psychotropic medication with exception of a low dose of a benzodiazepine (equivalent to 30 mg oxazepam daily) were also excluded. If psychotropic medication was used within the last 14 days (for fluoxetine, 6 weeks), participants were excluded. In addition, participants using corticosteroids, antidiabetics, estrogens, thyroid hormone, or herbal medication (eg, valerian, St John's wort) were excluded. All participants had a routine physical examination and laboratory blood tests. Before participation, written informed consent was obtained from all participants. The study was approved by the ethics committee of the Leiden University Medical Center.

2.2. Saliva cortisol measures

Instructions concerning saliva sampling prohibited eating, smoking, drinking tea or coffee, or brushing teeth within 15 minutes before sampling. Furthermore, no dental work 24 hours before sampling was allowed. Saliva samples were obtained using Salivettes (SARSTEDT, Nümbrecht, Germany) at 8 time points covering the cortisol day curve. Four samples were collected at awakening (T1) and 30 (T2), 45 (T3), and 60 (T4) minutes after awakening. Four additional samples were taken at 11:00 AM (T5), 3:00 PM (T6), 7:00 PM (T7), and 11:00 PM (T8). The cortisol curve of a single day is determined by situational factors and, to a smaller extent, by trait factors. Therefore, to reduce measurement error and the effects of day-to-day variation [31], participants were asked to provide saliva samples on 2 consecutive nonworking days. Nonworking days were chosen for both patients and controls because hardly any patients were working because of their illness. Samples were stored at 4°C until bringing them to the clinic, within 1 week after collection. After receipt, Salivettes were centrifuged at 2000*g* for 10 minutes, aliquoted, and stored at −20°C. Cortisol analysis was performed by competitive electrochemiluminescence immunoassay (Roche, Basel, Switzerland), as described in Van Aken et al [32]. The lower detection limit was less than 0.50 nmol/L. The intraassay coefficients of variance were lower than 7%; the interassay coefficients of variance were lower than 8%, except for the very low range. Per sampling point, *physiologically unlikely high values* (defined as >50 nmol/L) were excluded from further analyses (1.3% of the data). Saliva cortisol levels are reported as nanomoles per liter and showed a normal distribution. The 2 cortisol values obtained at the time points on the 2 days were significantly correlated, indicating moderate to good intraindividual stability over time (r between .42 and .68, $P \leq .01$). Therefore, mean cortisol values for each time point were computed for each subject and used in the analyses. If a sample was missing, then the value of the other day was used (for 2.9% of the data).

2.3. Anthropometric, lipid, and lipoprotein measures

Body weight and height were measured to calculate the BMI (kilograms per square meter). To calculate the WHR, the waist circumference was measured midway between the lower costal and iliac crest; and the hip circumference was measured at the level of the great trochanters.

Venous blood was sampled with standard venipuncture techniques. Nonfasting triglycerides, total cholesterol, and HDL cholesterol (plus third generation) were measured in serum by automated enzymatic colorimetric methods using a Modular P analyzer (Roche). Low-density lipoprotein cholesterol was calculated according to the Friedewald formula [33].

2.4. Statistical analyses

The area under the cortisol day curve ($AUC_{cortisol}$) was used as an indicator of the total cortisol excretion over the day, calculated using the trapezoid formula [34]. The AUC of the first 4 samples at awakening (ie, T1-T4) was added to the AUC of the last 4 samples (ie, T5-T8) because the time between the assessment of T4 and T5 varied depending on the time of awakening. For determination of the circadian variability in salivary cortisol ($variability_{cortisol}$), the within-individual variance between all cortisol assessments (8 samples × 2 days) was calculated. $Variability_{cortisol}$ was log-transformed because of its positively skewed distribution. For illustrative purposes, Fig. 1 represents 2 individual participants with, respectively, a high and low circadian cortisol variability.

Group differences for clinical characteristics, lipids, lipoproteins, BMI, WHR, and cortisol measures (ie, $AUC_{cortisol}$ and $variability_{cortisol}$) were assessed by independent *t* tests and 1-way analyses of variance for continuous variables and χ^2 tests for categorical variables. Next, associations between cortisol measures, lipoprotein profiles, and adiposity were examined in patients and controls. Lipid and adiposity indices were calculated for each subject. For the lipid index, a mean score of the individual *z* scores of triglycerides, LDL cholesterol, and inverted HDL cholesterol was calculated, corrected for sex and use of oral contraceptives [35]. For the adiposity index, a mean score of the individual *z* scores of BMI and WHR was calculated, corrected for sex and use of oral contraceptives. Univariate and multivariate linear regression analyses were conducted to determine the individual and independent contribution of $AUC_{cortisol}$ and $variability_{cortisol}$ in explaining the variance of, respectively, the lipid and adiposity index in the patient group and the control group. All regression analyses were adjusted for time of awakening, age, smoking (yes/no), and alcohol consumption (daily-weekly/monthly-none). Analyses were performed using Statistical Package for the Social Science version 16.0 (SPSS, Chicago, IL). *P* value less than .05 was considered statically significant.

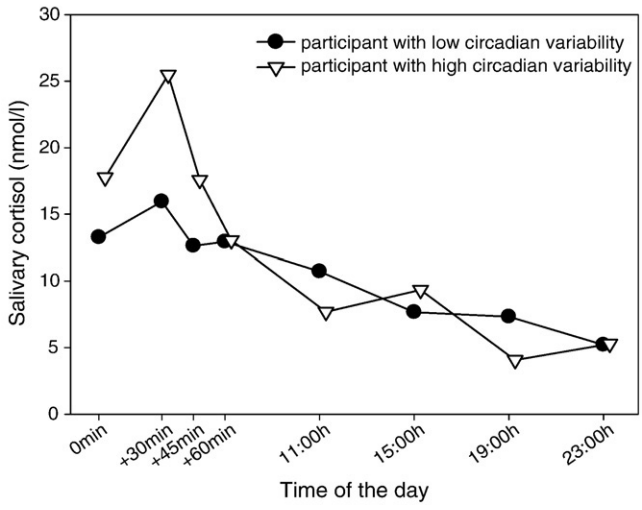

Fig. 1. Circadian cortisol variability. Graphical representation of salivary cortisol values (means from 2 sampling days) of 2 individual participants with either a high or low circadian cortisol variability. Figure is included for illustrative purposes to demonstrate the concept of circadian cortisol variability.

3. Results

3.1. Differences between patients and healthy controls

Clinical characteristics are presented in Table 1. Women showed significantly higher HDL cholesterol levels ($t = 3.5$, $P = .001$) and significantly lower WHR ($t = -9.0$, $P < .001$) than men. Therefore, lipid and adiposity indices were adjusted for sex (and oral contraceptives) to take the effects of confounding into account. Patients and controls did not differ statistically significantly for sex, age, BMI, and WHR. However, patients were more likely to smoke ($\chi^2 = 22.5$, $P < .001$) and, for the female participants, did more often use oral contraceptives ($\chi^2 = 6.4$, $P = .01$) as compared with controls. No statistically significant differences between patients and controls were found in serum lipid and lipoprotein levels, but patients showed lower HDL cholesterol levels than controls ($t = -3.3$, $P = .001$). Patients showed higher $AUC_{cortisol}$ values compared with controls ($t = 2.7$, $P = .01$), but a comparable $variability_{cortisol}$ ($t = -04$, $P = .97$).

3.2. Associations in the patients

The lipid and adiposity indices were significantly correlated ($r = .51$, $P \leq .001$). The correlation between $AUC_{cortisol}$ and $variability_{cortisol}$ showed a low correlation coefficient ($r = .22$, $P = .07$), indicating them to be relatively independent. In univariate regression analyses, $AUC_{cortisol}$ was a significant predictor of the lipid index. $Variability_{cortisol}$ was not significantly associated with the lipid index (Table 2). In multivariate models, however, $AUC_{cortisol}$ and $variability_{cortisol}$ were independently associated with the lipid index, after adjustment for age, smoking status, and alcohol consumption (Table 2). High $AUC_{cortisol}$ and a low $variability_{cortisol}$ were independently predictive for a less favorable lipid/lipoprotein profile.

Table 1
Clinical characteristics, serum lipid and lipoprotein levels, anthropometric measures, and cortisol measures in 72 patients with depressive and anxiety disorders and 42 healthy controls

	Patients (n = 72)	Controls (n = 42)	*P* value
Age	32.5 ± 11.3	33.3 ± 12.5	.72
Sex (% female)	47 (65.3%)	28 (66.7%)	.88
Smoking (% smokers)	39 (54.2%)	4 (9.5%)	<.001
Alcohol (% consumers)	38 (52.8%)	29 (69.1%)	.06
Oral contraceptives (% users in women)	30/47 (63.8%)	9/28 (32.1%)	.01
BMI (kg/m^2)	23.9 ± 4.1	24.3 ± 3.7	.63
WHR			
Men	.94 ± .07	.94 ± .05	.82
Women	.84 ± .05	.83 ± .04	.24
Total cholesterol (mmol/L)	4.80 ± 1.08	4.88 ± 1.11	.73
Triglycerides (mmol/L)	1.52 ± .86	1.41 ± .79	.53
LDL cholesterol (mmol/L)	3.11 ± .93	3.08 ± .99	.87
HDL cholesterol (mmol/L)	1.56 ± .40	1.82 ± .42	.001
$AUC_{cortisol}$ (nmol/[L h])	96.8 ± 32.0	81.8 ± 23.2	.01
$Variability_{cortisol}$ (nmol^2)[a]	36.9 ± 27.8	33.4 ± 19.7	.97

Data are presented as means ± standard deviation or number (percentage within group). To convert values for cholesterol and triglycerides from millimoles per liter to milligrams per deciliter, multiply, respectively, by 38.7 and 88.8.

[a] Log-transformed values were used in *t* test because of positively skewed distributions.

Table 3
Associations between serum lipid levels and cortisol measures in 72 patients with depressive and anxiety disorders

	Unadjusted		Adjusted[b]		Adjusted[c]	
	β	*P*	*β*	*P*	*β*	*P*
Cholesterol						
$AUC_{cortisol}$	.12	.34	.11	.39	.08	.53
$Variability_{cortisol}$[a]	.07	.60	−.17	.17	−.18	.14
BMI					.22	.06
Triglycerides						
$AUC_{cortisol}$	.24	.06	.18	.19	.12	.33
$Variability_{cortisol}$[a]	−.17	.18	−.26	.05	−.28	.02
BMI					.41	.001
HDL cholesterol						
$AUC_{cortisol}$	−.28	.02	−.31	.02	−.26	.03
$Variability_{cortisol}$[a]	.29	.02	.17	.17	.18	.12
BMI					−.32	.01
LDL cholesterol						
$AUC_{cortisol}$	.18	.15	.20	.15	.16	.23
$Variability_{cortisol}$[a]	−.02	.86	−.21	.11	−.22	.09
BMI					.25	.048

Standardized regression coefficients (*β*) and *P* values are presented.

[a] Log-transformed values because of skewed distribution of data.

[b] Adjusted for age, sex, use of oral contraceptives, smoking (yes/no), alcohol consumption (daily-weekly/monthly-none), and presence of depressive (yes/no) and/or anxiety disorders (yes/no).

[c] Additionally adjusted for BMI.

Univariate and multivariate models showed no significant associations between the 2 cortisol measures and the adiposity index (Table 2).

Next, we explored the associations with individual lipids and lipoproteins. Body mass index was added as predictor to the final model because of its strong association with lipid and lipoprotein levels. In the final model, $variability_{cortisol}$ was predictive for triglyceride levels; and $AUC_{cortisol}$ was predictive for HDL cholesterol. Body mass index was an independent predictor for almost all serum lipids and lipoproteins (Table 3). When analyses were repeated while adjusting for the presence of depressive disorder (yes/no) and/or anxiety disorder (yes/no), our main findings were not importantly affected (data not shown).

3.3. Associations in healthy controls

The lipid and adiposity indices were significantly correlated (r = .52, P = .001). Again, the correlation between $AUC_{cortisol}$ and $variability_{cortisol}$ was not statistically significant (r = .22, P = .16). Univariate and multivariate analyses showed no significant associations between $AUC_{cortisol}$ and $variability_{cortisol}$ and the lipid index. Furthermore, no significant associations were found

Table 2
Univariate and multivariate associations between lipid index, adiposity index, and cortisol measures in patients with depressive and anxiety disorders and in healthy controls

	Patients (n = 72)						Controls (n = 42)					
	Unadjusted (univariate)		Unadjusted (multivariate)		Adjusted[b] (multivariate)		Unadjusted (univariate)		Unadjusted (multivariate)		Adjusted[b] (multivariate)	
	β	*P*	*β*	*P*	*β*	*P*	*β*	*P*	*β*	*P*	*β*	*P*
Lipid index												
$AUC_{cortisol}$	.24	.048	.28	.02	.31	.02	.10	.54	.10	.57	.02	.89
Variability[a]	−.10	.42	−.17	.16	−.29	.02	.04	.81	.02	.89	.08	.64
Adiposity index												
$AUC_{cortisol}$	.09	.47	.05	.71	.09	.51	.08	.62	.03	.84	−.01	.97
$Variability_{cortisol}$[a]	.20	.10	.19	.13	.08	.54	.21	.19	.20	.23	.17	.30

Standardized regression coefficients (*β*) and *P* values are presented. Lipid index = mean score of the individual *z* scores for triglycerides, LDL cholesterol, and inverse HDL cholesterol, adjusted for sex and use of oral contraceptives. Adiposity index = mean score of the individual *z* scores for BMI and WHR, adjusted for sex and use of oral contraceptives.

[a] Log-transformed values because of positively skewed distribution.

[b] Adjusted for age, smoking, and alcohol consumption.

between $AUC_{cortisol}$ and $variability_{cortisol}$ and the adiposity index (Table 2).

4. Discussion

In the present study, higher basal cortisol concentrations were found in patients with depressive and/or anxiety disorders as compared with controls. In patients, elevated basal cortisol concentrations and lower circadian cortisol variability were independently associated with a less favorable lipoprotein profile (ie, higher scores on the lipid index). However, no associations were found between cortisol measures and indices of adiposity, although the adiposity index was strongly associated with dyslipidemia.

The elevated basal cortisol concentrations we found have been reported frequently for these patient groups [7,8]. Our findings on the association between elevated cortisol levels and dyslipidemia in our patient group (mean age, 32.8 ± 11.7 years) are in line with a study that showed associations between high 24-hour urinary cortisol levels and metabolic syndrome (which includes dyslipidemia) in elderly depressed patients (mean age, 74.1± 6.6 years) [11]. This indicates that the positive association between cortisol and dyslipidemia is not limited to elderly depressed patients. Associations were also found between glucocorticoid administration after organ transplant and hyperlipidemia [15,16,36]. Furthermore, it was previously shown in healthy subjects that a low circadian cortisol variability, measured in saliva samples, is related to a less favorable lipoprotein profile [21-23]. Such association was confirmed in our patients, but not in controls, maybe because our controls did not show low circadian variability. In summary, the present study supports the hypothesis that elevated basal cortisol concentrations and lower circadian cortisol variability induce dyslipidemia in patients with depressive and/or anxiety disorders.

In contrast to some previous studies [21,23], we did not find a relationship between cortisol and the adiposity index. Several factors might contribute to this difference. Firstly, the mean BMI of our participants was about 3 to 4 points lower than in most other studies [21,23]. Secondly, other important factors such as lifestyle behaviors might contribute more to the development of adiposity in patients with depressive and anxiety disorders than HPA-axis perturbations, more specifically, changes in dietary intake, sleep, and less physical activity [37]. Thirdly, adiposity might be a long-term consequence of cortisol excess via dyslipidemia. Our outpatient group might have been less chronically depressed to be able to assess this effect. Fourthly, individual differences in depressive symptoms (eg, high vs low appetite) may make it difficult to detect associations between cortisol and indices of adiposity. Fifthly, other neuroendocrine pathways might be involved, including the central sympathic nervous system, the gonadal and growth hormone axes, as well as leptin levels [38]. Lastly, hypercortisolism seems to be involved in central rather than peripheral adiposity [38]; and we did not directly assess the intraabdominal fat mass.

Our data support the hypothesis that the higher risk of CVD in patients with affective disorders may partly be explained through the direct effects of HPA-axis perturbations on lipoprotein metabolism. With respect to HPA-axis dysfunctions, an excess of glucocorticoids could contribute to insulin resistance, resulting in increased lipolysis through inhibition of lipoprotein lipase. Increased lipolysis results in increased serum levels of LDL cholesterol, total cholesterol, and triglycerides and decreased serum levels of HDL cholesterol [39]. Little is known about the associations between low circadian cortisol variability in patients with depressive and anxiety disorders and lipid metabolism. It could be hypothesized that a lower cortisol variability marks dysfunctions of the HPA axis and other endocrine axes that subsequently affect lipid metabolism [20,21,40].

Some methodological limitations of the present study should be mentioned. Firstly, participants were nonfasting before blood sampling for logistic reasons; and food intake is known to increase triglycerides levels. Furthermore, associations between lipid/lipoproteins and cortisol might have been weakened because blood was collected from participants at different time points during the day (mostly at 9:00 AM or at 2:00 PM). Nevertheless, significant associations between the index scores of dyslipidemia and cortisol measures were found. Secondly, no electronic monitoring of compliance to the sampling protocol was performed [41,42]. Therefore, nonadherence could have affected our data. Thirdly, although we adjusted for several potential confounders, other confounders might have influenced our outcome, such as the duration of the disease, the age of onset, and specific symptoms such as sleep disturbances. Fourthly, the sample size was relatively small. Lastly, the lumping of patients with depressive and anxiety disorders in a single group might have prevented us from finding more clear-cut results. However, in our opinion, this is justified because of the extensive comorbidity and indications for shared psychopathologic processes [43,44]. Moreover, we adjusted for the presence of a depressive and/or anxiety disorder; and this did not change our results.

We conclude that elevated basal cortisol concentrations and lower circadian cortisol variability were independently associated with a less favorable lipoprotein profile, but not with indices of adiposity, in patients with depressive and/or anxiety disorders. These associations were not found in healthy controls. Perturbations of the HPA axis in patients might partly explain the increased risk of CVD through its effects on lipoprotein metabolism. Our data need replication to confirm our results. Furthermore, prospective studies are needed to determine the impact of chronic psychologic stress on the HPA axis and its metabolic consequences.

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