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Depression and 24-Hour Urinary Cortisol in Medical Outpatients with Coronary Heart Disease: The Heart and Soul Study

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Abstract

Background—In patients with coronary heart disease (CHD), depression leads to worse cardiovascular outcomes. Depression has been associated with increased cortisol in medically healthy patients, suggesting that cortisol may act as a mediator in the pathway between depression and cardiovascular events. However, it is not known whether depression is associated with elevated cortisol levels in patients with CHD.

Methods—We examined the association between depression (assessed by the Computerized Diagnostic Interview Schedule) and 24-hour urinary cortisol in 693 medical outpatients with known CHD.

Results—Of 693 participants, 138 (20%) had current depression. Depressed participants had greater mean cortisol levels than those without depression (42 ± 25 vs. 36 ± 20 $\mu\text{g/day}$, $p < .01$). With each increasing quartile of cortisol concentration the frequency of depression increased ($p < .01$). Participants in the highest quartile of cortisol had a twofold increased odds of having depression, compared with those in the lowest quartile (odds ratio [OR] 2.1, 95% confidence interval [CR] 1.2–3.6, $p = .01$). This association remained strong after adjusting for potential confounding variables (OR 2.4, 95% CI 1.3–4.4, $p < .01$). In this cross-sectional analysis, elevated cortisol was not associated with worse cardiac function.

Conclusions—In patients with CHD, depression is associated with elevated cortisol levels.

Keywords

Coronary heart disease; cortisol; depression; HPA axis; medical illness; stress

Major depression and cardiovascular disease are the two leading causes of disability worldwide (Murray and Lopez 1997). Depression occurs in 17%–20% of patients with coronary heart disease (CHD; Rudisch and Nemeroff 2003) and is associated with an increased risk of future CHD events and mortality (Barefoot et al 2000; Blumenthal et al 2003; Burg et al 2003; Frasure-Smith et al 1993, 1995; Ladwig et al 1991; Lesperance et al 2000, 2002), yet little is known about the mechanisms linking depression with subsequent cardiac events (Carney and Freedland 2003; Joynt et al 2003).

Elevated cortisol due to enhanced activity of the hypothalamus-pituitary-adrenal (HPA) axis has been proposed as a possible mechanism by which depression may increase medical morbidity and mortality (Brown et al 2004; Gold and Chrousos 2002; McEwen 2003; Wolkowitz et al 2001). Depression is associated with elevated levels of cortisol in medically healthy patients (Anton 1987; Carroll et al 1976; Deuschle et al 1997; Halbreich et al 1985; Posener et al 2000; Young et al 1994); however, it is not known whether depression is associated with elevated cortisol in patients with CHD.

In patients with CHD, the potential association between depression and increased cortisol may be attenuated by comorbid medical conditions, medication use, and less severe depression. Alterations of cortisol secretion have been described in patients with diabetes (Roy et al 1998), hypertension (Litchfield et al 1998), and the metabolic syndrome (Rosmond et al 1998), all of which are common in patients with CHD. Moreover, some medications regularly prescribed for patients with CHD, such as beta-blockers or angiotensin receptor blockers, are known to influence cortisol secretion (Deininger et al 2001; Kizildere et al 2003). Finally, altered HPA function is present in only about 50% of depressed patients and is most pronounced in severe depression, especially the melancholic and psychotic subtype (Nelson and Davis 1997), and medical outpatients with CHD do not necessarily experience this same severity of depression.

We examined the association between depression and 24-hour cortisol levels in a cross-sectional study of 693 medical outpatients with known CHD. We hypothesized that depression would be associated with higher 24-hour urinary cortisol.

Methods and Materials

Participants

The Heart and Soul Study is a prospective cohort study of psychosocial factors and health outcomes in patients with CHD. Methods have been described previously (Ruo et al 2003). In brief, we used administrative databases to identify outpatients with documented CHD at two Department of Veterans Affairs Medical Centers (San Francisco VA Medical Center and the VA Palo Alto Health Care System, CA), one university medical center (University of California, San Francisco), and nine public health clinics in the Community Health Network of San Francisco. Patients were eligible to participate if they had at least one of the following: a history of myocardial infarction, angiographic evidence of $\geq 50\%$ stenosis in one or more coronary vessels, prior evidence of exercise-induced ischemia by treadmill or nuclear testing, a history of coronary revascularization, or a diagnosis of CHD by an internist or cardiologist.

Between September 2000 and December 2002, 1024 participants enrolled and completed a daylong study appointment at the San Francisco VA Medical Center. Of these, we excluded 192 participants whose cortisol was measured by a different method because the reference lab changed assays (from radioimmunoassay to high-performance liquid chromatography/tandem mass spectrometry) near the end of our enrollment period, 63 participants whose 24-hour urine collections were deemed inadequate (participant reported incomplete collection or urine volume was < 500 mL), 53 participants whose urine was inadvertently preserved with hydrochloric acid (rendering the cortisol assay inaccurate), 21 participants who reported use of oral corticosteroids, and 2 participants whose cortisol levels were considered extreme outliers (> 5 SD above the mean), leaving 693 participants for the analysis. The Heart and Soul Study protocol was approved by the Committee on Human Research at the University of California, San Francisco; the Research and Development Committee at the San Francisco VA Medical Center; the Medical Human Subjects Committee at Stanford University; the Human Subjects Committee at the VA Palo Alto Health Care System; and the Data Governance Board

of the Community Health Network of San Francisco. All participants provided written informed consent.

Major Depression

We measured the presence of current (past month) and past (lifetime) major depression according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) criteria. We used the modified Computerized National Institute of Mental Health Diagnostic Interview Schedule (CDIS-IV), a highly structured interview designed to yield psychiatric diagnoses (Robins et al 1981). The DIS has been used extensively to study the epidemiology and treatment of depression (Wells et al 1989). We also used the CDIS to assess the presence of generalized anxiety disorder and posttraumatic stress disorder (PTSD) during the past year. Trained research assistants administered the interview during the daylong baseline study appointment. Participants found to have current depression were informed that they were suffering from depression, instructed to discuss these symptoms with their primary care provider, and provided a list of local resources available for further evaluation and treatment. Throughout the text, we refer to major depression (assessed by CDIS) as depression.

To measure severity of depressive symptoms, we also administered the 9-item Patient Health Questionnaire (PHQ; Spitzer et al 1999) and categorized scores on this scale as representing no to minimal depressive symptoms (PHQ score 0-3), mild to moderate depressive symptoms (PHQ score 4-9), or severe depressive symptoms (PHQ score ≥ 10 ; Kroenke et al 2001). We defined severe depression as having clinical depression by the CDIS interview and PHQ score ≥ 10 , moderate depression as having clinical depression by the CDIS and PHQ score 4-9, and no depression as having no clinical depression by the CDIS and PHQ score < 4 .

24-Hour Urinary Cortisol

We used 24-hour urinary cortisol as a noninvasive, integrated measure of HPA activity that could be collected in subjects' home environments. Patients were instructed to collect all urine for 24 hours between the end of their study appointment and the time when a researcher visited their house the next day and to keep the urine collection jugs refrigerated at all times. No preservatives were added to the urine jugs. Research personnel arrived at patient homes exactly 24 hours after their appointment to ensure accurately timed specimens and to enhance compliance with the protocol. In our pilot testing, we found that this procedure was more likely to yield complete 24-hour collections than asking participants to start their 24-hour collection at 8 AM the next day. All patients were asked whether they were able to collect all urine or if some fraction had been inadvertently discarded. If the sample was reported to be incomplete or if the volume was less than 1 L, subjects were asked to repeat the collection, and research personnel returned 24 hours later to collect the urine. Similarly, if the 3-L collection jug was completely full, subjects were given two new jugs and asked to repeat the collection to ensure that no urine was inadvertently discarded. If subjects were unable to collect all urine for any reason or had urinary incontinence, their samples were deemed inadequate and no urinary cortisol data were recorded for these subjects.

Urinary cortisol was analyzed by radioimmunoassay at ARUP (Associated Regional and University Pathologists) laboratories, headquartered in Salt Lake City, Utah. The normal reference range for this assay was 20-90 $\mu\text{g/day}$ (where $\mu\text{g/day} = \mu\text{g/dL} \times \text{dL/day}$). The interassay coefficient of variance was $< 10\%$, and the intraassay coefficient of variance was $< 8\%$. The detection limit was 1.0 $\mu\text{g/dL}$. Cortisol levels for subjects whose cortisol levels were below this detection limit were coded as 1.0 $\mu\text{g/dL}$.

Potential Confounding Variables

Age, gender, and smoking were determined by self-report. We assessed medical history using a self-report checklist that included 45 common medical diagnoses. Alcohol use was determined by the AUDIT alcohol consumption questions (Bush et al 1998). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters, and obesity was defined as $\text{BMI} \geq 30 \text{ kg/m}^2$. Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. We measured systolic and diastolic blood pressure and assayed fasting glucose, glycosylated hemoglobin, total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) after a 12-hour fast.

Cardiac Disease Severity

On the day of the baseline study examination, all participants completed a resting echocardiogram for measurement of left ventricular ejection fraction, an exercise treadmill test for measurement of exercise capacity, and a stress echocardiogram for assessment of ischemia. We performed a symptom-limited, graded exercise treadmill test according to a standard Bruce protocol. We defined exercise capacity as the total number of metabolic equivalents (METs) and calculated the wall motion score index at peak exercise as our measure of ischemia.

We defined hypertension as systolic blood pressure $\geq 140 \text{ mm Hg}$ or diastolic blood pressure $\geq 90 \text{ mm Hg}$ or the use of antihypertensive medication; diabetes as current fasting glucose $> 126 \text{ mg/dL}$ and glycosylated hemoglobin concentration $> 6\%$ or patient's being prescribed antiglycemic medication; and dyslipidemia as $\text{LDL} \geq 130 \text{ mg/dL}$ or $\text{HDL} \leq 35 \text{ mg/dL}$ or patient's being prescribed lipid-lowering medications.

Statistical Analysis

The goal of this study was to examine the association between current (past month) major depression and 24-hour urinary cortisol concentration in patients with CHD. Differences in characteristics between participants with and without major depression were compared using *t* tests (or nonparametric equivalent) for continuous variables and chi-square tests for dichotomous variables. Analysis of covariance was used to compare mean cortisol levels in depressed and nondepressed participants, adjusted for potential confounding variables.

We used a Cochran–Armitage chi-square test for trend to examine the prevalence of depression by quartile of cortisol. To determine the unadjusted and adjusted association of cortisol and major depression, we used logistic regression analyses with quartile of cortisol as predictor and presence of major depression as the dependent variable. We repeated these analyses with cortisol entered as a continuous variable (per SD). To obtain adjusted risk estimates we entered all variables from Table 1 into a backward elimination logistic regression model that included the four quartiles of cortisol as dummy variables. Variables that were associated with depression (at $p < .10$) were retained in the model. We also examined the association of cortisol and depression, stratified by age (above or below the median), gender, diabetes, obesity ($\text{BMI} \geq 30$ vs. $< 30 \text{ kg/m}^2$), and smoking, and we tested for interactions between cortisol and each of these variables.

We used analysis of variance (ANOVA) to compare cortisol excretion in participants with current depression, participants with past but not current depression, and participants without depression. Follow-up comparisons between groups were done by *t* test. We also used ANOVA to compare cortisol excretion in participants who had severe depression (CDIS positive and $\text{PHQ} > 10$), mild to moderate depression (CDIS positive and $\text{PHQ} 4\text{--}9$), and no evidence of depression (CDIS negative and $\text{PHQ} < 4$). For this analysis of depression severity, we excluded 204 participants who reported depressive symptoms ($\text{PHQ score} \geq 4$) but did not meet criteria

for clinical depression by CDIS and 5 participants who had clinical depression by CDIS but without debilitating symptoms ($\text{PHQ} < 4$). Analyses were performed using Statistical Analysis Software (version 8, SAS Institute, Cary, North Carolina).

Results

Of 693 participants, 138 (20%) had current major depression according to the CDIS. Compared with participants who did not have depression, those with depression were younger, more likely to smoke, more likely to use psychotropic medication, and less likely to be male or to use statins (Table 1). Participants with depression had a greater mean left ventricular ejection fraction than those without depression. Depressed and nondepressed participants did not differ by history of congestive heart failure, hypertension, diabetes, myocardial infarction, or stroke. There was no difference in level of 24-hour urine creatinine between depressed and nondepressed participants. The prevalence of depression did not differ between the 693 participants in this analysis and in the overall sample of 1024 participants (20% vs. 19%; $p = .74$).

Cortisol and Depression

Depressed participants had higher 24-hour urinary free cortisol than patients without depression (mean $\pm$ SD: 42 ± 25 $\mu\text{g/day}$ vs. 36 ± 20 $\mu\text{g/day}$, $p < .01$). This association persisted after adjusting for age, gender, BMI, smoking, alcohol use, urinary creatinine, comorbid illnesses, medication use, and measures of cardiac function (adjusted mean $\pm$ SD: 41 ± 21 $\mu\text{g/day}$ vs. 36 ± 21 $\mu\text{g/day}$; $p = .01$). The proportion of participants with depression increased by quartile of cortisol (Figure 1). Participants in the highest quartile of cortisol had a twofold increased odds of having depression, compared with those in the lowest quartile of cortisol (Table 2). This association remained strong after adjusting for age, gender, BMI, smoking, alcohol use, urinary creatinine, comorbid illnesses, medication use, and cardiac function (Table 2). Results were similar when we examined the association between cortisol:creatinine ratio (quartile IV vs. I) and depression (adjusted odds ratio [OR] 1.9, 95% confidence interval [CI] 1.1-3.2, $p = .03$).

Overall, each standard deviation (21 mg/day) increase in cortisol concentration was associated with a 30% increased odds of depression (adjusted OR 1.3, 95% CI 1.1-1.6; $p = .01$). The association between cortisol and depression was similar in men and women, current smokers and nonsmokers, participants above and below the median age (67 years), participants with and without obesity, and participants with and without diabetes (all p values for interaction $> .3$).

Depression Severity

Mean cortisol values were 42 ± 28 $\mu\text{g/day}$ in the 68 participants with severe depression, 43 ± 23 $\mu\text{g/day}$ in the 65 participants with mild to moderate depression, and 36 ± 19 $\mu\text{g/day}$ in the 351 participants with no depression (overall $p = .007$). Among the depressed subjects, greater severity of depression was not associated with cortisol levels.

Current Versus Past Depression

We compared mean cortisol levels in the 138 participants with current depression (42 $\mu\text{g/day} \pm 25$), the 151 participants with past but no current depression (39 $\mu\text{g/day} \pm 21$), and the 404 participants with no history of depression (35 $\mu\text{g/day} \pm 19$; overall $p = .004$; Figure 2). Follow-up comparisons revealed significantly greater cortisol levels in current versus never depressed participants ($p < .05$) but nonsignificant differences in past versus never depressed participants.

Comorbid Anxiety

Ninety-seven (14%) participants met criteria for generalized anxiety disorder or PTSD in the past year, including 47% (65/138) of participants with current depression, 12% (18/151) of those with past depression, and 3% (14/404) of those with no history of depression. After excluding the 97 participants with anxiety or PTSD in the past year, depression remained associated with greater mean cortisol excretion (current depression: 43 ± 20 $\mu\text{g/day}$, past depression 38 ± 21 , no lifetime depression 35 ± 20 $\mu\text{g/day}$; overall F test $p = .007$). Mean cortisol levels were similar in the 65 depressed participants who had generalized anxiety disorder or PTSD (40.4 $\mu\text{g/day} \pm 21.5$) compared with the 73 depressed participants who did not have comorbid anxiety or PTSD (43.4 $\mu\text{g} \pm 27.7$) ($p > .1$).

Cortisol and Cardiac Disease Severity

We did not observe an association between quartile of cortisol and hypertension, BMI, diabetes, fasting glucose, glycosylated hemoglobin (HbA1c), HDL, or LDL (all $ps > .16$). Likewise, quartiles of cortisol were not associated with worse treadmill exercise capacity, decreased left ventricular ejection fraction, or greater ischemia by stress echocardiography.

Discussion

We found that current depression was associated with increased 24-hour cortisol levels among 693 medical outpatients with known CHD. Participants in the highest quartile of cortisol had a twofold increased odds of having current depression compared with those in the lowest quartile of cortisol. Even after adjusting for age, gender, BMI, smoking, alcohol use, urinary creatinine, comorbid medical conditions, medication use, and cardiac function, cortisol remained independently associated with major depression.

Major depression, especially the melancholic and psychotic subtype, was previously considered to be related to HPA axis alterations in about 50% of medically healthy patients (Nelson and Davis 1997); however, it was not known whether depression was associated with increased cortisol in patients with CHD. Despite the potentially confounding effects of comorbid illnesses and use of medications that are known to be associated with alterations in cortisol, we demonstrated an association between depression and increased cortisol levels in patients with CHD.

The causal direction between depression and cortisol cannot be determined with our cross-sectional study, however. There are four possible explanations for the observed association between depression and cortisol: 1) depression may lead to increased cortisol, 2) increased cortisol may lead to depression, 3) the relation could be bi-directional, or 4) another factor (or factors) could lead to both depression and elevated cortisol. The first model is supported by findings that certain symptoms of depression, such as sleep disturbances or decreased food intake, lead to increased cortisol (Sapolsky et al 2000; Spiegel et al 1999); evidence is also accumulating to suggest that alterations of the HPA axis are involved in the etiology and pathogenesis of depression (Gold and Chrousos 2002; Holsboer 1999; Wolkowitz et al 2001).

In support of the second model, patients with Cushing's syndrome have a high prevalence of depression, and medical patients chronically treated with synthetic glucocorticoids often develop depression (Wolkowitz et al 2001). Furthermore, certain classes of antidepressants normalize HPA activity and upregulate glucocorticoid receptors, thereby increasing negative feedback and lowering cortisol before eliciting their clinical effects (Holsboer and Barden 1996). This suggests that changes within the HPA axis may be causally involved in the antidepressant effects of these medications. Also, increased activity of the HPA axis, as

measured by the dexamethasone (DEX)-suppression test or the combined DEX/corticotropin releasing hormone (CRH) test, predicts early relapse in remitted patients with depression (Ribeiro et al 1993; Zobel et al 2001). Finally, several small and mostly open studies have shown that cortisol synthesis inhibitors (Wolkowitz and Reus 1999), CRH-receptor-antagonists (Zobel et al 2000), and glucocorticoid-receptor antagonists (Belanoff et al 2002) may have antidepressant effects.

It is also possible that there is a reciprocal relationship between depression and cortisol. Furthermore, other factors such as genetic predisposition or stressful life events could lead simultaneously to an elevation of cortisol and depression.

Elevated cortisol levels have been associated not only with depression but also coronary disease (Koertge et al 2002; Troxler et al 1977); we did not observe a cross-sectional association between cortisol and worse cardiac disease severity, however. One potential reason for the differences between our study and those demonstrating a link between cortisol and coronary atherosclerosis is that we did not use angiographic or carotid ultrasound measurements to determine level of atherosclerosis. Because anatomic findings do not necessarily correlate with severity of ischemia or risk of acute coronary syndromes (Ambrose et al 1988), angiography may be less accurate than functional studies, such as stress echocardiography, in identifying patients who have myocardium at risk for future events. Thus, it is possible that cortisol may be associated with anatomic level of atherosclerotic burden, but not with functional measures of cardiac disease severity, such as ejection fraction, exercise capacity, and inducible ischemia.

Furthermore, a lack of association between cortisol and baseline cardiac function does not rule out the possibility that elevated cortisol levels may contribute to the increased risk of subsequent coronary events associated with depression (Carney and Freedland 2003). Cortisol could contribute to greater long-term mortality by triggering or worsening acute cardiac events. Cortisol is strongly associated with the release of thromboxane A₂, a vasoconstrictor that is released after endothelial injury (Fimognari et al 1996). Moreover, cortisol has been shown to suppress the release of vasodilators such as nitric oxide and prostacyclin from vascular endothelium (Rogers et al 2002; Wallerath et al 1999). Finally, depressed patients show an increased cortisol response to psychological stress (Heim et al 2000), and mental stress has been shown to induce both cortisol release and cardiac ischemia (Ghiadoni et al 2000). Therefore, even if cortisol is not associated with worse baseline cardiac function, it is possible that cortisol contributes to worse outcomes in depressed patients by triggering subsequent coronary events.

Several limitations must be kept in mind when appraising our findings. Only 68% (693/1024) of Heart and Soul Study participants were included in this analysis; however, the prevalence of depression was similar in participants who were included or excluded from the analysis. Only 17% of our participants were women, thereby reducing our power to detect interactions by gender and limiting the generalizability of our results. Depressed patients were more likely to use antidepressants, anxiolytics, and anticonvulsants, all of which are known to reduce HPA activity (Holsboer and Barden 1996); however, adjustment for use of psychotropic medication did not affect the association between cortisol and depression. We relied on participants' self-report of compliance with the 24-hour urinary protocol and have no proof of complete collection; however, we tried to enhance compliance by visiting the subjects' home environment by requesting that they repeat any urine collection that seemed incomplete and by excluding any samples that were < 500 mL or otherwise deemed inadequate.

Because the psychiatric interviews were administered by lay research assistants, we cannot rule out the possibility that there were some inaccuracies concerning the diagnosis; however, our research assistants received extensive training, and the DIS is considered the gold standard

diagnostic instrument for assessment of depression by lay interviewers in epidemiologic studies (Robins et al 1981). Finally, most of the cortisol values in our sample were within the normal range and were not related to worse cardiac function; however, the Heart and Soul Study is an ongoing prospective study that will follow patients to determine whether greater cortisol at baseline predicts worse outcome at follow-up in patients with CHD.

In summary, we found that depression was associated with elevated cortisol levels in medical outpatients with CHD. Although elevated cortisol levels were not associated with worse cardiac disease severity in our cross-sectional analysis, increased cortisol levels may still contribute to the increased risk of CHD events in patients with depression.

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Figure 1. Proportion with depression by quartile of cortisol in 693 participants with coronary disease; p for trend = .008.

Figure 2.
Mean cortisol (with SE) by depression status; overall p from analysis of variance = .004.

Table 1Characteristics of 693 Participants with Coronary Artery Disease, Divided by the Presence of Depression^a

Variables	Current Depression ^b (<i>n</i> = 138)	No Current Depression (<i>n</i> = 555)	<i>p</i> Value
Demographic			
Age, mean (SD), years	62 (11)	68 (11)	<.0001
Male	96 (70)	483 (87)	<.0001
Current smoking	35 (25)	83 (15)	<.01
Regular alcohol use	46 (34)	149 (27)	.13
Medical History			
Congestive heart failure	23 (17)	92 (17)	.99
Hypertension	94 (68)	391 (71)	.55
Diabetes	39 (28)	149 (27)	.74
Myocardial infarction	67 (49)	312 (56)	.12
Stroke	23 (17)	78 (14)	.44
Asthma or COPD	25 (18)	86 (16)	.44
Kidney or renal disease	16 (12)	41 (7)	.11
Medication Use			
Antidepressants	58 (42)	60 (11)	<.0001
Anticonvulsants	30 (22)	39 (7)	<.0001
Anxiolytics	31 (22)	46 (8)	<.0001
Angiotensin receptor blockers	67 (49)	289 (52)	.46
Beta-blockers	75 (54)	336 (61)	.19
Statins	77 (56)	374 (67)	.01
Diuretics	34 (25)	171 (31)	.16
Hypoglycemic agents	29 (21)	100 (18)	.42
Cardiac Function			
Wall motion score index, mean (SD)	1.14 (0.32)	1.19 (0.36)	.17
Exercise capacity, mean (SD) METs	7.8 (3.7)	7.4 (3.4)	.21
Left ventricular ejection fraction, mean (SD)	64 (7)	61 (10)	<.01
Other Characteristics			
Body mass index, mean (SD) kg/m ²	28.9 (5.4)	28.3 (5.2)	.26
LDL, mean (SD) mg/dL	105 (36)	102 (32)	.33
HDL, mean (SD) mg/dL	47 (15)	46 (14)	.65
Glycosylated hemoglobin, mean (SD), %	6.0 (1.2)	6.0 (1.0)	.68
Fasting glucose, mean (SD) mg/dL	119 (43)	117 (36)	.59
Urine creatinine, mean (SD) mg/day	1380 (424)	1350 (414)	.46

COPD, chronic obstructive pulmonary disease; MET, metabolic units above resting; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

^aData expressed as number (%) unless otherwise indicated.^bBased on Diagnostic Interview Schedule for DSM-IV.

Table 2

Association Between Quartile of Cortisol and Depression in 693 Participants with Coronary Heart Disease

Quartile of Raw Cortisol	Proportion with Depression	Unadjusted OR (95% CI)	p Value	Adjusted OR (95% CI) ^a	p Value
I (< 23.1 $\mu\text{g/day}$)	14% (24/174)	1.0	—	1.0	—
II (> 23.1 to < 31.6 $\mu\text{g/day}$)	19% (32/173)	1.4 (.8–2.5)	.24	1.6 (.8–3.0)	.17
III (> 31.6 to < 47.4 $\mu\text{g/day}$)	23% (39/173)	1.8 (1.0–3.2)	.04	2.0 (1.1–3.7)	.03
IV (≥ 47.4 $\mu\text{g/day}$)	25% (43/173)	2.1 (1.2–3.6)	.01	2.4 (1.3–4.4)	.008

CI, confidence interval; OR, odds ratio.

^aFor this analysis, all variables from Table 1 were entered into a backward elimination logistic regression model (with $p < .10$) for inclusion in the model. The four cortisol quartiles were forced into the model as dummy (indicator) variables. The other variables associated with depression were age (OR per 11-year decrease 1.5, 95% CI 1.2–1.8), female gender (OR 2.5, 95% CI 1.5–4.1), antidepressant use (OR 4.7, 95% CI 2.9–7.6), anticonvulsant use (OR 2.3, 95% CI 1.3–4.2), and increased left ventricular ejection fraction (OR per 10% increase 1.3, 95% CI 1.0–1.6).