ORIGINAL ARTICLE

Cortisol and Catecholamines in Posttraumatic Stress Disorder

An Epidemiologic Community Study

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Background: Prior research has connected posttraumatic stress disorder (PTSD) to increased levels of catecholamines. However, studies of cortisol levels have produced mixed results.

Objective: To examine urinary catecholamine and cortisol levels in individuals with PTSD in a community sample.

Design: A representative cohort of young adult community residents, assessed periodically during a 10-year period for exposure to trauma and PTSD, was used to select a subset for urine collection studies conducted in a sleep laboratory across 2 consecutive nights and the intermediate day.

Setting: The sample of young adults was randomly selected from a large health maintenance organization and is representative of the geographic area except for the extremes of the socioeconomic status range.

Participants: A subsample was selected from the 10-year follow-up cohort (n=913; 91.1% of the initial sample). Eligibility criteria were: (1) persons exposed to trauma during the preceding 5 years, (2) other individuals who met PTSD criteria, and (3) a random preselected subsample. Of 439 eligible individuals, 292 (66.5%) participated, including 69 with lifetime PTSD.

Main Outcome Measures: Measures of cortisol and catecholamine levels in urine.

Results: The lifetime PTSD group demonstrated significantly higher catecholamine levels than the group exposed to trauma without PTSD and the nonexposed group. Individuals exposed to trauma without PTSD demonstrated significantly lower urine catecholamine levels than the nonexposed and the PTSD groups. Mean cortisol levels did not differ across groups. When analyzed by comorbidity with major depressive disorder (MDD), the PTSD-only group did not differ in cortisol levels from the groups with neither PTSD nor MDD. Women with MDD plus PTSD demonstrated significantly higher cortisol levels than women with neither disorder or with either disorder alone.

Conclusions: Trauma per se does not lead to sustained increases in cortisol or catecholamine levels. Posttraumatic stress disorder is associated with higher catecholamine levels. In contrast, persons with PTSD had neither an increase nor a decrease in mean urinary cortisol levels. Women with PTSD and comorbid MDD had higher cortisol levels.

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STRESS HAS BEEN VIEWED AS A precipitant for a number of psychiatric diseases. A unique form of stress, psychologic trauma is viewed in the *DSM* as linked in an essential way with a specific syndrome, that of posttraumatic stress disorder (PTSD).[1] It has been proposed that PTSD demonstrates a paradoxical cortisol profile in comparison with the expected response to stress, with evidence of low basal cortisol levels in urine and plasma and enhanced negative feedback to dexamethasone.[2-4] The low cortisol levels were accompanied by increased catecholamine secretion in urine, leading to the claim that there is a disconnect between basal cortisol and catecholamine in individuals with PTSD.[2,3] While there was some (but incomplete[5]) consistency among early studies with regards to the urinary cortisol findings in male combat veterans,[3] recent reports suggest that even these findings are uncertain.[6] The generalizability of these findings to the general community, where PTSD occurs predominantly in women, is questionable.

Studies in women with PTSD, generally recruited by advertising, have focused on childhood sexual abuse, which may not reflect the effects of trauma in adulthood. The results of these studies

are inconsistent, with one study suggesting increased cortisol levels,[7] and another, low cortisol levels,[8] while still another, no difference from control subjects.[9] Studies of individuals who have experienced natural disasters have focused on symptoms of anxiety or distress but not on *DSM*-defined PTSD.[10-14] An exception is a study by Maes et al,[13] which reported a higher mean urinary free cortisol (UFC) level in subjects with PTSD following natural disasters. However, in that study, subjects were volunteers and a comparison with persons exposed to trauma without PTSD was not included. Studies of individuals who have experienced disasters[10-14] have reported elevated mean cortisol levels in urine, saliva, or plasma. Boscarino[4] studied a representative sample of male veterans, but there have been no reports from representative community samples on basal cortisol levels in individuals exposed to trauma with PTSD.

Three studies have examined 24-hour urinary catecholamine levels in veterans with PTSD, yielding conflicting results. Kosten et al[15] and Yehuda et al[16] reported an increase in urinary epinephrine and norepinephrine levels in veterans with PTSD, compared with patients with other psychiatric disorders[15] or healthy control subjects.[16] Pittman and Orr[5] reported no difference in catecholamine levels between combat veterans with PTSD and combat veterans without PTSD. The nature of the control group might be critical because exposure to trauma may alter urinary epinephrine and norepinephrine levels. This possibility is supported by evidence of increased urinary norepinephrine levels in a civilian population exposed to the Three Mile Island nuclear accident, compared with individuals residing 80 miles away[17] and increased urinary catecholamine levels in American hostages shortly after they were freed from Iran.[18] Urinary catecholamine levels in persons exposed to trauma with and without PTSD compared with nonexposed persons have not been examined.

Because PTSD is highly comorbid with major depressive disorder (MDD),[19,20] the effect of MDD, which shows hypothalamic-pituitary-adrenal axis activation, on the neuroendocrine picture of PTSD is an important question. Results have been inconsistent. In earlier studies, the presence of comorbid MDD did not appear to alter the low cortisol findings in PTSD.[3] In contrast, a recent study reported that MDD and PTSD influenced 24-hour UFC levels in opposite directions, with no interaction, so that the comorbid group showed an intermediate cortisol excretion.[21]

In this report, we examine urinary catecholamine and cortisol levels in relation to PTSD and exposure to traumatic events. The study was conducted in the context of an ongoing longitudinal community study in the Detroit, Mich, metropolitan area. We present data on 24-hour UFC and catecholamine levels, collected from a subset of the sample in a sleep research center. The key questions addressed concern the association of exposure to trauma and PTSD with urinary cortisol and catecholamine levels and the role of comorbid MDD in the relationship of PTSD with these hormonal measures.

METHODS

SAMPLE AND PROCEDURES

The neurobiologic investigation was nested in a large-scale longitudinal community study of young adults. The study was described previously.[19,22] In brief, a sample of 1200 individuals was randomly selected from all 21- to 30-year-old members of a large health maintenance organization in southeast Michigan. The membership of the health maintenance organization was representative of the population of the geographic area as depicted in the 1990 US census, with the exception of the extremes of the socioeconomic status range. Personal interviews were conducted in 1989 with 1007 members (84%) of the sample. Follow-up personal interviews were conducted in 1992, 1994, and 1999 through 2001. In each wave, more than 90% follow-up completion was achieved. In the 10-year follow-up in 1999 through 2001, 913 members (91.1%) of the initial sample completed interviews. Biologic measures were collected on a subset of these respondents.

The following persons from among those who completed the 10-year follow-up were eligible for the sleep and urine collection study: (1) all persons who were exposed to traumatic events in the 5-year interval between 1994 and the last assessment, (2) other individuals (not from group 1) who met PTSD criteria in previous assessments, and (3) other individuals (not from groups 1 or 2) from a randomly preselected subsample of the total sample. Persons who moved away from the Detroit metropolitan area were not eligible. Persons with recent substance abuse, use of psychotropic medications, and smokers who reported that they could not abstain for the 8-hour sleep period were not eligible for this study. However, in this general population study, no subjects were excluded based on these criteria. Eligible respondents were invited to spend 2 consecutive nights and the intermediate day at the Sleep Center of Henry Ford Hospital, Detroit. Bedtimes were determined by matching the respondents' regular bedtimes at home. Respondents stayed in bed for 8 hours each night. Of a total 439 eligible individuals, 292 (66.5%) participated.

Urine collection during the 32-hour stay at the sleep center was made in 4 parts, with each covering an 8-hour period. The first collection covered the first night, the second collection covered 8 hours from rising to early afternoon, the third collection covered the late afternoon and evening, and the fourth, the second night. The procedure provided total 24-hour measures and had the added capacity to provide separate timed measures that captured the morning surge (in the 8 AM hour) and the evening low (in the 8 PM hour) for an examination of effects related to diurnal phase. At the time of collection, urine was split into 2 aliquots, with the urine for catecholamine level testing acidified with 7 mL of 6 N hydrochloric acid as a preservative, and the urine for cortisol level testing was frozen without further processing. Data on 13 persons were deleted because of low creatinine levels, defined as less than 1 g/24 h, leaving a sample of 275 persons for the analysis.

ASCERTAINING PTSD

The National Institute of Mental Health—Diagnostic Interview Schedule (NIMH-DIS)[23] for *DSM-III-R* was used to diagnose psychiatric disorders. The baseline interview in 1989 inquired about lifetime history of disorders, and each follow-up assessment inquired about disorders occurring during the interval period since the previous assessment. The diagnosis of PTSD in *DSM-III-R* requires exposure to a qualifying traumatic event and the presence of PTSD criterion symptoms that are linked to the traumatic event. Two earlier studies reported high concordance between NIHM-DIS–diagnosed PTSD and independent clinical reinterviews.[20,24] The latter[24] used the clinician-administered PTSD scale[25,26] and reported sensitivity of 76% and specificity of 97%.[24]

Table 1. Sample Characteristics: Sex, Race, Age, Lifetime Prevalence of Alcohol and Drug Use Disorders*

	Biologic Sample (n = 275)	Total Sample (n = 913)
Women	65.8	62.7
White	77.1	81.1
Education		
<High school	3.6	3.5
High school	22.6	20.8
Part college	44.0	46.2
College	29.8	29.5
Alcohol abuse or disorder	35.6	32.1
Drug abuse or disorder	16.4	14.6
Age†	37.5 (1.7)	36.8 (2.2)

*Values are expressed as percentages unless otherwise indicated.
†Values are expressed as mean (SD).

HORMONE ASSAYS

We assayed UFC levels with DPC Coat-a-Count cortisol kits (DPC, Los Angeles, Calif). Urine was extracted using dichloromethane following the instructions from the kit. Interassay variation for cortisol levels was 6%. Urine catecholamine levels were assayed by high-pressure liquid chromatography using a commercial laboratory (Warde Medical Laboratories, Ann Arbor, Mich).

STATISTICAL ANALYSIS

All statistical analyses were performed on log-transformed data, which normalized distributions of the hormone measures. Comparisons of nonsmokers who had never smoked (n=156), current smokers (n=58), and past smokers (n=61) showed no significant differences in total 24-hour UFC levels ($P=.44$). We found no significant effect of oral contraceptives (n=84) on 24-hour UFC levels ($P=.77$).

Two series of analyses were conducted for cortisol, epinephrine, norepinephrine, and dopamine levels. The first consisted of comparisons across 3 groups: (1) PTSD (n=69; 16 men, 53 women, 10 of whom met criteria for current PTSD at the time of the interview), (2) exposed to trauma without PTSD (n=105; 38 men, 67 women), and (3) no exposure to trauma (n=101; 40 men, 61 women). This provided 2 control groups with which PTSD could be compared, including a group of persons who were never exposed to trauma, according to the baseline interview and the 3 follow-up assessments. The second series examined comorbidity of PTSD with MDD and consisted of comparisons across 4 groups defined by history of PTSD and MDD: (1) neither disorder (n=139; 61 men, 78 women), (2) MDD only (n=67; 17 men, 50 women), (3) PTSD only (n=23; 5 men, 18 women), and (4) both disorders (n=46; 11 men, 35 women). All persons in the MDD group had reported at least 1 exposure in their lifetime, either preceding or following MDD onset. In each series of analyses and for each hormone, we first examined total 24-hour urine hormone levels and then we examined the night, morning (AM), and evening (PM) urine hormone levels, using an analytical approach that took into account diurnal variation.

Correlation of the first and second night cortisol levels was 0.43. The correlations of dopamine, epinephrine, and norepinephrine levels were higher, 0.67, 0.62, and 0.65, respectively. Differences between the 2 nights overall or across diagnostic groups were not significant, as tested by paired *t* tests, and consequently, hormone values of the 2 nights were averaged. Averaging across 2 nights yields a more reliable measure. Analysis of the 4 time periods, with each night treated separately, did not alter the results. For the total 24-hour measures, we combined the average of the 2 nights with the 8-hour AM and the 8-hour PM values.

We tested whether current PTSD or MDD cases (ie, with symptoms continuing in the preceding 12 months) differed from remitted cases but found no significant differences in cortisol or catecholamine levels. We therefore used lifetime disorders in the analyses. The neither-disorder group comprised 38 persons (27.3%) who were exposed to trauma and 101 who were never exposed. Comparison of these 2 subgroups in the neither-disorder group revealed significant differences only in dopamine levels, with persons who were exposed to trauma having a lower mean value than those never exposed. In a separate analysis, we used 2 no-disorder groups, classified by the presence vs the absence of exposure to trauma. The analysis with 2 no-disorder groups yielded the same results as the 4-group analysis.

Analysis of variance (ANOVA) was used to compare total 24-hour urinary measures across groups. Significant results were followed up with post hoc paired comparisons using the Tukey test. We tested the effects of sex, race, education, and interactions between group membership and these variables. When a significant covariate or an interaction was detected (using $\alpha=.05$), models that included these variables were displayed. Sample size was slightly smaller in the total 24-hour analyses because persons without 3 consecutive 8-hour urine collections (n=19) were excluded.

Multiple regression analysis was used, applying generalized estimating equations (GEEs),[27-29] to test and estimate associations between group membership and each of the 4 hormones across 3 time periods of the 24-hour diurnal cycle—night, AM, and PM. The GEE approach permits simultaneous modeling of the relationship between group classification and hormone measures at the 3 time periods. The GEE approach takes into account correlations within persons across the multiple measures and uses information on persons with incomplete data. Interaction terms were used to examine whether differences across groups varied by time and by covariates (eg, sex). No significant interactions between time and group membership were detected; post hoc tests of differences by group membership across night, AM, and PM were not performed. The estimated log-transformed means in the GEE results were averaged across the night, AM, and PM measures. In the analyses of cortisol levels, we found a significant interaction between diagnostic groups and sex. The final model for the cortisol analysis is illustrated in the equation

$$Y=\alpha+\beta_1\,(\text{group})+\beta_2\,(\text{sex})+\beta_3\,(\text{group}\times\text{sex})+\beta_4\,(\text{time})$$

where log cortisol measures at 3 times (night, AM, and PM) are the outcomes (Y).

RESULTS

No significant differences in the biologic subsample were observed in sex, race, age, education, and substance use disorders in comparison with the entire sample (**Table 1**). The 4 diagnostic groups defined by history of PTSD and MDD did not differ on these characteristics from the total sample.

URINARY CORTISOL LEVELS: EFFECTS OF TRAUMA EXPOSURE AND PTSD

The raw mean±SD of total 24-hour urinary cortisol levels for the entire sample with complete data (n=256) was

52.0±32.2 µg/24 h (143.5±88.8 nmol/d). The ANOVA of total 24-hour urinary cortisol levels in persons with PTSD, exposure to trauma without PTSD, and no exposure to trauma revealed neither a significant group difference nor a sex × group interaction. The GEE analysis on night, AM, and PM data (n=275) revealed a significant diurnal variation ($P<.001$) and a significant group × sex interaction ($P=.04$). However, sex-specific analyses detected no significant effects of group membership in either men ($P=.21$) or women ($P=.09$).

We explored the potential effect of type of trauma (assaultive vs nonassaultive) on cortisol levels and found no support for such an effect. We found no support for effects of early trauma (≤16 years of age) vs late trauma or history of prior exposure to trauma vs no prior exposure on cortisol levels. Recency of exposure (ie, within the preceding year) showed an effect on cortisol levels in men only, with those who were recently exposed exceeding significantly those who experienced a trauma more than 1 year ago, as well as those with no trauma exposure in their lifetime.

We explored whether restricting the analysis to current (active) PTSD would suggest different conclusions. There were no men with current PTSD; thus, the analysis was restricted to women. Current and past PTSD in women did not differ significantly ($P = .46$). Log mean ± SDs of no exposure to trauma and current PTSD in women were virtually identical, 2.50 ± 0.06 and 2.49 ± 0.18, respectively ($P = .97$).

URINARY CORTISOL LEVELS: COMORBIDITY WITH MDD

We evaluated the role of comorbidity of PTSD and MDD in total 24-hour UFC levels. Four groups were compared: MDD alone, PTSD alone, PTSD comorbid with MDD, and neither disorder. The ANOVA revealed a significant group × sex interaction ($P = .02$). However, sex-specific models revealed a nonsignificant group effect in men ($P = .12$) and women ($P = .07$).

The GEE analysis on night, AM, and PM UFC levels revealed a significant diurnal variation ($P<.001$) and group × sex interaction ($P = .003$). Group effects were significant in women ($P = .03$) and men ($P = .04$) (**Table 2**). In women, the PTSD/MDD comorbid group had significantly higher cortisol levels, compared with each of the other 3 groups (ie, MDD alone, PTSD alone, and no disorder). No other comparisons were significant. In men, the MDD group had a significantly higher mean cortisol level than the no-disorder and the comorbid PTSD/MDD groups. No other comparisons were significant. To illustrate the results, data on cortisol levels at night, AM, and PM from these analyses are displayed in **Figures 1** and **2**.

URINARY CATECHOLAMINE LEVELS: EFFECTS OF PTSD AND TRAUMA EXPOSURE

The sample raw mean±SD for 24-hour dopamine levels was 381.5±334.8 µg/24 h; epinephrine, 11.0±9.1 µg/24 h [60.1±49.7 nmol/d]; and norepinephrine, 50.3±8.2 µg/24 h [297.3±48.5 nmol/d]. **Table 3** presents comparisons of the PTSD, exposed to trauma without PTSD, and no exposure to trauma groups. There were significant effects of group membership on the 3 catecholamine levels. The group with PTSD had higher mean levels of all 3 urinary catecholamines, compared with the exposed to trauma without PTSD and no exposure groups. (See Table 3 for significant pairwise comparisons.) Pairwise comparisons also revealed significant differences between the exposed to trauma without PTSD and no exposure groups in dopamine ($P=.02$) and epinephrine ($P=.02$) levels, although in the opposite direction from the expected (ie, lower in the exposed to trauma without PTSD group than in the no exposure group). Subjects with past vs current PTSD did not differ significantly on any catecholamine measure ($P>.25$). The GEE models yielded similar results and, in addition, revealed significant diurnal variations ($P<.002$).

Table 2. Generalized Estimating Equations Model of Urinary Free Cortisol Levels (8 Hour) Controlling for Diurnal Variation (n = 275)*

	Degree of Freedom	*P* Value
Time	2	<.001
Group	3	.61
Sex	1	.03
Group × sex (interaction)	3	.003
Diagnostic Groups†	Men	Women
Neither MDD nor PTSD (n = 139)	2.68 (0.07)	2.48 (0.06)
MDD (n = 67)	2.98 (0.12)	2.38 (0.07)
PTSD (n = 23)	2.65 (0.23)	2.39 (0.12)
Both MDD and PTSD (n = 46)	2.46 (0.16)	2.72 (0.09)

Abbreviations: MDD, major depressive disorder; PTSD, posttraumatic stress disorder.

*Values are expressed as mean (SE) unless otherwise indicated.

†Significant differences in men: urinary free cortisol levels were higher in the MDD group than the neither MDD or PTSD group and than the both MDD and PTSD group. Significant differences in women: urinary free cortisol levels were higher in the group with both MDD and PTSD than all other groups.

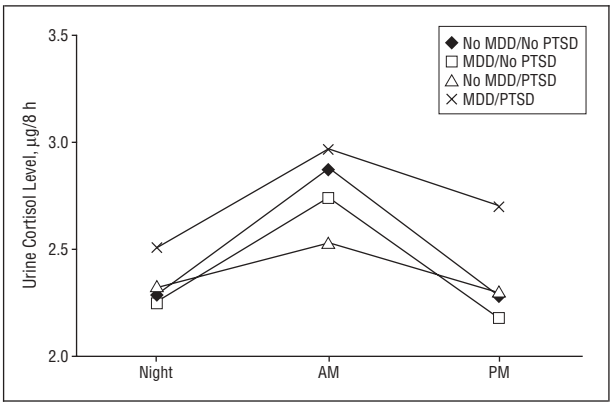

Figure 1. Urine cortisol excretion levels in the night, morning (AM), and evening (PM) in women by psychiatric diagnoses. The comorbid posttraumatic stress disorder (PTSD)/major depressive disorder (MDD) group demonstrated significantly elevated urinary free cortisol excretion levels compared with the other 3 groups; differences in the evening were particularly noticeable.

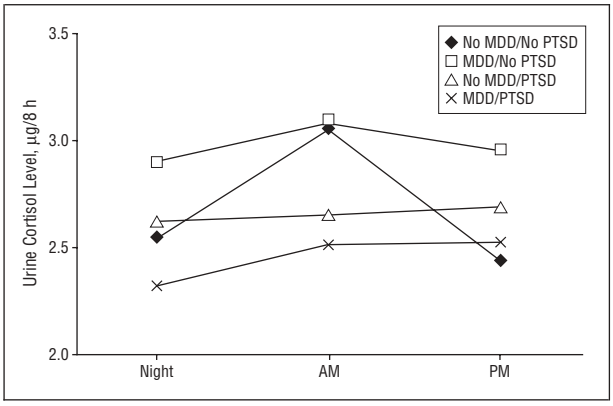

Figure 2. Urine cortisol excretion levels in the night, morning (AM), and evening (PM) in men by psychiatric diagnoses. The major depressive disorder (MDD) group differed significantly from the MDD/posttraumatic stress disorder (PTSD) group and the no-disorder group.

URINARY CATECHOLAMINE LEVELS: COMORBIDITY WITH MDD

Group means of total 24-hour urine dopamine, epinephrine, and norepinephrine levels across the 4 diagnostic groups are displayed in **Table 4**. A significant race difference was detected in the analysis of dopamine levels, with African American individuals' levels exceeding those of white individuals; the mean±SEs of dopamine levels in Table 4 are race-adjusted. For all 3 outcomes, there were significant effects of group membership. Pairwise comparisons showed that, across the 3 catecholamine measures, the comorbid group of PTSD plus MDD had significantly higher means than the groups with neither disorder and with MDD only. The group with PTSD only also exceeded the groups with neither disorder and with MDD on all 3 measures; however, the excess did not always reach significance (Table 4). A consistent finding across the 3 catecholamine measures was the absence of a significant difference between 2 PTSD groups (ie, the PTSD/MDD comorbid group and the PTSD-only group). The GEE analysis yielded similar results and, in addition, detected a significant diurnal variation ($P<.002$). The data for catecholamine levels across night, AM, and PM are shown in **Figures 3**, **4**, and **5**.

RELATIONSHIP BETWEEN CORTISOL AND CATECHOLAMINE LEVELS

Both urinary cortisol and catecholamine levels are indices of stress hormonal systems, but the extent to which these 2 systems are correlated is unclear. Using Spearman rank correlations, we examined whether there was evidence of a disconnect between the 2 systems in PTSD and, if observed, whether such a disconnect was unique to PTSD. We found that in the total sample, dopamine, epinephrine, and norepinephrine are robustly intercorrelated; Spearman rank correlations ranged from 0.47 to 0.69, with a mean of 0.60. However, none of the catecholamine levels had a significant correlation with cortisol levels ($\rho=0.04$-0.08). We further examined correlations between catecholamine and cortisol levels within subgroups (ie, exposed to trauma without PTSD, no trauma exposure, PTSD, MDD, and PTSD plus MDD), but, with one exception, correlations were less than 0.15 and not significant. There was a low but significant correlation (0.20) between cortisol and epinephrine levels in the group not exposed to trauma. We conclude there is no evidence of a disconnect between cortisol and catecholamine levels as a feature of PTSD.

COMMENT

The results for the 4 diagnostic groups, defined by history of PTSD and MDD, can be summarized as follows: (1) with respect to catecholamine levels, we found significantly higher mean levels of dopamine, epinephrine, and norepinephrine in persons with lifetime PTSD (with and without comorbid MDD), compared with persons with MDD alone or neither disorder; (2) with respect to cortisol levels, we found no distinct pattern associated with PTSD in either sex and no difference was detected between past and current PTSD; (3) a finding incidental to the PTSD-cortisol relationship was a significantly higher mean cortisol level in women with lifetime MDD comorbid with PTSD, compared with women with neither disorder or with either disorder alone and a significantly higher mean cortisol level in men with lifetime MDD alone, compared with men with neither disorder or with both disorders. Our analysis provides no support for the hypothesis that PTSD is associated with lower UFC levels.[3] Persons with PTSD did not show lower UFC levels than persons with no history of trauma or than persons with history of trauma but not of PTSD; neither did they show lower UFC levels than persons with a history of MDD or persons with neither disorder

Higher mean catecholamine levels have been reported in anxiety disorders, among them PTSD.[15,30-32] The noradrengergic and dopaminergic systems are implicated in arousal disturbance,[31] which is one of the hallmark symptoms of PTSD. Our findings of higher catecholamine levels in men and women with lifetime PTSD (alone or comorbid with MDD) are consistent with these reports. They extend the previous reports to lifetime PTSD in the general population.

Higher mean cortisol levels have been observed in patients with MDD compared with healthy control subjects.[33-35] Our finding of a higher mean urinary cortisol level in women with lifetime MDD comorbid with PTSD and in men with lifetime MDD alone is consistent with these reports. This finding in lifetime MDD is also consistent with a previous report that demonstrated higher mean saliva cortisol levels in women with past MDD compared with women with no history of MDD.[36]

Our results, taken together, are consistent with neurobiologic models of anxiety and MDD, namely, the involvement of the sympathetic nervous system in anxiety disorders and the involvement of the hypothalamic-pituitary-adrenal axis in MDD. Evidence of sympathetic nervous system involvement in PTSD was similar in both sexes, whereas evidence of hypothalamic-pituitary-adrenal axis activation in MDD varied by sex. In men, higher mean cortisol levels were observed in cases with lifetime MDD alone but not in the small number of cases

Table 3. Total 24-Hour Dopamine, Epinephrine, and Norepinephrine Levels in Groups Exposed to Trauma, Not Exposed to Trauma, and With Posttraumatic Stress Disorder (PTSD) (n = 256)*

	Degree of Freedom	DA†		E		NE	
		F Value	*P* Value	F Value	*P* Value	F Value	*P* Value
Group	2;247	9.3	<.001	7.3	.001	11.8	<.001
Race	1;247	15.9	<.001	. . .	. . .	. . .	. . .
				Mean (SE)			
Groups							
Not exposed to trauma (n = 101)		5.86 (0.07)		2.23 (0.06)		3.69 (0.05)	
Exposed to trauma (n = 105)		5.65 (0.07)		2.07 (0.05)		3.60 (0.05)	
PTSD (n = 69)		6.08 (0.08)		2.41 (0.07)		4.01 (0.07)	

Abbreviations: DA, dopamine; E, epinephrine; NE, norepinephrine.
*Statistics from analysis of covariance (DA), analysis of variance (E, NE), and adjusted log-transformed group means. Significant pairwise comparisons: all DA and E comparisons were significant, and the group with PTSD had NE levels higher than other 2 groups.
†Race-adjusted log-transformed means.

Table 4. Total 24-Hour Dopamine, Epinephrine, and Norepinephrine Levels Across Diagnostic Groups (n = 256)*

	Degree of Freedom	DA†		E		NE	
		F Value	*P* Value	F Value	*P* Value	F Value	*P* Value
Group	3;247	4.51	.004	3.67	.01	8.21	<.001
Race	1;247	12.99	<.001	. . .	. . .	. . .	. . .
				Mean (SE)			
Groups							
Neither MDD nor PTSD (n = 139)		5.76 (0.06)		2.18 (0.05)		3.69 (0.05)	
MDD (n = 67)		5.71 (0.08)		2.11 (0.07)		3.56 (0.07)	
PTSD (n = 23)		6.05 (0.14)		2.42 (0.12)		4.00 (0.12)	
Both MDD and PTSD (n = 46)		6.08 (0.10)		2.40 (0.08)		4.02 (0.08)	

Abbreviations: DA, dopamine; E, epinephrine; MDD, major depressive disorder; NE, norepinephrine; PTSD, posttraumatic stress disorder.
*Statistics from analysis of covariance (DA), analysis of variance (E, NE), and adjusted log-transformed means. Significant pairwise comparisons: the group with MDD and PTSD had higher DA levels than the groups with neither MDD nor PTSD and MDD alone; the group with PTSD alone had higher DA levels than the group with MDD alone; the group with both MDD and PTSD had higher E levels than the group with neither MDD nor PTSD and the group with MDD alone; the group with PTSD alone had higher E levels than the group with MDD alone; the group with both MDD and PTSD and the group with PTSD alone had higher NE levels than the group with neither MDD nor PTSD or the group with MDD alone.
†Race-adjusted log-transformed means.

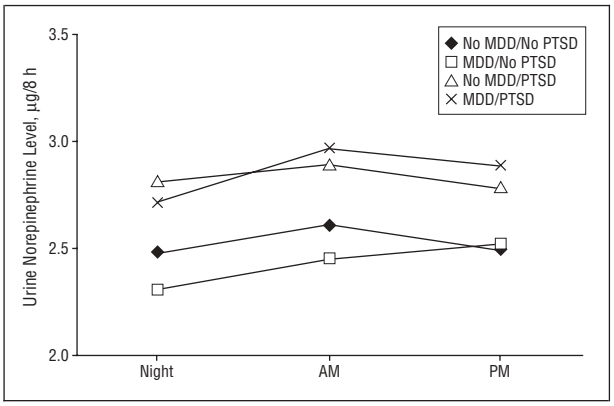

Figure 3. Urine norepinephrine excretion levels in night, morning (AM), and evening (PM) (men and women) by psychiatric diagnoses. The groups with posttraumatic stress disorder (PTSD) only and PTSD comorbid with major depressive disorder (MDD) had significantly higher levels than the other 2 groups.

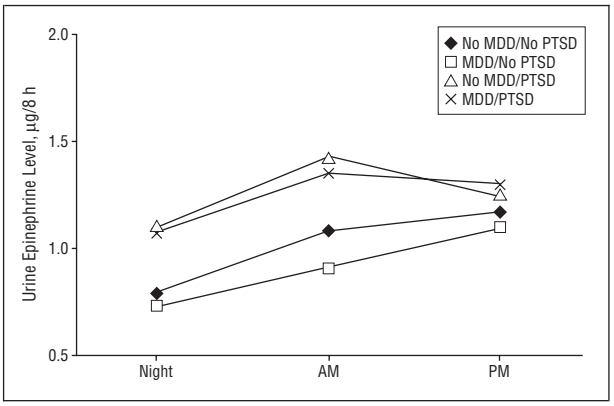

Figure 4. Urine epinephrine excretion levels in night, morning (AM), and evening (PM) (men and women) by psychiatric diagnoses. The groups with posttraumatic stress disorder (PTSD) only and PTSD comorbid with major depressive disorder (MDD) had significantly higher levels than the other 2 groups.

with MDD comorbid with PTSD. In women, higher mean cortisol levels were observed in comorbid cases but not in cases with lifetime MDD alone. Our results suggest that in women, MDD alone might be a less severe disorder than MDD combined with PTSD. Previous studies have reported that MDD comorbid with anxiety disorders is more severe than "pure" MDD in terms of depressive symptoms, course of illness, and treatment response.[37-42] The

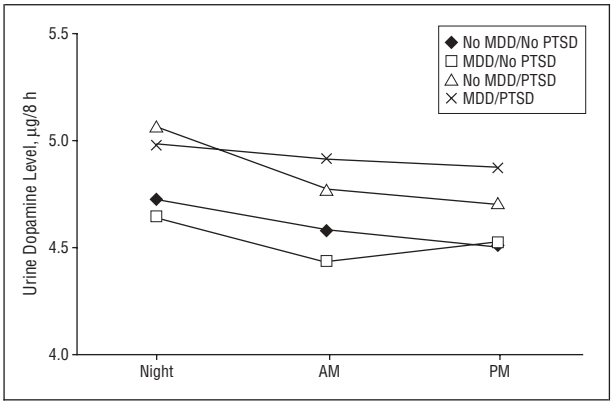

Figure 5. Urine dopamine excretion levels in night, morning (AM), and evening (PM) by psychiatric diagnosis (men and women). The groups with posttraumatic stress disorder (PTSD) alone and PTSD comorbid with major depressive disorder (MDD) had significantly higher levels than the MDD group, and the PTSD/MDD group had significantly higher levels than the group with neither disorder.

interpretation of the observed sex differences in urinary cortisol levels is unclear.

Our findings on UFC levels in women with MDD comorbid with PTSD are in agreement with a study by Heim et al,[43] which reported that depressed women with history of early trauma (11 of the 13 met criteria for PTSD) demonstrated enhanced cortisol secretion in response to a stressor, whereas women with MDD without early trauma showed normal cortisol responses, compared with healthy control subjects. A report by Rasmusson et al[9] of women with childhood abuse and PTSD also is consistent with these findings. The women with PTSD had either active or past MDD and showed enhanced cortisol responses to corticotropin-releasing factor and to corticotropin infusion, as well as a trend toward higher 24-hour UFC levels. A study by Lemieux and Coe[7] of women with childhood sexual abuse found higher 24-hour UFC levels in women with PTSD than with no PTSD. While the researchers did not report on comorbid MDD, they indicated that 5 of the 11 women with PTSD were taking antidepressants; the possibility that others may have had a history of depression was not ruled out. Our study and these previous studies converge in suggesting that alterations in hypothalamic-pituitary-adrenal axis, specifically a higher level of UFC, might be observed in women with MDD comorbid with PTSD. These studies highlight the importance of diagnosing both MDD and PTSD in research focusing on the neurobiology of either disorder.

An effect of exposure to trauma per se on urinary catecholamine levels was observed in both sexes. However, instead of a stress-like effect (ie, higher levels of these stress hormones), we observed lower levels in the exposed to trauma without PTSD group than the no exposure group. It is possible that the long-term adaptation to trauma exposure is associated with lower catecholamine levels. An alternative explanation is that exposure to trauma segregated individuals into a susceptible group (PTSD) and a nonsusceptible group (exposed to trauma without PTSD), who had before differed on baseline catecholamine levels before exposure to trauma. The nonexposed group (which showed higher mean catecholamine levels than the exposed group) might include a subset of persons who have a susceptibility to the PTSD-inducing effects of trauma but have never been exposed. A further possibility is that the subset of unexposed persons with a susceptibility to PTSD have a higher level of basal catecholamines. The presence of these persons would push upward the average level of catecholamines of the unexposed group as a whole. Evidence that preexisting anxiety disorders, which would be accompanied by increased secretion of catecholamines,[30,31] predict PTSD[19,44] supports this interpretation.

Four limitations in this study are noted. First, the 66.5% participation rate in the biologic studies, although high, considering respondents' burden, limits the generalizability of the results. However, the exceptionally high follow-up participation in the epidemiological study across multiple assessments allows us to evaluate and confirm the representativeness of the biologic sample on sociodemographic characteristics and history of substance use disorders. Differences on unmeasured variables cannot be ruled out. Second, although we found no difference between current and past PTSD, the small number of cases with current PTSD limits our ability to examine this question more definitively. Third, the small number of men with PTSD, either "pure" or comorbid with MDD, limits the reliability of our findings in men. The possibility of a sex difference in UFC levels merits further attention.

The fourth limitation is the use of the NIMH-DIS at baseline and across all follow-up assessments rather than a clinical assessment. However, the NIMH-DIS has been found to be highly specific but more conservative than a clinician-administered instrument.[24] Thus, cases designated as PTSD are "true" cases, although it is possible that some cases of PTSD undetected by the NIMH-DIS were included in the exposed to trauma without PTSD group. However, the availability of persons who were never exposed, according to baseline and multiple follow-up reassessments, addresses the concern that any misclassification of cases of PTSD might have obscured potential differences in cortisol levels associated with PTSD. The analyses comparing PTSD with the 2 control groups (exposed to trauma without PTSD and no exposure) showed no significant differences with regards to cortisol levels between PTSD and either of these control groups. In the analyses of comorbidity, the neither-disorder group (no PTSD/no MDD) was separated into (1) exposed to trauma without PTSD and (2) no exposure. No differences in cortisol levels were observed in a comparison that included only the no exposure group as reference from what was reported when the total group with neither disorder was used.

Important strengths of the study deserve mention. The most important strength is the representative community sample from which the data came. Previous studies on the neurobiology of PTSD in nonveteran populations have used clinical samples or samples of volunteers, which undoubtedly are biased in terms of severity of psychopathology, other clinical features, and social factors that influence self-selection to treatment and clinical research. In sharp contrast, our neurobiologic study is nested in a longitudinal epidemiologic study, with multiple psychiatric assessments during a 10-year period and an exceptionally high follow-up completion rate of the initial cohort. A comparison of the total sample with the sub-

set on whom data on 32-hour urine samples are available indicates that we have been successful in achieving a representative sample of the total cohort. The study thus offers an opportunity for an unbiased evaluation of neurobiologic factors in PTSD. The large sample size is another important strength. We also introduced a methodologic advance over previous studies that used total 24-hour urinary hormone secretion levels. It involved collecting urine in 8-hour increments linked to the wake-sleep cycle. This method revealed an overall circadian rhythm in cortisol and catecholamine levels. By taking into account the data from night, AM, and PM, GEE analysis offered enhanced statistical power for detecting differences across diagnostic groups, which were obscured in the analysis of total 24-hour UFC levels.

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