Article

Low Cortisol and Risk for PTSD in Adult Offspring of Holocaust Survivors

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Objective: The study examined the association between cortisol and putative risk factors for posttraumatic stress disorder (PTSD) in a sample of subjects at increased risk for the development of PTSD.

Method: Twenty-four-hour urinary cortisol excretion was measured in 35 adult offspring of Holocaust survivors and 15 healthy comparison subjects who were not offspring of Holocaust survivors. Subjects were also characterized with regard to clinical symptoms, presence or absence of psychiatric diagnoses including PTSD, and presence or absence of PTSD in their parents.

Results: Low cortisol levels were significantly associated with both PTSD in parents and lifetime PTSD in subjects, whereas having a current psychiatric diagnosis other than PTSD was relatively, but nonsignificantly, associated with higher cortisol levels. Offspring with both parental PTSD and lifetime PTSD had the lowest cortisol levels of all study groups.

Conclusions: Parental PTSD, a putative risk factor for PTSD, appears to be associated with low cortisol levels in offspring, even in the absence of lifetime PTSD in the offspring. The findings suggest that low cortisol levels in PTSD may constitute a vulnerability marker related to parental PTSD as well as a state-related characteristic associated with acute or chronic PTSD symptoms.

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We previously suggested that children of Holocaust survivors constitute a high-risk group for posttraumatic stress disorder (PTSD), since they were found to have a greater prevalence of lifetime PTSD compared to demographically similar persons who have experienced equivalent numbers and types of events that meet the DSM-IV definition of trauma (1). Adult children of Holocaust survivors also showed a greater prevalence of mood and other anxiety disorders (1). PTSD in children of Holocaust survivors appeared to be strongly related to parental PTSD. In a sample of Holocaust survivors and their children in which PTSD could be evaluated directly, lifetime PTSD was present in the children of parents with chronic PTSD but not in the children of parents who either had never developed PTSD or had recovered from PTSD within several years after World War II (2).

The idea that familial contributions can increase the likelihood of developing PTSD is supported not only by the observations summarized above but also by studies showing a relationship between psychological responses in trauma survivors and family history of psychopathology (reviewed in reference 3). As early as 1918, Wolfsohn demonstrated that 74% of 100 patients with war neuroses reported a family history of psychoneurosis compared to none of 100 matched comparison subjects (4). These observations were replicated by other investigators, who found similar associations in World War I (5–7) and World War II (8) veterans and their families, and by a later study of traumatized civilians exposed to disaster (9). The findings of these studies all described a significantly higher rate of familial mental illness in symptomatic trauma survivors with PTSD (or "shell shock") compared to either nonexposed subjects or similarly exposed survivors who did not develop posttraumatic syndromes. More recent community-based studies have confirmed that respondents with PTSD were three times more likely than trauma survivors without PTSD to report family mental illness, particularly anxiety, depression, psychosis, and antisocial behavior (10). Perhaps most compelling, however, is the finding of an increased prevalence of PTSD among trauma survivors who also had a twin with PTSD compared to trauma survivors whose exposed twin did not develop PTSD (11). The risk for developing PTSD after trauma exposure was significantly greater for monozygotic than for dizygotic twins, suggesting a role for genetic factors in conferring susceptibility to the development of these symptoms (12), possibly by influencing biological substrates associated with the pathophysiologic response to stress in PTSD.

Low ambient cortisol levels have been found in many groups of trauma survivors with PTSD (13–18). The observation of low cortisol levels in PTSD was initially considered counterintuitive, because cortisol levels have generally been found to be high in conditions of acute and chronic stress and in certain types of psychiatric disorders that are associated with stress (e.g., major depressive disorder) (reviewed in references 19, 20). In cases of chronic stress or chronic illness such as depression, increased cor-

tisol levels usually indicate that the hypothalamic-pituitary-adrenal (HPA) axis has grown resistant to the effects of cortisol. This cortisol resistance can be measured by the extent of "nonsuppression" of cortisol after the administration of dexamethasone. Indeed, about half of patients with major depressive disorder demonstrate a nonsuppression of cortisol on the dexamethasone suppression test (21). In contrast, low cortisol levels in PTSD are associated with enhanced cortisol suppression after dexamethasone administration (22), suggesting that the HPA axis may actually be overly responsive to stimulation (see reference 23 for review). The hypothesis that the HPA axis may be hypersensitive in PTSD is consistent with the more general phenomenology of increased reactivity to both explicit and implicit trauma reminders (e.g., reference 24) and as well as a more generalized hypervigilance in trauma survivors with this disorder.

According to current convention, phenomenological and biological differences between trauma survivors with and without PTSD are generally considered to be either consequences of the traumatic event or correlates of PTSD. However, given the evidence for familial transmission of vulnerability to PTSD or the more general idea of the existence of risk factors for the development of PTSD, it is reasonable to consider the possibility that variables that distinguish between trauma survivors with and without PTSD might also reflect risk factors for the development of PTSD and, as such, may be useful predictors of who will develop PTSD after exposure to trauma (25, 26).

The study of cortisol levels in the putative high-risk group of adult children of Holocaust survivors, especially those whose parents have PTSD, and comparison subjects provides an opportunity for determining the relationship between cortisol and putative risk factors for PTSD. Thus, in the study reported here, we evaluated 24-hour urinary cortisol levels in 35 adult children of Holocaust survivors and 15 comparison subjects. The evaluation of cortisol requires a consideration not only of the risk factor of parental trauma and PTSD, but also of the characteristics of the subject, particularly in regard to their own trauma exposure, presence of PTSD, or other psychiatric disorders. We therefore evaluated the association of cortisol to trauma exposure, parental survivor status, parental PTSD, personal PTSD, and other psychiatric diagnoses.

Method

Subjects

The study was approved by the Institutional Review Board of the Mount Sinai School of Medicine in New York City. All subjects provided written informed consent before their participation. Thirty-five offspring of Holocaust survivors (six men and 29 women) and 15 comparison subjects (eight men and seven women) participated in the study. The offspring were between the ages of 26 and 50 years, and the comparison subjects were between 23 and 51. Offspring were defined as having been raised by at least one biological parent who survived the Nazi Holocaust, but the majority (N=28) were raised by two biological parents who were survivors. The comparison subjects were Jewish, within the same age range, and did not have a parent who was a Holocaust survivor. The majority of the comparison subjects had two American-born parents, but two comparison subjects had one parent born in Israel.

There were two types of recruitment for the study. The clinical sample consisted of offspring who had participated in short-term group psychotherapy in the Mount Sinai Specialized Treatment Program for Holocaust Survivors and Their Families (N=19). The nonclinical sample consisted of volunteers solicited from lists obtained from the Jewish community (i.e., recruitment that did not identify the offspring status of subjects) or who had responded to newspaper advertisements and community group announcements for research participants. The nonclinical sample included both offspring (N=16) and comparison (N=15) subjects. Our previous study showed no substantial differences between offspring recruited by using these two methods in trauma history or in personal or parental history of PTSD (1). There were no formal exclusions for current or past psychiatric problems because we were interested in examining the contribution of such problems to cortisol levels. However, no subject in either group met criteria for a past or current psychotic disorder or substance dependence. Thus, the only past or current diagnoses present in the sample were substance abuse and mood, anxiety, and eating disorders. An earlier preliminary report of cortisol levels from a subset of this sample was reported in Yehuda et al. (27, 28).

Medical information on all subjects was obtained by the use of a medical checklist and was reviewed by a staff physician. Patients with major active medical conditions were excluded from the study, as were patients who had used benzodiazepines, lithium, β-blockers, or psychotropic medications within 2 months of the study. Subjects were not withdrawn from medications to participate in this protocol. One of the offspring had irregular and brief use of paroxetine, and one subject had taken trazodone as needed for sleep within 2 months of the study. Two subjects (one offspring and one comparison subject) reported occasional use of nonsteroidal asthma medication, five women (four offspring and one comparison subject) were taking either estrogen replacement or birth control pills, and three women (two offspring and one comparison subject) were taking low-dose levothyroxine sodium.

Clinical Assessment

Past and current lifetime trauma was assessed by using the Trauma History Questionnaire (B. Green, unpublished manuscript, 1995). The questionnaire lists 23 potentially traumatic (mostly potentially life-threatening) events, such as crime, physical and sexual assaults, and disaster, and includes an open-ended question for specifying other extraordinarily stressful situations or events. Subjects were asked the number of times they experienced each of these events and at what ages. The events were classified into four categories—crime, sexual abuse, disaster, and other—and then further classified as low-magnitude (e.g., mugging without a weapon, motor vehicle accident without injury) and high-magnitude (e.g., assault, rape) events. For events in the "other" category, repeated instances of hearing about traumatic events of the same type were counted only once.

After reviewing the responses to this questionnaire, the clinical rater asked the subject to identify the most traumatic life event from the list and used this event as the basis of inquiry about PTSD symptoms. PTSD symptoms were assessed by using the Clinician Administered PTSD Scale (29) and DSM-IV symptom criteria. If no event was present, or if no event was deemed life-threatening or as having resulted in a subjective response of intense fear, helplessness, or horror, the Clinician Administered PTSD Scale was not administered, and individual items were automatically scored as zero. Psychiatric diagnoses other than PTSD were made according to DSM-IV criteria by using the Structured Clinical Interview for DSM-IV (SCID) (30). The full diagnostic inter-

TABLE 1. Number of Lifetime Traumatic Events Reported by Offspring of Holocaust Survivors and Comparison Subjects Whose Parents Were Not Holocaust Survivors[a]

	Offspring (N=34)[b]		Comparison (N=15)		ANCOVA	
Traumatic Event[c]	Mean	SD	Mean	SD	F (df=1, 46)	p
Crime-related event	0.74	0.83	1.07	0.88	2.35	n.s.
Sexual abuse	0.47	0.86	0.07	0.26	0.34	n.s.
Disaster	0.82	1.24	0.67	0.82	0.06	n.s.
Other	1.91	2.71	1.27	1.03	0.00	n.s.
Low-magnitude event[d]	2.68	2.42	2.93	2.66	0.82	n.s.
High-magnitude event[d]	1.24	1.83	0.93	1.53	0.10	n.s.

[a] Mean without correction for age covariate.
[b] Data missing for one of 35 offspring of Holocaust survivors.
[c] Categories of traumatic events reflected subcategories on the Trauma History Questionnaire. Crime-related events included muggings, robberies, break-ins, domestic violence, and threats with weapons. Sexual abuse included rape, molestation, and forced sexual touching. Disaster included motor vehicle accidents, plane crashes, industrial accidents, sporting accidents, and natural disasters. Other traumas included war, witnessing sudden death, receiving information about death of loved ones, and life-threatening illness.
[d] Low-magnitude events included robberies and muggings without threat with weapon, molestation in adulthood that was not deemed subjectively threatening, or being the recipient of directed sexual exposure. High-magnitude events included potentially life-threatening events that caused subjective responses of fear, helplessness, or horror.

view was performed for only subjects who endorsed a positive response on one or more of the mental health screening questions at the beginning of the interview.

Parental PTSD was assessed in one of two ways. For 11 of the 35 offspring subjects, parents were interviewed directly by the investigators, who used the Clinician Administered PTSD Scale. (These parents could be interviewed because they participated in other ongoing research on Holocaust survivors at the Mount Sinai Traumatic Stress Studies Program.) For other subjects, determination of parental PTSD was made by the offspring, who completed a parental stress history assessment developed for this study. The scale required offspring to first describe the nature of the parent's Holocaust-related experience (i.e., concentration camp, ghetto, hidden in forest, etc.) and then complete a checklist based on the 17 DSM-IV symptoms of PTSD for each parent. The offspring estimated the average severity of each of the parent's symptoms, on the basis of recall from their childhood, adolescent, and early adult years. PTSD symptoms were rated on a 4-point Likert-type scale that had anchors similar to those on the Clinician Administered PTSD Scale. Although the accuracy of an adult child's estimate of the actual extent of parental PTSD symptoms is difficult to ascertain, particularly because PTSD symptoms may have fluctuated over the life course of the parent and some symptoms may not have been observable to the child and would therefore be underestimated, the questionnaire provided an index of the subjective perception of the parent's symptoms. It is noteworthy that this subjective assessment correlated well with our diagnostic conclusions when the parent could be rated with the Clinician Administered PTSD Scale. Nine of the 11 subjects whose parents we interviewed had completed the parental stress history scale. In each of these cases, our raters and the offspring generated the same conclusions regarding the presence or absence of PTSD.

In addition to this interview, subjects completed the Civilian Mississippi Scale (31) to determine the global effect of stressful events on individuals' lives. This scale provides a continuous measure of PTSD-like symptoms. Subjects also completed the Symptom Checklist (SCL-90) (32) to provide an estimate of general psychiatric symptom severity. The depression and anxiety subscales of this instrument were of interest for this study.

Cortisol Assessment

Urine was collected beginning at wake-up in 24-hour portions in 2-liter polyethylene bottles kept in freezers in the subjects' residences to ensure stability of cortisol, as previously described (18). Collections were scheduled to occur on days that were anticipated not to be particularly stressful to obtain samples that would reflect basal secretion (Mason et al. [13]). Typically, subjects planned to be at home for the 24-hour period to facilitate collection. Urinary free cortisol levels were determined by using an extraction procedure and radioimmunoassay kit from Clinical Assays, Inc. (Cambridge, Mass) (interassay coefficient of variation=4.0).

Statistical Analysis

One-way analysis of variance (ANOVA) was performed to determine group differences in age, height, weight, gender, education, and 24-hour urine volumes, as well as trauma exposure and clinical symptoms. The primary dependent variable in this study was cortisol level, which was substantially skewed; taking the log of cortisol level produced more nearly normally distributed values. Log-transformed cortisol levels of offspring and comparison subjects were used for all statistical analyses, but means and standard deviations of untransformed values are presented. Group means in cortisol levels were compared by using ANOVA. To further investigate whether group differences were attributable to demographic variables, gender, or trauma exposure, analysis of covariance (ANCOVA) or two-way ANOVA was performed. ANCOVAs, controlling for age, were performed to compare exposure to types of trauma between offspring and comparison subjects, as cumulative exposure may increase with age.

Additional analyses were performed to distinguish among the offspring by using characteristics that were either not evaluated (parental PTSD) or not present (lifetime PTSD, current major psychiatric diagnosis) among comparison subjects. Because all offspring with lifetime PTSD had a parent with PTSD, both variables could not be employed in factorial ANOVA. Instead, a trichotomy was constructed consisting of offspring 1) without parental PTSD or lifetime PTSD, 2) with parental PTSD but no lifetime PTSD, and 3) with both parental PTSD and their own lifetime PTSD. One-way ANOVA was performed to investigate cortisol differences in these three offspring groups and in comparison subjects. Another one-way ANOVA was performed to compare differences in log-transformed cortisol levels among offspring with and without current psychiatric diagnoses and comparison subjects. Two-way ANOVA was used to investigate whether the differences in log-transformed cortisol levels found among the three offspring types were affected by the presence of a current psychiatric diagnosis other than PTSD. Post hoc testing for the ANOVAs was performed using Tukey's honestly significant difference test or Dunnett's T3, if variances were unequal among the groups.

To complement these ANOVAs, correlational analyses with log-transformed cortisol levels were performed for offspring by using dichotomous indices of parental and lifetime PTSD and current psychiatric diagnosis. Parallel analyses were performed by using the Mississippi PTSD scale as a continuous measure of current PTSD symptoms in place of the dichotomous characterization of lifetime PTSD.

Results

The mean ages for children of Holocaust survivors and comparison subjects were 40.9 years (SD=6.4) and 32.7 years (SD=8.0), respectively ($F=14.59$, df=1, 48, $p<0.001$). Children of Holocaust survivors did not differ from comparison subjects in education (mean=17.0 years, SD=1.7,

TABLE 2. Symptom Severity of Offspring of Holocaust Survivors, Grouped by Presence of Lifetime Posttraumatic Stress Disorder (PTSD), and of Comparison Subjects Whose Parents Were Not Holocaust Survivors

	Score							
	Offspring With PTSD (N=10)		Offspring Without PTSD (N=25)		Comparison Subjects (N=15)		Analysis	
Symptom Severity Measure	Mean	SD	Mean	SD	Mean	SD	F (df=2, 47)	p
Civilian Mississippi Scale	94.5	23.3	76.7	20.2	65.7	13.4	6.76[a]	0.003
Symptom Checklist (SCL-90)								
Total score	74.2	51.6	52.3	39.6	31.5	36.6	3.25[b]	0.05
Depression subscale	1.29	0.98	0.84	0.68	0.43	0.56	4.32[c]	0.02
Anxiety subscale	1.18	0.97	0.43	0.51	0.32	0.38	7.14	0.002

[a] Significant post hoc difference (Tukey's honestly significant difference test) between offspring with PTSD and comparison subjects (p=0.002) and between offspring with PTSD and offspring without PTSD (p=0.04).
[b] Significant post hoc difference between offspring with PTSD and comparison subjects (Tukey's honestly significant difference test, p=0.04).
[c] Significant post hoc difference between offspring with PTSD and comparison subjects (Tukey's honestly significant difference test, p=0.02).

TABLE 3. Symptom Severity of Offspring of Holocaust Survivors, Grouped by Presence of Current Psychiatric Diagnosis, and of Comparison Subjects Whose Parents Were Not Holocaust Survivors

	Score							
	Offspring With Current Diagnosis (N=12)		Offspring Without Current Diagnosis (N=23)		Comparison Subjects (N=15)		Analysis	
Symptom Severity Measure	Mean	SD	Mean	SD	Mean	SD	F (df=2, 47)	p
Civilian Mississippi Scale	89.2	21.0	77.9	22.5	65.7	13.4	4.69[a]	0.01
Symptom Checklist (SCL-90)								
Total score	59.7	40.0	58.0	46.4	31.5	36.6	2.17	n.s.
Depression subscale	1.05	0.71	0.93	0.85	0.43	0.56	2.92	n.s.
Anxiety subscale	0.64	0.43	0.65	0.87	0.32	0.38	1.27	n.s.

[a] Significant post hoc difference between offspring with PTSD and comparison subjects (Tukey's honestly significant difference test, p=0.01).

and mean=16.8 years, SD=3.2, respectively) (F=0.04, df=1, 40, n.s.). An ANOVA analyzing the effects of group and gender failed to reveal significant group differences for height (F=0.28, df=1, 45, n.s.) or weight (F=3.66, df=1, 43, p=0.06). Significant gender effects were observed for height (F=20.10, df=1, 45, p<0.001) and weight (F=8.67, df=1, 43, p=0.005), but no interaction of group and gender was observed for either height (F=0.42, df=1, 45, n.s.) or weight (F=0.02, df=1, 43, n.s.). Offspring did not differ from comparison subjects in 24-hour urine volume (t=0.70, df=43, n.s.) or urinary cortisol concentration (t=1.36, df=43, n.s.).

Children of Holocaust survivors did not differ from comparison subjects in the types of lifetime traumatic experiences, as assessed by the Trauma History Questionnaire (Table 1). The mean number of traumatic events reported by children of Holocaust survivors (mean=4.1, SD=3.8) and comparison subjects (mean=3.9, SD=3.2) did not differ, covarying for age (F=0.38, df=1, 47, n.s.). However, offspring were more likely to develop PTSD after traumatic experiences. None of the comparison subjects met criteria for lifetime PTSD in response to their traumatic life experiences. In contrast, 28.6% of offspring (10 of 35 offspring) had lifetime PTSD, and two had current PTSD.

Table 2 and Table 3 provide a summary of self-reported symptom severity of the offspring, grouped by presence or absence of lifetime PTSD and current psychiatric diagnosis, and of the comparison subjects. Offspring with lifetime PTSD had significantly higher scores on the Mississippi PTSD scale than offspring without lifetime PTSD and comparison subjects, who did not differ significantly from each other. Offspring with lifetime PTSD also reported more psychiatric symptom severity than comparison subjects, as reflected by the SCL-90 total score. Offspring without lifetime PTSD were not significantly different from either of the other two groups on this measure. Significant group differences were observed on the depression and anxiety subscales of the SCL-90. Post hoc tests revealed significant differences in the number of current depressive symptoms endorsed by offspring with PTSD and comparison subjects, but no significant pair-wise group differences in anxiety ratings.

Twelve of the 35 offspring of Holocaust survivors met criteria for at least one current psychiatric diagnosis other than PTSD at the time of the evaluation. Five subjects had a mood disorder (either major depressive disorder or dysthymia) with generalized anxiety disorder, three met criteria for only a mood disorder, one had major depressive disorder with body dysmorphic disorder, one had dysthymia with an eating disorder, one met criteria for obsessive-compulsive disorder, and one had anorexia nervosa. Although these illnesses tended to be chronic, their severities were generally in the mild to moderate range at the time of assessment; only one subject had been treated with an antidepressant or psychotropic medication for any of these conditions within the previous 6 months. Three of the 12 subjects also had lifetime PTSD; one of these had current PTSD. None of the comparison subjects met the diagnostic criteria for current or past major psychiatric disorder.

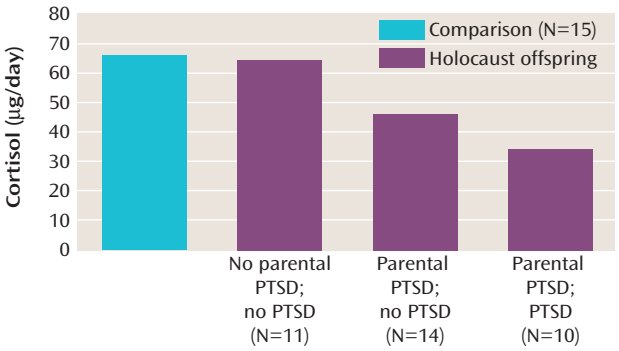
Offspring were classified by the presence or absence of current psychiatric diagnoses and compared on symptom

TABLE 4. Cortisol Levels in Offspring of Holocaust Survivors Grouped by Lifetime Posttraumatic Stress Disorder (PTSD), Parental PTSD, and Current Psychiatric Diagnosis Status

Group	Own Lifetime PTSD	Parental PTSD	Current Psychiatric Diagnosis	N	Cortisol Level (µg/day)[a] Mean	SD
1	Yes	Yes	No	7	29.48	11.09
2	Yes	Yes	Yes	3	45.03	29.39
3	No	Yes	No	10	33.88	16.72
4	No	Yes	Yes	4	76.10	49.35
5	No	No	No	6	64.59	10.80
6	No	No	Yes	5	63.44	19.06

[a] Significant difference in cortisol level between offspring with parental and lifetime PTSD, offspring with parental but not lifetime PTSD, and offspring with neither parental nor lifetime PTSD (F=4.60, df=2, 29, p=0.02). Significant difference in cortisol level between the offspring with and without current psychiatric diagnosis (F=4.34, df=1, 29, p=0.05). Significant difference in cortisol level between group 1 and group 3 (p=0.03, Tukey's honestly significant difference test) and between group 1 and group 5 (p=0.04, Tukey's honestly significant difference test).

FIGURE 1. Mean Cortisol Levels in Offspring of Holocaust Survivors and Comparison Subjects Whose Parents Were Not Holocaust Survivors, by Parental and Lifetime Posttraumatic Stress Disorder (PTSD) Status[a]



[a] Mean cortisol level of offspring of Holocaust survivors with both parental PTSD and lifetime PTSD was significantly different from that of offspring with no parental PTSD and no lifetime PTSD and that of comparison subjects (p<0.05, Tukey's honestly significant difference test).

rating scales to the comparison subjects (Table 2). Scores on the Mississippi PTSD scale were highest in the offspring with psychiatric diagnoses, three of whom also had lifetime PTSD. However, there were no differences between offspring with or without current psychiatric disorder on SCL-90 total scores or on the depression and anxiety subscales.

Assessment of parental PTSD indicated that 71.4% of the offspring (25 of 35 offspring) had at least one parent with chronic PTSD. All 10 offspring meeting criteria for lifetime PTSD were among these 25 offspring. Furthermore, for all 10 offspring with lifetime PTSD, both parents were Holocaust survivors.

As a group, children of Holocaust survivors showed significantly lower 24-hour urinary cortisol excretion (mean=48.3 µg/day, SD=27.0) than comparison subjects (mean=65.1 µg/day, SD=25.7) (F=5.62, df=1, 48, p=0.02), based on log-transformed cortisol values. When age was used as a covariate, this group difference was not substantially changed (F=5.13, df=1, 47, p=0.03). Covarying for the total number of traumatic life events in addition to age did not affect the group difference in cortisol level (F=5.11, df=1, 46, p=0.03). When gender was used as a main effect in a two-way ANOVA, the group difference was reduced (F=2.91, df=1, 46, p=0.10). However, there was no gender difference (F=0.66, df=1, 46, n.s.) or interaction of group and gender (F=0.15, df=1, 46, n.s.). There was no further reduction of significance when height and weight were added as covariates (F=2.94, df=1, 41, p=0.09). When education was used as a covariate, the group difference was still significant (F=4.41, df=1, 39, p=0.04).

Pooled within-group associations of cortisol level with other demographic observations were assessed by partial correlations, controlling for group. Log-transformed cortisol levels were not significantly correlated with age (r=–0.06, df=47, n.s.) or education (r=–0.15, df=39, n.s.). Partial correlations were not significant for total number of traumatic events (r=–0.04, df=46, n.s.), controlling for age in addition to group, or for height (r=0.22, df=43, n.s.) or weight (r=0.09, df=43, n.s.), controlling for gender in addition to group.

We divided the offspring sample into three categories: offspring with PTSD and parental PTSD, offspring without PTSD but with parental PTSD, and offspring without either PTSD or parental PTSD. Because all offspring with PTSD also had parental PTSD, it was not possible to distinguish fully between these two characteristics. A one-way ANOVA indicated significant differences in cortisol level among the comparison subjects and these three offspring categories (F=6.72, df=3, 46, p=0.001), as illustrated in Figure 1. Dunnett's T3 post hoc tests showed that offspring with both parental PTSD and their own PTSD differed from offspring without parental PTSD or their own PTSD (p=0.003), and also from comparison subjects (p=0.006).

When offspring were characterized by current psychiatric diagnosis, one-way ANOVA demonstrated differences in log-transformed cortisol levels among three groups, defined as offspring with (mean=63.1 µg/day, SD=33.2) and without (mean=40.6 µg/day, SD=19.8) current psychiatric diagnoses and comparison subjects (mean=65.1 µg/day, SD=25) (F=6.22, df=2, 47, p=0.004). Post hoc tests of log cortisol level that used Tukey's honestly significant difference test indicated that offspring with no current psychiatric diagnoses showed significantly lower mean 24-hour levels of cortisol excretion than offspring with psychiatric diagnoses (p=0.04) and comparison subjects (p=0.006).

A two-way ANOVA analyzing presence of current psychiatric diagnosis other than PTSD among offspring trichotomized by presence of parental PTSD and their own PTSD demonstrated significant main effects for both offspring group (F=4.60, df=2, 29, p=0.02) and diagnosis (F=4.34, df=1, 29, p=0.05) but a nonsignificant interaction (F=1.99, df=2, 29, n.s.). Table 4 presents the mean cortisol levels for offspring grouped by lifetime PTSD, parental PTSD,

and current diagnoses. Cortisol levels were generally low in offspring with both their own and parental PTSD and high in offspring with neither. Cortisol levels were generally higher in the groups with psychiatric diagnoses. Pairwise comparisons of groups using Tukey's honestly significant difference test of log cortisol levels demonstrated that, for the three groups without psychiatric diagnoses, offspring with both parental PTSD and lifetime PTSD had lower values than offspring with parental PTSD but no lifetime PTSD ($p=0.04$) and offspring with neither parental or lifetime PTSD ($p=0.03$).

Bivariate correlations demonstrated that in the offspring group, cortisol levels were more strongly negatively correlated with having parental PTSD ($r=-0.50$, $df=33$, $p=0.002$) than with lifetime PTSD ($r=-0.34$, $df=33$, $p=0.05$) and were positively correlated with having a current psychiatric diagnosis ($r=0.37$, $df=33$, $p=0.03$). After controlling for parental PTSD, the correlation between log-transformed cortisol level and lifetime PTSD was no longer significant ($r=-0.16$, $df=32$, n.s.). On the other hand, the relationship between log-transformed cortisol level and parental PTSD was maintained even after controlling for lifetime PTSD in the offspring ($r=-0.41$, $df=32$, $p=0.02$). The relationship between log-transformed cortisol level and parental PTSD was similarly demonstrated after controlling for current PTSD symptoms as reflected by the Mississippi PTSD scale ($r=-0.48$, $df=32$, $p=0.03$). The Mississippi scale score was, however, not significantly correlated with log-transformed cortisol level among the entire offspring sample ($r=-0.20$, $df=33$, n.s.). It is interesting to note that this index of PTSD symptoms was only moderately correlated with a diagnosis of PTSD among the offspring ($r=0.36$, $df=33$, $p=0.03$), indicating that PTSD symptoms were present in offspring even in the absence of a PTSD diagnosis (Table 2).

Discussion

The results demonstrate that some putative risk factors are associated with cortisol levels in offspring of Holocaust survivors, whereas other risk factors are not. Low cortisol levels in offspring were associated with parental PTSD but not with parental exposure to Holocaust-related trauma. This is consistent with our previous finding that risk for PTSD among offspring was related to parental PTSD status and not to exposure of the parent to the Holocaust (2).

Likewise, cortisol levels were associated with the development of PTSD in the offspring but not with the offspring's exposure to trauma. Because the development of PTSD in the offspring was limited to offspring with parental PTSD, it was not possible to distinguish completely between the effect of parental PTSD and the individual's own PTSD. Nonetheless, it appears that parental PTSD is an even more important correlate of cortisol levels in the offspring than whether or not the offspring developed his or her own PTSD after exposure to a traumatic event, as there was a significant correlation between cortisol level and parental PTSD even after controlling for the lifetime PTSD status of the offspring. Conversely, the correlation between PTSD and cortisol level in the offspring was no longer significant after controlling for parental PTSD.

This pattern of associations does not imply that the offspring's own PTSD was unrelated to cortisol level. Offspring with both parental PTSD and lifetime PTSD had significantly lower cortisol levels than either offspring without lifetime PTSD or comparison subjects. Offspring with only parental PTSD, but not lifetime PTSD, had an intermediate level of cortisol, which in this small sample was not significantly different from the levels in other groups. Thus, parental PTSD alone did not fully account for low cortisol levels in offspring.

In the context of discussions about biological correlates of risk, however, lifetime PTSD—that is, whether an individual ever developed PTSD—may be a more relevant variable than the current PTSD status at any given time after exposure to a traumatic event. The importance of this variable is illustrated by its association with current symptoms, not only as measured by the Mississippi PTSD scale but also by the SCL-90 total score and SCL-90 depression and anxiety subscale scores. Indeed, offspring with lifetime PTSD were more symptomatic in terms of current depression and anxiety symptoms than offspring without lifetime PTSD, while the presence of a current psychiatric disorder did not differentiate symptoms of the SCL-90. The association between lifetime PTSD and current psychiatric symptoms suggests that historical variables may be critical in determining current responses to the environment. Further, these results indicate that cortisol level, which has been considered to be a "state-related" measure because it is profoundly affected by day-to-day provocation, can be a legitimate correlate of historical variables such as past PTSD or even parental PTSD.

In this context, it should be noted that increased cortisol levels have been found in first-degree relatives of depressed patients and have been implicated as a risk factor for the development of major depressive disorder (33, 34). In fact, a variety of HPA parameters have been examined and found to be altered in nondepressed probands at genetic high risk for depression in a manner consistent with alterations observed in the depressed relatives, albeit not to the same extent (33, 34). Moreover, the HPA alterations were found to be stable when assessed 4 years later in the same high-risk probands (35). These studies demonstrate that cortisol parameters can be viewed as vulnerability markers in probands with high familial risk for depression.

Indeed, although PTSD and also parental PTSD appear to be associated with low cortisol levels, other psychiatric disorders such as major depressive disorder have been associated with increased cortisol levels (for review, see references 19 and 20). Having a psychiatric disorder is certainly a plausible outcome after exposure to trauma (36) and is compatible with and, some argue, predictive of (37)

the development of PTSD. In the current study, having a psychiatric diagnosis other than PTSD at the time of assessment was generally associated with levels of cortisol as high as those observed in comparison subjects. There were too few subjects in the sample to permit an analysis of cortisol by diagnosis, but this type of analysis may be of interest in future studies.

Nonetheless, in considering why cortisol levels were not significantly higher in offspring with psychiatric disorder compared with healthy volunteers, as one might expect based on the psychiatric literature, it may be that the cohort of subjects in this study, while meeting criteria for these disorders, were not symptomatic enough to show the cortisol elevations typically associated with psychiatric disorders. Supporting this view is the observation that there were no substantial differences in SCL-90 scores, particularly scores on the depression and anxiety subscales, for offspring with a psychiatric diagnosis compared to offspring without a psychiatric diagnosis or comparison subjects. Indeed, our exclusion of subjects taking psychotropic medications within the past 2 months may have generated a less symptomatic sample.

Alternatively, it may be that cortisol levels might have been more elevated in offspring with psychiatric disorder were it not for the presence of other factors that are associated with low cortisol levels. Indeed, having parental PTSD, and especially having lifetime PTSD in addition to parental PTSD, was generally associated with low cortisol levels. In the groups with parental PTSD and a current psychiatric diagnosis other than PTSD, the cortisol level was low for those with a lifetime PTSD diagnosis and high for those without a lifetime PTSD diagnosis. The message here is that a variety of intercorrelated factors contributing to risk for PTSD may be associated with different effects on cortisol. Thus, our findings represent the beginning of an exploration of this complex issue, which should be pursued to more carefully examine relationships among these factors and their individual or collective impact on risk and cortisol.

In considering unanswered questions and methodological limitations of the study, the reader should be reminded that the major risk factor examined in this study—that of parental PTSD—was largely based on the subjective assessment of the parent's PTSD by the offspring rather than by a direct examination of the parent. Yet, the subjective nature of the assessment may not be a serious methodological flaw in the context of examining the impact of parental status on the offspring. Indeed, the offspring's subjective evaluation may be at least as relevant to this issue as the objective reality of the parents' symptoms. PTSD may exert effects on the family because of the obvious distress of the afflicted parent. Although family members may not always know what intrusive thoughts are being recalled at any given time by the trauma survivor parent, family members may certainly notice the parent's distractibility, frequent references to the Holocaust, distress at reminders of the Holocaust, or explosive outbursts, or they may notice the effects of constriction of affect and numbing in the parent's life. It is important to note that although some offspring claimed their parents did not speak of the Holocaust, many of them still believed their parents were impaired by their experiences. It may be that witnessing symptoms, even in the absence of knowledge about the historical details of their parents' lives, is a salient aspect of conferring on offspring the vulnerability to PTSD after trauma exposure, as suggested by Solomon et al. (38). However, the converse case—a failure by the offspring to recognize parental PTSD—may not necessarily imply the absence of PTSD in that parent but only a lack of awareness of parental symptoms. This issue, too, can be addressed in a larger study examining the variability of cortisol levels in those who report no parental PTSD. Ultimately, it will be possible to determine whether a low cortisol level is differentially associated with subjective assessment or actual presence of PTSD in the parent(s) through direct examination of survivors and children.

Whatever the perception of offspring regarding parental psychopathology, parental rearing practices may be substantially affected by the presence of PTSD in one or both parents. Nongenomic transmission of stress response characteristics has been demonstrated in rats, and this process includes both a behavioral and neuroendocrine response bias (39, 40). Moreover, this effect of maternal behavior has recently been shown to persist across multiple generations (41) and to be associated with increased hippocampal glucocorticoid receptor expression. Thus, putative animal models exist that provide a template for generating hypotheses concerning the intergenerational transmission of stress vulnerability. The current findings represent the first clinical demonstration of this phenomenon that we are aware of. Clearly, additional studies are warranted to further explore this initial observation of the association of cortisol levels with the risk factor of parental PTSD.

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