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LONGITUDINAL COURSE OF ADOLESCENT DEPRESSION: NEUROENDOCRINE AND PSYCHOSOCIAL PREDICTORS

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Abstract

Objective—The study examined whether cortisol measures are associated with the clinical course of depression in adolescents. Further, the study evaluated whether the relationship between cortisol and clinical course is moderated by environmental stress and/or social support.

Method—Fifty-five adolescents with depression (age range 13–18) were recruited. In addition to a systematic diagnostic assessment, information was obtained on environmental stress and social support. Urinary free cortisol measures were collected on three consecutive nights during the index episode. Clinical follow-up evaluations were conducted at regular intervals over a 5-year period, documenting recovery from the index depressive episode and recurrent episodes. Information on environmental stress and social support also was gathered during each follow-up assessment.

Results—Consistent with prior reports, the majority of adolescents (92.2%) recovered from the initial depressive episode. A substantial proportion of the recovered youth (42.6%) experienced a subsequent episode during the follow-up period. Higher cortisol levels were associated with a longer time to recovery from the index depressive episode. The effect of cortisol on recovery was moderated by social support. The combination of elevated cortisol and recent stressful experiences predicted recurrence, whereas a higher level of social support was protective against recurrence.

Conclusions—These data, in conjunction with prior literature, suggest that depression reflects an underlying neurobiological vulnerability that may predispose individuals with high vulnerability to chronic, recurrent episodes. Psychosocial factors, independently or in combination with an underlying neurobiological vulnerability, also play an important role in determining the clinical course of depression.

Keywords

clinical course; depression; hypothalamic-pituitary-adrenal axis; social support; stress

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INTRODUCTION

Adolescence is the highest risk period for development of major depressive disorder.[1] Numerous studies also have documented that early depressive episodes persist or recur into adult life along with ongoing psychosocial difficulties. These difficulties include, but are not limited to, disruption in interpersonal relationships, early pregnancy, low educational attainment, poor occupational functioning and unemployment, as well as increased risk for suicidal behavior, resulting in substantial socioeconomic burden.[2] A better understanding of the factors that predispose youngsters to a chronic, recurrent course will be helpful in the development and implementation of more effective treatment and preventive strategies, thereby allowing such youth to achieve their full potential as adults.[3]

There has been considerable effort to determine the factors associated with the clinical course of depression in youngsters, but it remains unclear which variables exert a potent influence on the course of illness. Among the demographic and clinical variables that were examined, none has been shown yet to consistently predict the clinical course.[2–4] In addition, several psychological and social variables have been proposed as risk factors for chronic and/or recurrent illness, including high neuroticism, negative emotionality, negative cognitions, poor social support, and stressful experiences.[2–4]

There is a growing body of research examining neurobiological factors associated with the course of depression in adults. In particular, the hypothalamic-pituitary-adrenal (HPA) system has been studied quite extensively in relation to the pathophysiology and clinical course of depression, based on the theory that the HPA axis mediates/moderates the effects of stress on emotional, cognitive and behavioral responses.5,6 For example, a meta-analysis of dexamethasone suppression test (DST) results concluded that while cortisol response to dexamethasone administration does not have a prognostic value during a depressive episode, non–suppression of cortisol following successful treatment is a robust predictor of relapse in adults.7 Subsequent studies in recovered patients showed that abnormal cortisol responses to a combination of dexamethasone and corticotropin-releasing hormone (CRH) predicted recurrence.8,9

HPA dysregulation also has been linked to pediatric depression.[10] With respect to clinical course, higher cortisol secretion in the evening, a time when the HPA axis is relatively quiescent, predicted persistent depression after 72 weeks.[11] In a separate investigation, higher cortisol secretion near sleep-onset was associated with recurrence.[12] The present work extends these findings by examining the influence of cortisol on recovery and recurrence of depression in the same sample. Measures of environmental stress and social support also were incorporated because stressful experiences have been shown to precipitate depressive episodes both in adolescents and adults, whereas social support has been implicated as a protective factor.[2–4]

To the best of our knowledge, this is the first study to utilize HPA, stress and social support measures simultaneously in relation to the clinical course of adolescent depression. The following hypotheses were postulated: (1) adolescents with lower cortisol levels (measured at recruitment) would recover faster from the index depressive episode compared to their counterparts with higher cortisol levels; (2) the effect of cortisol on recovery from the index depressive episode would be moderated by the magnitude of persistent stress during adolescence, recent stressful life events and/or social support; (3) among adolescents who recovered from the index depressive episode, those having higher cortisol levels at baseline would be more likely to develop a recurrent depressive episode compared to those with

lower cortisol levels; and (4) psychosocial factors would moderate the effect of cortisol on the risk for recurrence.

METHOD

The data reported here are part of a larger study on the development and course of depression in adolescents, as well as the relationship between depression and substance use disorders.[13–15]

Participants

Fifty-five adolescent volunteers with depression were recruited from local mental health and pediatric clinics and schools. The participants met criteria for major depressive disorder, with a minimum duration of four weeks and a score of ≥15 on the first 17-items of the Hamilton Depression Rating Scale (HDRS).[16] All participants were between 13–18 years, and Tanner Stage III, IV or V of pubertal development.17,18 Exclusionary criteria included current or prior history of mania/hypomania, psychotic disorder or substance use disorder symptoms, and family history of bipolar disorder. Participants were free from psychotropic agents for at least eight weeks, and were medically healthy and free from alcohol or illicit drug use as confirmed by laboratory investigations and a urine screen. Other exclusionary criteria included weight greater than 150% of ideal body weight for age and gender, and weight or height less than one-third percentile. Prior to performing the research procedures, all adolescent participants signed a written assent form and parents signed an informed consent document, approved by the local Institutional Review Boards.

Diagnostic Evaluation

Diagnoses were based on a semi-structured interview, the Schedule for Affective Disorders and Schizophrenia for School-Age Children - the Present and Lifetime Version (K-SADS-PL).19 Inter-rater and test-retest reliability have been established for K-SADS-PL, as well as convergent and discriminant validity.19 The K-SADS-PL was administered separately to the adolescent and parent, and summary scores were tabulated. HDRS, Children's Global Assessment Scale (CGAS)20, Beck Depression Inventory (BDI)21, and Hollingshead Socioeconomic Scale22 also were completed.

The Family History-Research Diagnostic Criteria (FH-RDC), a semi-structured interview, was used for the evaluation of psychiatric disorders in family members.[23] A parent was interviewed regarding life-time psychiatric disorders in all first-degree relatives of the adolescent subject (including the self, spouse and all offspring). The FH-RDC is sensitive for obtaining information from knowledgeable relatives.24

Environmental Stress

In order to obtain information on chronic stress and acute stressful life experiences during adolescence, a semi-structured interview, the Chronic and Episodic Stress Interview for Adolescents was used.[25] Chronic stress consists of conditions that persist for 6 months or longer. In previous longitudinal studies, the magnitude of stress in pertinent domains remained stable across assessment periods.[26,27] In contrast, acute life experiences are discrete events with a clear period of onset and offset. Also, the type of events and the magnitude of stress associated with these events are more variable as compared to the chronic stress. Good inter-rater reliabilities have been established for the chronic and acute stress ratings.[28]

The magnitude of chronic stress in 10 content areas (family relationships, independence from the family, close friendships, romantic relationships, social life, school, work, finances,

health of the participant, and health of family members) was assessed in the past 6 months. The adolescent was interviewed on the quality of relationships and performance in each domain, and ratings were given by the interviewer for the magnitude of stress using objective and behaviorally-specific criteria (1 = not at all stressful, and 5 = extremely stressful).[25]

In addition to obtaining information on chronic stress, participants were probed systematically about the occurrence and timing of acute life events in the past 6 months.[25] Narrative summaries of the event and surrounding context were presented to a group of trained raters. In order to obtain ratings of the severity of stressors that were not distorted by participants' depressive symptoms, or misattribution of the meaning of the stressors, the raters were blind to the subject's diagnostic status and perception of stress. Consensus group ratings were given for the degree of stress (1 = not at all stressful, and 5 = extremely stressful) for each event, and whether the event was a positive, neutral or negative experience under the given circumstances. Symptom-related events were not scored. Only events that were considered negative were included in the analyses, and a summary score of stress impact from the negative events was tabulated.

Social Support

Two types of social support questionnaires were administered, perceived support and enacted (received) support. Perceived support represents the cognitive dimension of social support, whereas enacted support represents the behavioral aspect of support.[29] Perceived support is viewed as a global construct that remains stable over time and across relationships.[30,31] In contrast, enacted support is described in terms of frequency and quality of specific interactions and, thus, is expected to vary to a greater degree across time and situations.[29,30] The measure of perceived support included a short version of the Social Support Questionnaire (SSQ).32 Previous studies confirmed the reliability and validity of the SSQ in older adolescents.[30,31] The SSQ provides two measures of global perceived support: 1) a number score which includes the number of persons listed as providers of support in six pertinent domains; and 2) a satisfaction score in each domain scored as a 6-point Likert scale (1 = very dissatisfied; 6 = very satisfied). The average number of support providers and a mean satisfaction score were tabulated across all six domains. A composite score of social support was derived by combining these two scores.

The measure of enacted social support was a short version of the Social Support Inventory (SSI).33 Previous studies confirmed the reliability and validity of the SSI in older adolescents.[29,30] The SSI included 36 items and was designed to yield three sub-scales representing functional support (Information, Material Aid, and Emotional Support). A composite score was derived from the mean of these subscales.

Cortisol Measures

Each subject participated in a 3-night sleep-neuroendocrine study in the laboratory. Prior to these studies, sleep-wake schedules were regulated for at least one week, with participants going to bed between 10:00 to 11:00 p.m. and waking between 6:30 to 7:30 a.m.. The sleep-wake schedule was confirmed through diary and actigraphy. The participants were asked to void urine prior to switching off the lights. All urine voided during the night (including the sample obtained immediately upon awakening) was collected. A radioimmunoassay procedure was employed for the cortisol assays.[34] Free cortisol concentration and total amount excreted were determined. Samples from the same subject were analyzed in the same assay. In order to determine inter- and intra-assay coefficients of variation, replicate samples containing low, medium and high concentrations of cortisol were measured in each assay. The intra- and inter-assay coefficient of variation was 3.2% and 6.5%, respectively.

Follow-up Evaluation

After the baseline assessments, the participants were followed longitudinally at 6-month intervals in the first year and yearly thereafter, for up to 5 years. In addition to obtaining information from the K-SADS-PL during each follow-up evaluation, the Longitudinal Interval Follow-up Evaluation (LIFE)[35] was used to document the clinical course of depression using the 6-point Psychiatric Status Rating (PSR) to provide information on the severity of depressive symptomatology for each month.

Recovery from the index depressive episode was defined as a rating of ≤2 for ≥12 weeks on the PSR component of the LIFE. Recurrence was defined as a PSR rating of ≥5 for four or more weeks following recovery. The conventional criterion for remission/recovery is 8 weeks, and the minimum duration for recurrent depressive episode is 2 weeks.[36] In the current study, more stringent criteria were used for recovery and recurrence to ensure stability of symptoms because depressive symptoms in youngsters tend to be more variable, with greater heterogeneity in clinical response and course, than adults.[3] Information from the diagnostic assessments was presented to an independent clinician “blind” to diagnostic, stress, social support or cortisol measures.

Assessment of chronic and acute stress during follow-up was similar to the method used during initial evaluation.[25] Time frame included the period since the last interview. The adolescents also completed the SSQ and SSI during each follow-up evaluation.

Primary Dependent and Independent Variables

The primary outcome measures were time to recovery from the index depressive episode and the first depressive episode (recurrent episode) following recovery from the index episode. The independent variables included cortisol levels, stress (chronic as well as acute stress), and social support (both perceived and enacted support). Demographic (age, gender, race, and socioeconomic status) and clinical (body mass index, pubertal status, age of onset of depression, a prior history of depression, depression severity, duration of the depressive episode at intake, psychosocial function, suicidality, comorbid psychiatric disorders, a history of depression in the parent, and presence/absence of treatment during follow-up) variables served as potential covariates.

For cortisol measures, the first night was considered as an adaptation night and the mean values derived from Night 2 and Night 3 data were used. Timelines were generated for the onset of recurrent depressive episodes and stressful life events during the follow-up period. For each participant that developed a recurrent episode during the follow-up period, the total acute stress score for the 3 months preceding the onset of depression was computed. Each subject that did not have a depressive episode was paired with a participant with depression based on similar demographic information, and stressful events that he/she experienced in the corresponding 3 months were tabulated. This method was adopted instead of using a random 3-month period because events were not evenly distributed across the 5 years due to developmentally expected events (e.g., high school graduation and transition to college).

Statistical Methods

Cortisol variables were log-transformed and the psychosocial measures were standardized prior to the application of statistical tests for significance. Cortisol was not normally distributed and the range of scores varied across psychosocial measures. SPSS 17.0 Version for Windows was used for statistical analysis. Correlation procedures were utilized to examine associations between variables. Kaplan-Meier survival analysis was used to compute the probability of recovery from the index depressive episode or the probability of developing a recurrent episode during follow-up. In order to identify the predictors of

recovery/recurrence of depressive episodes, Cox proportional hazards regression procedure was utilized. Alpha was set at .05.

RESULTS

Demographic, Clinical, Psychosocial and Neuroendocrine Parameters

Demographic and clinical features at recruitment, as well as psychosocial and neuroendocrine parameters, are outlined in Table 1. Correlation co-efficients among the various demographic, clinical, psychosocial and neuroendocrine measures are depicted in Table 2. Higher scores on chronic stress were associated with higher cortisol levels, and cortisol concentration and total cortisol excretion correlated highly. The other measures showed only modest correlation. Gender and ethnic background did not significantly influence any of the clinical, psychosocial or neuroendocrine variables.

Follow-up Information

Four adolescents were assessed only at intake and did not complete any follow-up evaluations. Recruitment did not occur simultaneously and, therefore, not all subjects were studied longitudinally for the same period of time. Of the 51 adolescents that had follow-up information, 5.9% were followed for 12 months, 5.9% for 24 months, 13.7% for 36 months, 27.4% for 48 months, and 47.1% for 60 months (mean follow-up interval = 41.6 months; Median = 46.8 months).

Recovery from the Index Depressive Episode

Of the 51 adolescents with follow-up information, 47 (92.2%) recovered from the initial depressive episode. The mean time to recovery was 9.1 months (SE = 1.5, CI = 6.1–12.1), and the median time was 5.0 months (SE = 0.7, CI = 3.7–6.3) (see Figure 1). None of the demographic or clinical variables was significantly associated with recovery. Total cortisol excretion was used as the primary independent measure since urine volumes can affect cortisol concentration. After controlling for body mass index (BMI) and pubertal status, lower cortisol levels were associated with a faster time to recovery (OR = 0.5, CI = 0.3–0.7, p = .001; $\chi^2 = 11.59$, df = 4, p = .02).

In order to examine whether the psychosocial measures moderated the effect of cortisol on recovery, each psychosocial variable measured at baseline (namely, chronic stress, acute stress, perceived social support, and enacted social support) then was examined simultaneously with cortisol together with an interaction term (product of cortisol and each psychosocial measure). After accounting for the effect of cortisol, there was a non-significant trend for subjects with lower chronic stress levels to recover faster than those with higher stress levels (see Model 1, Table 3). However, chronic stress did not moderate the effect of cortisol on recovery time. Acute stress did not have an effect on recovery time (see Model 2, Table 3). Among adolescents with higher cortisol levels, those who reported higher levels of perceived social support recovered faster than their counterparts with lower levels of social support (see Model 3, Table 3; Figure 2). In contrast to perceived social support, enacted social support had no effect on recovery time (see Model 4, Table 3). Similar patterns emerged when the analyses were repeated with cortisol concentration as the primary predictor variable.

Recurrence of Depressive Episode during Follow-up

Of 47 youth that recovered from the index depressive episode, 20 (42.6%) developed a recurrent episode during follow-up. The mean time to recurrence was 37.5 months (SE = 3.4, CI = 30.8–44.1) (see Figure 3). None of the baseline demographic or clinical variables, as well as treatment during follow-up, was significantly associated with recurrence. After

controlling for BMI and pubertal status, adolescents who had higher cortisol levels at baseline had a greater probability of developing a recurrent episode than those who had lower cortisol levels (OR = 2.5, CI = 1.2–5.2, p = .02; χ^2 = 11.22, df = 4, p = .02).

In order to examine whether the psychosocial measures moderated the effect of cortisol on the risk for recurrence, each psychosocial variable measured at follow-up then was examined simultaneously with baseline cortisol values. Chronic stress did not have an effect on the probability of recurrence (see Model 1, Table 4). However, adolescents with higher levels of acute stress, particularly those with higher cortisol values, were more likely to develop a recurrent episode than those with lower levels of acute stress (see Model 2, Table 4). Perceived social support did not have an effect on the probability of recurrence (see Model 3, Table 4). After controlling for the effect of cortisol levels, adolescents who received more social support during follow-up were less likely to develop a recurrent episode than those who received less support (see Model 4, Table 4). However, enacted social support did not moderate the effect of HPA activity on recurrence (see Model 4, Table 4). Similar patterns emerged when the analyses were repeated with cortisol concentration as the primary predictor variable.

In order to graphically represent the combined effects of cortisol and acute stress on the risk for recurrence, the sample was stratified based on a median split of cortisol and stress measures: low-HPA activity and low-stress (n =13); high-HPA activity and low-stress (n = 10); low-HPA activity and high-stress (n = 10), and high-HPA activity and high-stress (n = 14). The four groups were then compared on the probability of recurrence during follow-up (χ^2 = 14.31, df = 3, p = .003; see Figure 4). In post-hoc comparisons, adolescents who had high HPA activity and also experienced high level of stress were more likely to develop a recurrent episode than those who had low HPA activity and experienced low level of stress (78.6% vs. 15.4%, χ^2 = 11.22, p = .001). Youth with both high HPA activity and high level of stress also were more likely to develop a recurrent episode than those who manifested elevated HPA activity but experienced low level of stress (78.6% vs. 30.0%, χ^2 = 4.86, p = .03). Adolescents who manifested low HPA activity, but experienced high level of stress, also were more likely to have a recurrent episode than those who had low HPA activity and experienced low level of stress (40.0% vs. 15.4%, χ^2 = 3.95, p = .05).

DISCUSSION

Consistent with prior reports, the majority of adolescents with depression recovered from the initial episode.[2,37,38] However, a substantial proportion of youth that recovered experienced a subsequent episode in less than five years.[2,37,38] None of the demographic or clinical features predicted recovery from the index depressive episode or recurrence. A summary of data from previous studies in youngsters and adults revealed no consistent predictors across studies.[2,4]

In contrast to the findings on demographic and clinical variables, cortisol and psychosocial factors predicted both recovery and recurrence of the depressive episode. Youngsters with higher baseline cortisol levels, and those with high levels of chronic stress (albeit not statistically significant), took a longer time to recover from the depressive episode. However, higher levels of social support were protective against a protracted depressive episode in those who had higher cortisol values. Similarly, the combination of higher baseline cortisol and recent stressful experiences was the most potent predictor of recurrence. These results replicate and extend prior findings in pediatric and adult depression. Increased cortisol secretion at baseline and recurrent stress were associated with a protracted time to recovery in a sample of depressed youngsters.[11] In an adult sample of remitted depressed patients, the combination of 24-hour cortisol excretion and fear

perception was the most powerful predictor of relapse during follow-up.39 These findings indicate that, although psychosocial and neurobiological measures individually have some utility in predicting the clinical course of depression,[4,7,12] a multi-dimensional approach across disciplines is more informative.[40,41]

Although the findings from the current study emphasize the interaction of neurobiological and psychosocial measures in determining the longitudinal clinical course of adolescent depression, these results should be considered preliminary because of the modest sample size. The sample comprised of volunteers with moderate levels of depression and stringent inclusion/exclusion criteria. Therefore, the findings might not be generalizable to community samples or to patients with more severe illness. Creatinine excretion was not measured simultaneously with cortisol, and individual differences in glomerular filtration rate and urine volume potentially could influence the cortisol values although all participants were medically healthy. Despite the statistical significance, the combined effect of cortisol and psychosocial measures on the clinical course of depression was only modest. Also, it is important to note that cortisol measures were collected only at intake, and a direct association between persistently high cortisol levels and chronic depression (or recurrence) could not be assessed. Although HPA measures are state-dependent,[42] evidence suggests that variations in HPA activity are heritable.43 Moreover, some investigations demonstrated that HPA dysregulation served as a premorbid marker of depression in at-risk individuals.[14,44] Therefore, HPA dysregulation may predispose individuals with high vulnerability to chronic, recurrent episodes. Psychosocial factors might interact with this underlying vulnerability and precipitate depressive episodes.

In the current study, chronic stress and perceived social support (which are relatively stable environmental factors) were better predictors of a chronic depressive episode, whereas acute stress and enacted support (which reflect changing environmental situations) were more robust predictors of recurrent episodes. In another investigation of adolescents, ongoing difficulties were associated with a protracted depressive episode,[11] whereas acute stress (within 3 months), but not chronic stress, was associated with recurrence.45

The clinical implications of these findings are three-fold. First, individual differences in HPA activity and their relation to the clinical course of depression indicate its potential utility as a prognostic indicator.[46] Evidence suggests that normalization of HPA dysregulation precedes the resolution of depressive symptoms,[47] and longitudinal assessment of HPA activity in depressed patients might be helpful in determining the propensity for chronicity and/or recurrence.[7,11] Individual differences in HPA regulation also might be helpful in the development of more specific interventions for the different subgroups and, ultimately, for an individual. For example, anti-glucocorticoid agents and CRH antagonists appear to have anti-depressant properties, and have been tested in humans for the treatment of depression.[48,49] It has been suggested that some antidepressants exert their clinical action via restoration of the glucocorticoid receptor gene expression and function, with subsequent normalization of the HPA feedback system.[47] Finally, the additional contribution of environmental stress and social support in determining the clinical course of depression suggests that such persons might benefit from adjunctive psychosocial interventions.[50] Future studies should evaluate the efficacy of pharmacotherapy and psychosocial interventions, singly and in combination, in depressed patients stratified on HPA activity and stress/social support levels.

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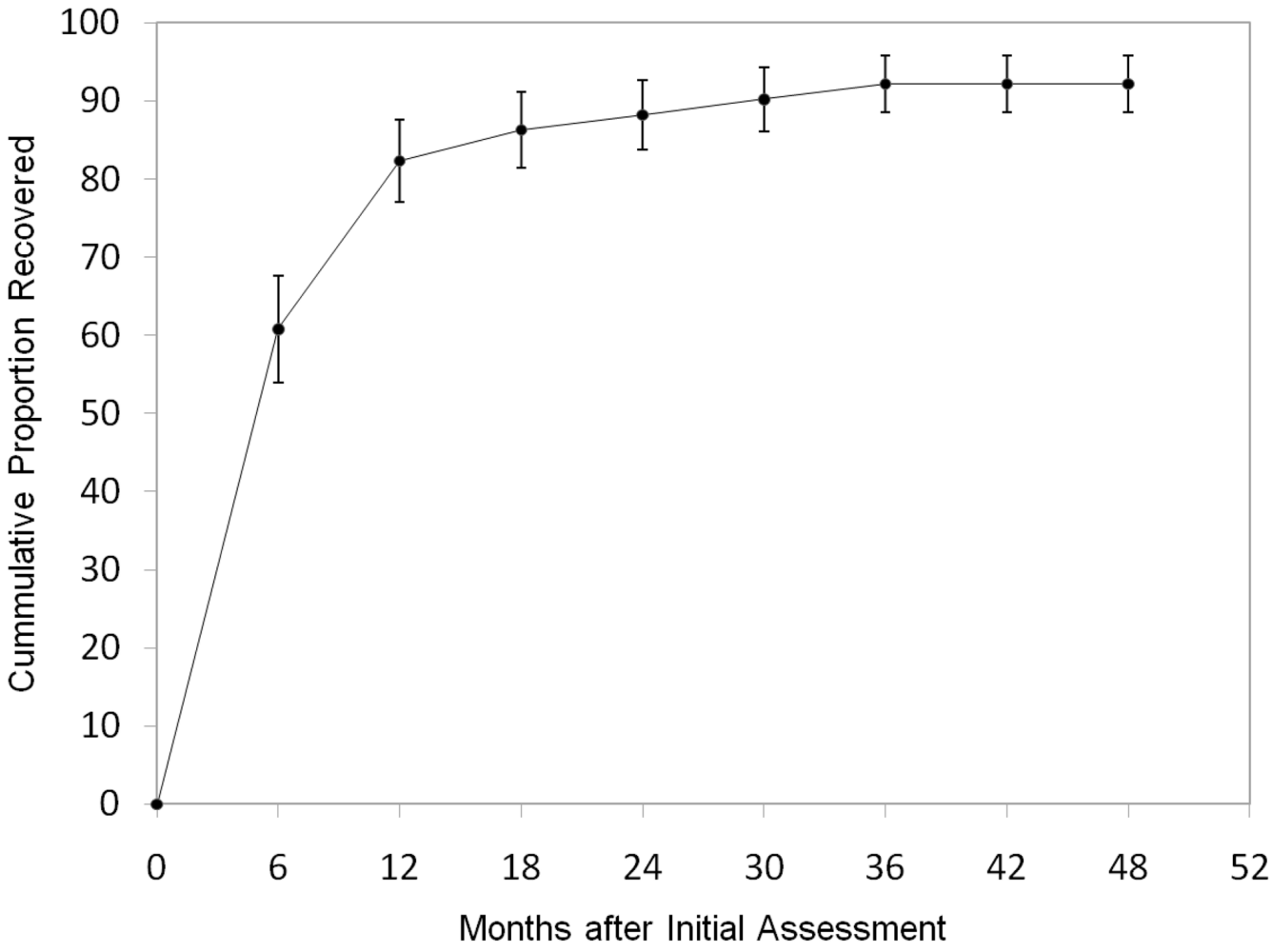

Figure 1.
Time to recovery from the index major depressive disorder (MDD) episode during prospective follow-up.

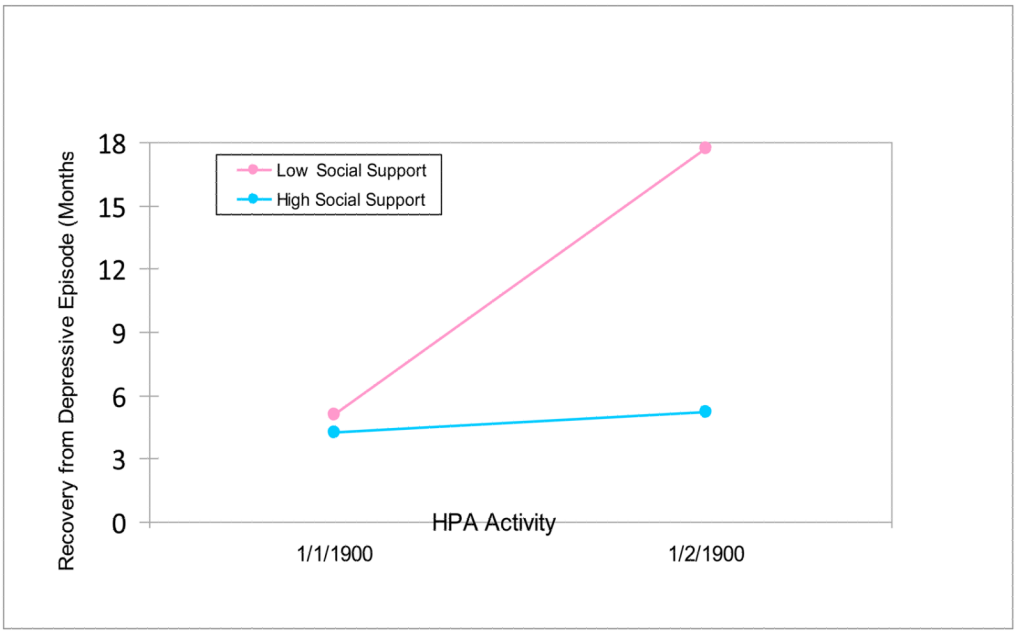

Figure 2.
Time to recovery from the index depressive episode during follow-up as a function of hypothalamic-pituitary-adrenal (HPA) activity and perceived social support measured at the time of recruitment.

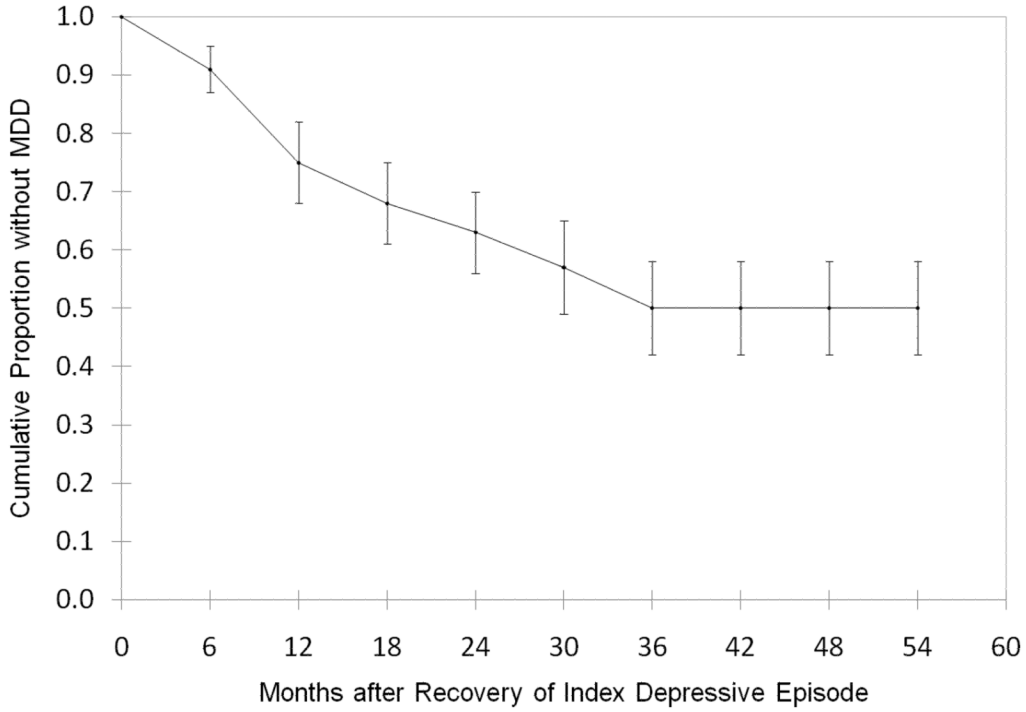

Figure 3.
Probability of survival from a recurrent major depressive disorder (MDD) episode during prospective follow-up.

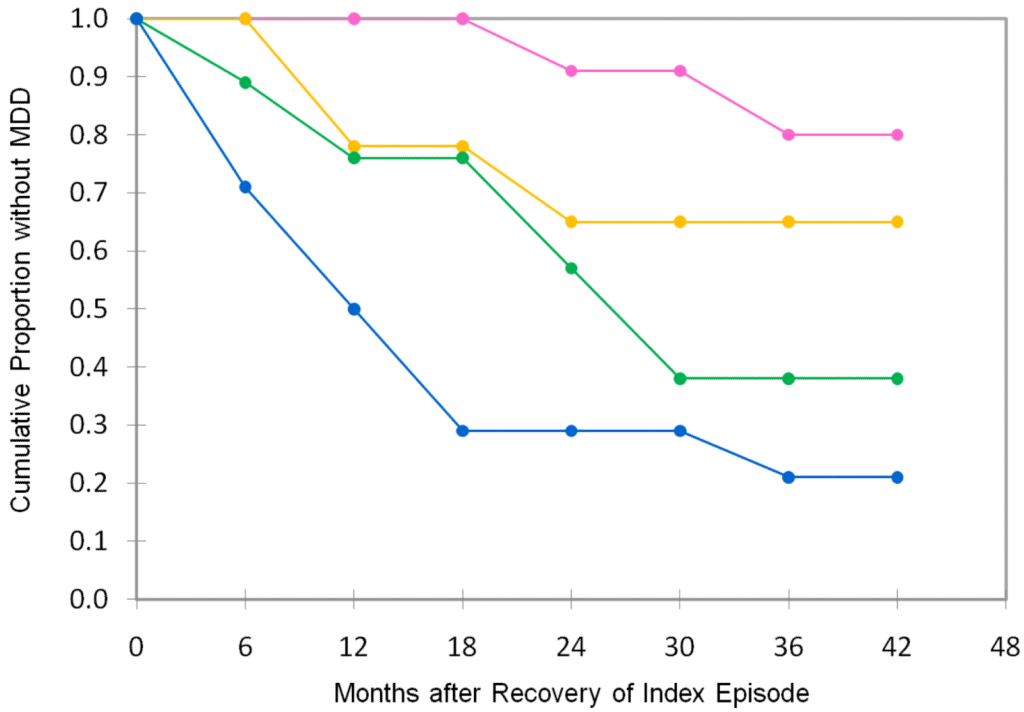

Figure 4.
Probability of survival from a recurrent major depressive disorder (MDD) episode during follow-up, stratified on hypothalamic-pituitary-adrenal (HPA) activity measured during the initial evaluation and stressful life experiences in the 3 months preceding the onset of recurrent MDD episode (pink = low-HPA activity and low-stress; yellow = high-HPA activity and low-stress; green = low-HPA activity and high-stress; and blue = high-HPA activity and high-stress).

Table 1

Demographic, clinical, psychosocial and neuroendocrine variables in the sample at initial (baseline) assessment

Demographic Characteristics	
age (years)[1]	15.3 ± 1.45 (13 – 18)
Gender[2]	
male	23 (41.8)
female	32 (58.2)
Race[2]	
Caucasian	29 (52.7)
Non-Caucasian (African, Asian & Mexican Americans)	26 (47.3)
socioeconomic status[1,3]	40.9 ± 11.2 (18 – 61)
Clinical Features	
body mass index (kg/m^2)[1]	21.5 ± 2.1 (17.4 – 26.5)
age of onset of depression (years)[1]	13.6 ± 2.5 (8 – 17)
prior history of a depressive episode[2]	10 (18.2)
duration of depressive episode at intake (months)[1]	5.0 ± 3.9 (2.4 – 27.5)
Hamilton Depression Rating Scale score[1]	19.8 ± 4.0 (15 – 32)
Beck Depression Inventory score[1]	18.4 ± 7.9 (14 – 37)
Clinical Global Assessment score[1,3]	50.7 ± 7.3 (41 – 75)
suicidality[2]	16 (29.1)
comorbid disorder (anxiety and/or disruptive disorders)[2]	24 (43.6)
depression in the parent[2]	28 (50.9)
Psychosocial Measures	
chronic stress[1]	22.3 ± 4.9 (10 – 37)
acute stress[1]	6.0 ± 5.5 (0 – 25)
perceived social support[1]	8.3 ± 2.9 (1.0 – 14.5)
enacted social support[1]	8.8 ± 1.8 (4.5 – 13.2)
Neuroendocrine Measures	
urinary free cortisol concentration (ng/ml)[1]	21.8 ± 11.7 (3.0 – 53.3)
total urinary cortisol excretion (μg)[1]	11.8 ± 5.8 (2.7 – 29.4)

[1] Values are presented as means and standard deviations along with ranges (in parentheses)

[2] Values are presented as raw values and percentages (in parentheses)

[3] A higher score represents higher socioeconomic status or better global functioning

Table 2

Spearman's correlation coefficients among demographic, clinical, psychosocial and neuroendocrine variables at initial assessment

	Age	SES	BMI	HDRS	BDI	CGAS	Chr. Str.	Ac. Str.	SS (P)	SS (E)	NUFC conc.	T. NUFC
Age	--	--	--	--	--	--	--	--	--	--	--	--
SES	.12	--	--	--	--	--	--	--	--	--	--	--
BMI	−.09	.08	--	--	--	--	--	--	--	--	--	--
HDRS	.06	−.01	.07	--	--	--	--	--	--	--	--	--
BDI	.07	−.05	.01	.14	--	--	--	--	--	--	--	--
CGAS	−.09	.14	−.03	−.24	.05	--	--	--	--	--	--	--
Chronic stress	−.01	−.10	−.03	−.23	.16	.07	--	--	--	--	--	--
Acute stress	−.05	−.08	−.11	.08	.02	−.04	.08	--	--	--	--	--
SS (P)	−.07	.03	−.06	.19	−.03	.01	−.16	−.05	--	--	--	--
SS (E)	.04	.15	−.13	.17	.10	.04	−.13	−.11	.22	--	--	--
NUFC conc.	.03	.01	.14	.17	−.03	−.11	.31*	.12	−.14	−.10	--	--
Total NUFC	.04	.03	.15	.16	−.03	−.06	.39*a*	.14	−.12	−.08	.89*b*	--

SES = socioeconomic status; BMI = body mass index; HDRS = Hamilton Depression Rating Scale; BDI = Beck Depression Inventory; CGAS = Children's Global Assessment Scale; SS (P) = perceived social support; SS (E) = enacted social support; NUFC conc. = nocturnal urinary free cortisol concentration; Total NUFC = total nocturnal urinary free cortisol excretion

* p ≤. 05;

a p ≤ .005;

b p ≤ .0001

Table 3

Cox regression models predicting recovery of the index depressive episode[1]

	β (SE)	Wald	OR (CI)	P
Model 1				
total urinary cortisol	−0.37 (0.17)	4.44	0.69 (0.49–0.98)	.04
chronic stress	−.29 (0.18)	2.67	0.77 (0.53–1.06)	.10
cortisol × chronic stress	0.18 (0.17)	1.11	1.20 (0.86–1.68)	.29
Model 2				
total urinary cortisol	−0.46 (0.21)	4.77	0.63 (0.42–0.95)	.03
acute stress	0.01 (0.19)	0.11	1.01 (0.69–1.47)	.97
cortisol × acute stress	−0.07 (0.30)	0.05	0.93 (0.52–1.68)	.82
Model 3				
total urinary cortisol	−0.47 (0.17)	7.75	0.63 (0.45–0.87)	.005
perceived social support	0.66 (0.18)	13.27	1.94 (1.36–2.78)	.0001
cortisol × perceived support	0.46 (0.18)	6.40	1.59 (1.11–2.27)	.01
Model 4				
total urinary cortisol	−0.45 (0.17)	6.97	0.64 (0.45–0.89)	.008
enacted social support	0.08 (0.17)	0.25	1.09 (0.78–1.51)	.62
cortisol × enacted support	0.29 (0.16)	3.17	1.34 (0.97–1.85)	.08

[1] All predictor variables comprised of data gathered at the time of recruitment

SE = standard error; OR = odds-ratio; CI = confidence interval

Model 1: χ^2 = 10.74, df = 3, p = .01

Model 2: χ^2 = 7.00, df = 3, p = .07

Model 3: χ^2 = 22.86, df = 3, p = .0001

Model 4: χ^2 = 10.15, df = 3, p = .02

Table 4

Cox regression models predicting recurrent depressive episode during follow-up[1]

	β (SE)	Wald	OR (CI)	P
Model 1				
total urinary cortisol	0.72 (0.35)	4.19	2.05 (1.03–4.08)	.04
chronic stress	−.07 (0.22)	0.10	0.93 (0.61–1.43)	.76
cortisol × chronic stress	−0.12 (0.26)	0.21	0.89 (0.53–1.49)	.65
Model 2				
total urinary cortisol	1.09 (0.50)	4.73	2.97 (1.11–7.94)	.03
acute stress	0.79 (0.25)	10.32	2.20 (1.36–3.56)	.001
cortisol × acute stress	1.11 (0.38)	8.40	3.02 (1.43–6.39)	.004
Model 3				
total urinary cortisol	0.83 (0.35)	5.54	2.30 (1.15–4.61)	.02
perceived social support	0.43 (0.34)	1.60	1.53 (0.79–2.96)	.21
cortisol × perceived support	0.21 (0.29)	0.51	1.23 (0.70–2.16)	.47
Model 4				
total urinary cortisol	0.64 (0.39)	2.72	1.90 (0.89–4.06)	.10
enacted social support	−0.73 (0.19)	15.06	0.48 (0.33–0.70)	.0001
cortisol × enacted support	−0.10 (0.20)	0.25	0.91 (0.62–1.33)	.91

[1] urinary cortisol was measured during recruitment and other measures were collected at follow-up

SE = standard error; OR = odds-ratio; CI = confidence interval

Model 1: $\chi^2 = 4.92$, df = 3, p = .18

Model 2: $\chi^2 = 16.89$, df = 3, p = .001

Model 3: $\chi^2 = 8.42$ df = 3, p = .04

Model 4: $\chi^2 = 19.30$, df = 3, p = .0001