The Relationship Between Stressful Life Events and Axis I Diagnoses Among Adolescent Offspring of Probands With Bipolar and Non-Bipolar Psychiatric Disorders and Healthy Controls: The Pittsburgh Bipolar Offspring Study (BIOS)

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ABSTRACT

Background: Previous studies have explored the role of stressful life events in the development of mood disorders. We examined the frequency and nature of stressful life events as measured by the Stressful Life Events Schedule (SLES) among 3 groups of adolescent offspring of probands with bipolar (BD), with non-BD psychiatric disorders, and healthy controls. Furthermore, we examined the relationship between stressful life events and the presence of *DSM-IV* Axis I disorders in these offspring. Stressful life events were characterized as dependent, independent, or uncertain (neither dependent nor independent) and positive, negative, or neutral (neither positive nor negative).

Methods: Offspring of probands with BD aged 13–18 years (n = 269), demographically matched offspring of probands with non-BD Axis I disorders (n = 88), and offspring of healthy controls (n = 81) from the Pittsburgh Bipolar Offspring Study were assessed from 2002 to 2007 with standardized instruments at intake. Probands completed the SLES for their offspring for life events within the prior year. Life events were evaluated with regard to current Axis I diagnoses in offspring after adjusting for confounds.

Results: After adjusting for demographic and clinical between-group differences (in probands and offspring), offspring of probands with BD had greater independent ($\chi^2 = 11.96$, $P < .04$) and neutral ($\chi^2 = 17.99$, $P < .003$) life events compared with offspring of healthy controls and greater number of more severe stressful life events than offspring of healthy controls, but not offspring of probands with non-BD. Offspring of BD probands with comorbid substance use disorder reported more independent stressful life events compared to those without comorbid substance use disorder ($P = .024$). Greater frequency and severity of stressful life events were associated with current Axis I disorder in offspring of both probands with BD and probands with other Axis I disorders regardless of dependency or valence. Greater frequency and severity of stressful life events were associated with greater current Axis I disorder in all offspring.

Conclusions: Offspring of probands with BD have greater exposure to independent and neutral life events than offspring of healthy controls. Greater frequency and severity of stressful life events were associated with Axis I disorder in offspring of both BD and non–BD affected probands.

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Bipolar disorder (BD) affects 2% to 4% of the population.[1,2] Adolescent offspring of probands with BD have elevated rates of *DSM-IV* Axis I disorders, especially BD, major depression, and anxiety disorders, compared to the general population.[3,4] Extant literature suggests a role of stressful life events in the development of Axis I disorders. For example, in adults with BD, incidence of negative stressful life events is increased prior to onset and recurrences of depressive and manic episodes.[5,6] Furthermore, in adolescents with BD, we have described greater exposure to negative, independent, and dependent stressful life events similar to rates described in depressed and anxious youth.[7] While a strong genetic basis of BD is clear,[8] environmental factors quite likely further contribute to and moderate the onset of BD and other Axis I disorders in offspring of BD probands.

The biopsychosocial model posits that biological, psychological, and socioenvironmental factors all play significant roles in the onset, course, and outcome of psychiatric illness. This model is evidenced by stressful life events preceding onset of Axis I disorders, including BD,[9] unipolar depression,[10–14] and anxiety disorders.[14] Specifically, total number of stressful life events during adolescence predicted future depression and anxiety episodes independent of initial symptoms.[15] Understanding the contribution of stressful life events in adolescence is relevant to onset and outcome of Axis I disorders. For example, adolescents who reported ongoing stressors had more persistent depressive symptoms.[11] In addition, adults who reported greater exposure to stressful life events in adolescence were shown to have slower response to treatment and slower remission time course in diagnoses of both depression[16] and anxiety disorder.[17]

Life events are characterized by valence and dependency. Life events may be stressful even if they have neutral (birth of a sibling) or positive (starting a new relationship) valence. In addition, life events may be independent (distinct from personal behavior) or dependent (associated with personal behavior).

Clinical Points

- Offspring of parents with bipolar disorder have high heritability of Axis I disorder compared to community samples.
- Stressful life events may contribute to the heritability of Axis I disorder in offspring of both parents with bipolar disorder and non-bipolar affected parents, suggesting a role for early intervention.

Individuals with mood disorder more often experience dependent, negative life events, both contributing to and potentially influenced by the chronic nature of mood disorders.[18]

It is unclear the extent to which having a parent with BD increases frequency and/or severity of stressful life events. However, there is evidence that the contribution of stressful life events to later psychiatric disorder is significantly influenced by genetic differences.[19] Stressful life events may also have greater impact on offspring with parents who have emotional disorder.[20] Offspring of BD probands, in particular, have a higher risk profile for sensitivity to stress, demonstrate more risky behavior, and have impaired coping strategies compared to offspring of controls.[21] Furthermore, individuals with a personal history of BD are more likely to report childhood adversities and recent stressors than individuals without BD.[22]

The Pittsburgh Bipolar Offspring Study (BIOS) is the largest study to date of offspring of probands with BD and offspring of community control probands. Prior results from intake assessment demonstrated that offspring of probands with BD had higher rates of anxiety, BD-I, and BD-spectrum (BD-I, BD-II, or subthreshold BD) disorders as compared to control offspring.[23,24] In this study, we evaluated adolescent offspring of probands with BD, community control probands with other Axis I disorder (offspring of probands with non-BD), and healthy control probands who presented with no Axis I disorder (offspring of healthy controls) with regard to their exposure to stressful life events. We evaluated stressful life events in the year preceding intake as reported by offspring and their parents, utilizing the Stressful Life Events Schedule (SLES).[25] We aim to (1) describe and quantify stressful life events in offspring of probands with BD compared with offspring of probands with non-BD and offspring of healthy controls, (2) explore the association between stressful life events and presence of current Axis I disorder in offspring of probands with BD, offspring of probands with non-BD, and offspring of healthy controls at study intake, and (3) examine whether specific categories of stressful life events are differentially associated with current Axis I disorders at intake. We hypothesized that offspring of probands with BD, as compared with offspring of probands with non-BD and offspring of healthy controls, would experience a higher number of stressful life events and greater severity of stressful life events in the year preceding intake, independent of demographic characteristics. We further hypothesized that greater severity and frequency of stressful life events would be associated with current Axis I disorder in all 3 offspring groups. Finally, we hypothesized that negative, dependent, and severe life events would have the greatest association with current Axis I diagnosis.

METHODS

The methods of BIOS have been described in detail in prior reports.[23,24] The University of Pittsburgh Institutional Review Board approved the study. Written informed consent and adolescent assent were obtained prior to study procedures. This study explored stressful life events at intake.

Sample

The sample was recruited via the probands from January 2002 to August 2007. Probands with BD were recruited via advertisement (53%), other studies (31%), and outpatient clinics (16%). Probands with BD met *DSM-IV* criteria for BD-I or BD-II disorders and lived within 200 miles of Pittsburgh, Pennsylvania. Exclusion criteria were lifetime diagnosis of schizophrenia, mental retardation, or mood disorder secondary to medical condition. Community control probands were recruited using random digit dialing and group matched to BD probands by age, sex, and neighborhood. In addition to the exclusion criteria used for BD probands, control probands could not have a parent or sibling with BD and the biological coparent could not have BD. There were no other diagnostic exclusions for control parent probands. The study included all offspring aged 13 to 18 years, to capture the effect of stressful life events during adolescence, unless the child had mental retardation.

Procedures

Parent probands, participating biological coprobands (31%), and psychiatric history for nonparticipating biological coprobands (assessed via interview with identified proband) were assessed using the Structured Clinical Interview for *DSM-IV* (SCID)[26] and the attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), and separation anxiety disorder sections of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL).[27] At intake, probands were interviewed (about offspring), and adolescents were interviewed using the K-SADS-PL. Symptoms contributing to more than 1 diagnosis (eg, distractibility) were not rated as fulfilling criteria for a mood disorder unless there was onset or worsening during a period of abnormal mood. Socioeconomic status was determined using the Hollingshead scale.[28] Interviewers had bachelor's or master's degrees, intensive training with the diagnostic instruments, and 80% agreement with certified raters. Interviewers who assessed offspring were blind to proband diagnosis. Assessments were presented to child psychiatrists blind to proband diagnosis for confirmation. Diagnostic reliability was assessed using audiotapes of 44 BIOS assessments rated by 2 to 8 BIOS interviewers (mean = 5.4). The κ statistic for diagnostic

Table 1. Demographic Variables for Offspring of Probands With Bipolar Disorder (OBD), Offspring of Probands With Non–Bipolar Disorder (ONBD), and Offspring of Healthy Controls (OHC)[a]

							Pairwise Comparisons			Pairwise Comparisons (FDR)		
Variable	OBD (n = 269)	ONBD (n = 88)	OHC (n = 81)	Statistic	*P* Value	*P* Value (FDR)	OBD vs ONBD *P* Value	OBD vs OHC *P* Value	ONBD vs OHC *P* Value	OBD vs ONBD *P* Value	OBD vs OHC *P* Value	ONBD vs OHC *P* Value
Gender, female	134 (49.81)	45 (51.14)	42 (51.85)	$\chi^2 = 0.12$	.94	1	.83	.75	.93	1	1	1
Lives with both parents	112 (41.64)	48 (54.55)	61 (75.31)	$\chi^2 = 28.97$	< .0001	.0001	.03	< .0001	.01	.30	< .0001	.06
Race, white	220 (81.78)	68 (77.27)	67 (82.72)	$\chi^2 = 1.06$	.59	1	.35	.85	.38	1	1	1
Age at first SLES, mean (SD), y	14.93 (1.31)	14.95 (1.35)	14.79 (1.25)	$F = 0.39$	.68	1	.9	.41	.44	1	1	1
Bipolar spectrum disorder	41 (15.24)	1 (1.14)	2 (2.47)	Fisher	.0001	.003	.0001	.001	.61	.003	.02	1
Anxiety	84 (31.23)	17 (19.32)	11 (13.60)	$\chi^2 = 12.45$	.002	.03	.03	.002	.32	.30	.03	1
Depression	86 (31.97)	18 (20.45)	3 (3.70)	Fisher	.0001	.003	.04	.0001	.001	.37	.003	.02
SUD	19 (7.06)	4 (4.55)	2 (2.47)	Fisher	.32	1	.4	.18	.68	1	1	1
OCD	10 (3.72)	1 (1.14)	0 (0)	Fisher	.15	1	.31	.12	1	1	1	1
MDE	63 (23.42)	11 (12.50)	2 (2.47)	Fisher	.0001	.003	.03	.0001	.02	.30	.003	.23
ADHD	78 (29.00)	18 (20.45)	9 (11.11)	$\chi^2 = 11.67$	.003	.04	.12	.001	.1	.99	.02	.85
DBD	68 (25.28)	13 (14.77)	7 (8.64)	$\chi^2 = 12.67$	.002	.03	.04	.001	.22	.37	.02	1
Any Axis I	180 (66.91)	47 (53.41)	30 (37.04)	$\chi^2 = 24.18$	< .0001	.0003	.02	< .0001	.03	.23	.0001	.30

[a]Values are n (%) unless otherwise stated.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BD = bipolar disorder, DBD = disruptive behavior disorders, FDR = false discovery rate, MDE = major depressive episode, OCD = obsessive-compulsive disorder, SLES = Stressful Life Events Schedule, SUD = substance use disorders.

Table 2. Proband Demographics[a]

Demographic	BD (n = 173)	Non-BD (n = 61)	Healthy Controls (n = 53)	Statistic	*P* Value	*P* Value (FDR)
SES, mean (SD)	34.72 (14.15)	36.56 (13.46)	39.40 (12.43)	$F = 2.43$	.09	.81
Age at offspring first SLES, mean (SD), y	40.28 (7.26)	42.45 (6.83)	41.49 (6.76)	$F = 2.29$	.1	.85
Gender, female	138 (79.77)	45 (73.77)	39 (73.58)	$\chi^2 = 1.45$	.48	1
Race, white	152 (87.86)	49 (80.33)	44 (83.02)	$\chi^2 = 2.34$	.31	1
DBD[b]	50 (28.90)	5 (8.20)	N/A	$\chi^2 = 10.75$	.001	.02
SUD[b]	114 (65.90)	30 (49.18)	N/A	$\chi^2 = 5.32$	.02	.23
Anxiety[b]	128 (73.99)	24 (39.34)	N/A	$\chi^2 = 23.78$	< .0001	.0001
ADHD[b]	35 (20.23)	3 (4.92)	N/A	Fisher	.004	.05
Psychotic[b]	5 (2.89)	1 (1.64)	N/A	Fisher	1	1
OCD[b]	25 (14.45)	1 (1.64)	N/A	Fisher	.004	.05
Any Axis I[b]	173 (100)	60 (98.36)	N/A	Fisher	.26	1

[a]Values are n (%) unless otherwise stated.
[b]Based on comparing BD and non-BD parents.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BD = bipolar disorder, DBD = disruptive behavior disorders, FDR = false discovery rate, N/A = not applicable, OCD = obsessive-compulsive disorder, SES = socioeconomic status, SLES = Stressful Life Events Schedule, SUD = substance use disorders.

reliability was 0.86 for bipolar spectrum disorders, 0.77 for BD-I/II versus BD–not otherwise specified versus no bipolar spectrum disorders, 0.64 for major depressive episode, 0.71 for any depressive episode, 0.86 for ADHD, 0.78 for anxiety disorders, 0.84 for ODD and/or CD, and 1.0 for substance use disorders (SUD).

Life Events Measure

Stressful life event frequency and severity were assessed at intake using the self-report SLES for offspring themselves and for probands about their offspring.[25] The SLES is an 80-item scale that directly asks if stressful events occurred in the year prior; effects are rated using 4-point Likert severity ratings (1–4) for each event. The SLES is derived from the Bedford College Life Events and Difficulties Schedule.[25,29] The SLES was developed to reduce participant burden and is cost-effective and useful for evaluation of stressful life events in adolescents. Total stressful life events concur well with those assessed by both the Life Events and Difficulties Schedule and the Life Events Checklist.[29] Events include those involving education, work, money, housing, crime, health, deaths, romantic relationships, and other relationships.

Independent, dependent, and uncertain (neither independent or dependent on participant behavior) (Supplementary eTable 1) life events were determined with comparison to independent ("My parents were not home because of work") and dependent ("I was fired from a job") variables on the Life Events Record,[15] the Life Events and Difficulties Schedule,[25] and ratings by 3 independent investigators with consensus. Events were also evaluated as negative ("I was robbed"), positive ("I started dating someone"), or neutral ("My parents had a baby") (Supplementary eTable 2) by 3 independent investigators with consensus.

Statistical Analyses (Tables 1–4)

Statistical analyses were conducted utilizing SAS, version 9.4 (SAS Institute, Inc). χ^2 tests were used for comparisons involving categorical variables, and analysis of variance (ANOVA) tests were used for those involving continuous variables for adolescent and proband demographic and clinical comparisons. Pairwise comparisons of offspring

Table 3. Stressful Life Events in Offspring[a]

Variable	OBD (n = 269)	ONBD (n = 88)	OHC (n = 81)	Negative Binomial GLMM χ^2	*P* Value	*P* Value (FDR)	Pairwise Comparisons OBD vs ONBD	OBD vs OHC	ONBD vs OHC	Pairwise Comparisons (FDR) OBD vs ONBD	OBD vs OHC	ONBD vs OHC
Total no. of events	13.89 (0.05)	12.91 (0.07)	10.22 (0.08)	9.97	.01	.10	.41	.001	.03	1	.02	.28
No. of events with effect = 4	3.78 (0.07)	2.75 (0.14)	1.92 (0.16)	15.75	.0004	.01	.05	.0001	.09	.40	.003	.69
No. of events with effect ≥ 3	7.45 (0.06)	6.35 (0.09)	4.62 (0.11)	13.95	.001	.02	.12	.0002	.03	.84	.01	.25
Severe	1.13 (0.09)	0.96 (0.18)	0.66 (0.16)	9.69	.01	.10	.42	.003	.11	1	.05	.78
Event count												
Independent	7.08 (0.05)	6.55 (0.08)	4.97 (0.08)	11.96	.003	.04	.43	.0003	.02	1	.01	.18
I/D	2.44 (0.05)	2.45 (0.07)	1.87 (0.10)	6.27	.04	.38	.94	.02	.03	1	.21	.28
Dependent	4.36 (0.06)	3.92 (0.09)	3.39 (0.11)	4.36	.11	.80	.30	.05	.31	1	.41	1
Negative	11.41 (0.05)	11.03 (0.07)	8.82 (0.08)	7.25	.03	.26	.70	.01	.04	1	.10	.38
P/N	2.00 (0.07)	1.47 (0.12)	1.02 (0.16)	17.99	.0001	.003	.02	.0001	.06	.21	.003	.46
Positive count, n (%)[b]	127 (47.21)	37 (42.05)	32 (39.51)	1.82	.4	1						
Severity	3.15 (0.09)	2.63 (0.19)	1.92 (0.17)	7.28	.03	.26	.40	.01	.22	1	.13	1
Total effect												
Independent	18.86 (0.06)	16.92 (0.08)	13.41 (0.09)	9.48	.01	.11	.28	.002	.06	1	.03	.50
I/D	6.32 (0.05)	6.11 (0.08)	5.14 (0.10)	3.34	.19	1	.73	.08	.19	1	.59	1
Dependent	11.57 (0.06)	9.74 (0.09)	8.67 (0.12)	5.81	.05	.44	.12	.03	.44	.84	.28	1
Negative	30.19 (0.05)	28.21 (0.08)	23.47 (0.09)	6.10	.05	.40	.48	.01	.12	1	.15	.84
P/N	5.13 (0.07)	3.46 (0.13)	2.70 (0.16)	17.20	.0002	.01	.01	.0003	.24	.11	.01	1
Positive	1.44 (0.07)	1.10 (0.14)	1.05 (0.17)	5.09	.08	.60	.10	.08	.82	.71	.64	1

[a]Values are mean (SE) unless otherwise stated. Standard errors are in log scale.
[b]Occurrence of positive event was modeled differently.
Abbreviations: FDR = false discovery rate, I/D = unclear dependency, GLMM = generalized linear mixed model, OBD = offspring of probands with bipolar disorder, OHC = offspring of healthy controls, ONBD = offspring of probands with non-bipolar disorder, P/N = neutral valence.

groups (offspring of probands with BD, offspring of probands with non-BD, and offspring of healthy controls) were performed for characteristics with omnibus test *P* values less than .05.

Analyses involving counts or total effects of stressful life events used generalized linear mixed models (GLMMs) with a random effect for family membership to account for within-family correlation. The total effect of an event type (eg, independent or negative) is the sum of the event severity ratings over all events of that given type. Multivariate models were used to adjust for possible demographic and clinical confounding variables. False discovery rate (FDR) correction was applied after multivariate adjustment to control for multiple comparisons.

All associations between event counts/total effects and proband group, except occurrence of the lone positive life event, were modeled using negative binomial GLMMs. A logistic GLMM was used to model occurrence of the positive event. Logistic GLMMs controlling for parent group modeled associations between event counts/total effects and current offspring Axis I diagnoses.

In multivariate analyses, all demographic characteristics and offspring diagnoses that exhibited significant overall between-group differences at the .10 level among the 3 parent groups were considered as candidates for confounding variables. Of the parental diagnosis variables with significant between-group differences at the .10 level, we chose SUD and anxiety since those occurred in at least 20 individuals from the BD parents and non-BD parents. Demographic confounders included whether or not offspring lives with both parents and parental socioeconomic status. Possible parental lifetime diagnosis confounders included SUD and anxiety, while possible offspring current diagnosis confounders included anxiety, depression, ADHD, and disruptive behavior disorders (DBD).

For multivariate analyses of associations between counts/total effects of life events and parent group (Table 3), covariates were cumulatively selected from demographic confounders, then parent lifetime diagnosis confounders, and finally offspring current diagnosis confounders. For each group of covariates, variables were selected for the final multivariate model by backward selection until all covariates were significant at the .10 level. The same procedure minus the adjustment for offspring current diagnosis confounders was used for multivariate analyses of associations between counts/total effects of life events and offspring current diagnoses (Table 4).

RESULTS

Participants

The sample included 438 offspring: 269 offspring of probands with BD, 88 offspring of probands with non-BD, and 81 offspring of healthy controls. Offspring did not differ in age, gender, race, or proband socioeconomic status. Offspring of probands with BD were less likely to live in intact families (Table 1 and Table 2).

Offspring Current Diagnoses at Assessment

In keeping with prior reports from this sample,[8,23,24,30] offspring of probands with BD as compared with offspring of probands with non-BD ($P < .002$) and offspring of healthy

Table 4. Stressful Life Events and Axis I Disorders

Variable	Current Any Axis I				Current MDE				Current ADHD			
	Odds Ratio	*t* Statistic	*P* Value	*P* Value (FDR)	Odds Ratio	*t* Statistic	*P* Value	*P* Value (FDR)	Odds Ratio	*t* Statistic	*P* Value	*P* Value (FDR)
Total no. of events	1.05	4.14	.002	.003	1.05	2.94	.004	.05	1.04	3.19	.002	.03
No. of events with effect = 4	1.14	4.21	<.0001	.002	1.18	4.37	<.0001	.002	1.03	1.12	.26	1
No. of events with effect ≥ 3	1.08	4.17	.001	.003	1.11	3.92	.0001	.003	1.03	1.67	.1	.73
Count												
Independent	1.07	3.09	.002	.03	1.08	2.27	.02	.21	1.07	2.79	.006	.09
I/D	1.27	3.94	.0001	.003	1.26	2.28	.02	.21	1.22	2.89	.005	.07
Dependent	1.15	4.51	<.0001	.002	1.18	3.47	.001	.02	1.11	3.07	.003	.05
Negative	1.06	4.20	<.0001	.002	1.07	2.97	.003	.05	1.05	3.31	.001	.02
P/N	1.18	2.71	.008	.10	1.20	2.00	.05	.42	1.15	2.15	.03	.28
Positive	1.28	1.17	.24	1	2.09	1.60	.11	.78	0.98	−0.06	.95	1
Total effect												
Independent	1.03	3.32	.001	.02	1.04	3.00	.003	.05	1.02	2.13	.03	.28
I/D	1.09	3.73	.0003	.01	1.10	2.57	.01	.12	1.05	2.04	.04	.36
Dependent	1.05	4.35	<.0001	.002	1.07	3.88	.0001	.003	1.02	1.90	.06	.48
Negative	1.02	4.27	<.0001	.002	1.03	3.59	.0004	.01	1.01	2.34	.02	.21
P/N	1.06	2.53	.01	.12	1.08	2.47	.01	.12	1.04	1.54	.13	.88
Positive	1.12	1.69	.09	.67	1.33	2.18	.03	.28	0.99	−0.09	.93	1
	Current DBD				Current SUD				Current Anxiety			
	Odds Ratio	*t* Statistic	*P* Value	*P* Value (FDR)	Odds Ratio	*t* Statistic	*P* Value	*P* Value (FDR)	Odds Ratio	*t* Statistic	*P* Value	*P* Value (FDR)
Total no. of events	1.08*	5.26	<.0001	.0001	1.08	3.86	.0002	.01	1.03	1.99	.05	.41
No. of events with effect = 4	1.12	3.69	.0003	.01	1.13	2.90	.004	.06	1.14	4.24	<.0001	.002
No. of events with effect ≥ 3	1.07	3.52	.001	.01	1.11	3.50	.001	.01	1.07	3.18	.002	.03
Count												
Independent	1.13	4.81	<.0001	.001	1.10	2.73	.01	.10	1.05	2.12	.04	.32
I/D	1.44*	4.82	<.0001	.0004	1.64	4.16	<.0001	.002	1.12	1.54	.13	.86
Dependent	1.19*	4.86	<.0001	.0004	1.27*	4.35	<.0001	.002	1.05	1.45	.15	1
Negative	1.09*	5.44	<.0001	.0001	1.10	3.90	.0001	.003	1.03	1.95	.05	.43
P/N	1.23*	3.17	.002	.03	1.29	2.51	.01	.15	1.13	1.84	.07	.52
Positive	1.57	1.62	.11	.78	4.47	2.59	.01	.12	0.92	−0.31	.76	1
Total effect												
Independent	1.04	4.42	<.0001	.002	1.04	3.03	.003	.05	1.02	2.67	.01	.11
I/D	1.11	3.79	.0002	.01	1.17	3.75	.0003	.01	1.06	2.40	.02	.19
Dependent	1.05	3.79	.0002	.01	1.09*	4.33	<.0001	.002	1.02	1.95	.05	.43
Negative	1.03	4.71	<.0001	.001	1.04	4.03	.001	.003	1.02	2.70	.01	.10
P/N	1.06*	2.45	.01	.16	1.09	2.23	.03	.27	1.05	1.87	.06	.49
Positive	1.11	1.23	.22	1	1.47	2.57	.01	.13	1.02	0.20	.84	1

*Model includes no random effect for family membership.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, DBD = disruptive behavior disorders, FDR = false discovery rate, I/D = unclear dependency, MDE = major depressive episode, P/N = neutral valence, SUD = substance use disorders.

controls ($P < .0001$) had significantly higher rates of any current Axis I disorder. Offspring of probands with BD had greater rates of bipolar spectrum illness than offspring of probands with non-BD ($P = .002$) and offspring of healthy controls ($P = .03$). Offspring of probands with BD had greater rates of anxiety ($P = .003$), depression ($P = .002$), ADHD ($P < .02$), and DBD ($P < .02$) than offspring of healthy controls.

Frequency of Stressful Life Events

Offspring groups did not differ significantly in total number of stressful life events reported. Offspring did differ in number of stressful life events rated severity 3 or 4 (ie, affected the participant "somewhat" or "a lot") ($P = .02$). Pairwise comparisons revealed that offspring of probands with BD reported greater frequency of stressful life events and greater number of stressful life events with severity ≥ 3 than offspring of healthy controls ($P = .003$, $P = .01$) (Table 3).

Categorization of Stressful Life Events

Groups differed significantly in number of independent stressful life events ($\chi^2 = 11.96$, $P < .04$, Supplementary eTable 1) and neutral stressful life events ($\chi^2 = 17.99$, $P < .003$). Increased independent and neutral life events, but not dependent events, compared with offspring of healthy controls were associated with offspring of probands with BD status ($P < .01$, $P = .003$). Offspring of probands with non-BD and offspring of healthy controls did not differ significantly with regard to type of stressful life event.

A multiple regression GLMM model revealed that offspring of probands with BD had greater frequency of independent stressful life events if the proband had comorbid SUD ($P = .024$). In addition, offspring of probands with BD with personal diagnosis of DBD experienced more stressful life events ($P = .044$). Offspring of probands with BD with a personal diagnosis of major depressive disorder (MDD) or BD had more independent life events

Table 5. Association Between SLES and Parent Group—Offspring Responses[a]

Variable	BD (n = 269)	Non-BD (n = 88)	HC (n = 81)	Negative Binomial GLMM χ^2	Negative Binomial GLMM *P* Value[b]	Pairwise Comparisons *P* Values: BD vs Non-BD	BD vs HC	Non-BD vs HC
Total no. of events	13.89 (0.05)	12.91 (0.07)	10.22 (0.08)	9.97	.0068	.41	.001	.03
No. of events with effect = 4	3.78 (0.07)	2.75 (0.14)	1.92 (0.16)	15.75	.0004	.05	.0001	.09
No. of events with effect ≥ 3	7.45 (0.06)	6.35 (0.09)	4.62 (0.11)	13.95	.0009	.12	.0002	.03
Severity	1.13 (0.09)	0.96 (0.18)	0.66 (0.16)	9.69	.008	.42	.003	.11
Event count								
Independent	7.08 (0.05)	6.55 (0.08)	4.97 (0.08)	11.96	.0025	.43	.0003	.02
Uncertain	2.44 (0.05)	2.45 (0.07)	1.87 (0.10)	6.27	.0435	.94	.02	.03
Dependent	4.36 (0.06)	3.92 (0.09)	3.39 (0.11)	4.36	.1131			
Negative	11.41 (0.05)	11.03 (0.07)	8.82 (0.08)	7.25	.0267	.70	.01	.04
Neutral	2.00 (0.07)	1.47 (0.12)	1.02 (0.16)	17.99	.0001	.02	.0001	.06
Positive count, n (%)[c]	127 (47.21)	37 (42.05)	32 (39.51)	1.82	.40	…	…	…
Total effect								
Severe	3.15 (0.09)	2.63 (0.19)	1.92 (0.17)	7.28	.0262	.40	.01	.22
Independent	18.86 (0.06)	16.92 (0.08)	13.41 (0.09)	9.48	.0087	.28	.002	.06
Uncertain	6.32 (0.05)	6.11 (0.08)	5.14 (0.10)	3.34	.1879	…	…	…
Dependent	11.57 (0.06)	9.74 (0.09)	8.67 (0.12)	5.81	.0547	…	…	…
Negative	30.19 (0.05)	28.21 (0.08)	23.47 (0.09)	6.10	.0473	.48	.01	.12
Neutral	5.13 (0.07)	3.46 (0.13)	2.70 (0.16)	17.20	.0002	.01	.0003	.24
Positive	1.44 (0.07)	1.10 (0.14)	1.05 (0.17)	5.09	.0786	…	…	…

[a]Values are mean (SE) unless otherwise stated. Standard errors are in log scale.
[b]None of these effects was significant after multivariate adjustment and FDR correction.
Abbreviations: BD = bipolar disorder, FDR = false discovery rate, GLMM = generalized linear mixed models, HC = healthy controls.
Symbol: … = not applicable.

than offspring of probands with BD with different Axis I diagnoses ($P = .028$).

Severity of Categorized Stressful Life Events

Severity was determined by maximum effect scoring on the SLES Likert scale, as above. Groups differed significantly only with regard to effect of neutral stressful life events scored 3 or 4 ($\chi^2 = 17.20$, $P < .01$). The effect was significantly greater in offspring of probands with BD than offspring of healthy controls ($P < .01$, Table 3).

Relationship of Stressful Life Events to Current Axis I Diagnosis (Table 4)

Total number, severity, and all categories of life events except positive and neutral events were associated with greater odds of any current Axis I disorder, adjusted for demographic group differences, and corrected for multiple comparisons (Table 4). The interaction between stressful life events and group (offspring of probands with BD or offspring of probands with non-BD) was not significant. Total number, severity, and all categories of life events except positive events were associated with DBD in offspring. Total number and severity of total life events, dependent life events, and negative life events were associated with greater rates of depression. Total number and severity of total life events and dependent, uncertain, and negative life events were associated with SUD. Total number of life events and negative life events were associated with ADHD. Only severity of life events (Likert scale ≥ 3) was associated with anxiety disorder.

Multivariate Analyses (Tables 5–8)

Multivariate analyses were completed utilizing parent and offspring responses, demographic confounders, parent lifetime diagnosis confounders, and finally offspring current diagnosis confounders. In multivariate analyses, the offspring responses to the SLES showed no significant effect for parent group after FDR correction (Table 5). When we utilized parental reports of the offspring stressful life events, the parent group effect was significant for stressful life event frequency, severity, and all SLES categories for parent responses except positive and neutral after FDR correction ($P < .001$, Table 7).

DISCUSSION

To our knowledge, this is the largest study to examine stressful life events and their relationship to current Axis I diagnoses in offspring of probands with BD. The relationship between stressful life events and Axis I disorder in offspring of probands with BD is important in that it may provide information about modifiable environmental contributions to the heritability of mood disorder. We hypothesized that offspring of probands with BD, as compared with offspring of probands with non-BD and offspring of healthy controls, would exhibit a higher number of stressful life events in the year preceding intake, independent of demographic characteristics.

Contrary to our hypothesis, after we adjusted for the presence of confounders (eg, demographics and between group parental and offspring psychopathology for the affected groups), offspring of probands with BD and offspring of probands with non-BD did not differ in total number of stressful life events or maximum effect of these stressful life events. However, offspring of probands with BD reported greater number of stressful life events affecting them "somewhat" or "a lot" (Likert scale ≥ 3) compared with offspring of healthy controls. Offspring of probands with BD also reported being exposed to more independent

Table 6. Association Between SLES and Current Pathology—Offspring Responses

	Current Any Axis I			Current MDE			Current ADHD			Current DBD			Current SUD			Current Anxiety		
Variable	Odds Ratio*	*t* Statistic	*P* Value[a]	Odds Ratio*	*t* Statistic	*P* Value	Odds Ratio[a]	*t* Statistic	*P* Value	Odds Ratio[a]	*t* Statistic	*P* Value	Odds Ratio*	*t* Statistic	*P* Value	Odds Ratio*	*t* Statistic	*P* Value
Total no. of events	1.06	4.60	<.0001*	1.05	2.94	.0035*	1.05	3.75	.0003**	1.08	5.77	<.0001*	1.08	3.86	.0002*	1.03	2.54	.0123
No. of events with effect = 4	1.15	4.59	<.0001*	1.18	4.37	<.0001*	1.05	1.70	.0911	1.13	4.32	<.0001*	1.13	2.90	.0043*	1.17	5.15	<.0001*
No. of events with effect ≥ 3	1.09	4.57	<.0001*	1.11	3.92	.0001*	1.04	2.24	.0265	1.08	4.14	<.0001*	1.11	3.50	.0006*	1.08	4.19	<.0001*
Count																		
Independent	1.08	3.58	.0005*	1.08	2.26	.0244	1.08	3.32	.0011	1.14	5.30	<.0001*	1.10	2.73	.0071	1.06	2.68	.0082
Uncertain	1.31	4.42	<.0001*	1.26	2.28	.0232	1.27	3.45	.0008**	1.49	5.35	<.0001*	1.64	4.16	<.0001*	1.12	1.67	.0973
Dependent	1.16	4.89	<.0001*	1.18	3.47	.0006*	1.12	3.53	.0006**	1.20	5.32	<.0001*	1.27	4.35	<.0001*	1.07	2.06	.0416
Negative	1.07	4.60	<.0001*	1.07	2.97	.0032*	1.06	3.78	.0002**	1.10	5.87	<.0001*	1.10	3.90	.0001*	1.03	2.37	.0193
Neutral	1.22	3.41	.0009	1.20	2.00	.0463	1.21	2.94	.0039	1.29	3.99	<.0001*	1.29	2.51	.0133	1.19	2.77	.0064
Positive	1.36	1.47	.1444	2.09	1.60	.1104	1.07	0.26	.7928	1.71	1.96	.0506	4.47	2.59	.0105	1.07	0.25	.8047
Total effect																		
Independent	1.03	3.82	.0002*	1.04	3.00	.0029*	1.02	2.75	.0067	1.04	5.04	<.0001*	1.04	3.03	.0029*	1.03	3.47	.0007*
Uncertain	1.10	4.22	<.0001*	1.10	2.57	.0104	1.07	2.65	.009	1.12	4.41	<.0001*	1.17	3.75	.0003*	1.07	2.75	.0067
Dependent	1.05	4.70	<.0001*	1.07	3.88	.0001*	1.03	2.34	.0205	1.05	4.24	<.0001*	1.09	4.33	<.0001*	1.03	2.80	.0059
Negative	1.02	4.69	<.0001*	1.03	3.59	.0004*	1.02	2.90	.0044	1.03	5.27	<.0001*	1.04	4.03	<.0001*	1.02	3.40	.0009*
Neutral	1.07	3.16	.0019	1.08	2.47	.0139	1.05	2.26	.0253	1.08	3.21	.0014	1.09	2.23	.0276	1.07	2.91	.0042*
Positive	1.13	1.92	.0574	1.33	2.18	.0295	1.01	0.18	.861	1.13	1.52	.1291	1.47	2.57	.0112	1.07	0.87	.387

[a]Controlling for parent group.
*Significant at .05 level after multivariate adjustment and FDR correction. **Significant at .01 level after multivariate adjustment and FDR correction.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, DBD = disruptive behavior disorders, FDR = false discovery rate, MDE = major depressive episode, SLES = Stressful Life Events Schedule, SUD = substance use disorders.

and neutral life events than offspring of healthy controls, while offspring of probands with non-BD did not. Greater exposure to independent life events in offspring of probands with BD indicates that they were more likely to be exposed to stressors in which they did not have a direct role. This finding is in agreement with previous studies indicating greater conferred risk in adolescents with a parent with BD and with less family cohesion[31–33] and may indicate need for early intervention to assist parents with BD in reducing environmental stressors for their offspring. The relationship between greater frequency of independent stressful life events and proband comorbid SUD for offspring of probands with BD is also worth noting. Our findings highlight a population for whom family interventions may greatly benefit both parent and child. Such intervention may reduce potential familial contributors to Axis I disorder in offspring of probands with BD. This is supported by findings that participants with bipolar spectrum disorders in family-focused treatment had less severe manic symptoms in the following year than participants in family psychoeducation alone.[34] It is interesting to note that socioeconomic status was not associated with the number or severity of stressful life events. This null finding may be related to the period of time assessed (1 year), or the greater contribution of proband psychopathology to assessed stressful life events may confound the role of socioeconomic status in this population.

There was an association between stressful life events and presence of Axis I disorder in offspring of all affected probands, after adjusting for confounders, which may have implications with regard to long-term resilience, coping strategies, and outcome, although the interaction between stressful life events and group (offspring of probands with BD and offspring of probands with non-BD) was not significant. Greater total number of life events was associated with DBD, greater rates of depression, SUD, and ADHD in offspring. Greater overall severity of life events was associated with DBD, depression, SUD, and anxiety in offspring. Except positive events, all categories of life events were associated with DBD in offspring. Dependent and negative life events were associated with greater rates of depression. Dependent, uncertain, and negative life events were associated with SUD. Negative life events were associated with ADHD. The broad impact of stressful life events and their relationship to Axis I disorder indicate potentially modifiable contributors to risk and suggest a need for early intervention in offspring of probands with BD and offspring of probands with non-BD.

Multivariate analyses controlling for parent group and incorporating parental responses as well as demographic, parent lifetime diagnosis, and offspring current diagnosis confounders indicated that parental group had a significant effect when utilizing parental responses, but not when considering offspring responses. This was an unexpected finding and may indicate an interaction between parental diagnosis and reporting of number and severity of stressful life events described by parents about their offspring. In contrast, it may be that offspring of bipolar parents evaluate

Table 7. Association Between SLES and Parent Group—Parent Responses[a]

Variable	BD n = 269	Non-BD n = 88	HC n = 81	Negative Binomial GLMM χ^2	Negative Binomial GLMM *P* Value	Pairwise Comparisons *P* Values BD vs Non-BD	BD vs HC	Non-BD vs HC
Total no. of events	11.39 (0.04)	9.80 (0.07)	6.52 (0.08)	36.82	<.0001*	.0795	<.0001	.0002
No. of events with effect = 4	3.45 (0.09)	2.32 (0.16)	1.33 (0.17)	25.40	<.0001*	.0261	<.0001	.0184
No. of events with effect ≥ 3	6.64 (0.06)	5.49 (0.11)	2.81 (0.13)	37.45	<.0001*	.1394	<.0001	<.0001
Event count								
Severity	0.68 (0.10)	0.51 (0.18)	0.25 (0.25)	14.23	.0008*	.1618	.0003	.0255
Independent	6.11 (0.05)	5.16 (0.08)	3.32 (0.09)	37.10	<.0001*	.0633	<.0001	.0002
Uncertain	1.92 (0.06)	1.93 (0.10)	1.10 (0.13)	16.13	.0003*	.9750	0.0001	.0009
Dependent	3.29 (0.06)	2.64 (0.11)	2.05 (0.12)	13.30	.0013	.0791	0.0005	.1198
Negative	9.32 (0.05)	8.08 (0.08)	5.57 (0.08)	29.04	<.0001*	.1097	<.0001	.0012
Neutral	1.64 (0.07)	1.40 (0.12)	0.72 (0.16)	23.07	<.0001*	.2516	<.0001	.0010
Positive count, n (%)[b]	75 (30.00)	15 (17.10)	20 (24.70)	5.77	.06	…	…	…
Total effect								
Severe	2.30 (0.13)	1.82 (0.22)	0.74 (0.25)	15.66	.0004	.3661	<.0001	.0084
Independent	16.50 (0.05)	13.42 (0.09)	7.54 (0.10)	48.37	<.0001*	.0544	<.0001	<.0001
Uncertain	5.68 (0.07)	5.42 (0.12)	3.04 (0.13)	18.09	.0001*	.7313	<.0001	.0012
Dependent	9.48 (0.08)	6.88 (0.13)	5.30 (0.14)	15.32	.0005	.0325	.0002	.1680
Negative	26.11 (0.05)	21.80 (0.09)	13.81 (0.09)	34.58	<.0001*	.0822	<.0001	.0005
Neutral	4.59 (0.08)	3.71 (0.14)	1.49 (0.16)	40.41	<.0001*	.1808	<.0001	<.0001
Positive	0.90 (0.15)	0.48 (0.27)	0.68 (0.27)	4.38	.112	…	…	…

[a]Values are mean (SE) unless otherwise stated. Standard errors are in log scale.
[b]Occurrence of positive event was modeled differently.
*Significant after multivariate adjustment and FDR correction.
Abbreviations: BD = bipolar disorder, GLMM = generalized linear mixed model, HC = healthy controls, SLES = Stressful Life Events Schedule.

and report stressful life events differently. In other words, it may be that parents with BD are more sensitive to stressful life events with higher likelihood of reporting, or it may be that offspring of bipolar parents are desensitized to stressful life events and/or underreport their frequency or severity.

There were limitations of the study. This report focused on adolescents aged 13–18 years only; future studies should include younger children. This study was cross-sectional, making it impossible to know whether life events for both proband and/or offspring preceded or followed the onset of psychopathology. Therefore, we report only an association. There is extensive literature supporting an association between life events and psychopathology, as well as the observation that families with a mood-disordered parent experience increased levels of stress. Proband and offspring disorder may have contributed to ratings of frequency and severity of stressful life events, and there is evidence that psychopathology may influence self-reported stressful life event severity.[35] However, ratings between offspring and probands were similar. The observation that probands reported more frequent and more severe stressful life events than their parents did may reflect a greater knowledge of personal life events especially because the sample only includes adolescents, minimization of stressful life events by parents, or a contribution of proband or offspring psychopathology. An additional limitation was that stressful life events were measured utilizing a self-report checklist rather than a semistructured interview with consensus. Although interview methods may provide greater detail and therefore greater certainty regarding the classification and severity of life events, the SLES provides a reliable estimate of the overall stress level and is feasible to use in large samples.[25] Stressful life events were measured only in the year prior to assessment. While this reduced the likelihood that events would be forgotten or underreported, we may have missed significant earlier events.

In univariate analyses, offspring of probands with BD were exposed to significantly more independent and neutral stressful life events than offspring of healthy controls. Explanations for higher rates of independent and neutral stressful life events in offspring of probands with BD may include limited social support or less cohesive family environments,[7,36,37] with contribution of impairment attributable to BD in the probands. Impaired family function and lower cohesion negatively impact outcome in youth BD, in particular.[33,38] Previous studies also have indicated greater risk for mood disorder in offspring exposed to parental BD and a role for intervention in families with a bipolar parent.[39] In particular, comorbid SUD in BD probands was associated with a greater number of independent stressful life events for offspring. This finding is consistent with previous reports of poorer outcomes in offspring of BD probands with SUD.[32,40] This strongly suggests a need for early intervention for parents with BD and SUD and suggests that treatment interventions for parents with this comorbidity are an important part of treating their offspring who are presenting with Axis I disorders as well. Finally, offspring of probands with BD with comorbid Axis I diagnoses who had personal diagnosis of MDD or BD also reported more frequent independent stressful life events. Familial treatment and individual treatment to address symptoms in adolescent offspring of probands with BD are indicated and have previously been shown to improve mood symptoms in these offspring at risk.[34]

In summary, these findings indicate that, while risk for any Axis I disorder in offspring of probands with BD

Table 8. Association Between SLES and Current Pathology—Parent Responses

	Current Any Axis I			Current MDE			Current ADHD			Current DBD			Current SUD			Current Anxiety		
Variable	Odds Ratio*	*t* Statistic	*P* Value	Odds Ratio[a]	*t* Statistic	*P* Value	Odds Ratio*	*t* Statistic	*P* Value	Odds Ratio[a]	*t* Statistic	*P* Value	Odds Ratio*	*t* Statistic	*P* Value	Odds Ratio[a]	*t* Statistic	*P* Value
Total no. of events	1.10369	5.43	<.0001*	1.062389	2.91	.0039	1.03975	2.56	.0115	1.08912	4.85	<.0001*	1.10838	4.02	<.0001*	1.03263	2.14	.0341
No. of events with effect = 4	1.18875	5.16	<.0001*	1.184712	4.43	<.0001*	1.04979	1.66	.0992	1.08807	2.96	.0033	1.15269	3.56	.0004*	1.13701	4.42	<.0001*
No. of events with effect ≥ 3 Count	1.12908	5.43	<.0001*	1.113825	4.15	<.0001*	1.03905	1.93	.0551	1.05919	2.96	.0033	1.12840	4.40	<.0001*	1.06669	3.36	.001*
Independent	1.11952	3.89	.0002*	1.069381	1.56	.1203	1.05096	1.77	.0783	1.10310	3.34	.0009	1.18258	3.79	.0002*	1.04889	1.72	.0885
Uncertain	1.48216	5.40	<.0001*	1.289688	2.24	.0257	1.24321	2.97	.0035	1.45790	4.72	<.0001*	1.68035	4.01	.0001*	1.15073	1.94	.054
Dependent	1.27724	5.57	<.0001*	1.237632	3.88	.0001*	1.10893	2.65	.009	1.29719	5.76	<.0001*	1.29033	4.03	<.0001*	1.08540	2.13	.035
Negative	1.12131	5.47	<.0001*	1.080399	3.05	.0024*	1.04677	2.54	.0124	1.10098	4.72	<.0001*	1.13906	4.28	<.0001*	1.04263	2.33	.0211
Neutral	1.25571	3.25	.0015	1.107716	0.85	.395	1.15431	2.02	.0455	1.36602	3.98	<.0001	1.26934	2.22	.0285	1.06061	0.81	.4194
Positive	1.73429	2.30	.0233	3.227152	2.59	.0099	1.23479	0.72	.472	2.10665	2.55	.0113	5.03544	3.01	.0031	1.05488	0.18	.8544
Total effect																		
Independent	1.04152	4.04	<.0001*	1.030485	1.95	.0519	1.02052	1.98	.0503	1.03277	3.08	.0022	1.07024	4.16	<.0001*	1.02654	2.55	.0121
Uncertain	1.14294	5.51	<.0001*	1.129189	3.17	.0016*	1.06426	2.47	.0147	1.11505	4.19	<.0001*	1.21179	4.39	<.0001*	1.05759	2.26	.0254
Dependent	1.07914	5.25	<.0001*	1.078251	4.29	<.0001*	1.02542	1.92	.0573	1.06607	4.76	<.0001*	1.08965	4.46	<.0001*	1.03846	2.96	.0037
Negative	1.03765	5.35	<.0001*	1.031228	3.47	.0006*	1.01407	2.23	.0275	1.02751	4.26	<.0001*	1.05209	5.15	<.0001*	1.02004	3.18	.0019
Neutral	1.08904	3.40	.0009	1.070633	1.83	.068	1.04739	1.77	.0793	1.09986	3.55	.0004	1.10672	2.33	.0216	1.04324	1.63	.1063
Positive	1.21046	2.50	.0137	1.444264	2.82	.005	1.02623	0.28	.7806	1.14740	1.48	.1386	1.45107	2.46	.0152	1.07873	0.86	.394

[a]Controlling for parent group only.
*Significant at .05 level after multivariate adjustment and FDR correction.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, DBD = disruptive behavior disorders, MDE = major depressive episode, SLES = Stressful Life Events Schedule, SUD = substance use disorders.

is highly heritable in comparison with community samples, there are contributions to risk for onset of Axis I disorder from stressful life events. Offspring of probands with BD may experience greater severity of effect of stressful life events than offspring of healthy controls. Offspring of probands with BD, in particular, report exposure to an increased number of independent and neutral life events. Greater frequency and severity of stressful life events were associated with current Axis I disorder in offspring of both BD and non–BD affected probands, suggesting a role for early intervention in offspring of patients with Axis I disorders, but particularly in offspring of BD probands.

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Supplementary material follows this article.

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Supplementary Material

Article Title: The Relationship Between Stressful Life Events and Axis I Diagnoses Among Adolescent Offspring of Probands With Bipolar and Non-Bipolar Psychiatric Disorders and Healthy Controls

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List of Supplementary Material for the article

1. eTable 1 Stressful Life Events Scale-Dependent Events
2. eTable 2 Stressful Life Events Scale-Negative Events

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1. Stressful Life Events Scale-Dependent Events

4. I was fired from a job.
7. Male: My girlfriend was pregnant.
19. I had problems at my job.
20. I did not get accepted to a school.
22. I lived with my boyfriend/ girlfriend.
24. I told someone really bad news.
26. I started dating someone.
27. I broke up with my boyfriend/ girlfriend.
28. I argued with my boyfriend/ girlfriend.
31. I was in the hospital or had an operation.
35. I fought more with my parents.
36. I argued more with other relatives (not parents).
38. I tried out for a sports team or club and did not make it.
40. I changed in physical appearance and did not like it (acne, etc.).
46. I was caught committing a crime.
52. I stopped talking to a good friend.
53. I fought with a good friend.
56. My job affected other aspects of life (school, homelife, social life).
65. I had problems being liked by classmates.
71. Females: I got pregnant. how did it affect you?
74. I stopped going to school. how did it affect you?
75. I fought with someone at school. how did it affect you?
76. I fought more with my brother/ sister.
78. I told someone that I was bisexual or homosexual.
79. I ran away from home.

Supplementary eTable 2. Stressful Life Events Scale-Negative Events

1. I had trouble with grades or schoolwork.
3. My parents were not home because of work.
4. I was fired from a job.
5. My parents hit each other (fight).
6. I testified in court.
7. Male: My girlfriend was pregnant.
8. My parents have problems at work.
9. I was robbed.
10. I got really bad news.
11. My pet died or ran away.
14. My family had money problems.
15. My parents divorced or separated.
16. My close friends or family members had trouble with the police.
17. I applied for a job and did not get hired.
19. I had problems at my job.
20. I did not get accepted to a school.
21. I had a bad accident or health problems.
24. I told someone really bad news.
25. A close friend died.
27. I broke up with my boyfriend/ girlfriend.
28. I argued with my boyfriend/ girlfriend.
31. I was in the hospital or had an operation.
32. A close friend or family member was robbed.
33. My close friend or relative was really sick.
34. I had problems with someone at work.
35. I fought more with my parents.
36. I argued more with other relatives (not parents).
37. A close relative died.
38. I tried out for a sports team or club and did not make it.
40. I changed in physical appearance and did not like it (acne, etc.).
41. I was sexually harrassed at school or work.
42. I broke off an engagement.
43. My family had problems buying or selling a house.
44. I was physically/ sexually abused by my boyfriend/girlfriend.
45. I was hurt or punched by someone.
46. I was caught committing a crime.
47. My close friend or family member was in the hospital or had an operation.
48. Females: I had an abortion.
49. I was bullied at school or in my neighborhood.

50. I did poorly on an important test.
51. There were problems with my house (overcrowded, needs to be fixed up, mice or insects).
52. I stopped talking to a good friend.
53. I fought with a good friend.
54. I had problems with family members, close friends, or classmates.
56. My job effected other aspects of life (school, homelife, social life).
57. I was sexually hurt or touched in private parts.
60. My parent was out of work or not working.
62. I had long term health problems.
63. My neighborhood was not safe (violence, crimes, gangs).
64. A close friend or family member was hurt badly.
65. I had problems being liked by classmates.
66. My close friends or family tried to hurt themselves.
67. My parents or brother/ sister died.
68. My parent was fired from his/ her job.
69. My brother/ sister fought more with my parents.
70. I saw something bad happen.
72. My parents had trouble getting along.
73. My home was damaged because of fire, flood, storm, tornado or other event.
74. I stopped going to school.
75. I fought with someone at school.
76. I fought more with my brother/ sister.
77. Males: My girlfriend had an abortion.
79. I ran away from home.