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Is Liability to Recurrent Major Depressive Disorder Present Before First Episode Onset in Adolescence or Acquired After the Initial Episode?

Jeremy W. Pettit,
Florida International University

Chelsey Hartley,
Florida International University

Peter M. Lewinsohn,
Oregon Research Institute

John R. Seeley, and
Oregon Research Institute

Daniel N. Klein
Stony Brook University

Abstract

Many individuals who experience a major depressive episode will subsequently develop recurrent episodes. Although numerous studies have investigated predictors of recurrent episodes, methodological limitations have made it difficult to determine the extent to which liability to recurrent major depressive disorder (rMDD) exists prior to first onset or develops after first onset. This study used a prospective design in a community sample of adolescents to examine variables before and after first onset MDD as predictors of rMDD over a 12 year follow-up. Among 59 adolescents who experienced first onset MDD, 72.88% developed rMDD during the follow-up period. Parental history of rMDD and lifetime history of minor depression prior to MDD onset significantly predicted rMDD. These two effects replicated in ancillary analyses in an expanded sample of N=205. Following MDD onset, a higher number of major life events significantly predicted rMDD. Liability to rMDD exists prior to MDD onset in the form of familial risk and less severe mood disturbances, whereas liability to rMDD in the form of elevated stress may develop following a first onset in adolescence.

Keywords

depression; onset; recurrence; risk factors; adolescence

An extensive literature documents the recurrent course of major depressive disorder (MDD), with recurrence defined as a new episode of MDD after full recovery from a prior episode (Frank et al., 1991). Estimates of recurrent episodes range from 35–85% depending on sample characteristics and follow-up length (e.g., Curry et al., 2011; Eaton et al., 2008; Mueller et al., 1999; Pettit, Lewinsohn, & Joiner, 2006). Theoretical and empirical work on recurrent MDD (rMDD) typically emphasizes stable liability models or scar models (Burcusa & Iacono, 2007; Monroe & Harkness, 2005; Wichers, Geschwind, van Os, &

Correspondence: Jeremy Pettit, Department of Psychology, Florida International University, Miami, FL 33199.

Peeters, 2010). Stable liability models assert that a trait-like susceptibility to depression exists prior to a first lifetime major depressive episode (FLED; Monroe & Harkness, 2011) and remains present after remission of the FLED. As long as the liability remains present, individuals remain susceptible to developing episodes of depression. Scar models posit that the experience of a FLED creates a liability that did not exist prior to the episode, which in turn increases risk for future episodes. It is possible that stable liabilities and scars each contribute to rMDD.

Numerous investigations have examined predictors of recurrent depressive episodes (see Burcusa & Iacono, 2007; Monroe & Harkness, 2005). Findings have been mostly unsupportive of scar models (e.g., Beevers, Rohde, Stice, & Nolen-Hoeksema, 2007; Ormel, Oldehinkel, & Vollebergh, 2004; Rohde, Lewinsohn, & Seeley, 1990), whereas findings that heritability estimates for rMDD exceed those for a single lifetime episode of depression (SLED; Monroe & Harkness, 2011) are consistent with a stable genetic liability to rMDD (e.g., Gershon, Weissman, Guroff, Prusoff, & Leckman, 1986; Kendler, Gardner, & Prescott, 1999). In a recent review, however, Monroe and Harkness (2011) delineated two primary methodological limitations that have impeded the field's ability to test predictors of rMDD, and by extension, to draw conclusions about whether liability to rMDD exists prior to FLED onset or develops after FLED onset.

The first limitation is the failure to distinguish between variables that predict rMDD versus a SLED and variables that predict any recurrent episode of depression. In many studies, participants were assessed during or following an index episode and then tracked to examine which variables predicted a recurrent episode. Regrettably, no distinction was made between individuals whose index episode was a FLED and individuals whose index episode was itself a recurrence. It is possible that predictors of the transition from FLED to rMDD differ from predictors of one recurrent episode to another recurrent episode (Monroe & Harkness, 2011).

The second limitation is the failure to assess predictors of rMDD prior to onset of a FLED. To our knowledge, only one study has addressed this limitation (Eaton, et al., 2008). In a study of 92 adults from the Baltimore Epidemiologic Catchment Area Followup who experienced FLED onset during the follow-up, an early onset age was the only significant predictor of rMDD. Unfortunately, the breadth of risk factors investigated was minimal because identifying predictors of rMDD was not the main focus of the study.

Thus, in spite of numerous investigations on predictors of recurrent depression, two important questions remain unanswered. First, does liability to rMDD exist before onset of a FLED? Second, is liability to rMDD acquired following onset of a FLED? Obtaining empirical data to answer these two questions may shed light on the identification of individuals at risk for rMDD and inform prevention strategies to alter that risk.

The purpose of the present study was to address these two questions with empirical data from the Oregon Adolescent Depression Project (OADP), a large, prospective study of psychological disorders among school-based adolescents. Potential predictors of rMDD were selected based on empirical research linking them to recurrent depression (Bockting, Spinhoven, Koeter, Wouters, & Schene, 2006; Dunn & Goodyer, 2006; Lewinsohn, Allen, Seeley, & Gotlib, 1999; Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2000; Mueller, et al., 1999). Based on evidence that heritability estimates for rMDD exceed those for a SLED, we hypothesized that parental history of rMDD would significantly predict participant rMDD. Such a pattern would be consistent with a stable liability model, in which some adolescents are at high familial risk for rMDD even prior to FLED onset. Because evidence in support of

scar models has been weak (Wichers, et al., 2010), we did not expect liability variables following FLED onset to significantly predict rMDD.

Method

OADP participants were randomly selected from nine high schools in Oregon. A total of 1709 adolescents (mean age=16.6) completed an initial evaluation (T_1). One year later, 1507 (88%) returned for a second evaluation (T_2). Differences between participants and those who declined to participate or dropped out of the study before T_2 were small (Lewinsohn, Hops, Roberts, Seeley, & Andrews, 1993). At age 24, all participants with a history of psychopathology by T_2 (n=644) and a random sample with no history of psychopathology (n=457) were invited to a third (T_3) evaluation. Of 1101 T_2 participants selected for T_3, 941 (85%) completed the evaluation. At age 30, all T_3 participants were invited to a T_4 evaluation; 816 (87%) completed the interview.

Near the time of the T_3 evaluation, lifetime psychopathology in participants' biological parents was assessed. Of 941 participants with T_3 data, parental diagnostic data were available for 803 (85%).

For primary analyses, the sample included 59 participants with no T_1 lifetime history of MDD who experienced FLED onset between T_1–T_2 and remained in the study through T_4. The latter requirement ensured follow-up of sufficient length to classify participants as SLED or rMDD. On average, follow-up from T_2 until T_4 was 12.43 years (SD=1.09) and time from FLED offset to T_4 was 12.54 years (SD=1.66). An additional 15 participants experienced FLED onset between T_1–T_2 but dropped out of the study prior to T_4, and parental diagnostic data were not available for five participants (8.5%). No significant differences on measured variables were found between those who completed T_4 and those who did not, or between those with and without parental diagnostic data (*p*s>.10).

Ancillary analysis on T_1 predictor variables were run among 205 participants with no T_1 lifetime history of MDD who experienced FLED onset between T_1–T_3. This approach provided greater statistical power to detect effects for a stable liability model. Among these 205, 59 participants described above had FLED onset between T_1–T_2 and an additional 146 participants had FLED onset between T_2–T_3. Mean time from FLED offset to T_4 was 9.46 years (SD=2.77). We were unable to examine predictor variables measured after FLED onset among these 205 participants because the assessment battery was changed substantially after T_2.

Diagnostic interviews

Participants were interviewed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS; Orvaschel, Puigantich, Chambers, Tabrizi, & Johnson, 1982) at T_1, T_2, and T_3. In conjunction with the K-SADS, the Longitudinal Interval Followup Evaluation (LIFE; Keller et al., 1987) was used to evaluate the presence and course of disorders since the previous interview. T_4 diagnoses were based on the Structured Clinical Interview for Axis I DSM-IV Disorders–Non-Patient Edition (SCID-NP; First, Spitzer, Gibbon, & Williams, 1995), with the LIFE also used to evaluate disorder presence and course since T_3.

Interviewers had advanced degrees in a mental health field, completed a 70-hour course in diagnostic interviewing, and completed a minimum of two supervised training interviews. Independent review of randomly selected cases indicated good-excellent interrater reliability for diagnoses used in this study (Lewinsohn, et al., 1993).

T_1 diagnostic status—Dichotomous variables represented lifetime diagnosis of any anxiety disorder, alcohol or substance use disorder, disruptive behavior disorder, and minor depressive disorder (mDep).

T_1– T_2 FLED clinical characteristics—FLED duration and number of DSM criteria symptoms present during the FLED were obtained from the K-SADS/LIFE. Duration was defined as the length of time from first meeting MDE criteria to the point at which episode recovery criteria were first met (see below). A dichotomous variable represented mental health treatment utilization for the FLED. Any psychosocial or pharmacological treatment for the FLED was coded as positive for mental health treatment utilization.

MDD recurrence—A dichotomous variable represented the recurrence of MDD by T_4. Recurrence was operationalized as a new episode of MDD after full recovery (i.e., a minimum of eight consecutive weeks with no more than 1–2 mild depressive symptoms).

Parental diagnosis—Effort was made to obtain two sources of diagnostic data for each parent: 76% of parents were directly interviewed using the SCID-NP; data via informants (i.e., participants and/or another first degree relative) were collected on all parents using the Family Informant Schedule and Criteria (FISC; Mannuzza & Fyer, 1990), supplemented with items necessary to derive DSM-IV diagnoses. Lifetime best-estimate DSM-IV diagnoses were derived independently by two senior diagnosticians from all available information. Interrater reliabilities of diagnoses from direct and family history interviews and best-estimates were good-excellent (Klein, Lewinsohn, Seeley, & Rohde, 2001). Five dichotomous (0=neither parent met criteria; 1=one or both parents met criteria) variables represented parental lifetime diagnostic history: MDD, SLED, rMDD, anxiety disorder, and substance use disorder.

T_1 and T_2 psychosocial measures

The following psychosocial measures with established reliability and validity in the OADP (see Andrews, Lewinsohn, Hops, & Roberts, 1993; Mathew, Pettit, Lewinsohn, Seeley, & Roberts, 2011) were assessed at T_1 and again at T_2.

Academic problems—This construct was assessed with seven items (α = .68), such as "Were you satisfied with your grades?"

Coping—Coping skills assessed the ways in which individuals cope with stressful situations, using 17 items (α= .76).

Dysfunctional attitudes—Intensity of dysfunctional attitudes was assessed with nine items (α= .74) from the Dysfunctional Attitudes Scale (Weissman & Beck, 1978).

Family social support—This construct was measured with eight items (α=.77), such as "How well do you get along with your parents?"

Friend social support—This construct was assessed with seven items (α=.72), such as "How many close friends do you have?"

Health problems—This construct was assessed with six items (α = .61), such as "In the past year, have you been unable to work and/or participate in school activities because of some illness or injury?"

Interpersonal dependency—The extent to which participants desired more support and approval from others, were anxious about being alone or abandoned, and were interpersonally sensitive was assessed with the 10-item emotional reliance subscale of the Interpersonal Dependency Inventory (Hirschfeld et al., 1977) (α= .83).

Major Life Events—This measure assessed the occurrence of 14 low frequency major life events in the preceding year.

Analytic Strategy

Separate logistic regression models were used to examine the association between each predictor and rMDD. To test whether liability to rMDD existed prior to FLED onset, T_1 participant variables and parental history of psychopathology were examined as predictors of recurrence status. To test whether liability to rMDD developed after FLED onset, T_2 participant variables were examined as predictors of recurrence status. Because the statistical power available to detect effects for T_2 participant variables was low, we focused on examination of effect sizes in addition to tests of statistical significance. Full Information Maximum Likelihood was used to estimate missing values for the five cases without parental diagnostic data.

Results

All 59 participants experienced remission of the FLED. Mean FLED duration was 21.44 weeks. Two participants (3.39%) met DSM-IV criteria for the chronic episode specifier. Forty-three participants (72.88%) experienced a recurrence and were classified as rMDD: 25 experienced two episodes, eight experienced three episodes, and 10 experienced 4–7 episodes. Mean length of time from FLED offset to onset of a recurrent episode was 60.09 months (SD=42.28). The other 16 participants (27.12%) did not experience a recurrence and were classified as SLED. Mean length of time from FLED offset to T_4 evaluation did not significantly differ across SLED and rMDD cases, $t(58)=0.91$, p=ns.

Is liability to rMDD present prior to a FLED onset?

The effects of T_1 variables on recurrence status are presented in Table 1. The odds of rMDD were significantly higher among participants with a T_1 history of mDep and among participants with a parental history of rMDD. No other variable was a significant predictor of recurrence status. When mDep and parental rMDD were entered simultaneously as predictors of rMDD, the effect of parental rMDD remained significant, odds ratio (OR)=4.80, 95% CI=1.03, 22.35, p=.04, and the effect of mDep decreased to a trend level, OR=6.88, 95% CI=0.78, 60.80, p=.08.

To examine whether the combination of mDep and parental rMDD predicted the development of rMDD with higher accuracy than either risk factor alone, predictive power was calculated using an “and” decision rule and an “or” decision rule with these two risk factors. The former indicates that only adolescents who met both criteria were predicted to develop rMDD; the latter indicates that only one of the two criteria must be met. As shown in Table 2, the “and” rule produced perfect specificity and positive predictive value, but low sensitivity, negative predictive value, and overall accuracy. The “or” rule also produced high specificity and positive predictive value, and moderate sensitivity, negative predictive value, and overall accuracy. Overall accuracy of the “or” rule exceeded that of either predictor alone and the “and” rule.

Ancillary analyses—Analyses were repeated among 205 participants who experienced FLED onset between T_1 and T_3. Mean FLED duration was 21.64 weeks and all participants

experienced remission. Eight participants (3.90%) met DSM-IV criteria for the chronic episode specifier. One-hundred fifteen participants (56.09%) experienced a recurrence and were classified as rMDD: 75 experienced two episodes, 22 experienced three episodes, and 18 experienced 4–7 episodes. Mean length of time from FLED offset to onset of a recurrent episode was 57.70 months (SD=35.83).

Results from logistic regression models among the 205 participants were identical to those among the 59 participants in terms of statistical significance: mDep (OR=2.89, 95% CI=1.29, 6.51, $p<.01$) and parental rMDD (OR=1.85, 95% CI=1.06, 3.24, $p<.05$) were the only variables that significantly predicted rMDD. When mDep and parental rMDD were entered simultaneously as predictors of rMDD, the effect of mDep remained significant, OR=2.84, 95% CI=1.20, 6.76, $p=.02$, and the effect of parental rMDD decreased to a trend level, OR=1.72, 95% CI=0.98, 3.02, $p=.06$.

Is liability to rMDD acquired after a FLED onset?

The effects of T_2 variables on recurrence status are presented in Table 3. Seventeen of 59 participants (28.80%) were currently in the FLED at the time of the T_2 evaluation. Current T_2 FLED status did not significantly predict recurrence status, OR=1.30, 95% CI=0.35, 4.79, $p=.69$.

Inspection of ORs in Table 2 revealed consistently small effect sizes, with the exception of a medium yet nonsignificant effect of treatment utilization. Findings did not differ when psychological treatment and pharmacological treatment were examined separately. Major event stress was the only T_2 variable that significantly predicted recurrence status. To determine whether the significant effect was accounted for by current depression, we included T_2 MDD status as a covariate; the predictive effect of major event stress remained statistically significant, OR=1.65, 95% CI=1.00, 2.75, $p < .05$. When T_2 major event stress, mDep, and parental rMDD were all entered simultaneously as predictors, none was a statistically significant predictor of rMDD (all $ps>.09$).

Discussion

This study examined whether liability variables for rMDD could be identified prior to and shortly following onset of a FLED in adolescence. Over 70% of 59 adolescents who experienced a FLED developed rMDD over a 12 year follow-up. The rate of rMDD was 56% among 205 participants in ancillary analyses using a shorter follow-up period (mean=9 years). These recurrence rates are similar to those reported in some previous investigations that used follow-ups of a decade or more (Fombonne, Wostear, Cooper, Harrington, & Rutter, 2001; Mueller, et al., 1999), but are considerably higher than the 35% rate reported in the only other study that prospectively tracked participants in a FLED over a lengthy period (Eaton, et al., 2008). The higher rate found in the present study may be due to the young age at which participants experienced a FLED, as an early onset of MDD may portend a more recurrent course (Eaton, et al., 2008; Pettit, Lewinsohn, Roberts, Seeley, & Monteith, 2009).

Prior history of mDep and parental history of rMDD were the only variables that significantly predicted development of rMDD. This was the case in primary analyses and in ancillary analyses with an expanded sample. The finding that adolescents with a past history of mDep were at elevated odds of rMDD suggests a chronic life course of mood disturbance, beginning with subthreshold depressive symptoms before mid-adolescence, escalating to syndromal FLED during adolescence, and proceeding to rMDD by early adulthood. This is consistent with a model of stable liability to experience mood disturbances of varying

intensity, although the possibility that the experience of mDep left a "scar" that increased odds of rMDD cannot be ruled out (Wichers, et al., 2010).

The finding that a positive parental history of rMDD was associated with elevated odds of offspring rMDD is consistent with a stable familial risk liability model (Gershon, et al., 1986; Kendler, et al., 1999). A previous study (Eaton, et al., 2008) did not find a significant association between parental depression and offspring rMDD. However, parental rMDD was not assessed. The present findings indicate that odds of offspring rMDD are elevated only in the presence of parental rMDD, not parental SLED.

Examination of combinations of mDep and parental rMDD using "and" and "or" decision rules revealed that both rules led to high specificity and positive predictive power, but modest to low sensitivity and negative predictive power. In addition, multivariate models indicated that parental rMDD and mDep remained significant or trend level predictors of rMDD when entered jointly. As such, the presence of either mDep or parental history of rMDD provides a useful index for clinicians and researchers to identify adolescents in a FLED who are at very high risk for rMDD.

After adolescents had experienced a FLED, the number of major life events in the past year was the only significant predictor of rMDD. The finding that a higher number of major life events after, but not before, the onset of a FLED significantly predicted rMDD is consistent with the possibility of a scarring effect of a FLED.

This study's findings should be viewed in light of limitations. The small sample constrained statistical power available to detect effects for predictors of rMDD measured after FLED onset. Given the early age of MDD onset, caution should be used in generalizing the findings beyond adolescent onset MDD. It is possible that some participants classified as SLED will subsequently transition to rMDD. It also is possible that recurrent episodes may have been missed due to memory bias given the six-year intervals between T_2, T_3, and T_4. Finally, several of the psychosocial measures have relatively low temporal stability and their impact on depression may be constrained to short time intervals (e.g., the impact of major events on depression is strongest in the first few months following events). Future research is encouraged to include variables that may have more distal, enduring effects.

In summary, lifetime history of mDep and parental history of rMDD predicted the development of rMDD among adolescents who had not yet experienced a major depressive episode. Following onset of a first major depressive episode, a higher level of major life events predicted the development of rMDD. These findings suggest some liabilities to rMDD may be present before FLED onset and others may be acquired following FLED onset. Among adolescents who are experiencing a FLED, a history of less severe mood disturbances such as mDep or a parental history of rMDD indicate a high risk for recurrence. Such adolescents may represent ideal candidates for maintenance treatments following response to acute phase treatments (Jarrett et al., 1998).

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Table 1

T_1 Predictors of Recurrence

Predictors	SLED (n=16)	rMDD (n=43)	Odds Ratio (95% CI)	Nagelkerke R^2
Female Gender	68.75%	67.44%	1.06 (0.31, 3.61)	.001
Lifetime Psychological Disorder				
Anxiety Disorder	12.5%	9.30%	0.72 (0.12, 4.36)	.003
Substance Use Disorder	0.0%	2.33%	--	.016
Disruptive Behavior Disorder	12.50%	4.65%	0.34 (0.04, 2.66)	.025
mDep	**6.25%**	**37.21%**	**8.89 (1.07, 73.80)**	**.154**
Psychosocial Variables[a]				
Family Support	9.74 (6.81)	8.18 (6.99)	0.97 (0.89, 1.05)	.014
Friend Support	30.27 (3.60)	29.84 (3.84)	0.97 (0.83, 1.13)	.004
Health Problems	1.00 (1.25)	1.33 (1.40)	1.21 (0.75, 1.95)	.017
Academic Impairment	7.88 (2.06)	8.86 (3.35)	1.12 (0.92, 1.37)	.031
Major Event Stress	1.00 (1.37)	1.21 (1.26)	1.15 (0.71, 1.84)	.008
Coping Skills	49.31 (9.49)	45.79 (9.25)	0.96 (0.90, 1.02)	.041
Dysfunctional Attitudes	31.94 (4.09)	30.91 (6.85)	0.97 (.089, 1.07)	.008
Interpersonal Dependency	25.88 (7.47)	23.60 (6.65)	0.95 (0.87, 1.04)	.031
Parental Lifetime				
Psychological Disorder				
MDD	40.0%	69.23%	3.38 (0.98, 11.62)†	.100
SLED	26.67%	30.77%	1.22 (0.32, 4.63)	.002
rMDD	**13.33%**	**48.71%**	**6.18 (1.23, 31.07)**	**.160**
Anxiety Disorder	31.25%	38.71%	0.85 (0.24, 2.97)	.002
Substance Use Disorder	56.25%	51.16%	0.82 (0.26, 2.59)	.003

Note. N=59.

[a]Mean scores (standard deviations) are presented for Psychosocial Variables. SLED=single lifetime major depressive episode; rMDD=recurrent major depressive disorder; mDep=minor depression. Bold font indicates statistical significance at p<.05;

†p=.054.

Table 2

Screening Properties for T_1 Risk Factor Combinations

Predictor of rMDD	Sensitivity	Specificity	PPV	NPV	Overall accuracy
mDep	.37	.94	.94	.36	.43
Parental rMDD	.44	.88	.90	.37	.56
mDep OR parental rMDD	.63	.81	.90	.45	.67
mDep AND parental rMDD	.19	1.00	1.00	.31	.41

Note. mDep=minor depression; rMDD=recurrent major depressive disorder; PPV=positive predictive value; NPV=negative predictive value.

Table 3

T_2 Predictors of Recurrence

Predictors	SLED (n=16)	rMDD (n=43)	Odds Ratio (95% CI)	Nagelkerke R^2
T_2 Psychosocial Measures				
Family Support	13.05 (8.94)	8.59 (7.40)	0.93 (0.86, 1.01)	.084
Friend Support	28.93 (3.49)	30.17 (3.85)	1.09 (0.93, 1.29)	.031
Health Problems	1.27 (1.01)	1.37 (1.02)	1.10 (0.56, 2.17)	.002
Academic Impairment	8.93 (4.04)	9.13 (3.43)	1.02 (0.85, 1.20)	.001
Major Event Stress	**0.80 (0.94)**	**1.72 (1.67)**	**1.66 (1.01, 2.76)**	**.111**
Coping Skills	48.88 (8.41)	46.60 (7.96)	0.93 (0.86, 1.01)	.082
Dysfunctional Attitudes	32.50 (5.69)	31.84 (7.52)	0.99 (0.91, 1.07)	.003
Interpersonal Dependency	24.38 (5.48)	24.58 (7.33)	1.01 (0.92, 1.09)	.001
FLED Characteristics				
Duration in Weeks	14.69 (21.67)	6.79 (5.71)	1.00 (0.99, 1.01)	.012
Number of DSM Symptoms	5.56 (2.03)	6.24 (1.25)	1.35 (0.91, 2.02)	.057
Treatment Utilization	12.50%	25.58%	2.41 (0.47, 12.31)	.022

Note. N=59. Mean scores (standard deviations) are presented for all variables except Treatment Utilization. Percentages are presented for Treatment Utilization. SLED=single lifetime major depressive episode; rMDD=recurrent major depressive disorder; FLED=first lifetime major depressive episode. Bold font indicates statistical significance at p<.05.