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The Temporal Relation between Depression and Comorbid Psychopathology in Adolescents at Varied Risk for Depression

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Abstract

Background—This study examined the temporal comorbidity of depressive disorders with anxiety, externalizing, and substance use disorders in adolescents who varied in risk for depression.

Methods—Participants were 240 adolescents and their mothers who had either a history of depression (high-risk, $n=185$) or were lifetime-free of psychiatric disorders (low-risk, $n=55$). Children (54.2% females) were first evaluated in 6th grade (mean age = 11.86, $SD = .57$) with the K-SADS-PL to assess current and lifetime diagnoses, and then annually through 12th grade with the A-LIFE to assess diagnoses since the previous evaluation.

Results—For girls, the rate of depression was high regardless of prior anxiety, whereas for boys, the odds that those with prior subthreshold anxiety would have subsequent subthreshold depression were 1.5 times those of boys with no prior subthreshold anxiety, controlling for risk. In addition, the odds that girls with prior substance use disorders would have a threshold depressive disorder subsequently were three times those of girls with no prior substance use disorders, controlling for risk.

Conclusions—These results highlight the importance of early detection of various forms of psychopathology in youth who then can be targeted for intervention. The prospective paths to comorbidity differed by sex, thus suggesting that interventions need to be constructed with sensitivity to these distinct diagnostic trajectories.

Keywords

Depression; Comorbidity; Adolescents; High-risk Offspring

Depression in youth rarely occurs in “pure” forms (Angold, Costello, & Erkanli, 1999; Sorensen, Nissen, Mors, & Thomsen, 2005). Comorbidity is the rule rather than the exception. The presence of major depressive disorder (MDD) or dysthymic disorder (DD) in children and adolescents is estimated to increase the likelihood of another disorder at least twenty-fold (Angold & Costello, 1993). Comorbidity is associated with a greater likelihood of recurrence, longer episodes, suicide attempts, increased utilization of mental health services, and functional impairment (Birmaher et al., 1996; Ezpeleta, Domenech, & Angold, 2006). Diagnoses frequently comorbid with MDD in youth include anxiety disorders, conduct disorders, and substance abuse and dependence (Wagner, 2003).

Depression and anxiety are among the most commonly co-occurring conditions, with estimates ranging from 16% to 50% (Angold et al., 1999; Seligman & Ollendick, 1998) and as high as 70% in clinical samples of depressed youth (Birmaher et al., 1996). A meta-

analysis of studies of comorbidity in children revealed a median odds ratio of 8.2 between anxiety and depression, 6.6 between conduct disorder and depression, and 3.3 between substance use disorders and depression (Angold et al., 1999; Armstrong & Costello, 2002).

Less is known about the temporal course of disorders co-occurring with depression in youth. That is, to what extent does the occurrence of one disorder increase the likelihood of others? Results of studies of the developmental sequence of depression and other forms of psychopathology have varied. In a longitudinal study of a community sample, Costello, Mustillo, Erkanli, Keeler, and Angold (2003) found that, controlling for other comorbidities, anxiety significantly predicted depression, depression significantly predicted anxiety, ADHD significantly predicted oppositional defiant disorder, and anxiety significantly predicted substance use disorders. In a follow-up of a clinical sample, Kovacs, Gatsonis, Paulauskas, and Richards (1989) reported that two thirds of children with comorbid depression and anxiety disorders experienced the anxiety disorder prior to the depression. Similarly, the Oregon Adolescent Depression Project (Rohde, Lewinsohn, & Seeley, 1991) showed that anxiety, externalizing, and substance use disorders all preceded depression. Additionally, Weissman, Fendrich, Warner, and Wickramaratne (1992) found that among offspring of depressed parents, 28.6% of those with an initial diagnosis of conduct disorder developed depression over the next two years, which is consistent with the finding by Lahey, Loeber, Burke, Rathouz, and McBurnett (2002) that CD preceded depression in clinic-referred boys.

Few studies, however, have examined within the same individuals the prospective relation between prior psychopathology and subsequent depression as well as the reverse (i.e., prior depression predicting subsequent psychopathology). The purpose of the present longitudinal study was to investigate the temporal relations of depression with anxiety, externalizing, and substance use disorders (SUDS) through adolescence. Given the episodic nature of depressive disorders, examining these diagnoses prospectively within the same individuals decreased the chances of inadvertently missing disorders when they occurred and strengthened our ability to test temporal precedence.

The present study explored these relations in a sample of offspring of mothers who either had histories of mood disorders ('high risk') or were lifetime-free of psychiatric disorders ('low risk'). Given the higher rates of depression, anxiety, conduct, and substance use disorders among high-risk youth compared to their low-risk counterparts (Beardslee et al., 1996; Weissman, Wickramaratne, Moreau, & Olfson, 1997; Weissman, Warner, Wickramaratne, Moreau, & Olfson, 2000), the current sample was particularly appropriate for studying comorbidity (Avenevoli & Merikangas, 2006).

In addition, we explored whether the relations between depression and comorbid psychopathology varied as a function of sex. The developmental trajectories of comorbid disorders have been found to differ for initially depressed male and female adolescents (Kovacs, Obrosky, & Sherrill, 2003). In contrast, Sorensen and colleagues (2005) found no sex differences in disorders comorbid with depression symptoms. Clarifying the complex temporal link between depression and other disorders in males and females could help to inform future investigations about the processes underlying these conditions and guide the formulation of gender-specific interventions.

Finally, studies have highlighted the importance of investigating subsyndromal symptoms, that is, symptoms that do not meet all the criteria for a threshold diagnosis (Georgiades, Lewinsohn, Monroe, & Seeley, 2006; Lewinsohn, Shankman, Gau, & Klein, 2004). Adolescents with subthreshold depression are at elevated risk of developing MDD, SUDs, and anxiety disorders (e.g., Lewinsohn, Solomon, Seeley, & Zeiss, 2000; Pickles et al.,

2001), and subthreshold depressive disorders are associated with impaired psychosocial functioning (Rapaport & Judd, 1998). Therefore, we examined the temporal relations between depression and other psychopathology at both the threshold and subthreshold levels of the disorders.

Method

Participants

Participants were 240 mothers and adolescents first assessed in 6th grade (mean age = 11.86, $SD = .56$). The sample of adolescents was 54.2% female, 82% Caucasian, 14.7% African-American, and 3.3% other (Hispanic, Asian, Native American). Family socioeconomic status was predominantly working- to middle-class ($M=41.84$, $SD = 13.25$) (Hollingshead, 1975). Only one child per family (i.e., the student in 6th grade) was included in the study.

Procedure

A letter describing the project and a brief health history questionnaire were sent to over 3500 parents of 5th-grade public school children. Of the 1495 respondents, telephone screening interviews were conducted with the 587 who endorsed a history of depression, use of antidepressants, or no history of psychopathology. Based on these screening calls, 349 mothers were identified as having a history of depressive symptoms ($n=247$) or no history of psychiatric problems ($n=102$). They then were interviewed in person with the Structured Clinical Interview for *DSM* diagnoses (SCID; Spitzer, Williams, Gibbon, & First, 1990) to confirm the presence or absence of a diagnosis of a depressive disorder. The final sample of 240 families consisted of 185 mothers with histories of a depressive disorder and 55 mothers who were lifetime free of psychiatric diagnoses. At baseline, high risk (HR) and low risk (LR) youth did not differ significantly in age (HR: $M=11.84$, $SD=.56$; LR: $M=11.91$, $SD=.55$), sex (HR: 55.7% female; LR: 49.1% female), or race/ethnicity [HR: 83.8% Caucasian, 13.5% African-American, and 2.7% other (Hispanic, Asian, Native American); LR: 74.6% Caucasian, 18.2% African-American, and 7.3% other (Hispanic, Asian, Native American)].

Youth were first assessed in sixth grade and then annually through 12th grade. Prior to beginning the evaluations, informed consent and assent were obtained from all participating mothers and adolescents, respectively. All procedures were approved by the Behavioral Sciences Institutional Review Board at Vanderbilt University. Interviewers about adolescents' psychopathology were unaware of parents' psychiatric histories. Although interviewers were aware of adolescents' prior diagnoses, they were not informed about any hypotheses regarding the temporal relations among disorders over time.

Measures

The Schedule for Affective Disorders and Schizophrenia for School-aged Children – Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) was used at baseline to assess adolescents' current and history of psychopathology. The Longitudinal Interval Follow-up Evaluation for adolescents (A-LIFE; Keller et al., 1987), which parallels the K-SADS-PL, was used at the annual evaluations to assess adolescents' disorders since the previous interview. Interviewers received their training and weekly supervision from an expert clinician (JG). A second rater who was unaware of the primary interviewer's ratings reviewed a random 25% of the audio-taped interviews. Inter-rater reliability for all diagnoses yielded kappas $\geq .78$ (depression = .82; anxiety = .78; externalizing = .85, substance use = .79).

Both threshold and subthreshold levels of disorders were analyzed. Threshold depression included DSM-IV-defined diagnoses of MDD or DD. Threshold anxiety included diagnoses

of separation anxiety (SAD), overanxious (OAD), generalized anxiety (GAD), panic, phobias (social, specific), obsessive-compulsive disorder (OCD), or post-traumatic stress disorder (PTSD). Threshold externalizing disorders included diagnoses of oppositional defiant disorder (ODD) or conduct disorder (CD). Subthreshold diagnoses of depression, anxiety, or externalizing disorders were defined as having at least half the criterion symptoms plus functional impairment (e.g., Fergusson, Horwood, Ridder, & Beaudrais, 2005). Because the frequency of threshold SUDs was relatively low in this sample, however, we combined subthreshold and threshold alcohol and substance abuse and dependence into a single category of SUDs.

To assess the temporal relations of depression with these other disorders, we identified the *first* lifetime occurrence of a depressive diagnosis at either a subthreshold or threshold level, and then estimated the odds of another disorder occurring later at a subthreshold or threshold level. We also examined these relations in reverse. That is, we identified the *first* lifetime occurrence of one disorder (i.e., anxiety, externalizing, SUDs) at either a subthreshold or threshold level, and then examined the odds that depression (subthreshold or threshold) occurred subsequently. For example, if a child had an anxiety disorder at age 6 and again at age 11, only the *first* occurrence at age 6 was included in the analyses; that is, we examined whether threshold or subthreshold depression followed that first diagnosis of an anxiety disorder. For a small subset of the sample (N=14; 5.8%), both the first and subsequent disorders occurred prior to the baseline interview. Thus, for the majority (94.2%) of participants, the second disorder was diagnosed at an annual follow-up evaluation conducted after baseline.

Data Analysis

To test whether one disorder predicted another over time, we fit three series of logistic regression analyses examining the bidirectional relations between anxiety and depression, externalizing and depression, and substance use and depression. Risk and sex were dummy-coded, using high risk and females, respectively, as the comparison group (see Table 1 for frequencies of diagnoses by risk and sex). The first series of models investigated the relations between anxiety and depression (see Table 2), controlling for risk and sex. Model 1 (M1) examined threshold anxiety predicting threshold depression; M2 tested threshold anxiety predicting subthreshold depression. M3 tested the prediction of subthreshold anxiety to threshold depression; M4 tested subthreshold anxiety predicting subthreshold depression. In the next four models, the predictors and outcomes were reversed such that threshold depression predicted threshold anxiety (M5) and subthreshold anxiety (M6), and subthreshold depression predicted threshold (M7) and subthreshold anxiety (M8).

The next two series of logistic regression models investigated the relations of externalizing (Models 9–16) and substance use disorders (SUD) (Models 17–20) to depression in a similar manner, with sub- and threshold levels of one disorder predicting sub- and threshold levels of the other, and then reversing predictors and outcomes. Because sub- and threshold substance use diagnoses were combined, fewer substance use models were fit.

After fitting the main effect models for all three series, the interaction between sex and prior psychopathology (defined as first lifetime occurrence) was added to each model to examine whether the temporal relations between the other disorders (i.e., anxiety, externalizing, or substance use) and depression, and the reverse, differed by sex.

Missing Data

A total of 207 participants had complete interview data. Differences between completers and noncompleters were examined using t-tests for continuous variables and chi-square analyses

for categorical variables. Participants missing interview data were more likely to be male than those with complete data [$\chi^2(1) = 11.75, p < .01$]. Participants' sex was included as a control variable in all analyses. No other significant differences were found between completers and noncompleters on study variables.

Results

Main Effects

Previous Psychopathology Predicting Odds of Subsequent Psychopathology (Table 2, columns 3 and 4)—Overall, prior subthreshold externalizing disorders significantly predicted subsequent threshold depressive disorders ($OR = 2.07, p < .05$), controlling for sex and risk (M11, columns 3 and 4). That is, the fitted odds that youth diagnosed with a prior subthreshold externalizing disorder would develop a subsequent threshold depressive disorder (versus not) were more than twice those of youth not diagnosed with a prior subthreshold externalizing disorder, controlling for sex and risk. No other main effects were found for previous psychopathology predicting later psychopathology.

Risk Predicting Odds of Lifetime Psychopathology (Table 2, columns 5 and 6)—High-risk youth had an average 12 times the odds of having had a subthreshold or threshold depressive disorder compared to low-risk youth, controlling for prior subthreshold or threshold anxiety disorders and sex (M1–M4, OR range=9.47–15.06, $p < .001$), controlling for prior subthreshold or threshold externalizing disorders and sex (M9–M12, OR range=9.12–15.28, $p < .001$), and controlling for prior subthreshold or threshold SUDs and sex (M17–M18, OR range=10.08–15.13, $p < .001$). Compared to low-risk youth, high-risk adolescents had more than 4 times the fitted odds of having had a subthreshold or threshold anxiety disorder (M5–M8, OR range=3.48–5.82, $p < .05$), more than 11 times the fitted odds of having had a subthreshold or threshold externalizing disorder (M13–M16, OR range=10.92–11.38, $p < .001$), and more than 6 times the fitted odds of having had a subthreshold or threshold SUD (M19–M20, OR range=5.25–6.97, $p < .05$), controlling for prior subthreshold or threshold depression and sex.

Sex Predicting Odds of Psychopathology (Table 2, Columns 7 and 8)—The fitted odds that girls would have been diagnosed with a subthreshold or threshold anxiety disorder (versus not) were approximately twice those of boys, controlling for prior subthreshold or threshold depression and risk (M5–M8, OR range=1.97–2.57, $p < .05$). The fitted odds that girls would have been diagnosed with a subthreshold or threshold depressive disorder were 1.5 times those of boys, controlling for prior subthreshold and threshold anxiety and risk, although this finding was not significant (M1–M4, OR range=1.43–1.63, $p < .24$). The fitted odds that boys would have been diagnosed with a subthreshold or threshold externalizing disorder were almost twice those of girls, controlling for prior subthreshold or threshold depression and risk (M13–M16, OR range=.44–.49, $p < .05$). No main effects for sex were found for substance use disorders.

Moderation Effects of Sex

Relation between Depression and Anxiety—When added to the main effects models in Table 2, sex significantly moderated the relation between subthreshold anxiety and subthreshold depression. The proportional improvement in fit when the sex by anxiety interaction term was added to the model with the main effects of these predictors and risk (M4) was a 2% reduction in the X^2 statistic (X^2 difference= 4.39, df difference=1, $p < .05$). For girls, the rates of depression were high regardless of prior anxiety; the effect of anxiety on subsequent depression was not significant. For boys, the fitted odds that those with

previous subthreshold anxiety would have a subsequent subthreshold depression (versus not) were one and a half times the odds of boys with no prior subthreshold anxiety, controlling for risk ($OR=1.55, p<.04, CI: .05-.90$). Among youth with a prior history of subthreshold anxiety, the fitted odds that males would have subsequent subthreshold depression were 1.97 times the fitted odds for females.¹

Relation between Depression and Substance Use Disorders—The sex by prior SUD interaction significantly incremented the main effects model (M17), which included risk, sex, and prior substance use (combined subthreshold and threshold) as predictors of subsequent depression. The proportional improvement in fit when the sex by SUD interaction term was included was a 3% reduction in the X^2 statistic (X^2 difference=7.16, df difference=1, $p<.05$). The fitted odds that girls with a prior SUD would have a subsequent threshold depressive disorder were more than 3 times those of girls without a prior SUD, controlling for risk ($OR=3.36, p<.01, 95\% CI: 1.67-93.46$). Among youth with a prior history of SUD, the fitted odds that girls would have a subsequent threshold depressive disorder were 13.24 times the fitted odds for boys.

Discussion

The present study examined the predictive relations of depression with anxiety, externalizing, and substance use disorders in a sample of youth who varied with regard to their risk for mood disorders and explored whether these relations differed by sex. As expected (e.g., Beardslee, Versage, & Gladstone, 1998), offspring of mothers with a history of mood disorders (high risk) were more likely to be diagnosed with depressive, anxiety, externalizing, and substance use disorders, controlling for prior psychopathology and sex, than offspring of mothers without lifetime psychiatric diagnoses (low risk). This finding was true for both threshold and subthreshold levels of the disorders.

Regarding the main effect of previous psychopathology predicting subsequent psychopathology, prior subthreshold externalizing predicted subsequent depressive disorders (i.e., MDD, DD). This result is consistent with the finding that CD often is followed by mood disorders (Zoccolillo, 1992) and that for 70% of children with CD, the CD preceded depression (Ezpeleta et al., 2006). Importantly, the findings of this study suggest that even subthreshold levels of externalizing disorders are potent enough to increase the risk of developing a threshold depressive disorder.

The odds of girls having been diagnosed with an anxiety disorder were twice those of boys, controlling for prior depression and risk, and the odds of girls having been diagnosed with a depressive disorder were one and a half times those of boys, controlling for prior anxiety and risk. These findings parallel other studies showing that females have higher rates of anxiety and depressive disorders than males (Breslau, Chilcoat, Peterson, & Schultz, 2000; Eaton et al., 1997). Also consistent with the literature (e.g., Kovacs, 2003; Offord, Boyle, & Racine, 1989), was the finding that the odds of boys having been diagnosed with an externalizing disorder were almost twice those of girls, controlling for prior depression and risk.

¹We reran all analyses excluding the 14 participants for whom both disorders occurred before the baseline assessment and found that the results remained essentially the same, with two exceptions. Sex significantly moderated the relation between *threshold* anxiety and subthreshold depression, such that the fitted odds that boys with previous threshold anxiety would experience later subthreshold depression were over four times those of boys without previous threshold anxiety ($OR = 4.08, CI: .019-.956, p=.045$); the interaction with sex in the relation between *subthreshold* anxiety and subthreshold depression was now only marginal ($OR = 1.30, CI: .052-1.168, p = .078$). Second, an externalizing by sex interaction effect emerged such that the fitted odds that girls with previous threshold depression would experience later subthreshold externalizing disorders were almost one and a half times those of girls without previous threshold depression ($OR = 1.42, CI: 1.086-45.180, p = .041$).

Several interesting findings emerged with regard to sex differences. First, the relation between anxiety and depression differed for males and females. Whereas for girls the rates of depression were high regardless of prior anxiety, the odds of boys with prior subthreshold anxiety disorders having subsequent subthreshold depression were one and a half times those of boys without prior subthreshold anxiety. These findings highlight the pernicious effects of anxiety symptoms in boys. Perhaps for boys, having anxiety is more debilitating in a culture where boys are socialized to be “tough.” For anxious boys, social support and acceptance may be less forthcoming, thereby leading to feelings of rejection and depression. These results mirror those of other investigators who also have shown that anxiety predicts depressive symptoms in males (Frost, Reinherz, Pakiz-Camras, Giaconia, & Lefkowitz, 1999) and suggest that anxious males may be particularly vulnerable to depression (Breslau et al., 2000).

In addition, sex moderated the relation between SUDs and depression. The odds of girls with prior SUDs receiving a subsequent diagnosis of a depressive disorder were thirteen times the odds of boys with prior SUDs receiving such a diagnosis. These results parallel those of other studies that have found that comorbid substance use and depression in adolescents is particularly high among females (Clark et al., 1997; Whitmore et al., 1997). Rao, Daley, and Hammen (2000) showed that for adolescent girls, SUDs predicted future MDD but the reverse was not the case. Roberts, Roberts, and Xing (2007) found that alcohol dependence conferred an increased risk for depression, particularly for females (odds of 8.0 for females and 3.7 for males). Similarly, the use of illegal substances in adolescent girls has been found to predict an increased risk of depressive symptoms three years later (Frost et al., 1999).

Thus, the temporal relations between depression and anxiety and depression and substance use disorders differed for males and females. One explanation for comorbidity may be that it is the consequence of attempts to cope with stress, albeit maladaptive attempts (Hammen & Compas, 1994). These results highlight the importance of early detection of vulnerable individuals so that they might be targeted for intervention. Moreover, such intervention efforts may need to differ for males versus females because of their distinct patterns of temporal comorbidity.

One limitation as well as strength of this study was that the sample consisted primarily of offspring of depressed mothers. Given the increased rates of psychopathology in children of depressed parents (Beardslee et al., 1998), this high-risk sample allowed for greater frequency and variability in the occurrence of symptoms and disorders than would be found in a nonselected community sample. This feature of the sample likely increased our chances of diagnosing sufficient numbers of disorders and thereby facilitated our ability to explore the complex relations among them over time. These results may not generalize to a purely normative sample, however.

Another strength of this study was that it involved a relatively long follow-up period of approximately seven years. However, these adolescents are likely to continue having new onsets into their adult years. Following the sample into early adulthood would provide a more extensive picture of the temporal relations between depression and other disorders during an important developmental epoch. Additionally, although we examined diagnoses separately for each individual for each analysis, some individuals could have had a complex constellation of disorders (e.g., anxiety to depression to SUD); future studies should explore these more complicated relations over time.

Given the relatively low rates of any particular anxiety disorder, it was not possible to examine the relations between depression and specific anxiety diagnoses. Separation

anxiety, overanxious disorder, and phobias often precede the onset of MDD (Lewinsohn, Zinbarg, Seeley, Lewinsohn, & Sack, 1997). Larger samples are needed to have sufficient power to detect the relation of these specific disorders with depression. Avenues for future research also include examining pubertal status, mothers' non-depressive psychopathology, number of mood episodes, age of onset, length of illness, and fathers' psychiatric history in relation to the sequence of comorbid disorders in children and adolescents. Future studies of comorbidity also should explore through what mechanisms (e.g., biological, psychosocial) one disorder precedes another. How does anxiety lead to depression (Flannery-Schroeder, 2006)? Do anxiety and depression share a common underlying diathesis that simply takes longer for the depression to unfold (Grillon et al., 2005; Kendler, Gardner, & Prescott, 2002), or does being anxious generate circumstances that increase the likelihood of the onset of depression (Hammen, 2006)?

The present prospective study exploring the predictive relations between depression and other psychiatric disorders has potential clinical implications with regard to whom and what might be targeted in interventions aimed at treating and preventing depression. For example, depression prevention programs should target anxiety, even at the subthreshold level, particularly among high-risk boys, and substance use, particularly among high-risk girls. In addition, given such gender differences, the use of same-sex groups might be advised, particularly if different comorbid disorders are the focus of the intervention.

KEY POINTS

- Few studies have examined in the same individuals the prospective relations between prior psychopathology and subsequent depression as well as the reverse. Little is known about whether sex differences exist in the temporal relations between depression and other psychopathology.
- This study examined the temporal comorbidity of depressive disorders with anxiety, externalizing, and substance use disorders in adolescents who varied in risk for depression.
- The results of this study indicate that the temporal relations between depression and anxiety and depression and substance use disorders differed for males and females.
- The findings of the present study have potential clinical implications with regard to whom and what might be targeted in interventions aimed at preventing depression. For example, depression prevention programs should target subthreshold anxiety among high-risk boys, and substance use among high-risk girls.

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REFERENCES

- Andrews JA, Lewinsohn PM. Suicidal attempts among older adolescents: Prevalence and co-occurrence with psychiatric disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1992; 31:655–662. [PubMed: 1644728]
- Angold A, Costello EJ. Depressive comorbidity in children and adolescents: empirical, theoretical, and methodological issues. *American Journal of Psychiatry*. 1993; 150:1779–1791. [PubMed: 8238631]

- Angold A, Costello EJ, Erkanli A. Comorbidity. *Journal of Child Psychology and Psychiatry*. 1999; 40:57–87. [PubMed: 10102726]
- Armstrong TD, Costello EJ. Community studies on adolescent substance use, abuse, or dependence and psychiatric comorbidity. *Journal of Consulting and Clinical Psychology*. 2002; 70:1224–1239. [PubMed: 12472299]
- Avenevoli S, Merikangas KR. Implications of high-risk family studies for prevention of depression. *American Journal of Preventive Medicine*. 2006; 31:126–235.
- Axelson DA, Birmaher B. Relation between anxiety and depressive disorders in childhood and adolescence. *Depression and Anxiety*. 2001; 14:67–78. [PubMed: 11668659]
- Beardslee WR, Keller MB, Siefer R, Lavori PW, Staley J, Podorekfsky D, Shera D. Prediction of adolescent affective disorder: Effects of prior parental affective disorders and child psychopathology. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1996; 35:279–288. [PubMed: 8714315]
- Beardslee WR, Versage EM, Gladstone TRG. Children of affectively ill parents: A review of the past 10 years. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1998; 37:1134–1141. [PubMed: 9808924]
- Birmaher B, Ryan ND, Williamson DE, Brent DA, Kaufman J, Dahl RE, Perel J, Nelson B. Childhood and adolescent depression: A review of the past 10 years. Part 1. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1996; 35:1427–1439. [PubMed: 8936909]
- Breslau, N.; Chilcoat, HD.; Peterson, EL.; Schultz, LR. Gender differences in major depression: The role of anxiety. In: Frank, E., editor. *Gender and its effects on psychopathology*. American Psychiatric Press; Washington, D.C.: 2000. p. 131-149.
- Clark DB, Pollock N, Bukstein OG, Mezzich AC, Bromberger JT, Donovan JE. Gender and comorbid psychopathology in adolescents with alcohol dependence. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1997; 36:1195–1203. [PubMed: 9291720]
- Cole DA, Peeke LG, Martin JM, Truglio R, Seroczynski AD. A longitudinal look at the relation between depression and anxiety in children and adolescents. *Journal of Consulting and Clinical Psychology*. 1998; 66:451–460. [PubMed: 9642883]
- Costello EJ, Foley DL, Angold A. 10-year research update review: The epidemiology of child and adolescent psychiatric disorders: II. Developmental epidemiology. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2006; 45:8–24. [PubMed: 16327577]
- Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. *Archives of General Psychiatry*. 2003; 60:837–844. [PubMed: 12912767]
- Eaton WW, Anthony JC, Gallo J, Cai G, Tien A, Romanoski A, Lyketsos C, Chen L. Natural history of diagnostic interview schedule/DSM-IV major depression: The Baltimore Epidemiologic Catchment Area follow-up. *Archives of General Psychiatry*. 1997; 54:993–999. [PubMed: 9366655]
- Ezpeleta L, Domenech JM, Angold A. A comparison of pure and comorbid CD/ODD and depression. *Journal of Child Psychology and Psychiatry*. 2006; 47:704–712. [PubMed: 16790005]
- Flannery-Schroeder EC. Reducing anxiety to prevent depression. *American Journal of Preventive Medicine*. 2006; 31:136–142.
- Frost AK, Reinherz HZ, Pakiz-Camras B, Giaconia RM, Lefkowitz ES. Risk factors for depressive symptoms in late adolescence: A longitudinal community study. *American Journal of Orthopsychiatry*. 1999; 69:370–381. [PubMed: 10439851]
- Georgiades K, Lewinsohn PM, Monroe SM, Seeley JR. Major depressive disorder in adolescence: The role of subthreshold symptoms. *American Academy of Child and Adolescent Psychiatry*. 2006; 45:936–944.
- Grillon C, Warner V, Hille J, Merikangas KR, Bruder GE, Tenke CE, Nomura Y, Leite P, Weissman MM. Families at high and low risk for depression: A three-generation startle study. *Biological Psychiatry*. 2005; 57:953–960. [PubMed: 15860334]
- Hammen C. Stress generation in depression: Reflections on origins, research, and future directions. *Journal of Clinical Psychology*. 2006; 62:1065–1082. [PubMed: 16810666]

- Hammen C, Compas BE. Unmasking unmasked depression in children and adolescents: The problem of comorbidity. *Clinical Psychology Review*. 1994; 14:585–603.
- Hankin BL, Abramson LY, Moffitt TE, Silva PA, McGee R, Angell KE. Development of depression from preadolescence to young adulthood: Emerging gender differences in a 10-year longitudinal study. *Journal of Abnormal Psychology*. 1998; 107:128–140. [PubMed: 9505045]
- Hollingshead, AB. Four factors of social status. Yale University, Department of Sociology; New Haven, CT: 1975.
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. The Schedule for Affective Disorders and Schizophrenia for School-aged Children: Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1997; 36:980–988. [PubMed: 9204677]
- Keller MB, Lavori PW, Friedman B, Nielsen E, Endicott J, McDonald SP, Andreasen NC. The longitudinal interval follow-up evaluation: A comprehensive method for assessing outcome in prospective longitudinal studies. *Archives of General Psychiatry*. 1987; 44:540–548. [PubMed: 3579500]
- Kendall PC, Kortlander E, Chansky TE, Brady EU. Comorbidity of anxiety and depression in youth: Treatment implications. *Journal of Consulting and Clinical Psychology*. 1992; 60:869–880. [PubMed: 1360989]
- Kendler KS, Gardner CO, Prescott CA. Toward a comprehensive developmental model for major depression in women. *American Journal of Psychiatry*. 2002; 159:1133–1145. [PubMed: 12091191]
- Kovacs M, Gatsonis C, Paulauskas SL, Richards C. Depressive disorders in childhood. IV. A longitudinal study of comorbidity with and risk for anxiety disorders. *Archives of General Psychiatry*. 1989; 46:776–782. [PubMed: 2774847]
- Kovacs M, Obrosky DS, Sherrill J. Developmental changes in the phenomenology of depression in girls compared to boys from childhood onward. *Journal of Affective Disorders*. 2003; 74:33–48. [PubMed: 12646297]
- Lahey BB, Loeber R, Burke J, Rathouz PJ, McBurnett K. Waxing and waning in concert: Dynamic comorbidity of conduct disorder with other disruptive and emotional problems over 17 years among clinic-referred boys. *Journal of Abnormal Psychology*. 2002; 111:556–567. [PubMed: 12428769]
- Lewinsohn PM, Solomon A, Seeley JR, Zeiss A. The clinical implications of “subthreshold” depressive symptoms. *Journal of Abnormal Psychology*. 2000; 109:345–351. [PubMed: 10895574]
- Lewinsohn PM, Shankman SA, Gau JM, Klein DN. The prevalence and comorbidity of subthreshold psychiatric conditions. *Psychological Medicine*. 2004; 34:613–622. [PubMed: 15099416]
- Lewinsohn PM, Hops H, Roberts RE, Seeley JR, Andrews JA. Adolescent psychopathology: I. Prevalence and incidence of depression and other DSM-III-R disorders in high school students. *Journal of Abnormal Psychology*. 1993; 102:133–144. [PubMed: 8436689]
- Lewinsohn PM, Zinbarg R, Seeley JR, Lewinsohn M, Sack WH. Lifetime comorbidity among anxiety disorders and between anxiety disorders and other mental disorders in adolescents. *Journal of Anxiety Disorders*. 1997; 11:377–394. [PubMed: 9276783]
- McClellan JM, Rubert MP, Reichler RJ, Sylvester CE. Attention deficit disorder in children at risk for anxiety and depression. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1990; 29:534–539. [PubMed: 2387787]
- Offord DR, Boyle MH, Racine Y. Ontario Child Health Study: Correlates of disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1989; 28:856–860. [PubMed: 2808255]
- Pickles A, Rowe R, Simonoff E, Foley D, Rutter M, Silberg J. Child psychiatric symptoms and psychosocial impairment: Relationship and prognostic significance. *British Journal of Psychiatry*. 2001; 179:230–235. [PubMed: 11532800]
- Rao U. Links between depression and substance abuse in adolescents. *American Journal of Preventive Medicine*. 2006; 31:161–174.

- Rao U, Daley SE, Hammen C. Relationship between depression and substance use disorders in adolescent women during the transition to adulthood. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2000; 39:215–222. [PubMed: 10673833]
- Rapaport MH, Judd LL. Minor depressive disorder and subsyndromal depressive symptoms: Functional impairment and response to treatment. *Journal of Affective Disorders*. 1998; 48:227–232. [PubMed: 9543213]
- Reinherz HZ, Giaconia RM, Pakiz B, Silverman AB, Frost AK, Lefkowitz ES. Psychosocial risks for major depression in late adolescence: a longitudinal community study. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1993; 32:369–377. [PubMed: 8444767]
- Roberts RE, Roberts CR, Zing Y. Comorbidity of substance use disorders and other psychiatric disorders among adolescents: Evidence from an epidemiologic survey. *Drug and Alcohol Dependence*. 2007; 88:4–13.
- Rohde P, Lewinsohn PM, Seeley JR. Comorbidity of unipolar depression: II. Comorbidity with other mental disorders in adolescents and adults. *Journal of Abnormal Psychology*. 1991; 100:214–222. [PubMed: 2040773]
- Seligman LD, Ollendick TH. Comorbidity of anxiety and depression in children and adolescents: An integrative review. *Clinical Child and Family Psychology Review*. 1998; 1:125–144. [PubMed: 11324302]
- Spitzer, RL.; Williams, JBW.; Gibbon, M.; First, MB. User's guide for the Structured Clinical Interview for DSM-III-R. American Psychiatric Press; Washington, D.C.: 1990.
- Sorensen MJ, Nissen JB, Mors O, Thomsen PH. Age and gender differences in depressive symptomatology and comorbidity: An incident sample of psychiatrically admitted children. *Journal of Affective Disorders*. 2005; 84:85–91. [PubMed: 15620389]
- Wager KD. Major depression in children and adolescents. *Psychiatric Annals*. 2003; 33:266–270.
- Weissman MM, Fendrich M, Warner V, Wickramaratne P. Incidence of psychiatric disorder in offspring at high and low risk for depression. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1992; 31:640–648. [PubMed: 1644726]
- Weissman MM, Leckman JF, Merikangas KR, Gammon GD, Prusoff BA. Depression and anxiety disorders in parents and children. *Archives of General Psychiatry*. 1984; 41:845–952. [PubMed: 6466043]
- Weissman, MM.; Warner, V.; Wickramaratne, P.; Moreau, D.; Olfson, M. Offspring at risk: Early-onset major depression and anxiety disorders over a decade. In: Rapoport, JL., editor. *Childhood onset of "adult" psychopathology: clinical and research advances*. American Psychiatric Publishing, Inc.; Washington, D.C.: 2000. p. 245-258.
- Weissman MM, Wickramaratne P, Moreau D, Olfson M. Offspring of depressed parents: 10 years later. *Archives of General Psychiatry*. 1997; 54:932–940. [PubMed: 9337774]
- Weissman MM, Wickramaratne P, Nomura Y, Warner V, Pilowsky D, Verdelli H. Offspring of depressed parents: 20 years later. *American Journal of Psychiatry*. 2006; 163:1001–1008. [PubMed: 16741200]
- Whitmore EA, Mikulich SK, Thompson LL, Riggs PD, Aarons GA, Crowley TJ. Influences on adolescent substance dependence: Conduct disorders, depression, attention deficit hyperactivity disorder, and gender. *Drug and Alcohol Dependence*. 1997; 47:87–97. [PubMed: 9298330]
- Wickramaratne PJ, Weissman MM. Onset of psychopathology in offspring by developmental phase and parental depression. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1998; 37:933–942. [PubMed: 9841243]
- Zoccolillo M. Co-occurrence of conduct disorder and its adult outcomes with depressive and anxiety disorders: a review. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1992; 31:547–556. [PubMed: 1592790]

Table 1

Frequency of Diagnoses by Risk and Sex

	High Risk N=185	Low Risk N=55	Females N=130	Males N=110	Total N=240
Diagnosis	N (%)	N (%)	N (%)	N (%)	N (%)
Threshold Depression	68 (36.8%)	2 (3.6%)	43 (33.1%)	27 (24.5%)	70 (29.2%)
Sub-threshold Depression	26 (14.1%)	2 (3.6%)	17 (13.1%)	11 (10%)	28 (11.7%)
Threshold Anxiety	31 (16.8%)	2 (3.6%)	24 (18.5%)	9 (8.2%)	33 (13.8%)
Sub-threshold Anxiety	53 (28.6%)	8 (14.5%)	37 (28.5%)	24 (21.8%)	61 (25.4%)
Threshold Externalizing	38 (20.5%)	0 (0%)	15 (11.5%)	23 (20.9%)	38 (15.8%)
Sub-threshold Externalizing	33 (17.8%)	3 (5.5%)	19 (14.6%)	17 (15.5%)	36 (15.0%)
Combined (sub-or threshold) Substance Abuse/Dependence	47 (25.4%)	3 (5.5%)	22 (16.9%)	28 (25.5%)	50 (20.8%)

Table 2

Series of fitted main-effects logistic regression models examining the temporal relations between depression, anxiety, externalizing, and substance use disorders, controlling for child sex and risk.

1.	2. Prior Psychopathology	3.	4.	5. High-Risk	6.	7. Female	8.	9. Outcome
Model		OR	95% CI	OR	95% CI	OR	95% CI	
M1	Threshold Anxiety	1.12	.45–2.78	15.06***	3.54–63.95	1.45	.80–2.64	Threshold Depression
M2	Threshold Anxiety	1.01	.41–2.46	9.47***	2.83–31.69	1.54	.85–2.80	Subthreshold Depression
M3	Subthreshold Anxiety	1.38	.74–2.59	14.59***	3.43–61.98	1.43	.79–2.61	Threshold Depression
M4	Subthreshold Anxiety	.61	.30–1.22	10.04***	3.00–33.64	1.63	.89–2.97	Subthreshold Depression
M5	Threshold Depression	.59	.24–1.47	5.81*	1.33–25.71	2.49*	1.09–5.68	Threshold Anxiety
M6	Threshold Depression	.49~	.22–1.06	3.81***	1.73–8.41	2.00*	1.14–3.53	Subthreshold Anxiety
M7	Subthreshold Depression	.57	.23–1.42	5.82*	1.33–25.58	2.57*	1.12–5.86	Threshold Anxiety
M8	Subthreshold Depression	.85	.43–1.67	3.48*	1.57–7.72	1.97*	1.12–3.46	Subthreshold Anxiety
M9	Threshold Externalizing	.96	.38–2.45	15.28***	3.59–65.06	1.45	.79–2.68	Threshold Depression
M10	Threshold Externalizing	.95	.40–2.29	9.54***	2.84–31.99	1.54	.84–2.79	Subthreshold Depression
M11	Subthreshold Externalizing	2.07*	1.05–4.11	12.90***	3.01–55.18	1.72~	.92–3.22	Threshold Depression
M12	Subthreshold Externalizing	1.18	.60–2.32	9.12***	2.71–30.70	1.57	.86–2.85	Subthreshold Depression
M13	Threshold Depression	1.00	.45–2.23	~a	~a	.44*	.21–.91	Threshold Externalizing
M14	Threshold Depression	.81	.39–1.72	10.92***	.23–36.93	.49*	.27–.88	Subthreshold Externalizing
M15	Subthreshold Depression	.71	.31–1.64	~a	~a	.44*	.21–.92	Threshold Externalizing
M16	Subthreshold Depression	.65	.30–1.37	11.38***	3.36–38.54	.49*	.27–.88	Subthreshold Externalizing
M17	Substance Use Disorder	1.05	.45–2.45	15.13***	3.56–64.28	1.47	.81–2.66	Threshold Depression
M18	Substance Use Disorder	.65	.29–1.46	10.08***	3.01–33.77	1.50	.83–2.73	Subthreshold Depression
M19	Threshold Depression	1.81~	.90–3.64	5.25**	1.53–18.05	.53~	.28–1.02	Substance Use Disorder
M20	Subthreshold Depression	.64	.30–1.37	6.97*	2.04–23.80	.56~	.29–1.06	Substance Use Disorder

OR=Odds Ratio; CI=Confidence Interval

~ $p < .10$

* $p < .05$

100
**
 $p < .d$

d = not able to calculate due to small cell size