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Co-morbidity between major depressive disorder and anxiety disorders: shared etiology or direct causation?

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Abstract

Background—Major depressive disorder (MDD) and anxiety disorders (ANX) are debilitating and prevalent conditions that often co-occur in adolescence and young adulthood. The leading theoretical models of their co-morbidity include the direct causation model and the shared etiology model. The present study compared these etiological models of MDD–ANX co-morbidity in a large, prospective, non-clinical sample of adolescents tracked through age 30.

Method—Logistic regression was used to examine cross-sectional associations between ANX and MDD at Time 1 (T1). In prospective analyses, Cox proportional hazards models were used to examine T1 predictors of subsequent disorder onset, including risk factors specific to each disorder or common to both disorders. Prospective predictive effect of a lifetime history of one disorder (e.g. MDD) on the subsequent onset of the second disorder (e.g. ANX) was then examined. This step was repeated while controlling for common risk factors.

Results—The findings supported relatively distinct profiles of risk between MDD and ANX depending on order of development. Whereas the shared etiology model best explained co-morbid cases in which MDD preceded ANX, direct causation was supported for co-morbid cases in which ANX preceded MDD.

Conclusions—Consistent with previous research, significant cross-sectional and prospective associations were found between MDD and ANX. The results of the present study suggest that different etiological models may characterize the co-morbidity between MDD and ANX based upon the temporal order of onset. Implications for classification and prevention efforts are discussed.

Keywords

Anxiety; co-morbidity; depression; etiology

Introduction

Major depressive disorder (MDD) and anxiety disorders (ANX) are common and highly co-morbid disorders (e.g. Maser & Cloninger, 1990; Lewinsohn *et al.* 1993; Merikangas *et al.* 1998; Mineka *et al.* 1998; Angold *et al.* 1999; Kessler *et al.* 2003). Research data have indicated a lifetime prevalence rate of 16.2% for MDD (Kessler *et al.* 2003) and 28.8% for ANX (Kessler *et al.* 2005). Fifty-nine percent of adults with lifetime MDD also met criteria for lifetime ANX (Kessler *et al.* 2003). Whereas MDD onset is spread across adolescence and early adulthood (interquartile range from ages 18–43; Kessler *et al.* 2005), ANX onset tends to be concentrated in a narrow developmental span characterized by an interquartile range from ages 6–20 (Kessler *et al.* 2005).

Several studies have called for greater specificity of the conceptualization of anxiety disorders (e.g. Widiger & Clark, 2000; Merikangas *et al.* 2003). Empirical work supports the division of anxiety disorders into fear and distress conditions (Watson, 2005). Although MDD has shown substantial comorbidity with anxiety disorders in both conditions, this overlap is particularly noted with regard to the distress condition of generalized anxiety disorder (GAD; e.g. Moffitt *et al.* 2007; Kessler *et al.* 2008).

Compared to non-co-morbid presentations of the disorders, co-morbid MDD–ANX is associated with greater symptom severity (Coryell *et al.* 1988; Mitchell *et al.* 1988; Bernstein, 1991), higher rates of suicidal behavior (Reich *et al.* 1993; Lewinsohn *et al.* 1995; Rohde *et al.* 2001), higher rates of mental health treatment utilization but poorer treatment response (Lewinsohn *et al.* 1995; Brent *et al.* 1998; Emslie *et al.* 1998), higher medical costs (Marciniak *et al.* 2005), and an increased risk of recurrence (Emslie *et al.* 1998). Given the high level of overlap between MDD and ANX, and the severe impairment and cost incurred by their co-morbidity, understanding the development of co-morbid MDD–ANX represents a pressing need. The primary aim of the present study was to address that need by evaluating models of their co-morbidity among adolescents and young adults.

Theory-driven models of co-morbidity

Two theoretical models of co-morbidity between ANX and MDD that have received considerable research attention are direct causation and shared etiology. The direct causation model states that one disorder causes or lowers the threshold for the expression of the other disorder (Avenevoli *et al.* 2001). To date, evidence indicates that ANX often temporally precedes MDD (Kovacs *et al.* 1989; Alloy *et al.* 1990; Hagnell & Grasbeck, 1990; Regier *et al.* 1990; Breslau *et al.* 1995; Wittchen, 1998; Breslau *et al.* 2000; Merikangas *et al.* 2003) and predicts the course of MDD (Sanford *et al.* 1995), leading some to suggest that ANX may play a causal role in the development of MDD (Brady & Kendall, 1992). However, it is not yet clear whether the relationship is causal or explained by other factors.

The shared etiology model, also referred to as the correlated liabilities model (Neale & Kendler, 1995), posits that a common set of risk factors leads to the development of both MDD and ANX. Research has shown that MDD and ANX share several putative risk factors, such as severely stressful life events (Finlay-Jones & Brown, 1981; Miller & Ingham, 1983; Brown, 1993; Brown & Harris, 1993; Cicchetti & Toth, 1998; D’Imperio *et al.* 2000), socio-economic disadvantage, non-intact family structure, family dysfunction, and peer problems (see Shanahan *et al.* 2008 for review). Parental psychiatric disorders also have been implicated (e.g. Turner *et al.* 1987; Puig-Antich *et al.* 1989; Last *et al.* 1991; Harrington *et al.* 1993; Kovacs *et al.* 1997; Klein *et al.* 2003). Thus, it is possible that common risk factors may account for a substantial proportion of the co-occurrence of MDD and ANX.

Risk factors for MDD

Numerous risk factors for MDD have been identified. Multiple indicators of poor interpersonal functioning have been linked to elevated risk of MDD, including low family social support (Lewinsohn *et al.* 1994, 1998; Bond *et al.* 2001), loneliness (Joiner *et al.* 2002), and emotional reliance or interpersonal dependence (Lewinsohn *et al.* 1995). Certain cognitive variables have also been shown to enhance risk of MDD, such as low self-esteem (Brown *et al.* 1986) and negative attributional style (Abramson *et al.* 1989; Lewinsohn *et al.* 1994, 1998). Additionally, the presence of other psychiatric conditions, such as subthreshold depressive symptoms (Judd *et al.* 1996, 1998; Lewinsohn *et al.* 1998, 2003; Pine *et al.* 1998), alcohol abuse (Kandel *et al.* 1997; Armstrong & Costello, 2002) and drug use (Brook *et al.* 2002), predicts MDD onset. Finally, status variables such as female gender and a single-parent home, in addition to stressful events and academic problems, represent risk factors for MDD (Andrews & Lewinsohn, 1992; Lewinsohn *et al.* 1993, 1998).

Risk factors for ANX

Risk factors for ANX overlap considerably with those for MDD, and include female gender, stressful events and poor interpersonal functioning (Coie *et al.* 1992; Panak & Garber, 1992; Keiley *et al.* 2003; Kessler *et al.* 2005). Cigarette smoking and subthreshold symptoms of anxiety constitute additional risks (Lewinsohn *et al.* 1997; Armstrong & Costello, 2002; Klein *et al.* 2003). A cognitive factor that may predict the development of ANX is tendency to worry (Roemer & Borkovec, 1993).

Current study

In summary, there is preliminary support for both theoretical models of the co-morbidity between MDD and ANX. Nevertheless, prior work has often failed to consider a range of risk factors for MDD and ANX and to examine both models within the same study. The current study extends findings by Olinio *et al.* (2010) on the longitudinal associations between anxiety and depressive disorders by examining theoretical models of co-morbidity in a large, non-clinical sample of adolescents who were tracked through age 30.

Method

Participants

Participants were drawn from the Oregon Adolescent Depression Project (OADP). OADP probands were randomly selected from nine high schools in western Oregon. A total of 1709 adolescents (ages 14–18 years, mean = 16.6, *s.d.* = 1.2) completed an initial (T1) assessment between 1987 and 1989. Approximately 1 year later, 1507 (88%) returned for a second evaluation (T2). Differences between the sample and the larger population from which it was selected, and between participants and those who declined to participate or dropped out of the study before T2, were small (Lewinsohn *et al.* 1993). At age 24, all probands with a history of psychopathology (*n* = 644) by T2 and a random sample with no history of psychopathology (*n* = 457) were invited to participate in a third (T3) evaluation. Of the 1101 T2 participants selected for a T3 interview, 941 (85%) completed the age 24 evaluation. The T2 diagnostic groups did not differ on the rate of participation at T3. Lastly, at age 30, all T3 participants were invited to participate in a T4 evaluation. Of the 941 T3 participants, 816 (87%) completed the T4 interview. The 816 T4 participants included 484 (59%) women. Among those invited to the T3 and T4 assessments, women were more likely than men to complete evaluations ($\chi^2 > 5.99$, $p < 0.05$). Participation did not differ as a function of other demographic variables or previous diagnoses.

The reference sample for the current investigation included the 1507 probands who completed T1 and at least one follow-up assessment.

Diagnostic interviews

Participants were interviewed with a version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) at T1, T2 and T3. The version of the K-SADS used combined features of the Present Episode and Epidemiologic versions (Orvaschel *et al.* 1982; Chambers *et al.* 1985). In conjunction with the K-SADS, the Longitudinal Interval Follow-Up Evaluation (LIFE; Keller *et al.* 1987) was used to evaluate the presence and course of disorders since participation in the previous diagnostic interview. T4 diagnostic assessments were based on the Structured Clinical Interview for Axis I DSM-IV Disorders – Non-Patient Edition (SCID-NP; First *et al.* 1995), with the LIFE also used to evaluate disorder presence and course since T3. Symptom endorsements during these interviews were subsequently evaluated in conjunction with DSM-III-R criteria (APA, 1987) at T1 and T2 and DSM-IV criteria (APA, 1994) at T3 and T4. Interviews at T3 and T4 were conducted by telephone, which generally provides comparable validity to face-to-face interviews (Sobin *et al.* 1993; Rohde *et al.* 1997).

T1 diagnostic status—Two dichotomously coded variables were created to reflect lifetime ANX and lifetime MDD. In addition, two dichotomously coded variables were created to reflect lifetime alcohol use disorder and any lifetime substance use disorder (excluding alcohol).

T1 lifetime subthreshold depression and anxiety—Subthreshold diagnoses were coded dichotomously and assigned according to the definitions from Lewinsohn *et al.* (2004) and Shankman *et al.* (2008). Subthreshold depression was defined as an episode of depressed mood or loss of interest or pleasure lasting at least 1 week, plus at least two of the seven associated symptoms (yielding a total of at least three symptoms). Probands could not have subthreshold depression if they previously met criteria for dysthymic disorder or bipolar disorder. Subthreshold anxiety was defined as the presence of at least three anxiety symptoms across the following anxiety disorders: panic disorder, agoraphobia without a history of panic, social phobia, simple phobia, obsessive–compulsive disorder (OCD), separation anxiety (SA), overanxious disorder (OD), acute stress disorder, GAD and post-traumatic stress disorder (PTSD). Probands could not have subthreshold anxiety if they previously met criteria for any anxiety disorder.

T1 psychosocial measures

The following psychosocial measures were selected based on their theoretical relevance to ANX, MDD, or both.

Family social support—Eight continuously scored items were specified as loading on a latent Family Social Support construct. The model provided an acceptable to excellent fit on the basis of the model error index [root mean square error of approximation (RMSEA) = 0.05] and fit indices [Comparative Fit Index (CFI) = 0.99, Tucker–Lewis Index (TLI) = 0.99]. Internal consistency was adequate ($\alpha = 0.77$).

Friend social support—Seven continuously scored items were specified as loading on a latent Friend Social Support construct. The model provided a good to excellent fit (RMSEA = 0.04, CFI = 0.98, TLI = 0.96) and internal consistency was adequate ($\alpha = 0.72$).

Dysfunctional attitudes—Nine items from the Dysfunctional Attitudes Scale (DAS; Weissman & Beck, 1978) measured the tendency to generalize from specific bad outcomes to a sense of negative self-worth. The measure demonstrated acceptable internal consistency ($\alpha = 0.74$).

Worry—The tendency to worry was assessed with five items drawn from the Minnesota Multiphasic Personality Inventory (Hathaway & McKinley, 1943) and the Maudsley Obsessional Compulsive Inventory (Hodgson & Rachman, 1977). The measure demonstrated acceptable internal consistency ($\alpha = 0.69$).

Loneliness—Loneliness was assessed with an eight-item scale adapted from the UCLA Loneliness Scale (Roberts *et al.* 1993), which measures feelings of solitude, disconnection and lack of closeness. Acceptable internal consistency ($\alpha = 0.78$) was demonstrated.

Emotional reliance—Excessive emotional reliance was assessed with 10 items of the extent to which the individual desires excessive support and approval from others, is anxious about being alone or abandoned, and is interpersonally sensitive (Emotional Reliance Scale; Hirschfeld *et al.* 1976). The measure demonstrated good internal consistency ($\alpha = 0.83$).

Self-esteem—Self-esteem was assessed with three items on satisfaction with specific body parts (Body Parts Satisfaction Scale; Berscheid *et al.* 1973), three items on general satisfaction with physical appearance (Physical Appearance Evaluation subscale; Winstead & Cash, 1984), and three items on self esteem (Self-Esteem Scale; Rosenberg, 1965). The measure demonstrated acceptable internal consistency ($\alpha = 0.81$).

Analytic strategy

Logistic regression was used to examine T1 cross-sectional associations between ANX and MDD, and also associations between theoretically derived risk factors and lifetime history of MDD or ANX. Each risk factor was significantly associated with MDD, ANX, or both at T1, and was therefore retained for prospective analyses (results available upon request to first author). In prospective analyses, we first examined the prospective relationships between the T1 risk factors and the subsequent onsets of MDD and ANX. Risk factors that predicted only MDD or ANX were considered ‘specific’, whereas those that predicted both conditions were considered ‘common’. Next, we examined the prospective predictive effect of a T1 lifetime history of one disorder (e.g. MDD) on the subsequent onset of the second disorder (e.g. ANX). This step was then repeated while controlling for common risk factors identified in step 1. Our rationale was that, if the predictive effect of one disorder on the other decreased to non-significance after controlling for common risk factors, then a shared etiology model would be supported (i.e. the relationship between MDD and ANX is explained by the presence of risk factors common to each disorder). If the predictive effect of one disorder on the other remained statistically significant after controlling for common risk factors, then a direct causation model would be supported (i.e. one disorder temporally precedes the other and the relationship is not spurious; Garber & Hollon, 1991). Based on prior research, we expected to find bidirectional predictive effects between MDD and ANX, and that these effects would decrease to non-significance after controlling for common risk factors.

Cox proportional hazards models were used to examine T1 predictors of subsequent disorder onset. Cox models take into account the onset of a disorder and the time to onset. Cox models appropriately handle information from censored cases, or those individuals who did not develop MDD or ANX over the course of the study. The probability of developing a disorder was expressed as a hazard ratio (HR) with a 95% confidence interval (CI). An interval variable representing time was created by computing (a) the number of months from the first assessment wave to disorder onset or (b) the number of months from the first assessment wave to the final assessment wave among those who did not develop a disorder. The diagnostic status for each disorder was coded dichotomously. All non-binary predictor variables were standardized prior to analysis so that HRs indicate the change in risk for one

standard deviation of the predictor. The proportional hazards assumption was tested in each model by including a time $\times$ predictor interaction term. When the proportional hazards assumption was not met, the predictor, time variable, and the time $\times$ predictor interaction term were retained in the model (Tabachnick & Fidell, 2001). As measures of standardized effect size, we used odds ratios (ORs) for logistic regression models and generalized R^2 for Cox proportional hazards models (O'Quigley *et al.* 2005). In addition to examining the statistical significance of predictors before and after controlling for common risk factors, we also calculated the percentage change in HR (Batty *et al.* 2006).

Given the stratified sampling procedure used at T3, weights reflecting the probability of selection for the T3 follow-up were used in analyses. Cox proportional hazards models including the weighting variable were run in Mplus, version 5 (Muthén & Muthén, 1998–2007). Missing data were modeled using maximum likelihood estimation.

Results

We first examined cross-sectional associations between the disorders at T1 in the entire sample ($n = 1507$; Table 1). As expected, the association between MDD and ANX at T1 was statistically significant when examining lifetime diagnostic status ($n = 1507$, OR 4.71, 95% CI 3.31–6.71) and current diagnostic status ($n = 1507$, OR 7.94, 95% CI 3.11–20.24).

Prospective predictors of disorder onset

MDD—The reference sample for predicting MDD onset (comorbid or non-co-morbid) included 1222 participants (602 women) with no lifetime history of MDD at T1. Of these, 309 (25.29%) developed MDD by the final assessment in which they participated. Significant univariate predictors of MDD were female gender, family social support, friend social support, negative attributional style, worry, subthreshold depression, loneliness, and emotional reliance (Table 2).

ANX—The reference sample for predicting ANX onset (co-morbid or non-co-morbid) included 1358 participants (700 women) with no lifetime history of ANX at T1. Of these, 109 (8.03%) developed ANX by the final assessment in which they participated. Significant univariate predictors of ANX were female gender, family social support, friend social support, worry, self-esteem, loneliness, and emotional reliance (Table 2).

From the preceding sets of analyses, common predictors of MDD and ANX were female gender, family social support, friend social support, worry, loneliness, and emotional reliance. Higher levels of negative attributional style and subthreshold depression were specific predictors of MDD whereas lower self-esteem was a specific predictor of ANX.

Dimensions of ANX—Secondary analyses were conducted with anxiety disorders divided into fear and distress disorders (Watson, 2005). Fear disorders were defined as any form of lifetime panic disorder (with or without agoraphobia) or any form of lifetime phobia disorder (specific phobia, social phobia, or agoraphobia). Of the 1450 participants with no history of these conditions at T1 (767 women), 82 (4.99%) developed a fear disorder while in the study. Significant predictors of fear disorders were female gender, family social support, friend social support, worry, substance abuse/dependence, number of parents in the home, self-esteem, loneliness, and emotional reliance (Table 3).

Models were then run for distress disorders. Distress disorders were defined as lifetime GAD, PTSD, OCD, OD or SA[†]. Of those 1426 participants (751 women) with no identified history of a distress disorder at T1, 60 (4.21%) developed a distress disorder while in the

study. Significant predictors of distress disorders were female gender, friend social support, worry, and loneliness (Table 3).

Prospective relationships between MDD and ANX

In the total sample ($n = 1507$), 207 participants met lifetime criteria for both MDD and ANX by the final assessment wave in which they participated. Of these, 125 (61.88%) developed ANX prior to MDD, with a mean time of 8.41 years from ANX onset to MDD onset. Seventy-four (36.63%) developed MDD prior to ANX, with a mean time of 6.04 years from MDD onset to ANX onset. Eight participants (3.96%) reported simultaneous MDD and ANX onsets.

T1 ANX predicting MDD onset—Lifetime ANX at T1 was examined as a prospective predictor of MDD onset by the final assessment. As expected, T1 ANX significantly predicted the onset of MDD in those with no history of MDD at T1 ($n = 1222$, HR 2.32, 95% CI 1.70–3.16). When common predictors were added, T1 ANX (HR 1.94, 95% CI 1.42–2.67), gender (HR 0.55, 95% CI 0.43–0.70) and emotional reliance (HR 1.19, 95% CI 1.05–1.35) remained significant predictors of MDD onset. All other predictors decreased to non-significance. The addition of common predictors led to a 40.43% reduction in the T1 ANX HR for MDD.

Analyses were then run separately examining fear and distress disorders as predictors of MDD onset. Fear ($n = 1222$, HR 1.76, 95% CI 1.05–2.97) and distress disorders ($n = 1222$, HR 2.75, 95% CI 1.85–4.08) were each significant univariate predictors of MDD onset in those with no history of MDD at T1. When common predictors were included, fear disorders decreased to non-significance whereas female gender and emotional reliance remained significant predictors of MDD. Distress disorders remained significant, along with female gender and emotional reliance, as a multivariate predictor of MDD (Table 4).

T1 MDD predicting ANX onset—T1 MDD significantly predicted the onset of ANX in those with no history of ANX at T1 ($n = 1358$, HR 1.81, 95% CI 1.21–2.70). When common predictors were added, female gender remained the only significant predictor of ANX onset whereas T1 MDD and all other predictors decreased to non-significance (Table 4). The addition of common predictors led to a 74.07% reduction in the T1 MDD HR for ANX.

Analyses were also run separately with MDD as a predictor of fear and distress disorders. T1 MDD was a significant predictor of fear disorder onset in those with no history of fear disorders at T1 ($n = 1428$, HR 1.95, 95% CI 1.23–3.08). T1 MDD was also a significant predictor of distress disorder onset in those with no history of distress disorders at T1 ($n = 1408$, HR 1.79, 95% CI 1.05–3.07). Each of these relationships decreased to non-significance when common predictors were added. Female gender and loneliness remained significant predictors of fear disorders and there were no significant multivariate predictors of distress disorders (Table 4).

Discussion

Consistent with expectations and prior research, significant cross-sectional and prospective associations were found between MDD and ANX. A combination of shared and distinct risk factors best explained the development of MDD and ANX over time. Attributional style and subthreshold MDD were identified as specific risk factors for MDD. Low self-esteem

[†]Models were run with both the more inclusive (GAD, PTSD, OCD, OD, SA) and the less inclusive (GAD, PTSD, OCD) distress conditions and the findings did not differ meaningfully.

specifically predicted ANX. Finally, female gender, family social support, friend social support, worry, loneliness, and emotional reliance were identified as predictors common to MDD and ANX.

The results of the present study suggest that different etiological models may characterize the comorbidity between MDD and ANX based upon the temporal order of onset. T1 ANX remained a significant predictor of subsequent MDD onset, even after controlling for common risk factors. This is consistent with previous research, which has generally supported the temporal precedence of and predictive relationship from ANX to MDD (Kendell, 1974; Reinherz *et al.* 1989; Angst *et al.* 1990; Orvaschel *et al.* 1995; Pine *et al.* 1998). Furthermore, it extends prior work by demonstrating that the predictive effect of ANX on later MDD was not spurious, or entirely accounted for by other variables in this study. It should be noted, however, that the addition of common risk factors did lead to a 40% reduction in the HR for MDD onset. By contrast, T1 MDD did not continue to significantly predict subsequent ANX onset when common predictors were included in analyses, and the addition of common risk factors led to a 74% reduction in the HR for ANX onset. Thus, temporal precedence and a significant association were found, but the association between MDD and later ANX was due to the presence of common risk factors. This is most consistent with a shared etiological path from MDD to the development of ANX.

Interesting findings emerged with regard to cognitive, interpersonal and psychopathological risk factors for disorder onset. First, although worry is commonly viewed as a risk factor for or a symptom of anxiety disorders, the present findings indicated that worry in adolescence conferred prospective risk for both ANX and MDD. This is consistent with a large body of work indicating substantial overlap between MDD and GAD (Kendler *et al.* 1992; Brawman-Mintzer *et al.* 1993; Wittchen *et al.* 1994; Carter *et al.* 2001). Second, the cognitive factor of negative attributional style was shown to be a specific predictor of MDD. This finding is consistent with the reformulated model of learned helplessness (Abramson *et al.* 1978), which hypothesizes negative attributional style to relate specifically to MDD and not to other emotional disorders. Third, poor interpersonal functioning in adolescence, including loneliness, emotional reliance and impaired relationships with family and peers, conferred risk for both MDD and ANX. This finding suggests that poor interpersonal functioning is not specifically associated with the development of MDD, but may reflect the joint presence of social anxiety and mood disturbance. Finally, prior work has found that subthreshold depressive symptoms increase the risk of MDD (Broadhead *et al.* 1990; Lewinsohn *et al.* 2000; Fergusson *et al.* 2005). The present findings were consistent with that research and further indicated that subthreshold depression was a specific risk for MDD.

Interesting findings also emerged with regard to the separate dimensions of ANX. Whereas risk factors for the distress disorders were common to MDD and ANX, two risk factors for fear disorder onset were specific. Consistent with research on the correlates of panic disorder (e.g. Zvolensky *et al.* 2006), substance use was found to specifically predict fear disorders. Additionally, a lower number of parents in the home also specifically predicted fear disorders.

The current study has several strengths. The use of a large non-clinical sample increases confidence in the external validity of the results. The study also incorporated reliable diagnostic procedures using criteria from DSM-III-R and DSM-IV and repeated assessments with a follow-up period of approximately 15 years, providing an opportunity to carefully document the onset and course of psychiatric conditions. Finally, the study assessed an array of psychosocial variables, which permitted analysis of common and specific risk factors for the disorders.

Limitations should also be noted. Despite the large sample, there were fewer cases of ANX than in other community samples, and therefore low statistical power to detect predictive effects for ANX. Although this is a limitation, it also suggests that new onset of ANX after mid-adolescence is rare. As a consequence of this limitation, we were unable to examine anxiety disorders by specific diagnoses, even though anxiety disorders may differ based on onset age. Our analyses of ANX by fear and distress conditions may also have been limited by the DSM-III-R criteria used in the T1 assessments. Although the diagnostic criteria for some anxiety disorders were modified in the DSM-IV, very high rates of agreement have been found between anxiety disorders diagnosed using the two sets of criteria (Kendall & Warman, 1996). An additional limitation is that temperament (e.g. neuroticism or negative affect; Mineka *et al.* 1998) was not examined as a common risk factor, although the psychosocial risk factors included in this study probably correlate meaningfully with temperament (e.g. Prenoveau *et al.* 2009).

The age range of the sample was also limited in that it did not extend past 30 years and information for some participants may not be complete because of different follow-up periods. As new cases of psychiatric disorders, particularly MDD, may develop after early adulthood (Kessler *et al.* 2005), it is recommended that prospective studies examine MDD and ANX into later development periods. A final limitation is that a relatively high number of analyses were run without correcting for inflated error rate. This analytic strategy was adopted to balance concerns of Type I and Type II errors, given the low statistical power to detect effects in some analyses.

Clinical implications of the present study are most relevant to prevention efforts. The support for a possible causal link from ANX to MDD suggests that successful prevention of and intervention for ANX in youth may prevent the development of MDD (see Kessler & Price, 1993). These findings therefore underscore the importance of efficacious prevention and early intervention efforts for anxiety (see Rapee, 2002; Barrett & Farrell, 2009). Furthermore, because the prospective predictive effect of MDD on later ANX decreased to non-significance after accounting for female gender, adolescent girls may represent a particularly at-risk population for intervention efforts.

In summary, the results of the present study supported different etiological models of MDD–ANX comorbidity depending on which condition developed first. The path from ANX to later MDD is most consistent with a direct causation model, whereas the path from MDD to later ANX is most consistent with a shared etiology model. Future research is encouraged to cross-validate these findings in samples with greater economic and ethnic diversity, and also with a higher prevalence of ANX.

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Table 1
Prevalence of MDD and ANX by T1 and at any point in the study after T1

	T1	Any point in study after T1
MDD	285 (18.9)	594 (39.4)
Non-co-morbid MDD	215 (14.3)	389 (25.8)
ANX	149 (9.9)	258 (17.1)
Non-co-morbid ANX	66 (4.4)	53 (3.5)
Fear disorders	65 (4.3)	147 (9.8)
Distress disorders	92 (6.1)	152 (10.1)
Co-morbid MDD–ANX	58 (3.8)	205 (13.6)
MDD – Fear	29 (1.9)	113 (7.5)
MDD – Distress	40 (2.7)	116 (7.7)

Values given as *n* (%).

Table 2
T1 bivariate predictors of MDD and ANX

	MDD HR (95% CI)	Generalized R^2	ANX HR (95% CI)	Generalized R^2
Male gender	0.51 ** (0.40–0.64)	0.1039	0.40 ** (0.26–0.62)	0.1573
Academic problems	1.07 (0.97–1.20)	0.0053	1.18 (0.99–1.41)	0.0281
Family social support	1.14 * (1.02–1.27)	0.0176	1.28 ** (1.08–1.53)	0.0657
Friend social support	1.21 ** (1.08–1.35)	0.0311	1.47 ** (1.23–1.77)	0.1458
Negative attributional style	1.14 * (1.02–1.28)	0.0145	1.08 (0.90–1.30)	0.0052
Worry	1.27 ** (1.14–1.42)	0.0540	1.46 ** (1.21–1.76)	0.1408
Subthreshold depression	1.63 ** (1.30–2.04)	0.0585	1.18 (0.79–1.77)	0.0057
Subthreshold anxiety	1.18 (0.91–1.54)	0.0049	1.23 (0.82–1.85)	0.0088
Alcohol abuse/dependence	1.42 (0.84–2.38)	0.0057	1.64 (0.83–3.24)	0.0186
Substance abuse/dependence	1.16 (0.77–1.77)	0.0016	1.69 (0.99–2.87)	0.0345
Cigarette smoking	1.46 (0.99–2.15)	0.0119	1.14 (0.61–2.13)	0.0016
Number of parents in home	0.83 (0.68–1.01)	0.0115	0.79 (0.58–1.07)	0.0212
Self-esteem	0.92 (0.82–1.02)	0.0098	0.77 ** (0.65–0.92)	0.0721
Loneliness	1.21 ** (1.08–1.36)	0.0337	1.42 ** (1.19–1.68)	0.1408
Emotional reliance	1.30 ** (1.17–1.45)	0.0693	1.35 ** (1.13–1.61)	0.0840

HR, Hazard ratio; CI, confidence interval.

*
 $p < 0.05$

**
 $p < 0.01$.

Table 3
T1 bivariate predictors of fear and distress disorders

	Fear HR (95% CI)	Generalized R^2	Distress HR (95% CI)	Generalized R^2
Male gender	0.28 ** (0.16–0.48)	0.2717	0.46 ** (0.27–0.79)	0.1154
Academic problems	1.20 (0.98–1.47)	0.0360	1.01 (0.78–1.29)	0.0049
Family social support	1.36 ** (1.12–1.66)	0.1188	1.22 (0.97–1.55)	0.0329
Friend social support	1.36 ** (1.10–1.68)	0.0858	1.54 ** (1.22–1.96)	0.1697
Negative attributional style	1.02 (0.82–1.26)	0.0003	1.30 (1.03–1.66)	0.0520
Worry	1.48 ** (1.19–1.84)	0.1663	1.35 * (1.05–1.74)	0.0835
Subthreshold depression	0.97 (0.60–1.55)	0.0002	1.17 (0.71–1.93)	0.0055
Subthreshold anxiety	1.20 (0.75–1.93)	0.0065	0.94 (0.54–1.62)	0.0008
Alcohol abuse/dependence	2.06 (0.99–4.27)	0.0456	1.66 (0.72–3.84)	0.0205
Substance abuse/dependence	2.71 ** (1.59–4.62)	0.1591	1.58 (0.81–3.08)	0.0255
Cigarette smoking	1.80 (0.97–3.31)	0.0422	1.50 (0.74–3.01)	0.0183
Number of parents in home	0.69 * (0.49–0.98)	0.0502	0.89 (0.60–1.33)	0.0047
Self-esteem	0.72 ** (0.60–0.87)	0.1411	0.86 (0.67–1.10)	0.0148
Loneliness	1.53 ** (1.26–1.86)	0.2019	1.40 ** (1.12–1.76)	0.1303
Emotional reliance	1.49 ** (1.21–1.82)	0.1741	1.20 (0.94–1.53)	0.0521

HR, Hazard ratio ; CI, confidence interval.

*
 $p < 0.05$

**
 $p < 0.01$.

Table 4
Multivariate prospective associations between MDD and ANX

	ANX	Fear	Distress
T1 MDD predicting ANX onset			
T1 MDD	1.21 (0.79–1.86)	1.20 (0.73–1.96)	1.34 (0.75–2.40)
Male gender	0.45 ** (0.29–0.70)	0.30 ** (0.17–0.52)	0.63 (0.36–1.10)
Family social support	1.06 (0.87–1.29)	1.12 (0.89–1.40)	1.05 (0.81–1.36)
Friend social support	1.17 (0.85–1.61)	0.73 (0.51–1.03)	1.53 (0.97–2.39)
Worry	1.16 (0.93–1.45)	1.04 (0.80–1.36)	1.10 (0.82–1.50)
Loneliness	1.14 (0.84–1.55)	1.73 ** (1.24–2.39)	0.94 (0.61–1.46)
Emotional reliance	1.08 (0.88–1.32)	1.25 (0.99–1.57)	0.95 (0.72–1.26)
MDD			
T1 ANX predicting MDD onset			
T1 ANX	1.94 ** (1.42–2.67)		
Male gender	0.55 ** (0.43–0.70)		
Family social support	1.06 (0.94–1.20)		
Friend social support	1.04 (0.86–1.25)		
Worry	1.06 (0.93–1.21)		
Loneliness	1.08 (0.89–1.32)		
Emotional reliance	1.17 * (1.04–1.33)		
T1 Fear predicting MDD onset			
T1 Fear	1.42 (0.84–2.40)		
Male gender	0.53 ** (0.42–0.67)		
Family social support	1.05 (0.93–1.18)		
Friend social support	1.02 (0.84–1.23)		
Worry	1.08 (0.94–1.23)		
Loneliness	1.10 (0.90–1.34)		
Emotional reliance	1.19 ** (1.05–1.35)		
T1 Distress predicting MDD onset			
T1 Distress	2.37 ** (1.59–3.55)		
Male gender	0.54 ** (0.42–0.68)		
Family social support	1.06 (0.94–1.20)		
Friend social support	1.02 (0.84–1.23)		
Worry	1.06 (0.92–1.21)		
Loneliness	1.12 (0.92–1.36)		
Emotional reliance	1.18 ** (1.04–1.33)		

Vales given as hazard ratio (95% confidence interval).

*
 $p < 0.05$

**
 $p < 0.01$.