What Characteristics of Primary Anxiety Disorders Predict Subsequent Major Depressive Disorder?

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Objective: The goal of this study was to examine the associations between specific anxiety disorders and the risk of major depressive disorder and to explore the role of various clinical characteristics of anxiety disorders in these relationships using a prospective, longitudinal design.

Method: The data are from a 4-year prospective, longitudinal community study, which included both baseline and follow-up survey data on 2548 adolescents and young adults aged 14 to 24 years at baseline. DSM-IV diagnoses were made using the Munich-Composite International Diagnostic Interview.

Results: The presence at baseline of any anxiety disorder (odds ratio [OR] = 2.2 [95% CI = 1.6 to 3.2]) and each of the anxiety disorders (specific phobia, OR = 1.9 [95% CI = 1.3 to 2.8]; social phobia, OR = 2.9 [95% CI = 1.7 to 4.8]; agoraphobia, OR = 3.1 [95% CI = 1.4 to 6.7]; panic disorder, OR = 3.4 [95% CI = 1.2 to 9.0]; generalized anxiety disorder, OR = 4.5 [95% CI = 1.9 to 10.3]) was associated with a significantly ($p < .05$) increased risk of first onset of major depressive disorder. These associations remained significant after we adjusted for mental disorders occurring prior to the onset of the anxiety disorder, with the exception of the panic disorder association. The following clinical characteristics of anxiety disorders were associated with a significantly ($p < .05$) increased risk of developing major depressive disorder: more than 1 anxiety disorder, severe impairment due to the anxiety disorder, and comorbid panic attacks. In the final model, which included all clinical characteristics, severe impairment remained the only clinical characteristic that was an independent predictor of the development of major depressive disorder (OR = 2.2 [95% CI = 1.0 to 4.4]).

Conclusion: Our findings suggest that anxiety disorders are risk factors for the first onset of major depressive disorder. Although a number of clinical characteristics of anxiety disorders appear to play a role in the association between anxiety disorders and depression, severe impairment is the strongest predictor of major depressive disorder.

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Previous studies using both clinical and population-based samples have consistently shown that anxiety disorders typically begin early in life (during childhood and adolescence), whereas the onset of depressive disorders generally occurs later during young to middle adulthood.[1–3] Numerous findings have demonstrated high rates of comorbidity between anxiety and depressive disorders.[1,4–6] Several cross-sectional studies have reported statistically significant associations between primary anxiety disorders and secondary depressive disorders, suggesting that anxiety disorders increase the risk of subsequent depression.[4,7,8] Recent data from longitudinal studies further show that anxiety disorders co-occur with an increased risk of depression.[9–11] To our knowledge, only 1 longitudinal study has not found a significant association between anxiety disorders (specific and social phobia) in adolescence and major depressive disorder during adulthood.[12]

Although the results of several studies suggest that anxiety disorders increase the risk of subsequent depressive disorders, little is known about the role of clinical characteristics of anxiety disorders in this association.[13]

There is some evidence for a possible key role of panic attacks in the development of psychopathology. For instance, panic attacks are strongly related to the subsequent development of a variety of mental disorders, not just

panic disorder and agoraphobia.[14] Goodwin and Hamilton[15] report nonspecific relations between panic attacks and risk of psychiatric morbidity, and other analyses show that panic attacks act as an independent predictor of major depressive disorder among adults in the community, after adjustment for other anxiety comorbidity.[11] Other findings indicate an association between the level of anxiety disorder morbidity and risk of subsequent mental disorders. Specifically, significant associations have been found between the number of anxiety disorders reported in adolescence and risk of major depressive disorder.[9]

The goal of the current study was to examine the associations between specific anxiety disorders and the risk of major depressive disorder while overcoming the methodological problems of previous studies. Specifically, we used a strictly prospective design to reduce measurement error with regard to the chronological order of development of anxiety disorders and major depressive disorder. As anxiety disorders are frequently comorbid with each other as well as with other mental disorders,[2,6,16,17] we will also examine the effects of anxiety disorders on the onset of major depressive disorder by adjusting for anxiety and other mental disorders occurring prior to the onset of each anxiety disorder in order to reduce bias in causal inference.[18] In addition, we will examine the role of clinical features of anxiety disorders in the risk of the subsequent onset of major depressive disorder by investigating (1) the association between anxiety disorders at baseline, measured both in the aggregate and separately, and the risk of first onset of major depressive disorder during the follow-up period; and (2) the role of clinical characteristics of anxiety disorders at baseline (i.e., number of comorbid anxiety disorders—1 anxiety disorder vs. at least 2 anxiety disorders), DSM-IV panic attacks, and impairment level of anxiety disorder (nonsevere vs. severe) in the risk of major depressive disorder during follow-up.

METHOD

Sample

The data are from the Early Developmental Stages of Psychopathology (EDSP) study. The EDSP study is a prospective longitudinal study designed to collect data on the prevalence, comorbidity, risk factors, and course of mental disorders in a representative sample. The sample consists of 3021 adolescents and young adults aged 14 to 24 years at baseline. The study includes a baseline survey, 2 follow-up surveys, and a family history component. The baseline sample was drawn in 1994 from government registries in metropolitan Munich, Germany. Because the study focuses on the early developmental stages of mental disorders, 14- to 15-year-old individuals were sampled at twice the probability of people aged 16 to 21 years, and 22- to 24-year-old individuals were sampled at half the probability of people aged 16 to 21 years.

At baseline, a total of 3021 interviews were completed (response rate: 70.8%). The first follow-up survey was conducted only for the younger cohort aged 14 to 17 years at baseline, whereas the second follow-up survey was conducted for all subjects. At the first follow-up survey 14 to 25 months after baseline, a total of 1228 interviews were completed, resulting in a response rate of 88%. Of the 3021 subjects who participated in the baseline survey, a total of 2548 took part in the second follow-up survey 33 to 50 months after baseline (response rate: 84.3%). For respondents aged 14 to 17 years at baseline, the complete follow-up status from baseline to second follow-up was assessed from the aggregation of information obtained from the first and second follow-up interviews. For probands older than 17 years at baseline, the complete follow-up status was assessed from the second follow-up questions, which cover the time between baseline and second follow-up. A more detailed description of the study and the demographic characteristics of the sampled population and the respondents have been reported elsewhere.[19,20] Findings presented in this article are based on baseline and follow-up data of 2548 adolescents and young adults aged 14 to 24 years at baseline.

Assessments

Subjects were interviewed with the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI),[21,22] an updated version of the World Health Organization CIDI.[23] The DIA-X/M-CIDI allows for the assessment of symptoms and syndromes and the diagnosis of 48 mental disorders, along with providing information about onset, duration, severity, and psychosocial impairment. The diagnosis of mental disorders discussed in this article was based on the M-CIDI/DSM-IV algorithms. The DIA-X/M-CIDI is supplemented by a separate booklet for respondents that includes disorder-specific questionnaires as well as symptom lists and cognitive aids to assist the respondent in dating symptom onset and recency, answering complicated symptom questions, and identifying course patterns. Test-retest reliability and validity for the full DIA-X/M-CIDI have been reported elsewhere,[24–26] along with descriptions of the DIA-X/M-CIDI format and coding conventions.

Interviewers

A total of 57 clinical interviewers conducted the M-CIDI interviews. Most of the interviewers were clinical psychologists with extensive experience in diagnostic interviewing. At baseline, 25 professional health research interviewers recruited from a survey company (Infratest Gesundheitsforschung, Munich, Germany) were also involved. All interviewers received 1 week of intensive training on the M-CIDI, followed by at least 10 closely monitored practice interviews and additional 1-day booster sessions throughout the study.

Anxiety Disorders Included in the Analysis

The following anxiety disorders were included in our analyses: specific phobia, social phobia, agoraphobia, panic disorder, and generalized anxiety disorder (GAD). Because of low base rates of posttraumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) and to reduce variability (thus to increase statistical power in the multivariate analyses), we did not examine these 2 conditions separately. It is noteworthy, though, that except for 1 case, all PTSD and OCD cases were included, because the patients met criteria for at least 1 of the anxiety disorders as well. Clinical characteristics of baseline anxiety disorders were defined as follows. (1) Number of comorbid anxiety disorders: we differentiated between respondents with only 1 anxiety disorder and respondents who met the criteria for 2 or more anxiety disorders. (2) Nonsevere versus severe impairment: we differentiated between respondents reporting no or low impairment of daily life (nonsevere impairment) and those reporting severe or more severe impairment (severe impairment) at the worst time of their fear/anxiety or their avoidance of anxiety situations. (3) With versus without panic attacks: panic attack patients were defined as having at least 1 panic attack according to DSM-IV without meeting diagnostic criteria for panic disorder.

Data Analysis

Data were weighted to consider different sampling probabilities as well as systematic nonresponse at baseline. The Stata Software package[27] was used to compute robust variances, confidence intervals, and p values (by applying the Huber-White sandwich matrix) required when basing analyses on weighted data.[28] Logistic regressions with odds ratios (ORs) were used to describe the associations between anxiety disorders at baseline and risk of major depressive disorder during the follow-up period. Only those who did not have a lifetime diagnosis of major depressive disorder at baseline were included in the regression models. We analyzed 2 sets of models. First, all analyses were adjusted for age and gender. Second, to reduce the bias of odds ratios as measures of the causal effect on onset of major depressive disorder, we additionally adjusted our analyses for mental disorders occurring prior to the onset of the anxiety disorder. Here, the control variable was set to 1 if a respondent had an anxiety disorder and the other mental disorder preceded the anxiety disorder or if a respondent did not have an anxiety disorder and the other disorder was present until the median age at onset of anxiety disorders (the median was calculated separately in age groups). Otherwise, the control variable was set to 0. For cases in which the age at onset was the same for the anxiety disorder and the other mental disorder, the control variable was set to missing, and thus the case was omitted.

Additionally, we fitted a series of multiple logistic regression models to assess whether specific diagnoses, the presence of more than 1 anxiety disorder, impairment, and panic attacks were independent predictors of incident major depressive disorder among those with an anxiety disorder at baseline. These analyses served to estimate conditional associations on an individual level as well as to assess the predictive value of several sets of covariates on the public-health level, taking the frequencies of conditions into account. For the latter purpose, we calculated the area under the receiver operating characteristic curve (AUC)[29] based on the model probability of incident major depressive disorder and the true occurrence of incident major depressive disorder.

RESULTS

Association Between Anxiety Disorders at Baseline and Risk of Incident Major Depressive Disorder

Presence of any anxiety disorder and each of the anxiety disorders individually at baseline was associated with a significantly increased risk of major depressive disorder, compared with that in the reference group (Table 1). GAD showed the strongest link (OR = 4.5), followed by panic disorder (OR = 3.4), agoraphobia (OR = 3.1), social phobia (OR = 2.9), and specific phobia (OR = 1.9). After adjustment for all mental disorders with onsets prior to the onset of anxiety disorders, these associations remained relatively stable with only slightly smaller odds ratios in most cases, with the exception of panic disorder, which was no longer statistically significant.

Association Between Number of Comorbid Anxiety Disorders at Baseline and Risk of Incident Major Depressive Disorder

Among respondents with any anxiety disorder at baseline, both having only 1 (OR = 1.8) and having more than 1 (OR = 5.0) anxiety disorder were associated with a significantly increased risk of major depressive disorder compared with having no anxiety disorder at baseline (Table 2). Additionally, the risk of depression was significantly higher among those with more than 1 anxiety disorder compared with 1 anxiety disorder at baseline (OR = 2.8). These associations remained stable after adjustment for comorbid mental disorders occurring prior to the onset of each specific anxiety disorder under investigation. Specific phobia with at least 1 comorbid anxiety disorder at baseline was strongly associated with an increased risk of major depressive disorder (OR = 5.7), whereas specific phobia alone was not significantly associated with an increased risk of depression (OR = 1.4). Furthermore, specific phobia with at least 1 comorbid anxiety disorder showed a higher risk for first onset of major depressive disorder than specific phobia alone (OR = 4.1), suggesting that the presence of a specific phobia with a comorbid anxiety disorder at baseline is important in predicting the onset of major depressive disorder, yet specific phobia

Table 1. Association Between the Presence of Anxiety Disorders at Baseline and the Risk of Incident Major Depressive Disorder During Follow-Up

	Incident Major Depressive Disorder During Follow-Up					
			Adjusted for Age and Gender		Adjusted for Age, Gender, and Previous Mental Disorder[a]	
Anxiety Disorder at Baseline	Weighted N	Weighted %	OR	95% CI	OR	95% CI
Any anxiety disorder[b]						
No	136	7.6	ref		ref	
Yes	77	16.6	2.2*	1.6 to 3.2	2.1*	1.5 to 3.1
Specific phobia						
No	162	8.4	ref		ref	
Yes	51	15.7	1.9*	1.3 to 2.8	1.8*	1.2 to 2.8
Social phobia						
No	182	8.6	ref		ref	
Yes	31	22.5	2.9*	1.7 to 4.8	2.3*	1.3 to 3.9
Agoraphobia						
No	201	9.1	ref		ref	
Yes	12	27.3	3.1*	1.4 to 6.7	3.0*	1.2 to 7.4
Panic disorder						
No	206	9.2	ref		ref	
Yes	7	28.5	3.4*	1.2 to 9.0	2.5	0.4 to 14.2
Generalized anxiety disorder						
No	202	9.1	ref		ref	
Yes	11	33.3	4.5*	1.9 to 10.3	3.9*	1.1 to 13.2

[a]Mental disorders that occurred prior to the onset of anxiety disorders (substance use disorders, other anxiety disorders, obsessive-compulsive disorder, posttraumatic stress disorder, dysthymia, hypomanic/manic episodes, somatoform disorders, eating disorders).
[b]Includes specific phobia, social phobia, agoraphobia, panic disorder, and generalized anxiety disorder.
*$p < .05$.
Abbreviation: ref = reference group.

with no other comorbid anxiety disorder is not. These associations remained relatively stable after adjusting for comorbid mental disorders. The data do not suggest that social phobia, agoraphobia, panic disorder, or GAD with an additional anxiety disorder at baseline are more important in predicting the onset of major depressive disorder than the presence of social phobia, agoraphobia, panic disorder, or GAD alone. Interestingly, among those with agoraphobia at baseline, having a comorbid anxiety disorder did not appear to increase the risk of major depressive disorder (27.8% for agoraphobia alone vs. 26.8% for agoraphobia with another anxiety disorder; OR = 0.9).

Association Between Severity of Anxiety Disorder–Related Impairment and Risk of Incident Major Depressive Disorder

Any anxiety disorder (OR = 1.7), social phobia (OR = 2.7), and agoraphobia (OR = 3.4) with nonsevere impairment were associated with a significantly increased risk of depression (Table 3). Severe impairment was associated with a significantly increased risk of depression among those with any anxiety disorder (OR = 5.0), specific phobia (OR = 5.9), social phobia (OR = 3.5), panic disorder (OR = 4.1), and GAD (OR = 5.0), but not among those with agoraphobia, for which the low number of cases should be considered. With the exception of social phobia and panic disorder with severe impairment, the associations remained significant after adjusting for comorbid mental disorders occurring prior to the onset of the anxiety disorder under investigation. There was a significantly greater risk of major depressive disorder associated with severe versus nonsevere impairment among participants with any anxiety disorder (OR = 3.0) and specific phobia (OR = 4.2) at baseline. These associations remained relatively stable with slightly smaller ORs after adjustment for prior comorbid mental disorders.

Association Between Anxiety Disorders With Comorbid Panic Attacks and the Risk of Incident Major Depressive Disorder

Any anxiety disorder at baseline was associated with a significantly increased risk of major depressive disorder among both those with (OR = 6.4) and those without (OR = 2.0) comorbid panic attacks, compared with those who had no anxiety disorder at baseline (Table 4). These associations persisted after adjustment for prior comorbid mental disorders. Furthermore, the test comparing anxiety disorders without panic attacks and anxiety disorders with panic attacks indicated significant difference (OR = 3.2), showing that the presence of comorbid panic attacks is associated with an increased risk of major depressive disorder. However, this association did not remain significant after we adjusted for prior comorbid mental disorders. Among individuals with agoraphobia or GAD at baseline, comorbid panic attacks did not appear to increase the risk of major depressive disorder.

Final Model

To examine whether clinical characteristics of anxiety disorders (presence of panic attacks, number of comorbid

Table 2. Comorbid Anxiety Disorders at Baseline and Onset of Major Depressive Disorder During Follow-Up

	Incident Major Depressive Disorder During Follow-Up					
			Adjusted for Age and Gender		Adjusted for Age, Gender, and Previous Mental Disorder[a]	
Anxiety Disorder at Baseline	Weighted N[b]	Weighted %	OR	95% CI	OR	95% CI
No anxiety disorder[c]	136	7.6	ref		ref	
Any anxiety disorder[d]						
(A) only 1 anxiety disorder	53	13.6	1.8*	1.2 to 2.6	1.7*	1.1 to 2.6
(B) more than 1 anxiety disorder	25	31.4	5.0*	2.7 to 9.0	4.9*	2.6 to 9.0
(B) vs (A)			2.8*	1.4 to 5.3	2.9*	1.4 to 5.7
Specific phobia						
(A) specific phobia alone	28	10.9	1.4	0.8 to 2.3	1.4	0.8 to 2.2
(B) specific phobia and other anxiety disorder	23	34.3	5.7*	3.0 to 10.6	6.3*	3.2 to 12.3
(B) vs (A)			4.1*	1.9 to 8.5	4.7*	2.1 to 10.2
Social phobia						
(A) social phobia alone	13	15.6	2.2*	1.0 to 4.4	2.1*	1.0 to 4.2
(B) social phobia and other anxiety disorder	18	32.5	5.6*	2.7 to 11.4	5.1*	2.4 to 10.5
(B) vs (A)			2.6	0.9 to 6.9	2.4	0.9 to 6.4
Agoraphobia						
(A) agoraphobia alone	6	27.8	4.2*	1.3 to 13.0	3.8*	1.1 to 11.9
(B) agoraphobia and other anxiety disorder	6	26.8	3.9*	1.4 to 10.4	4.1*	1.2 to 13.0
(B) vs (A)			0.9	0.2 to 4.0	1.1	0.2 to 5.2
Panic disorder						
(A) panic disorder alone	1	16.8	2.5	0.2 to 23.4	…	…
(B) panic disorder and other anxiety disorder	6	32.8	5.7*	1.9 to 16.8	4.4	0.9 to 20.2
(B) vs (A)			2.3	0.1 to 25.9	…	…
Generalized anxiety disorder						
(A) generalized anxiety disorder alone	4	24.9	4.2*	1.1 to 16.0	7.7*	1.8 to 32.7
(B) generalized anxiety disorder and other anxiety disorder	7	42.8	8.5*	2.7 to 26.1	6.4*	1.6 to 25.4
(B) vs (A)			2.0	0.3 to 11.3	0.8	0.1 to 5.9

[a]Mental disorders that occurred prior to the onset of anxiety disorders (substance use disorders, obsessive-compulsive disorder, posttraumatic stress disorder, dysthymia, hypomanic/manic episodes, somatoform disorders, eating disorders). Cases in which the disorder of interest and at least 1 control disorder began in the same year were omitted from this analysis.
[b]Since the weighted Ns were rounded, the sum of the individual weighted Ns does not always equal the total weighted N.
[c]No specific phobia, social phobia, agoraphobia, panic disorder, or generalized anxiety disorder.
[d]Includes specific phobia, social phobia, agoraphobia, panic disorder, and generalized anxiety disorder.
*$p < .05$.
Abbreviation: ref = reference group.

anxiety disorders, impairment) were independent predictors for the development of incident major depressive disorder (Table 5), we included all factors in the final logistic model. Severe impairment (OR = 2.2) and female gender (OR = 2.7) remained significantly associated with first onset of major depressive disorder after adjustment for gender, age, and the other clinical characteristics of anxiety disorders simultaneously. Moreover, we calculated the AUC to estimate the predictive value of different models predicting first onset of major depressive disorder. An AUC of 0.5 indicates that the predictive value of a model for the development of major depressive disorder is not better than a decision by chance. As shown in Table 5, the model containing gender and age alone yielded an AUC of 0.59. After impairment was added to that model, the AUC increased considerably (AUC = 0.68). Interestingly, the AUC did not substantially increase after the addition of other clinical characteristics (number of anxiety disorders, occurrence of panic attacks; AUC = 0.70).

DISCUSSION

The goal of this study was to examine the associations between anxiety disorders and the risk of major depressive disorder and to explore the role of various clinical characteristics of anxiety disorders in these associations. Limitations of the study should be noted prior to a discussion of our findings. Although we used a prospective design to explore the association between anxiety disorders and subsequent major depressive disorder, diagnoses of anxiety disorders at baseline were retrospective and therefore subject to possible recall bias. Yet, potential biases were probably attenuated in this relatively young sample. Despite the use of a fairly large overall sample, some of our findings are based on relatively few cases and should be interpreted with caution. In preparation for more detailed predictor analyses, we have included at this stage only a limited range of possible constructs and clinical features of anxiety disorders. Future analyses will include

Table 3. Severity of Anxiety Disorder–Related Impairment at Baseline and Onset of Major Depressive Disorder During Follow-Up

	Incident Major Depressive Disorder During Follow-Up					
			Adjusted for Age and Gender		Adjusted for Age, Gender, and Previous Mental Disorder[a]	
Anxiety Disorder at Baseline	Weighted N[b]	Weighted %	OR	95% CI	OR	95% CI
Any anxiety disorder[c]						
No anxiety disorder[d]	136	7.6	ref		ref	
Nonsevere impairment	47	12.7	1.7*	1.1 to 2.4	1.7*	1.1 to 2.5
Severe impairment	31	31.2	5.0*	2.9 to 8.6	4.5*	2.5 to 8.1
Severe vs nonsevere impairment			3.0*	1.6 to 5.6	2.7*	1.4 to 5.2
Specific phobia						
No specific phobia	162	8.4	ref		ref	
Nonsevere impairment	35	12.2	1.4	0.9 to 2.2	1.5	0.9 to 2.4
Severe impairment	17	38.4	5.9*	2.7 to 12.7	5.3*	2.1 to 13.0
Severe vs nonsevere impairment			4.2*	1.8 to 9.6	3.5*	1.3 to 9.2
Social phobia						
No social phobia	182	8.6	ref		ref	
Nonsevere impairment	21	21.0	2.7*	1.4 to 4.9	2.5*	1.3 to 4.5
Severe impairment	10	26.2	3.5*	1.4 to 8.3	1.9	0.7 to 4.9
Severe vs nonsevere impairment			1.3	0.4 to 3.7	0.8	0.2 to 2.3
Agoraphobia						
No agoraphobia	201	9.1	ref		ref	
Nonsevere impairment	11	29.3	3.4*	1.4 to 7.8	3.2*	1.3 to 7.8
Severe impairment	1	16.3	1.7	0.2 to 13.7	…	…
Severe vs nonsevere impairment			0.5	0.0 to 4.7	…	…
Panic disorder						
No panic disorder	206	9.2	ref		ref	
Nonsevere impairment	2	24.1	2.5	0.4 to 13.9	3.7	0.4 to 28.7
Severe impairment	5	31.2	4.1*	1.2 to 13.6	1.1	0.1 to 13.4
Severe vs nonsevere impairment			1.7	0.2 to 13.5	0.3	0.0 to 7.6
Generalized anxiety disorder						
No generalized anxiety disorder	202	9.1	ref		ref	
Nonsevere impairment	3	27.8	3.5	0.9 to 13.0	3.7	0.9 to 13.8
Severe impairment	8	36.0	5.0*	1.7 to 14.0	5.4*	1.2 to 23.5
Severe vs nonsevere impairment			1.4	0.2 to 7.5	1.5	0.2 to 10.5

[a]Mental disorders that occurred prior to the onset of anxiety disorders (substance use disorders, other anxiety disorders, obsessive-compulsive disorder, posttraumatic stress disorder, dysthymia, hypomanic/manic episodes, somatoform disorders, eating disorders). Cases in which the disorder of interest and at least 1 control disorder began in the same year were omitted from this analysis.
[b]Since the weighted Ns were rounded, the sum of the individual weighted Ns does not always equal the total weighted N.
[c]Includes specific phobia, social phobia, agoraphobia, panic disorder, generalized anxiety disorder.
[d]No specific phobia, social phobia, agoraphobia, panic disorder, or generalized anxiety disorder.
*$p < .05$.
Abbreviation: ref = reference group.

family history, temperamental factors (e.g., behavioral inhibition), and childhood disorders. Although a number of studies have suggested that depression might also be a risk factor for subsequent anxiety disorders,[7,30] we did not examine this pathway due to the lack of statistical power.

Associations Between Anxiety Disorders and Major Depressive Disorder

Consistent with both previous cross-sectional and longitudinal studies, these results show strong associations between anxiety disorders and the development of subsequent major depressive disorder.[4,7–11] Furthermore, these data provide some evidence suggesting a potentially direct link between anxiety disorders and subsequent major depressive disorder, as these associations remain significant after adjusting for almost all mental disorders occurring prior to the onset of anxiety disorders. Therefore, it appears that anxiety disorders as defined according to CIDI/DSM-IV criteria, measured both in the aggregate and separately (social phobia, agoraphobia, GAD), appear to make an independent contribution to the risk of the onset of major depressive disorder among adolescents and young adults. Specific phobias seem to be different in this regard, as their association with secondary major depressive disorder is significant only if complicating factors are present (comorbid conditions, severe impairment).

Clinical Characteristics of Anxiety Disorders

In our investigation of clinical characteristics that may play a role in the increased risk of depression among persons with anxiety disorders, we found anxiety comorbidity to be additionally important in this link. There seems to be a dose-response relationship in terms of the association between number of comorbid disorders and risk of major depressive disorder. In the unadjusted model, a dose-response relationship appeared to characterize the associations between all of the clinical features examined (i.e., number of comorbid disorders, severity of impairment,

Table 4. Presence of DSM-IV Panic Attacks at Baseline and Onset of Major Depressive Disorder During Follow-up

	Incident Major Depressive Disorder During Follow-Up					
			Adjusted for Age and Gender		Adjusted for Age, Gender, and Previous Mental Disorder[a]	
Anxiety Disorder at Baseline	Weighted N[b]	Weighted %	OR	95% CI	OR	95% CI
Any anxiety disorder[c]						
No anxiety disorder[d]	136	7.6	ref		ref	
Without panic attacks	62	14.9	2.0*	1.3 to 2.8	2.0*	1.3 to 2.9
With panic attacks	8	35.6	6.4*	2.3 to 17.5	5.6*	2.0 to 15.4
With vs without panic attacks			3.2*	1.1 to 9.2	2.8	0.9 to 8.1
Specific phobia						
No specific phobia	162	8.4	ref		ref	
Without panic attacks	47	15.0	1.8*	1.2 to 2.7	1.7*	1.1 to 2.7
With panic attacks	5	33.2	5.2*	1.5 to 17.8	4.7*	1.0 to 21.2
With vs without panic attacks			3.0	0.8 to 10.4	2.7	0.5 to 12.6
Social phobia						
No social phobia	182	8.6	ref		ref	
Without panic attacks	26	20.7	2.6*	1.5 to 4.5	2.1*	1.2 to 3.7
With panic attacks	5	45.9	8.1*	1.7 to 36.9	6.3*	1.1 to 34.8
With vs without panic attacks			3.1	0.6 to 15.1	3.0	0.5 to 17.5
Agoraphobia						
No agoraphobia	201	9.1	ref		ref	
Without panic attacks	11	26.8	3.0*	1.3 to 6.8	3.4*	1.4 to 8.5
With panic attacks	1	34.5	3.8	0.3 to 40.9	…	…
With vs without panic attacks			1.3	0.1 to 15.2	…	…
Generalized anxiety disorder						
No generalized anxiety disorder	202	9.1	ref		ref	
Without panic attacks	9	32.2	4.1*	1.6 to 10.3	4.0*	1.0 to 15.4
With panic attacks	2	41.5	7.9	0.9 to 65.7	2.6	0.3 to 22.3
With vs without panic attacks			1.9	0.2 to 18.9	0.7	0.0 to 8.0

[a]Mental disorders that occurred prior to the onset of anxiety disorders (substance use disorders, other anxiety disorders, obsessive-compulsive disorder, posttraumatic stress disorder, dysthymia, hypomanic/manic episodes, somatoform disorders, eating disorders). Cases in which the disorder of interest and at least 1 control disorder began in the same year were omitted from this analysis.
[b]Since the weighted Ns were rounded, the sum of the individual weighted Ns does not always equal the total weighted N.
[c]Includes specific phobia, social phobia, agoraphobia, generalized anxiety disorder.
[d]No specific phobia, social phobia, agoraphobia, panic disorder, or generalized anxiety disorder.
*$p < .05$.
Abbreviation: ref = reference group.

presence of panic attacks) and the risk of depression associated with anxiety disorders.

Specifically, respondents with 2 or more anxiety disorders had a significantly higher risk of first onset of major depressive disorder compared with individuals with 1 anxiety disorder. This finding is consistent with previous reports suggesting a monotonic association between the number of anxiety disorders reported in adolescence and later risks of major depressive disorder.[9] Specific phobias uncomplicated by comorbidity with other anxiety disorders do not convey per se an increased risk for major depressive disorder.

Consistent with previous results showing an association between level of anxiety morbidity and risk of depression, these data also expand knowledge in this area by showing some degree of specificity in the strength of each anxiety disorder to increase risk of depression. From these data, it is not possible to determine the reason for this apparent specificity in risk associated with comorbid and noncomorbid disorders. For instance, the reason that specific phobia, when not comorbid with other disorders, is the only anxiety disorder not associated with an increased risk of major depressive disorder may be that the link between anxiety disorders and major depressive disorder in young persons is impairment and increased avoidance resulting in disability. To highlight this theory with an example, it is conceivable that some specific phobias (e.g., snake phobia in metropolitan Munich) may not be related to daily impairment, and therefore alone may not increase the risk of depression. Specifically, anxiety disorders that currently impair severely or extremely a subject's functioning in 1 or more social role areas are associated with a significantly greater risk of major depressive disorder. This observation has previously been suggested by Kessler and colleagues[7,8] in their analyses on active and nonactive disorders. Alternatively, a genetic link might exist between anxiety and depression that does not apply to specific phobia alone as strongly as to other anxiety disorders (e.g., GAD[31]). Other explanations are conceivable, including the possibility that environmental/psychosocial and genetic factors contribute to this link. Future studies that can more closely investigate these possibilities are needed as a next step. Consistent with previous findings,[11,14,15] we also found that, among individuals with anxiety disorders, panic attacks were associated with a significantly greater risk for the first onset of major depressive disorder.

Table 5. Multiple Model for Incidence of Major Depressive Disorder Among Cases With an Anxiety Disorder at Baseline

Variable	Value
Clinical characteristics of anxiety disorders, OR (95% CI)	
No. of comorbid anxiety disorders (> 1 vs 1)	1.7 (0.7 to 4.0)
Impairment (severe vs nonsevere)	2.2 (1.0 to 4.4)*
Panic attacks (yes vs no)	1.5 (0.5 to 4.0)
Sociodemographic characteristics, OR (95% CI)	
Gender (female vs male)	2.7 (1.3 to 5.3)*
Age at baseline	1.0 (0.9 to 1.2)
Model, AUC	
Gender and age	0.59
Gender, age, impairment	0.68
Gender, age, panic attacks	0.61
Gender, age, no. of anxiety disorders	0.68
Gender, age, impairment, no. of disorders, panic attacks	0.70

*$p < .05$.
Abbreviation: AUC = area under receiver operating characteristic curve.

In the final model, which included all clinical features, severe impairment associated with anxiety disorders emerged as the most important predictor of incident major depressive disorder. This result provides some support for traditional theories saying that the severity of impairment due to avoidance behavior might lead to an accumulation of stressful experiences that trigger the onset of depression.[32,33] It is also possible that the presence of severe anxiety leads to other life-course changes such as reduced academic or occupational performance or fewer social relationships, which in turn lead to the onset of depression. Future analyses of our dataset will address more precisely these potential pathways.

The stable associations between anxiety disorders and the development of subsequent major depressive disorder evident within our prospectively designed study, even after adjusting for mental disorders occurring prior to the onset of the anxiety disorder, suggest that anxiety disorders in general, as well as features of their specific phenomenology, might act as risk factors for the first onset of major depressive disorder according to the taxonomy of Kraemer et al.[34] The qualifying characteristics of anxiety disorders (presence of comorbid anxiety disorders, severity of impairment, occurrence of panic attacks) might also serve as powerful cues for the clinician to make more precise prognostic decisions about a patient's future risk of developing secondary depressive disorders. Future analyses will attempt to test the potential causal role of anxiety disorders for first onset of depression prospectively by including additional vulnerability and risk factors.

Clinical Implications

Specifying the possible key role of anxiety disorders in the development of major depressive disorder is important for understanding the etiology of depression, improving efficacy of treatment, and developing effective prevention strategies, especially early intervention programs. Given the high prevalence of secondary depression—even in young people[19,35]—and the high risk of a poorer prognosis in depression with an early onset,[36,37] effective strategies for preventing major depressive disorder are increasingly important. As our findings suggest that particularly severely disabling anxiety disorders are associated with an increased risk of subsequent major depressive disorder, effective treatment of anxiety disorders, specifically those associated with extreme disability, might be important for targeted primary prevention of major depressive disorder. Our results regarding the influence of clinical features of anxiety disorders on the risk of subsequent major depressive disorder could contribute to the identification of individuals at highest risk for first onset of major depressive disorder and a more malignant course of illness.[10] As clinical inquiry into the extent of impairment associated with an anxiety disorder can take place in a time-efficient and cost-effective manner, identification of such individuals in clinical settings may be possible.

Although data on this topic remain preliminary, Goodwin and Olfson,[38] for instance, showed that treatment of anxiety disorders (e.g., panic attacks) may reduce the risk of developing major depressive disorder. Estimates from Kessler and colleagues[8] suggest that approximately 10% of mood disorders may be prevented by successful early intervention in social phobia. Longitudinal studies are needed next to explore the relation between treatment of anxiety disorders and the risk of major depressive disorder.

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