

Incidence and Risk Patterns of Anxiety and Depressive Disorders and Categorization of Generalized Anxiety Disorder

Katja Beesdo, PhD; Daniel S. Pine, MD; Roselind Lieb, PhD; Hans-Ulrich Wittchen, PhD

Context: Controversy surrounds the diagnostic categorization of generalized anxiety disorder (GAD).

Objectives: To examine the incidence, comorbidity, and risk patterns for anxiety and depressive disorders and to test whether developmental features of GAD more strongly support a view of this condition as a depressive as opposed to an anxiety disorder.

Design: Face-to-face, 10-year prospective longitudinal and family study with as many as 4 assessment waves. The DSM-IV Munich Composite International Diagnostic Interview was administered by clinically trained interviewers.

Setting: Munich, Germany.

Participants: A community sample of 3021 individuals aged 14 to 24 years at baseline and 21 to 34 years at last follow-up.

Main Outcome Measures: Cumulative incidence of GAD, other anxiety disorders (specific phobias, social phobia, agoraphobia, and panic disorder), and depressive disorders (major depressive disorder, and dysthymia).

Results: Longitudinal associations between GAD and depressive disorders are not stronger than those between GAD and anxiety disorders or between other anxiety and depressive disorders. Survival analyses reveal that the factors associated with GAD overlap more strongly with those specific to anxiety disorders than those specific to depressive disorders. In addition, GAD differs from anxiety and depressive disorders with regard to family climate and personality profiles.

Conclusions: Anxiety and depressive disorders appear to differ with regard to risk constellations and temporal longitudinal patterns, and GAD is a heterogeneous disorder that is, overall, more closely related to other anxiety disorders than to depressive disorders. More work is needed to elucidate the potentially unique aspects of pathways and mechanisms involved in the etiopathogenesis of GAD. Grouping GAD with depressive disorders, as suggested by cross-sectional features and diagnostic comorbidity patterns, minimizes the importance of longitudinal data on risk factors and symptom trajectories.

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Author Affiliations: Institute of Clinical Psychology and Psychotherapy, Technische Universitaet Dresden, Dresden, Germany (Drs Beesdo and Wittchen); Section on Development and Affective Neuroscience, National Institute of Mental Health, Bethesda, Maryland (Dr Pine); Max Planck Institute of Psychiatry, Munich, Germany (Drs Lieb and Wittchen); and Institute of Psychology, Epidemiology, and Health Psychology, University of Basel, Switzerland (Dr Lieb).

ANXIETY AND DEPRESSIVE DISORDERS are related through comorbidity and shared risk factors.¹⁻³ Although some particular anxiety disorders may show relatively weak associations with depressive disorders, clinical⁴ and epidemiological^{5,6} studies find that anxiety and depressive disorders rarely occur in pure forms. Factor analytic approaches suggest that these data reflect the influence of a higher-order “internalizing” factor.⁷⁻¹⁰ In the process of revising DSM-IV,^{11,12} these findings have stimulated calls for rethinking of diagnostic classes^{13,14} based on data regarding similarities and differences in risk factors.¹⁴

Particularly intense inquiry focuses on generalized anxiety disorder (GAD) and major depression.^{15,16} Factor analysis links GAD more closely to depressive disorders (internalizing anxious-misery dimension) than to

other anxiety disorders, such as phobias and panic disorder (internalizing fear dimension).^{7,9,10} Research on genetics,¹⁷⁻²⁰ personality,²¹⁻²³ and adversities^{24,25} also supports this view. However, this view is challenged by many other observations,^{15,16,26} including those regarding familial factors,^{25,27} temperament,^{25,28} life events,^{29,30} biological characteristics,³¹ comorbidity,^{24,32,33} illness course,^{28,34} cognitive biases,^{35,36} and treatment.^{16,37} Despite the considerable research on the relationship between GAD and major depression,^{24,25,38} to our knowledge, no prior study has used a longitudinal approach to quantify the degree to which similarities and differences in risk profiles and symptom trajectories support a grouping of GAD with depressive as opposed to anxiety disorders. Beyond major depression, considering dysthymia is important given findings regarding comorbidity,^{32,39-43} structure,^{7,9,10} and disease course.¹²

The present study provides data on similarities and differences in developmental features and risk factors of anxiety and depressive disorders. Specifically, we test whether developmental features of GAD are more consistently associated with depressive as opposed to anxiety disorders. Using data from a prospective, longitudinal community study, we will (1) compare incidence and comorbidity patterns of GAD with depressive disorders (major depression and dysthymia) and selected anxiety disorders (panic disorder and phobias) and (2) examine putative family-genetic, temperamental/personality, and environmental factors that might be differentially associated with specific conditions.

METHODS

SAMPLE

The prospective longitudinal Early Developmental Stages of Psychopathology (EDSP) study assessed mental disorders and associated risk factors in a representative sample of 3021 adolescents and young adults aged 14 to 24 years at baseline (T0). The study also includes follow-up surveys (T1, T2, and T3), a family history component (T0, T2, and T3), and parent surveys (T1 and T3). Study methods and design and information on representativeness and response rates have been previously described.⁴⁴⁻⁴⁷

The baseline sample was selected in 1994 from government registries (greater Munich area, Germany). The study emphasized development by sampling 14- to 15-year-old individuals at twice the probability rate and 22- to 24-year-old individuals at half the probability of 16- to 21-year-old individuals. Sample weights account for this sampling scheme in the subsequent analyses.

A total of 3021 interviews were conducted at baseline. The response rate was 70.9%, equal or superior to rates in other large-scale epidemiological studies.^{48,49} At T1 (range, 1.2-2.1 years after baseline), 1228 interviews (88.0%) were conducted among participants aged 14 to 17 years at baseline. At T2 (range, 2.8-4.1 years after baseline), 2548 participants (84.3%) were interviewed; 2210 (73.2%) were interviewed at T3 (range, 7.3-10.6 years after baseline). For 2797 participants, at least 1 follow-up assessment is available; the overall response rate of 92.6% compares favorably with other studies.^{50,51} There was no selective attrition from baseline to the 10-year follow-up assessment for participants with GAD (odds ratio, 0.9; 95% confidence interval [CI], 0.5-1.9; $P = .81$) or other disorders considered herein (all P values $> .05$).

All participants older than 18 provided written informed consent; for respondents 18 years and younger, parental consent was provided. The EDSP program has been approved by the Ethics Committee of the Medical Faculty of the Technische Universität Dresden.

DIAGNOSTIC ASSESSMENT

Face-to-face interviews were conducted by trained clinical interviewers using the computer-assisted Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI).^{52,53} Reliability and validity have been reported previously.⁵³⁻⁵⁵ At baseline, the lifetime version of the DIA-X/M-CIDI was used; at follow-up interviews, the interval version was used. All diagnoses were obtained using M-CIDI/DSM-IV algorithms.⁵² The impairment criterion for phobias was applied when participants were 18 years or older.⁵⁶

Analyses use aggregated data from baseline to T3 for the following outcomes: (1) anxiety disorders, comprising specific pho-

bias, social phobia, agoraphobia without panic disorder, and panic disorder with and without agoraphobia; (2) depressive disorders, comprising major depressive disorder and dysthymia (excluding bipolar disorders); and (3) GAD (without applying the diagnostic exclusion criteria). These outcomes were chosen based on analyses by Krueger⁷ and others.^{9,10} Posttraumatic stress disorder, obsessive-compulsive disorder, and bipolar disorder were excluded from the main analyses because of conflicting findings in structural models^{5,10,57,58}; separation anxiety disorder was assessed in the T1 subsample only. However, these diagnoses were considered in supplementary analyses.

The test-retest reliability ranged from a κ of 0.45 for GAD to 1.00 for panic disorder.⁵³ Inconsistencies in GAD were mainly owing to different responses with regard to the 6-month time duration; however, test-retest reliability of the GAD stem question was good and in the range of other disorders ($\kappa, 0.70$). Supplementary analyses considered GAD with a shorter minimum duration. Validity of the DSM-IV/M-CIDI diagnoses compared with independent clinical consensus diagnoses by treating physicians was estimated, with κ ranging from 0.54 for dysthymia to 0.79 for any anxiety disorder, including GAD, to 0.96 for major depressive episodes.⁵⁴ Age-of-onset reliability estimates were also established with intraclass coefficients ranging from 0.45 for specific phobia, environmental subtype, to 0.97 for GAD and major depressive episodes.^{53,56}

ASSESSMENT OF RISK FACTORS

Based on the literature,^{16,24-27,59,60} we examined the following putative risk factors.

Parental Mental Disorders

As previously reported,⁶¹ parental diagnoses were based on 2 sources: (1) parent interviews at T1 and/or T3 and (2) family history information provided by the offspring at T0, T2, and T3. Interviewed parents ($n = 1189$) underwent the same assessment procedures as their offspring (DIA-X/M-CIDI). Family history items were designed using a modified version of the Family History Research Diagnostic Criteria⁶² as a model. At T0, DIA-X/M-CIDI stem questions and questions about treatment were used; at T2 and T3, an extended family history module covered DSM-IV criteria. Parental disorders were aggregated using a priority hierarchy that was determined following examination of agreement patterns between family history report and available parent interview data. This examination demonstrated the highest agreements regarding parental diagnoses, especially in terms of specificity (tends to cause higher bias) at T3 compared with T2 and T0. Parent interview information from T1 and T3 interviews was considered to be the most reliable and was used if available. If parent interview data were not available, T3 family history reports were used, and if these reports were not available, then T2 family history reports and, last, T0 family history reports were used. In the present study, we consider parental GAD (307 of 3021 parents [9.7%]), anxiety disorders (specific phobia, social phobia, agoraphobia, and panic disorder; 770 [21.5%]), depressive disorders (major depression, and dysthymia; 858 [27.7%]), and substance-use disorders (alcohol abuse or dependence, and illicit drug abuse or dependence; no baseline family history information available; 356 of 2764 [12.6%]).

Temperament/Personality

The German version of the Retrospective Self-Report of Inhibition (RSRI)⁶³ was used at baseline to assess behavioral inhibition, defined as consistent restraint in response to social and nonsocial situations. The RSRI consists of 30 questions about

specific childhood behaviors. Internal consistency of the RSRI was considered acceptable in clinical and nonclinical samples. Validity is high, which is reflected by a strong agreement between individuals (self-reports) and their parents (observer reports) regarding the individual's inhibited behaviors as a child, a positive relationship of retrospective self-report and contemporary measures of inhibition, and accounts for variance in general and specific measures of mental health.⁶³ The psychometric properties of the German RSRI were comparable to those of the English version.⁶⁴ The total mean behavioral inhibition score is used herein.

The German version of the 100-item Tridimensional Personality Questionnaire⁶⁵ was used at T3 to assess 11 subscales that load on 3 distinct dimensions: novelty seeking, reward dependence, and harm avoidance.^{66,67} Novelty seeking reflects exploratory activity and aversion to monotony, whereas reward dependence is characterized by the maintenance of reward-inducing behavior and reduction of punishment-eliciting behavior. Harm avoidance indicates the tendency toward behavioral inhibition to avoid punishment, novel stimuli, and nonreward. The Tridimensional Personality Questionnaire is based on Cloninger's general theory of personality and is conceptualized to measure stable traits by self-report. Reliability and construct validity of the German version indicate sufficient psychometric properties.⁶⁵

A modified German version of the Resilience Scale⁶⁸ was used at T1 to assess the degree of individual resilience, defined as a protective personality factor that enhances individual adaptation to high-risk status, acute stressors, or recovery from trauma. Resilience has been associated with healthy development among children, adolescents, and adults.⁶⁹ Reliability and validity of the German Resilience Scale have been established.^{68,70}

Environmental Factors

Early separation events (492 [15.8%]) were assessed at baseline within the family history section of the DIA-X/M-CIDI and included death of a parent (57 [2.0%]) and parental separation or divorce (436 [13.8%]) before age 10.

The German version of the Questionnaire of Recalled Parental Rearing Behavior⁷¹ administered at T1 is based on the Swedish EMBU (Egna Minnen Beträffande Uppfostran)⁷² and involved offspring assessment of the perceived parental rearing styles with regard to parental rejection, emotional warmth, and overprotection. Reliability and validity of the Questionnaire of Recalled Parental Rearing Behavior have been reported to be high.^{71,73}

The McMaster Family Assessment Device⁷⁴ was used at T1 to assess 6 dimensions of family functioning via parental interviews. The general functioning scale is used herein (higher scores reflect dysfunctional family functioning), representing the overall family climate. Reliability and validity of the scale have been established.⁷⁵

STATISTICAL ANALYSIS

Data are weighted by age, sex, and geographic location at baseline to match the distribution of the sampling frame; frequencies (numbers) are unweighted. Stata statistical software, version 10.0,⁷⁶ was used to compute robust variances, CIs, and *P* values (by applying the Huber-White sandwich matrix) required when basing analyses on weighted data.⁷⁷

Age-specific cumulative incidence rates were estimated with the Kaplan-Meier method in survival analysis. Consistent with prior reports,⁴⁷ disorder age of onset was based on the minimum age reported by the respondent at any of the assessment waves. This definition corresponded well (>90%) with other age-of-onset aggregation methods (eg, using the first or mean of re-

ported ages of onset); the absolute values of differences were at most 1 year, except for major depression and specific phobias, for which the agreement between the mean and minimum methods was slightly lower (86.9% and 83.1%, respectively). For the diagnostic outcome categories, the lowest age of onset of the specific disorders was used. Cox regression analyses with hazard ratios (HRs) were used to assess associations between family-genetic (parental disorders), temperamental/personality (behavioral inhibition, Tridimensional Personality Questionnaire, and resilience), and environmental (early separation, rearing, and family climate) factors and diagnostic outcomes in probands (GAD, anxiety disorder, and depressive disorder). To improve comparability of results, the questionnaire scores were standardized in Cox regressions, resulting in a mean (SD) of 0 (1) in the weighted total sample; the reported associations thus indicate the change in outcome (natural logarithm of HR in Cox regression) per 1-SD increase. All Cox regressions were conducted using age and sex as stratification variables; ie, different curves are fitted according to the values of these variables before assessing the covariates of interest.⁷⁸ Time-dependent covariates (eg, GAD before outcome) were defined as having ever had the condition before time *t* using age-of-onset data. Some data were missing because of missing age-of-onset information in outcome or time-dependent covariates.

RESULTS

INCIDENCE AND COMORBIDITY PATTERNS

The estimated age-specific cumulative incidence for GAD at age 34 is 4.3% (*n* = 106); incidence is 23.2% (*n* = 732) for other anxiety disorders (phobia or panic disorder), and 28.6% (*n* = 686) for any depressive disorder (major depressive disorder or dysthymia) (**Figure 1A**). The cumulative age-of-onset distribution (**Figure 1B**) reveals the earliest onset for anxiety disorders; GAD shows an age-of-onset slope more similar to the depressive than the anxiety disorders, with core incidence periods occurring in adolescence and early adulthood. The considerable degree of heterogeneity among the anxiety disorders should be noted; panic disorder and agoraphobia have a similarly delayed age-of-onset as GAD (**Figure 1C**). These patterns contrast with social phobia and particularly specific phobias, for which first onset almost never occurs after adolescence.

Overall, GAD is strongly associated with anxiety disorders (panic and phobias: odds ratio, 7.06; 95% CI, 4.40-11.34; *P* < .001) and depressive disorders (4.44; 2.83-6.97; *P* < .001). Phobias (odds ratio, 2.40; 95% CI, 1.94-2.97; *P* < .001) and panic disorder (3.61; 2.28-5.73; *P* < .001) also are strongly associated with depressive disorders.

Table 1 presents time-lagged associations between prior and subsequent disorders. Phobias and panic disorder, GAD, and depressive disorders significantly predict the onset of each other. Highest HRs emerge for GAD predicting anxiety disorders (HR, 4.14) and, vice versa, anxiety disorders predicting GAD (5.05). For both directions, the associations of anxiety disorders or GAD with depressive disorders are consistently smaller (HRs, 1.88-2.54) than the anxiety-GAD associations. There were no interactions with time, except that depressive disorders occurred earlier among participants who had experienced prior phobias or panic (main effect for prior anxiety HR, 7.90; *P* < .001; anxiety × time interaction effect HR, 0.92; *P* < .001). When adjusting for comorbidity with

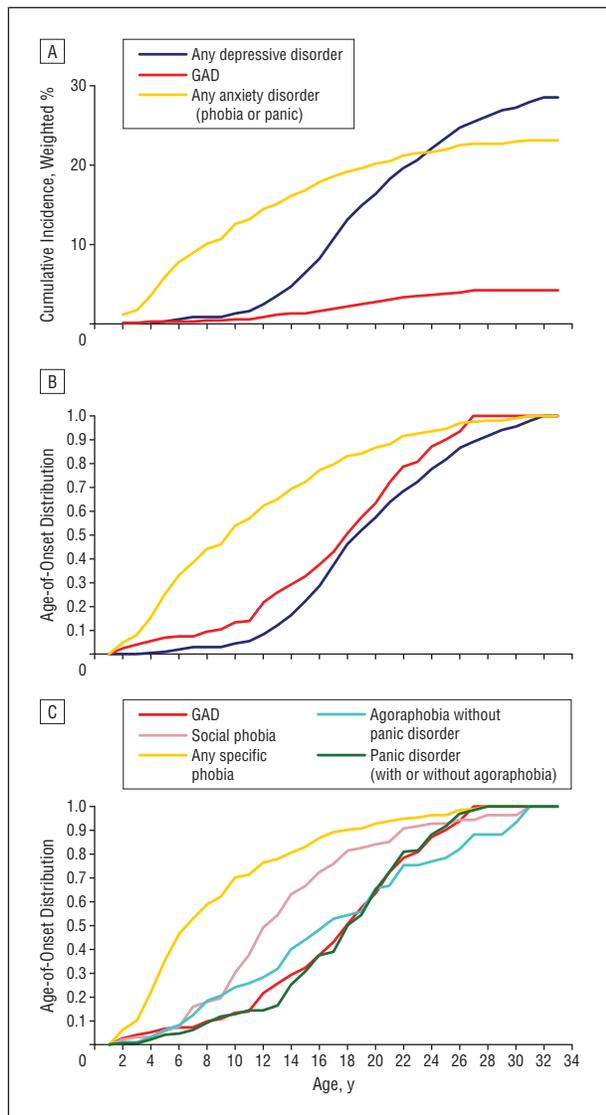


Figure 1. Incidence of generalized anxiety disorder (GAD) and other mental disorders. Estimated age-specific cumulative incidence (A) and age-of-onset distribution (B and C).

disorders occurring before the outcome, HRs decreased but remained significant, except that the association between prior depressive disorder and subsequent GAD was reduced to nonsignificance.

ASSOCIATIONS WITH PUTATIVE RISK FACTORS

Given the significant associations among disorders, we first examined putative risk factors for any depressive or anxiety disorder, including GAD (**Table 2**). Compared with individuals without anxiety and depression, affected individuals were characterized by a broad familial liability, temperamental/personality, and environmental risk profile.

To examine differential risk profiles and, specifically, whether factors associated with GAD are more closely related to depressive than anxiety disorders, we generated the following diagnostic outcome groups: (A) GAD (n=106), (B) anxiety alone (phobias or panic disorder but

no GAD or depressive disorder; n=429), (C) depression alone (major depressive disorder or dysthymia but no GAD or anxiety disorder; n=388), and (D) comorbid depressive and anxiety disorder but no GAD (n=234). Groups B through D do not include cases with GAD. Group A consisted of few cases without lifetime phobias or panic and depressive disorders (15 [14.4%]) and somewhat more with phobias and panic alone (27 [25.9%]) or depressive disorder alone (22 [19.2%]); the largest subgroup had both anxiety and depressive disorders (42 [40.5%]).

Table 3 shows the frequencies and means for putative risk factors for the 4 diagnostic outcome groups and **Table 4** shows the respective associations. Partly different factors are associated with anxiety alone and depression alone. Harm avoidance and, less clearly, parental comorbid anxiety and depressive disorders are associated with both anxiety and depressive disorders. However, parental depressive disorders alone, low resilience, low parental emotional warmth, and high parental rejection appear to be specific to offspring depressive disorders; parental GAD, high behavioral inhibition, exposure to childhood separation events, and parental overprotection, in contrast, appear to be specific to anxiety disorders.

The factors associated with GAD overlap with all those that are specific for anxiety disorders (parental GAD, behavioral inhibition, childhood separation events, and parental overprotection). However, they overlap only partly with those that are specific to depressive disorders (parental depressive disorders alone). Furthermore, unlike anxiety and/or depressive disorders, GAD is associated with reward dependence and dysfunctional family functioning.

Similar to GAD, comorbid cases with anxiety and depressive disorders reveal a broad range of strong risk associations. Since GAD cases (group A) revealed comorbidity, we repeated the analysis adjusting for comorbid anxiety and depressive disorders with onsets before GAD. Although the depression-overlap association between parental depressive disorder alone and offspring GAD was diminished (HR, 1.65; 95% CI, 0.96-2.84; $P = .07$), the anxiety-overlap associations with parental GAD (3.08; 1.86-5.12; $P < .001$), behavioral inhibition (1.64; 1.34-2.00; $P < .001$), and childhood separation events (1.94; 1.19-3.17; $P = .008$) remained significant. Furthermore, the GAD-specific association with reward dependence remained unchanged (HR, 1.43; 95% CI, 1.09-1.87; $P = .01$). Associations for overprotection and family functioning decreased to nonsignificance, likely owing to limited power in the smaller subsample.

In supplementary analyses, we explored first whether separation anxiety disorder as an early, childhood-onset disorder is a differential predictor for the 4 diagnostic outcome groups. Results reveal that separation anxiety disorder is a significant and specific predictor for phobias and panic alone (HR, 3.48; 95% CI, 1.73-7.00; $P < .001$) and GAD (7.65; 1.40-41.82; $P = .02$).

Second, we explored the robustness of findings in Tables 3 and 4 by using different outcome definitions. Based on epidemiological evidence suggesting that current criteria for GAD may be too strict,^{40,79,80} particularly for youth,^{32,51} and given that other studies manipulated the threshold definitions for GAD to increase

Table 1. Longitudinal Associations Between Prior and Subsequent Disorders

Prior Condition	Risk for Onset of Subsequent Disorders					
	GAD		Anxiety Disorder (Phobia or Panic)		Depressive Disorder	
	HR (95 % CI)	P Value	HR (95 % CI)	P Value	HR (95 % CI)	P Value
GAD						
Unadjusted	4.14 (2.13-8.05)	<.001	2.25 (1.36-3.75)	.002
Adjusted ^a	3.31 (1.61-6.82)	.001	1.72 (1.01-2.94)	.05
Anxiety disorder (phobia or panic)						
Unadjusted	5.05 (3.24-7.87)	<.001	1.88 (1.56-2.27)	<.001
Adjusted ^a	4.69 (2.99-7.36)	<.001	1.80 (1.49-2.19)	<.001
Depressive disorder						
Unadjusted	2.54 (1.38-4.65)	.003	2.38 (1.61-3.51)	<.001
Adjusted ^a	1.72 (0.94-3.14)	.08	2.16 (1.44-3.23)	<.001

Abbreviations: CI, confidence interval; ellipses, not applicable; GAD, generalized anxiety disorder; HR, hazard ratio from Cox regression with time-dependent covariates, stratified for sex and age.

^aHazard ratio was adjusted for comorbid anxiety and depressive disorders occurring before the respective outcome.

Table 2. Putative Risk Factors Among Cases With or Without GAD, Anxiety, or Depressive Disorder

Putative Risk Factor	GAD and Anxiety or Depressive Disorders ^a			
	No (n=1864)	Yes (n=1157)	Association	
			HR (95% CI)	P Value
Parental disorders				
GAD ^b	127 (6.4)	180 (15.1)	1.93 (1.60-2.32)	<.001
Anxiety disorder but no depressive disorder ^c	214 (9.0)	159 (12.2)	1.35 (1.12-1.62)	.002
Depressive disorder but no anxiety disorder ^c	221 (12.8)	193 (17.8)	1.30 (1.11-1.54)	.002
Anxiety and depressive disorder ^c	119 (4.8)	117 (9.0)	1.71 (1.40-2.10)	<.001
Substance-use disorder but no anxiety or depressive disorder ^c	58 (3.1)	37 (3.4)	1.00 (0.70-1.42)	.99
Temperament/personality, mean (SD)				
Behavioral inhibition ^d	2.03 (0.30)	2.24 (0.38)	1.69 (1.58-1.81)	<.001
Novelty seeking ^d	16.42 (4.72)	16.74 (5.17)	1.02 (0.95-1.11)	.56
Harm avoidance ^d	11.23 (5.46)	14.53 (6.17)	1.50 (1.39-1.62)	<.001
Reward dependence ^d	17.43 (4.23)	18.22 (4.62)	1.05 (0.96-1.14)	.28
Resilience ^{d,e}	139.94 (11.49)	136.04 (12.32)	0.78 (0.71-0.86)	<.001
Environmental factors				
Childhood separation events	245 (12.4)	247 (21.4)	1.66 (1.41-1.95)	<.001
Parental emotional warmth, mean (SD) ^{d,e}	23.71 (3.79)	22.94 (4.35)	0.83 (0.75-0.92)	<.001
Parental rejection, mean (SD) ^{d,e}	9.37 (1.53)	10.03 (2.14)	1.29 (1.20-1.39)	<.001
Parental overprotection, mean (SD) ^{d,e}	13.12 (2.78)	14.09 (3.18)	1.26 (1.15-1.37)	<.001
Dysfunctional family functioning, mean (SD)	1.60 (0.42)	1.68 (0.43)	1.18 (1.07-1.29)	.001

Abbreviations: CI, confidence interval; GAD, generalized anxiety disorder; HR, hazard ratio from survival analyses with Cox regressions, stratified by sex and age.

^aData are given as unweighted number of participants (weighted percentage) unless otherwise indicated; $P < .05$ indicates statistical significance.

^bIncludes comorbid cases.

^cDoes not include cases with comorbid GAD.

^dUnstandardized scores were used for mean and standard deviation, and standardized scores were used for associations.

^eAssessed at the first follow-up assessment (T1; subsample only).

comparability with major depressive disorder,^{17,18,25} we repeated the analyses using GAD with a shorter minimum duration (3 months and 1 month) (eTable 1; <http://www.archgenpsychiatry.com>). Despite decreasing HRs with decreasing GAD minimum duration, 3 of the 4 GAD anxiety-specific associations remained (parental GAD, behavioral inhibition, and childhood separation events), whereas significance of the GAD depression-specific factor (parental depressive disorder) was attenuated in GAD. When performing analyses using a minimum duration of 3 months for GAD, another indication for risk overlap for GAD and depression was found (low resilience).

Next, following structural models, we chose to consider in our primary analyses only some of the anxiety disorders, focusing on those with consistent loadings on the fear dimension (phobias and panic).^{7,9,57,58,81} We omitted the DSM-IV anxiety disorders posttraumatic stress disorder and obsessive-compulsive disorder because of conflicting results in structural analyses.^{5,10,57,58} Including posttraumatic stress disorder and obsessive-compulsive disorder within the anxiety outcome group did not change the primary results (eTable 2).

Then, contrary to procedures in other studies,^{24,25,38} we considered major depression and dysthymia in our pri-

Table 3. Putative Risk Factors for GAD, Anxiety, and/or Depressive Disorders as Separate Groups^a

Putative Risk Factor	GAD ^b		Anxiety Disorder but No Depressive Disorder ^c		Depressive Disorder but No Anxiety Disorder ^c		Anxiety and Depressive Disorder ^c	
	No (n=2915)	Yes (n=106)	No (n=2592)	Yes (n=429)	No (n=2633)	Yes (n=388)	No (n=2787)	Yes (n=234)
Parental disorders								
GAD ^b	277 (8.9)	30 (29.2)	238 (8.8)	69 (15.7)	267 (9.6)	40 (10.2)	266 (9.2)	41 (16.0)
Anxiety disorder but no depressive disorder ^c	356 (10.1)	17 (15.0)	310 (10.0)	63 (11.9)	327 (10.1)	46 (11.4)	340 (10.0)	33 (13.1)
Depressive disorder but no anxiety disorder ^c	391 (14.3)	23 (22.4)	363 (15.0)	51 (12.2)	335 (13.5)	79 (21.8)	374 (14.5)	40 (17.1)
Anxiety and depressive disorder ^c	226 (6.3)	10 (7.8)	192 (6.0)	44 (9.3)	200 (6.1)	36 (8.3)	209 (6.1)	27 (10.4)
Substance-use disorder but no anxiety or depressive disorder ^c	93 (3.3)	2 (2.3)	82 (3.2)	13 (3.3)	84 (3.3)	11 (2.9)	84 (3.1)	11 (5.1)
Temperament/personality, mean (SD)								
Behavioral inhibition ^d	2.09 (0.33)	2.42 (0.50)	2.09 (0.34)	2.24 (0.36)	2.10 (0.35)	2.14 (0.33)	2.09 (0.34)	2.34 (0.36)
Novelty seeking ^d	16.56 (4.92)	16.33 (4.53)	16.52 (4.82)	16.70 (5.41)	16.49 (4.87)	16.87 (5.12)	16.52 (4.88)	16.79 (5.18)
Harm avoidance ^d	12.39 (5.92)	16.14 (6.13)	12.28 (5.89)	14.26 (6.25)	12.35 (5.97)	13.68 (5.89)	12.27 (5.87)	15.68 (6.28)
Reward dependence ^d	17.67 (4.40)	19.52 (4.01)	17.74 (4.31)	17.80 (4.96)	17.66 (4.39)	18.23 (4.43)	17.70 (4.39)	18.25 (4.56)
Resilience ^{d,e}	138.44 (11.92)	135.76 (14.39)	138.67 (12.15)	137.11 (11.09)	138.70 (11.73)	135.66 (13.67)	138.77 (11.87)	134.29 (12.43)
Environmental factors								
Childhood separation events	460 (15.3)	32 (28.4)	409 (15.1)	83 (20.8)	425 (15.7)	67 (16.6)	427 (14.8)	65 (27.7)
Parental emotional warmth, mean (SD) ^{d,e}	23.40 (4.02)	22.94 (5.37)	23.42 (4.02)	23.29 (4.17)	23.57 (4.00)	21.94 (4.21)	23.40 (4.01)	23.37 (4.48)
Parental rejection, mean (SD) ^{d,e}	9.64 (1.84)	9.99 (1.56)	9.61 (1.86)	9.80 (1.68)	9.56 (1.70)	10.33 (2.61)	9.59 (1.75)	10.17 (2.44)
Parental overprotection, mean (SD) ^{d,e}	13.45 (2.98)	14.67 (3.00)	13.41 (2.94)	14.01 (3.15)	13.48 (2.96)	13.87 (3.21)	13.44 (2.95)	14.38 (3.25)
Dysfunctional family functioning, mean (SD) ^{d,e}	1.63 (0.43)	1.83 (0.47)	1.62 (0.43)	1.67 (0.42)	1.63 (0.43)	1.66 (0.44)	1.62 (0.43)	1.69 (0.42)

Abbreviation: GAD, generalized anxiety disorder.

^aData are given as the unweighted number of participants (weighted percentage) unless otherwise indicated.

^bIncludes comorbid cases.

^cDoes not include cases with comorbid GAD.

^dUnstandardized scores.

^eAssessed at the first follow-up assessment (T1; subsample only).

mary analyses following structural^{7,9,10} and comorbidity findings,^{32,39-43} but we chose to exclude bipolar cases because of inconclusive results from structural analyses.^{5,58} Repeating the analyses by focusing on major depression with and without exclusion of mania/hypomania cases did not change the primary results (eTable 3).

Last, we explored whether the anxiety-specific predictors from Tables 3 and 4 appear consistently across the specific anxiety disorders and GAD without comorbid depression. As shown in **Figure 2**, despite some variations, similarly directed risk patterns emerged across the specific anxiety disorders, except that panic disorder without depression was not associated with increased rates of parental GAD.

COMMENT

Strong comorbidity between anxiety and depressive disorders raises questions about the need to reconceptualize these disorders,^{13,14,58,82} with particularly intense focus on GAD. The present study contributes novel data relevant to these questions by comparing GAD, other anxiety disorders, and depressive disorders in terms of developmental features and risk factors.

Our results suggest some similarities and differences among GAD, other anxiety disorders, and depressive disorders. Although the age-of-onset distribution for GAD appears more similar to depressive disorders than specific and social phobias, panic disorder and agoraphobia also

resembled GAD and depression. Furthermore, temporal comorbidity for GAD showed at least as strong a tie to other anxiety disorders as to depressive disorders. More persuasive evidence linking GAD to anxiety comes from our findings of risk associations in familial, temperamental/personality, and environmental variables. Our findings differentiate patterns for anxiety and depressive disorders, with GAD showing more similarities to anxiety than depression.

The diagnosis of GAD first appeared in the *DSM-III*,⁸³ when the traditional concept of anxiety neuroses was abandoned in favor of descriptive, phenomenological approaches. Although originally a residual diagnostic class, GAD gained status as a unique condition based on steadily accumulating evidence.^{32,84-86} At the same time, however, debate has surrounded the categorization of GAD as an anxiety disorder as opposed to a depressive disorder. Most prominently, this debate is fueled by data on comorbidity and factor structure,^{7,9,10,13,14,38,58} yet other, more substantial work also influences this discussion.^{15-27,29,31,35-37,82} To date, however, few studies have examined similarities and differences in developmental features and risk factors by directly comparing GAD with other diagnostic groups. Most prior studies compared selected features of GAD and major depression^{16,24,25} without considering relationships to other anxiety disorders. The present study fills this gap by comparing developmental patterns and risk factors among GAD, anxiety disorders, and depressive disorders, including major depression and dysthymia.

Table 4. Associations Between Putative Risk Factors and GAD, Anxiety, and/or Depressive Disorders

Putative Risk Factor	GAD ^a		Anxiety but No Depressive Disorder ^b		Depressive but No Anxiety Disorder ^b		Anxiety and Depressive Disorder ^b	
	HR ^c (95% CI)	P Value	HR ^c (95% CI)	P Value	HR ^c (95% CI)	P Value	HR ^c (95% CI)	P Value
Parental disorders								
GAD ^a	3.77 (2.27-6.26)	<.001 ^d	1.75 (1.31-2.34)	<.001	1.05 (0.73-1.50)	.80	1.54 (1.06-2.25)	.03
Anxiety disorder but no depressive disorder ^b	1.76 (0.97-3.18)	.06	1.13 (0.83-1.54)	.45	1.25 (0.89-1.76)	.20	1.31 (0.88-1.96)	.19
Depressive disorder but no anxiety disorder ^b	1.77 (1.05-2.98)	.03	0.79 (0.56-1.11)	.18	1.71 (1.31-2.22)	<.001	1.21 (0.83-1.77)	.32
Anxiety and depressive disorder ^b	1.46 (0.70-3.01)	.31	1.46 (1.02-2.09)	.04	1.46 (0.99-2.14)	.05	1.61 (1.04-2.49)	.03
Substance-use disorder but no anxiety or depressive disorder ^b	0.60 (0.17-2.16)	.43	1.04 (0.54-2.00)	.91	0.76 (0.39-1.48)	.42	1.67 (0.85-3.26)	.14
Temperament/personality								
Behavioral inhibition ^e	1.97 (1.66-2.33)	<.001 ^d	1.39 (1.26-1.53)	<.001	1.08 (0.98-1.20)	.14	1.62 (1.45-1.81)	<.001
Novelty seeking ^e	0.94 (0.76-1.15)	.53	1.01 (0.88-1.16)	.89	1.10 (0.96-1.25)	.16	1.01 (0.86-1.20)	.87
Harm avoidance ^e	1.69 (1.37-2.09)	<.001 ^d	1.29 (1.14-1.47)	<.001	1.21 (1.06-1.37)	.003	1.57 (1.35-1.83)	<.001
Reward dependence ^e	1.43 (1.07-1.90)	.02 ^d	0.91 (0.78-1.06)	.24	1.09 (0.95-1.25)	.21	1.00 (0.83-1.21)	.98
Resilience ^{e,f}	0.84 (0.55-1.29)	.43	0.90 (0.78-1.02)	.11	0.79 (0.66-0.95)	.01	0.72 (0.61-0.86)	<.001
Environmental factors								
Childhood separation events	2.44 (1.54-3.85)	<.001 ^d	1.35 (1.02-1.79)	.04	1.07 (0.80-1.43)	.65	2.05 (1.49-2.83)	<.001
Parental emotional warmth ^{e,f}	0.91 (0.55-1.51)	.72	0.92 (0.79-1.06)	.24	0.69 (0.57-0.83)	<.001	0.96 (0.77-1.19)	.69
Parental rejection ^{e,f}	1.20 (0.94-1.53)	.14	1.11 (0.99-1.25)	.08	1.34 (1.18-1.51)	<.001	1.33 (1.13-1.56)	<.001
Parental overprotection ^{e,f}	1.48 (1.07-2.05)	.02	1.16 (1.02-1.32)	.02	1.12 (0.92-1.36)	.25	1.34 (1.13-1.59)	.001
Dysfunctional family functioning ^{e,f}	1.48 (1.05-2.07)	.02	1.13 (0.98-1.30)	.08	1.11 (0.91-1.35)	.30	1.12 (0.92-1.37)	.26

Abbreviations: CI, confidence interval; GAD, generalized anxiety disorder; HR, hazard ratio.

^aIncludes comorbid cases.

^bDoes not include cases with comorbid GAD.

^cHazard ratio calculated from survival analyses with Cox regressions, stratified by sex and age.

^dSignificant at the .05 level after adjusting for comorbid anxiety and depressive disorders.

^eStandardized scores were used for calculations.

^fAssessed at the first follow-up assessment (T1; subsample only).

Comparing first anxiety disorders alone and then depressive disorders alone, some common risk associations as well as considerable differences were found. For both groups, harm avoidance was an associated factor, and shared familial liability, reflected by parental comorbid anxiety and depression, was indicated. Parental GAD, behavioral inhibition, childhood separation events, and overprotective rearing, however, were specific to anxiety disorders; a history of parental depression alone, low parental emotional warmth, and high degrees of parental rejection were specific to offspring depressive disorders. These findings are largely consistent with evidence from prior studies suggesting commonalities but also some specificity in the etiopathogenesis of anxiety and depressive disorders.^{2,3,87-95} Also consistent with prior research^{25,90} is our finding that comorbid anxiety and depressive disorders reveal an overall broader risk profile. In this context, it should be emphasized that anxiety disorders may themselves be a risk factor for the development of depressive disorders,² possibly owing to impairments or other characteristics associated with the respective condition.^{47,96} The incidence and temporal priority patterns indicate a considerable earlier onset of any anxiety disorder compared with depression, particularly owing to the early onset of specific and social phobias. Despite indications for the existence of bidirectional associations between anxiety and depressive disorders, mostly owing to the later-onset agoraphobia and panic disorder, this supports the view that anxiety disorders are powerful risk factors for secondary depression as the most frequent trajectory. This is in agreement with findings from many other studies^{1,51,97-102} and has led some to suggest that, similar to somatic disorders, staging models may be of potential value

for specifying the complexity of developmental patterns of mental disorders.¹⁰³

Against expectations arising from comorbidity and factor-structure findings, our study provides little evidence that GAD is more similar to depressive than anxiety disorders. As in other studies,^{24,38,79,104} we do find that GAD and depressive disorders exhibit similar age-of-onset patterns and strong bidirectional associations. However, the predictive association of depression with GAD was attenuated when adjusting for prior anxiety disorders. Moreover, we found an onset pattern in agoraphobia and panic disorder that appeared similar to GAD; we also found strong bidirectional associations between GAD and anxiety disorders, associations that are at least as strong as those to depression. As with other data,^{32,33,43,105} these observations challenge the suggestion that GAD relates more strongly to depression than to anxiety disorders.

Most important, risk profiles revealed that overlapping factors were either not specific for GAD and depressive disorders (harm avoidance) or were accounted for by comorbidity (parental depressive disorder alone). In contrast, other factors (parental GAD, behavioral inhibition, childhood separation events, and parental overprotection) showed a more consistent pattern of overlap between GAD and anxiety disorders. Therefore, with the possible exception of a familial liability for depressive disorders, no evidence was found for common risk factors for depressive disorders and GAD differing from those of anxiety disorders; relatively consistent evidence was found, however, for specific commonalities in risk associations for anxiety disorders and GAD that differ from those of depressive disorders. These findings are generally in line with previous indications that,

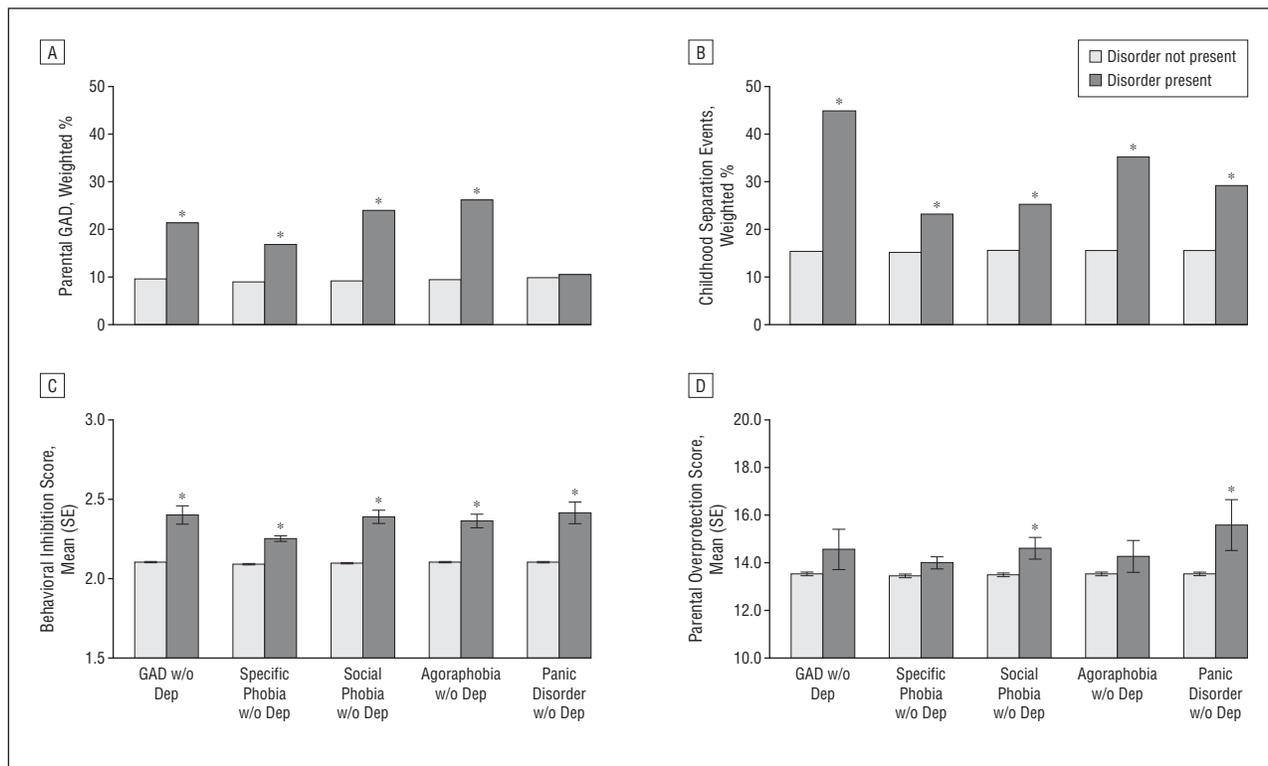


Figure 2. Comparison of anxiety-specific risk variables among anxiety disorders without comorbid depression (Dep). Risk variables are parental generalized anxiety disorder (GAD) (A), childhood separation events (B), behavioral inhibition (C), and parental overprotection (D). For all the specific anxiety disorders, interanxiety comorbidity was possible. *Hazard ratio is significant at the .05 level.

although the genetic contributions to GAD and major depression may be the same,¹⁷⁻¹⁹ other, environmentally mediated factors may differ.^{15-19,24-30}

Only a few prior studies examined the question of differential risk factors in GAD and major depression.^{16,24,25} One methodologically sound study²⁵ compared pure GAD and pure major depression in a large representative birth cohort and found, consistent with our study, a set of risk factors for GAD that is not shared with major depression. Beyond this, our study adds evidence that, in terms of risk constellations, GAD seems to be more closely related to anxiety than depressive disorders. Specifically, GAD was associated with each of the factors for which anxiety specificity was indicated (parental GAD, behavioral inhibition, childhood separation events, and parental overprotection), factors previously shown to be related to various anxiety disorders.^{106,107}

Overall, our data suggest that there is little evidence for GAD being more closely related to depressive than anxiety disorders. Of significance, this conclusion appears to be robust even with variations in methods. Findings in our risk analyses were largely retained when, in accordance with the procedures of other studies, the minimum duration requirement for GAD was decreased to increase comparability to major depression (eTable 1),^{17,18,25} when the depression group was restricted to major depression cases with or without consideration of hypomania or mania (eTable 3),^{24,25,38} and when posttraumatic stress disorder and obsessive-compulsive disorder were additionally considered among the anxiety disorders (eTable 2), as suggested by the *DSM-IV*.¹² Additional support for our con-

clusion comes from the finding that childhood separation anxiety disorder, consistent with earlier studies,¹⁰⁸ was found to be a strong predictor for both GAD and phobias/panic but not for depressive disorders. Moreover, GAD was still related with the anxiety-specific predictors when adjusting for comorbidity and when considering only GAD without comorbid depression. Therefore, none of the analyses revealed findings in favor of a different conclusion.

Of note, although anxiety-specific predictors were found across various individual anxiety disorders, there was also some indication for heterogeneity. Particularly for GAD, reward dependence and adverse family functioning appeared as specific predictors. Although the high levels of reward dependence in our participants with GAD were unexpected given previous findings from patient studies,^{109,110} overall, our findings favorably agree with prior research on family dysfunction and distress^{111,112} as well as indications for poor childhood attachment experiences and vulnerable current state of mind with respect to attachment in GAD.¹¹³ However, more work is needed to understand the specific contribution of these factors in the development of GAD. More generally, our findings suggest increasing research on genetic, biological, and environmental factors as well as their interplay in critical time periods¹¹⁴⁻¹¹⁶ to identify diagnosis-specific etiological pathways and mechanisms involved in the development of complex psychopathological conditions.

Of course, our study is not without limitations. First, with a maximum age of 34 years, our sample is relatively young. Individuals with anxiety disorder alone and depressive disorder alone may still develop comorbidity with

the other group. Second, owing to the sample including relatively few GAD cases without any comorbid lifetime anxiety or depressive disorder, we were not able to perform analyses among cases with GAD alone. Third, consistent with other studies,^{24,25,38} we did not apply the *DSM-IV* diagnostic exclusion rules for GAD. However, this poses a tough test of our research question because this procedure avoids artificially lowering comorbidity with depressive disorders. Of note, a body of research shows that applying exclusion criteria does not drastically decrease prevalence rates for GAD,¹⁰⁵ and even GAD without comorbid depression is characterized by functional impairments and disabilities¹¹⁷; eliminating the exclusion criterion for GAD has been suggested.¹¹⁸ Fourth, the relatively low test-retest reliability of the GAD *DSM-IV/M-CIDI* diagnosis should be noted. Still, the test-retest reliability of the GAD stem question was good,⁵³ and supplementary analyses considering GAD with shorter minimum durations revealed similar results. Fifth, we did not use a strictly prospective analysis approach for all risk factors¹¹⁹ because this would have drastically limited the study power and, thus, the generalizability of the results. The selection of predictor variables was based on empirical evidence suggesting the temporal precedence of these factors in the development of mental disorders. For example, although one could consider the assessment as being confounded, we included temperamental/personality measures as predictors because personality and temperament are conceptualized as traits, largely genetically determined, measurable early in life, and relatively stable over time.¹²⁰⁻¹²⁴ Finally, we examined a restricted number of predictor variables and cannot exclude the possibility that more overlapping risk profiles would emerge under consideration of more or other factors. The choice of variables must be carefully considered when validating diagnoses for purposes of accurate classification.¹²⁵

To conclude, based on our findings and considerations, anxiety and depressive disorders appear to be remarkably different with regard to risk constellations and temporal longitudinal patterns. Generalized anxiety disorder appears to clearly differ from depression, and our study results provide novel evidence that GAD is in fact closer to anxiety disorders than to depressive disorders. Although more work is needed on the unique etiological pathways for GAD, it seems premature, at the least, to classify GAD with the depressive disorders.

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Correspondence: Katja Beesdo, PhD, Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Chemnitz St 46, 01187 Dresden, Germany (Katja.Beesdo@tu-dresden.de).

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