ORIGINAL ARTICLE

Incidence of Social Anxiety Disorder and the Consistent Risk for Secondary Depression in the First Three Decades of Life

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Context: Epidemiological findings demonstrating an increased risk for individuals with social anxiety disorder (SAD) to develop depression have been challenged by discrepant findings from prospective longitudinal examinations in childhood and early adolescence.

Objectives: To examine patterns of SAD incidence, the consistency of associations of SAD with subsequent depression, and distal and proximal predictors for subsequent depression.

Design: Face-to-face, 10-year prospective longitudinal and family study of up to 4 waves. The *DSM-IV* Munich–Composite International Diagnostic Interview was administered by clinically trained interviewers.

Setting: Community sample in Munich.

Participants: Three thousand twenty-one individuals aged 14 to 24 years at baseline and 21 to 34 years at follow-up.

Main Outcome Measures: Cumulative incidence of SAD and depression (major depressive episode or dysthymia).

Results: Cumulative incidence for SAD was 11.0%; for depression, 27.0%. Standardized person-years of incidence for SAD were highest for those aged 10 to 19 years (0.72%) and were low before (0.20%) and after (0.19%) that age range. Depression incidence was different, characterized by delayed and continued high rates. Social anxiety disorder was consistently associated with subsequent depression, independent of age at onset for SAD (relative risk range, 1.49-1.85, controlling for age and sex). Crude Cox regressions showed significant distal (eg, parental anxiety or depression, behavioral inhibition) and proximal SAD characteristics (eg, severity measures, persistence) as predictors. Most associations were attenuated in multiple models, leaving behavioral inhibition (hazard ratio, 1.30 [95% confidence interval, 1.04-1.62; $P=.02$]) and, less consistently, panic (hazard ratio, 1.85 [95% confidence interval, 1.08-3.18; $P=.03$]) as the remaining significant predictors.

Conclusions: Social anxiety disorder is an early, adolescent-onset disorder related to a substantially and consistently increased risk for subsequent depression. The demonstration of proximal and particularly distal predictors for increased depression risks requires further exploration to identify their moderator or mediator role. Along with previous evidence that comorbid SAD is associated with a more malignant course and character of depression, these results call for targeted prevention with the aim of reducing the burden of SAD and its consequences.

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Large-scale epidemiological studies worldwide have provided relatively convergent prevalence estimates of *DSM-IV* social anxiety disorder (SAD) and its correlates and associations with other mental disorders, particularly depression, in the general population (eg, the National Comorbidity Survey [NCS],[1-3] Mental Health Stratified subsample of the Supplement to the Ontario Residents of Households Health Survey [MHS-OHS],[4] the Netherlands Mental Health Survey and Incidence Study [NEMESIS],[5,6] Early Developmental Stages of Psychopathology [EDSP] Study,[7-9] German Health Interview and Examination Survey [NHS],[10,11] Australian Mental Health Survey [ANMHS],[12] European Study of the Epidemiology of Mental Disorders [ESEMeD],[13,14] National Institute on Alcohol Abuse and Alcoholism National Epidemiological Survey on Alcohol and Related Conditions [NIAAA-NESARC],[15] and National Comorbidity Survey Replication [NCS-R][16,17]). Owing to the retrospective nature of these mostly cross-sectional studies and the wide age range (16 to ≥65 years), however, it remains unclear whether SAD actually predicts the onset of subsequent depression. Moreover, patterns of incidence for SAD remain understudied, particularly with regard to the period that has been suggested in retrospective studies as the peak risk phase, ie, the first 3 decades of life.[18,19] A better de-

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scription of the incidence patterns of SAD in its early developmental stages is important for a better understanding of the etiologic factors involved in the first onset of SAD and in particular the temporal patterns and potential causal mechanisms involved in the onset of subsequent depression. Furthermore, such data are essential to early intervention and the prevention of more severe stages of SAD and its complications as the onset of subsequent depression.

Several reports from clinical[20,21] and nonclinical studies[3,8,9,22-25] suggest that SAD predicts an increased risk for depression. However, few studies use prospective designs in epidemiological samples, and most of those that do focus on adults. Because SAD may start as early as childhood, studies examining the longitudinal association between SAD and depression should ideally begin at least in early adolescence and must ensure a sufficient observation period into adulthood to examine the risk of depression. To our knowledge, only 2 prospective epidemiological studies have examined the association between childhood or adolescent SAD and adult depression risk. Pine et al[26] found no association between the 2 conditions in an upstate New York sample, but the adult follow-up only extended into the middle 20s. Because onset of depression might also occur later, that study may have underestimated the strength of the relationship. Stein et al[8] and Bittner et al[22] used 4 to 5 years of prospective longitudinal data in 14- to 24-year-old individuals from the EDSP Study and demonstrated, using different methods, that SAD is prospectively associated with an increased risk for incident depression. However, Stein et al[8] also analyzed separate cohorts (aged 14-17 and 18-24 years at baseline) and found that this association seems to be restricted to the older cohort of individuals aged 18 to 24 years at baseline. As with Pine et al,[26] it has been speculated that the absence of the SAD-depression association for the younger cohort (aged 14-17 years at baseline) may be attributed to the fact that, owing to the relatively short follow-up, these SAD cases had not yet passed through the peak period for first onset of depression.

The present study reexamines these issues by using 10 years of recently available prospective data from the EDSP Study, thus extending the examination by Stein et al[8] by an additional 5 years of observation. We further provide for the first time a more complete description of incidence patterns of SAD and depression from the early adolescent period to 34 years of age and will examine the consistency of the association between SAD and adult depression for different SAD age-at-onset groups. In addition, several distal risk factors and proximal SAD characteristics will be explored in their ability to predict onset of subsequent depression.

METHODS

SAMPLE

The EDSP Study is a prospective longitudinal study designed to collect data on the prevalence, incidence, comorbidity, risk factors, and course of mental and substance use disorders in a representative sample that originally included 3021 adolescents and young adults aged 14 to 24 years at baseline (T_0). The study also includes 3 follow-up surveys (T_1, T_2, and T_3), a family history component, and direct information from the parents assessed at T_1.[7,27,28]

The baseline sample was drawn in 1994 from government registries in the greater Munich area of registrants expected to be aged 14 to 24 years at the T_0 interview in 1995. Because the study emphasized early developmental stages of psychopathology, individuals aged 14 to 15 years were sampled at twice the probability of those aged 16 to 21 years, and individuals aged 22 to 24 years were sampled at half the probability of those aged 16 to 21 years.

Most interviews throughout the study took place in the respondents' homes or, in some instances, at another location preferred by the respondent. Approximately one-third of the sample received a financial incentive ($10-$20) to participate. Participants provided informed consent; parental consent was provided for respondents 18 years or younger.

The baseline sample (N=3021) is representative of the greater Munich population aged 14 to 24 years; baseline response rate was 70.8%. Refusal to participate in the survey (18.2%) was by far the most frequent reason for nonresponse, followed by a reported lack of time (3.3%), failure to contact anyone in the identified household (3.1%), and failure to contact the sampled individual in the household (3.0%) (1.6% were lost owing to other reasons). The first follow-up survey (T_1) was conducted only for individuals aged 14 to 17 years at baseline, whereas the second (T_2) and third (T_3) follow-up surveys were conducted for all individuals. At T_1 (median interval since baseline, 1.6 years; interval range, 1.2-2.1 years), 1228 interviews were completed (response rate, 88.0%). A total of 2548 of the original 3021 individuals (response rate, 84.3%) took part in T_2 (median interval since baseline, 3.5 years; interval range, 2.8-4.1 years). In all, 2210 individuals participated in T_3 (response rate, 73.2%; median interval since baseline, 8.2 years; interval range, 7.3-10.6 years). A more detailed description of the study and the demographic characteristics of the sampled population and the respondents has been reported elsewhere.[7,27,28]

DIAGNOSTIC ASSESSMENT

Individuals were interviewed with the computer-assisted Munich–Composite International Diagnostic Interview (DIA-X/M-CIDI)[29,30] and its embedded assessment modules.[7,27,28] The DIA-X/M-CIDI allows for the assessment of symptoms and syndromes and for the diagnosis of 48 mental disorders, along with information about onset, duration, severity, and psychosocial impairment. Trained clinical interviewers (ie, clinical psychologists) performed the 2- to 3-hour face-to face interviews. Diagnoses of mental disorders were obtained by using the M-CIDI *DSM-IV* algorithms. The DIA-X/M-CIDI is supplemented by a separate respondent's booklet 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,[30-32] along with descriptions of the DIA-X/M-CIDI format and coding conventions.

At baseline, the lifetime version of the DIA-X/M-CIDI was used. At each of the follow-up assessments, we applied the DIA-X/M-CIDI interval version, which refers to the period between the last and the current assessment. Findings presented herein are based on the aggregation of all available information for each participant from baseline to T_3 (for individuals aged 14-17 years at baseline, T_0, T_1, T_2, and T_3; for individuals aged 18-24 years at baseline, T_0, T_2, and T_3).

The diagnosis of SAD was assigned according to the *DSM-IV* DIA-X/M-CIDI diagnostic algorithms.[9] *Depressive disorder* was defined as meeting *DSM-IV* criteria for 1 or more episodes of

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major depression (MDE) or dysthymia (without using the exclusion criteria). The test-retest reliability of diagnostic categories ranged from κ values of 0.68 for major depression to 0.72 for SAD.[30] The validity of these DIA-X/M-CIDI diagnoses compared with independent clinical consensus diagnoses by treating physicians was estimated with κ values of 0.54 for dysthymia, 0.80 for SAD, and 0.96 for MDE.[31]

All SAD characteristics reported herein were also derived from the DIA-X/M-CIDI SAD section.[9] Age-at-onset information was based on the lowest age at onset reported by the respondent at any of the assessment waves.[33] This definition of age at onset agreed well (>90%) with other age-at-onset aggregation methods (ie, first and mean age at onset over the 4 EDSP assessments); ie, the absolute value of differences were at most 1 year for both SAD and depression, besides that lower agreement rates (about 70%) were found for depression when the mean method was used. *Duration* of SAD was calculated as the number of years between age at onset of SAD and the highest reported age at recency. *Degree of avoidance* refers to the frequency at which social situations were avoided owing to anxiety (never, rarely, frequently, or always; mean across all completed waves). If respondents reported no avoidance, they were further asked whether they had always tolerated such situations. A negative response was used as an indicator of rare avoidance. The SAD severity indicators included the following:

1. The *number of social situations* refers to the number of reported social situations in the M-CIDI avoided or endured with anxiety by the respondent (range, 1-7).
2. The *number of anxiety cognitions* refers to the reported count of having 1 or more of the following M-CIDI cognitions: (1) something embarrassing or shameful could happen; (2) being regarded as dumb or weak; (3) being regarded as crazy; (4) to experience an anxiety (panic) attack; (5) to be confused; (6) to be ashamed; (7) to throw up; (8) to lose control over intestinal organs; or (9) to turn red whenever one was in a social situation, thought about it, or was about to enter such a situation.

Degree of impairment reflects how much the anxiety of social situations or avoidance interfered with life and daily activities (not at all, a little, much, or very much). For each of these indicators, a total mean score across all completed waves was generated. *Persistence* of SAD is based on an index constituting the following elements: (1) degree of SAD expression at each wave (0 indicates none; 1, symptomatic; 2, subthreshold; and 3, threshold); (2) persistence of anxiety or avoidance of social situations for months or years (1 indicates no persistence; 2, persistence); (3) degree of avoidance (1 indicates partial; 2, complete avoidance); and (4) frequency of anxiety and avoidance (1 indicates none; 2, rarely; 3, sometimes; and 4, always). The persistence index was calculated by multiplying the mean scores of the 4 components; the resulting overall persistence score ranged from 0.75 to 24.00.

From the DIA-X/M-CIDI response booklet, the following scales were selected to examine risk factors and SAD-related characteristics in greater detail. The German version of the Retrospective Self-Report of Inhibition[34] (assessed at baseline) is composed of a set of 30 questions about specific childhood behaviors reflecting behavioral inhibition (BI), defined as consistent restraint in response to both social and nonsocial situations (sympathetic nervous system activity, fear of things, etc). The total mean BI score was chosen because the 2-dimensional scores did not reveal notably different findings. Internal consistency of the Retrospective Self-Report of Inhibition was found to be acceptable in clinical and nonclinical samples with the Cronbach coefficient α for the 30 questions of 0.77 or greater and median item-to-total correlations of $r \geq 0.31$. Validity was high as 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 relation of retrospective self-report and contemporary measures of inhibition, and accounts for variance in general and specific measures of mental health.[34] The self-reported Liebowitz Social Anxiety Scale,[35] a reliable and valid measure of SAD in patient samples,[36] was used at T_2 to assess the degree of anxiety in (0 indicates none; 1, mild; 2, moderate; and 3, severe) and the frequency of avoidance of (0 indicates never; 1, occasionally; 2, often; and 3, always) 23 social situations. For each of these scales, a sum score was generated (theoretical range, 0-69). The German version[37] of the Symptom Checklist-90–Revised was used at baseline to assess the presence of a broad range of psychological problems and symptoms of psychopathology referring to the past 7 days. In the present report, the phobic-anxiety subscale is used for the characterization of SAD individuals. The 1-week retest reliability of the subscales was found to be satisfactory to good (student sample; N=80; r_{tt}, 0.69-0.92). Internal consistencies (Cronbach coefficient α) for the subscales ranged in nonclinical samples from 0.51 to 0.83.

For the present article, the scores from these questionnaires were standardized, resulting in a mean of 0 (SD, 1) in the weighted total sample; the reported associations thus indicate the change in outcome (or transformed outcome, respectively, eg, ln[odds] [the natural logarithm of the odds] in logistic regressions) per increase by 1 SD.

As previously reported,[38] *parental mental disorders* assessment was based on direct DIA-X/M-CIDI interviews with parents (n=1053) as part of the T_1 family assessments or on family history information as obtained in the family history module at T_2 and T_3 with the respondent as informant. Family history items were designed to take the family history research diagnostic criteria[39] as a basic model. Diagnostic information about parental mental disorders was aggregated, with predominance given to direct information from the interviewed parent (T_1) over indirect family history information (T_2/T_3); ie, whenever direct information was available, indirect information was ignored. Only the presence of any parental *DSM-IV* anxiety or depressive disorder was used herein.

STATISTICAL ANALYSIS

Data are weighted by age, sex, and geographic location at baseline to match the distribution of the sampling frame; frequencies are reported unweighted. The Stata software package, version 9.0,[40] was used to compute robust variances, 95% confidence intervals (CIs), and *P* values (by applying the Huber-White sandwich matrix), which are required when analyses are based on weighted data.[41]

Our analyses are based on a total sample of 3021 individuals and a subsample of 319 individuals who met the SAD criteria at any assessment wave. Two individuals with missing age-at-onset data were excluded. Associations between the cumulative SAD and depression occurrences were assessed with odds ratios (ORs) from logistic regressions while adjusting for sex and age. The association between SAD and subsequent depression was assessed with risk ratios from risk ratio regressions (procedure BINREG in Stata software[40,42]) and risk differences derived from logistic regressions (procedures LOGISTIC and Mfx in Stata software[40,43]). Referring to Greenland,[44] we prefer risk differences as a more appropriate measure than ORs or risk ratios when assessing interactions. Age-specific cumulative lifetime incidence rates were estimated with the Kaplan-Meier method. Cox regressions with hazard ratios (HRs) were used to assess factors of the transition from SAD and risk of subsequent depressive disorders. Our analyses on factors for the transition from SAD to depression are based on the time-dependent covariate SAD(t) in the person-year data file, de-

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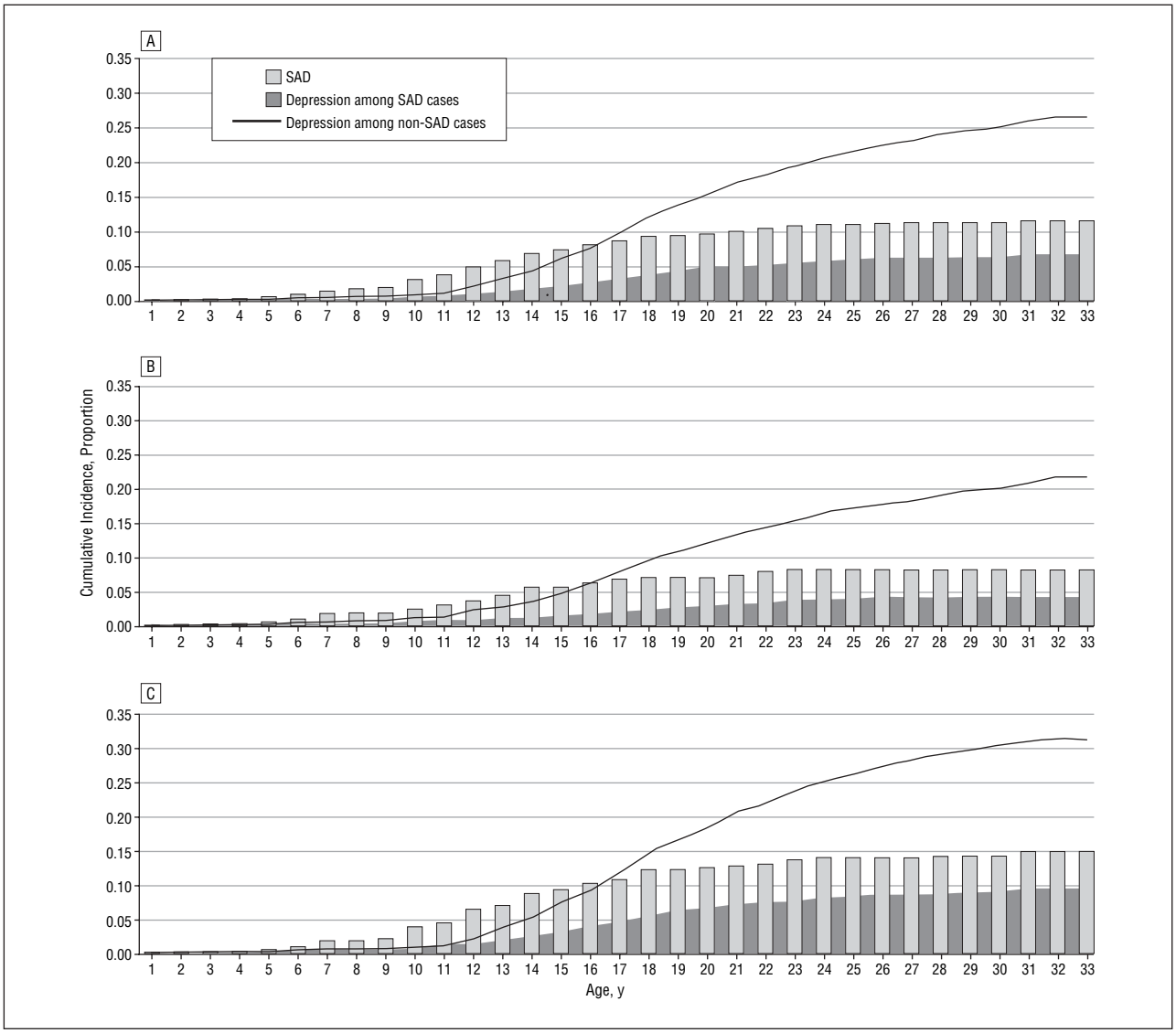

Figure. Overall age-dependent cumulative lifetime incidence of social anxiety disorder (SAD) and of depression (major depressive episode or dysthymia) in cases with or without the presence of SAD to age 33 years (based on a total of 3021 subjects [A], including 1533 males [B] and 1488 females [C] in up to 4 waves).

fined as 1 if SAD had ever been present before the age of t (assessed with age-at-onset data) and 0 otherwise. For the overall sample, the person-year data file included 36 753 units of observation; for the subsample with SAD(t), 1427 units were available. For some predictors, this number decreases slightly (by ≤5%) owing to missing information on the predictor. All Cox regressions were conducted using the strata variables age cohort and sex to adjust for effects of these variables.[45] We also calculated standardized incidence rates per person-year, defined as 100 times the number of incident cases in the risk period divided by the total number of person-years under risk.[46]

RESULTS

CUMULATIVE INCIDENCE

The overall cumulative incidence for SAD up to T_3 was 11.0% for the total sample (weighted; unweighted number, 319 of 3021), 8.0% for males (weighted; unweighted number, 120 of 1533), and 14.0% for females (weighted; unweighted number, 199 of 1488). The estimated age-dependent cumulative incidence rate for SAD at 33 years of age was 11.6%, and 8.2% and 14.9% for men and women, respectively (**Figure**). The incidence of SAD increased steeply after 9 years of age and then gradually decreased, with the inflection point occurring around 17 years of age in boys and 19 years of age in girls. The standardized incidence rates per person-year were highest (0.72%) from 10 to 19 years of age (0.50% for males and 0.95% for females); considerably lower rates were found below (≤9 years, 0.20%) and above (20-34 years, 0.19%) this age range.

The overall cumulative incidence for depression (dysthymia and MDE) was 27.0% for the total sample (weighted; unweighted number, 782 of 3021), 20.8% for males (weighted; unweighted number, 302 of 1533), and 33.0% for females (weighted; unweighted number, 480 of 1488). The age-dependent cumulative incidence for depressive disorders at 33 years of age was 31.9%, and 25.2% and 38.5% for men and women, respectively. The Figure shows a considerably different—namely, delayed—

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Table 1. Risk for Subsequent Depression Among Individuals With or Without SAD by Onset of SAD Before a Specific Age

Age at Onset of SAD, y	No. of Subjects With SAD	Frequency of Subsequent Depression Among Cases, No. (Weighted %)		RR (95% CI)[a]	*P* Value	RD (95% CI)[a]	*P* Value
		Without Prior SAD	With Prior SAD				
<11	88	693 (25.2)	33 (46.1)	1.64 (1.24-2.16)	<.001	0.18 (0.06-0.30)	.004
<12	114	671 (24.8)	42 (45.1)	1.64 (1.27-2.11)	<.001	0.18 (0.07-0.29)	.002
<13	150	617 (23.6)	57 (47.0)	1.85 (1.49-2.30)	<.001	0.22 (0.12-0.31)	<.001
<14	179	568 (22.4)	54 (40.5)	1.70 (1.34-2.14)	<.001	0.17 (0.08-0.26)	<.001
<15	214	512 (21.1)	57 (38.0)	1.71 (1.35-2.16)	<.001	0.16 (0.07-0.24)	<.001
<16	228	451 (19.4)	52 (36.0)	1.77 (1.40-2.25)	<.001	0.15 (0.07-0.23)	<.001
<17	247	384 (17.6)	41 (30.5)	1.60 (1.22-2.11)	<.001	0.11 (0.03-0.19)	.006
<18	260	321 (15.4)	32 (24.2)	1.49 (1.08-2.05)	.02	0.07 (0.00-0.15)	.05
<19	279	255 (12.7)	34 (25.1)	1.83 (1.33-2.50)	<.001	0.10 (0.03-0.17)	.005
<20	283	215 (10.9)	24 (18.9)	1.63 (1.12-2.38)	.01	0.06 (0.00-0.12)	.05

Abbreviations: CI, confidence interval; RD, risk difference; RR, risk ratio; SAD, social anxiety disorder.
[a] Adjusted for sex and age.

age-dependent incidence function for depression among both individuals with and individuals without SAD as compared with the incidence function of SAD. Incidence rates for depression were increasing across the age spectrum considered in both sexes. Besides the overall higher cumulative incidence, the incidence curve for depression differed among lifetime SAD and non-SAD cases. Although there were continuing high incidences of depression among non-SAD cases, depression incidence decreased after 25 years of age in men and after 26 years of age in women. By 21 years of age in women and 26 years of age in men, the cumulative incidence of depression among SAD cases had reached about 50% of the cumulative incidence of SAD; a further increase of this proportion at higher ages was observed for women only (about 65% at 33 years of age).

SAD AND RISK FOR DEPRESSION

Overall, 50.2% (weighted; unweighted number, 152 of 319) of respondents with SAD also had a depressive disorder during the observation period. The overall association between SAD and depression was substantial (OR, 3.18 [95% CI, 2.45-4.14]) and decreased only slightly when controlling for age (OR, 3.12 [95% CI, 2.40-4.06]), sex (OR, 2.98 [95% CI, 2.28-3.89]), or age and sex (OR, 2.92 [95% CI, 2.23-3.81]; for all, $P<.001$). Social anxiety disorder was found to be the temporal primary disorder in most of the cases (59.3% [weighted; unweighted number, 89 of 150]); 11.7% (weighted; unweighted number, 18) reported an onset in the same year, and 28.4% (weighted; unweighted number, 43) reported an onset of depression before SAD. There were no significant differences between SAD cases with prior, same-year, or subsequent onset of depression on sociodemographic and clinical characteristics. As shown by Cox regressions, the risk for subsequent depression was 2-fold in individuals with SAD compared with respondents with no SAD (HR, 2.02 [95% CI, 1.59-2.57]) and almost 3-fold in individuals with SAD compared with respondents with no anxiety disorder (HR, 2.60 [95% CI, 2.03-3.34; for both, $P<.001$]). (Note: The conditional risk for depression by SAD status is not displayed in the Figure; the Figure shows the overall cumulative lifetime incidence of SAD and depression.) This increase in depression risk was found for both the generalized (HR for the comparison with no SAD, 2.64 [95% CI, 1.84-3.79]; HR for the comparison with no anxiety disorder, 3.39 [95% CI, 2.35-4.88]) and the nongeneralized subtype of SAD (HR for the comparison with no SAD, 1.76 [95% CI, 1.31-2.38]; HR for the comparison with no anxiety disorder, 2.27 [95% CI, 1.67-3.08; for all, $P<.001$]). The difference in depression risk between individuals with generalized compared with the nongeneralized subtype of SAD was not significant (HR, 1.47 [95% CI, 0.93-2.34; $P=.10$]).

ROLE OF AGE AT ONSET OF SAD FOR SUBSEQUENT DEPRESSION RISK

To examine whether the occurrence of SAD in different developmental stages is associated with a different probability for subsequent depression, we examined the proportion of depression occurrences (overall, n=782) in individuals who had or did not have SAD up to a certain age (**Table 1**). Because almost all SAD onsets occurred before the age of 20 years, only ages younger than 11 years to ages younger than 20 years were considered. Table 1 shows that the eligible SAD cases in each age-at-onset row had a significantly higher risk for onset of subsequent depression compared with cases without SAD. Although this difference occurred irrespective of the age at onset of SAD, it was most pronounced for onsets from younger than 11 years to younger than 16 years.

Recent prospective studies with a shorter follow-up period extending only to the mid 20s[8,26] did not find an association between SAD and incident depression among younger adolescents but did find one among older adolescents and young adults. Using our 10-year follow-up data extending up to the mid 30s, we examined interactions for the older birth cohort (aged 18-24 years at baseline) vs the younger birth cohort (aged 14-17 years at baseline) in the prediction of subsequent depression among cases with SAD onset to a certain age. No interactions were found for birth cohort (a table is available from the authors on request). Both younger and older partici-

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Table 2. Variables Predicting the Onset of Depression Among Those Who Have Ever Had SAD Before the Respective Age (Cox Regression With Time-Dependent Covariate)

Predictors for Subsequent Depression Among SAD Cases	Crude Associations (n = 2591)[a]	*P* Value	Multiple Model (n = 2476)[b]	*P* Value	Separate Models[c]	*P* Value
Distal characteristics						
Sex (female vs male)	1.69 (1.11-2.56)	.01	1.48 (0.87-2.52)	.15	1.54 (0.93-2.53)	.09
Familial vulnerability (any anxiety disorder or MDE among parents)[d]	1.74 (1.09-2.77)	.02	1.14 (0.69-1.88)	.61	1.25 (0.81-1.93)	.32
Dispositional vulnerability (BI, standardized total score)[e]	1.41 (1.18-1.69)	<.001	1.34 (1.02-1.76)	.03	1.30 (1.04-1.62)	.02
No. of comorbid anxiety disorders before depression[f]						
1 vs 0	1.33 (0.78-2.28)	.30	1.30 (0.74-2.31)	.36	1.30 (0.77-2.21)	.33
2 vs 0	1.66 (0.95-2.90)	.08	1.11 (0.49-2.48)	.81	1.29 (0.68-2.45)	.44
≥3 vs 0	3.51 (1.62-7.62)	.002	1.68 (0.54-5.22)	.37	1.99 (0.89-4.45)	.09
Proximal SAD characteristics						
Avoidance						
Degree of avoidance[g]	1.17 (0.83-1.65)	.38	0.87 (0.51-1.48)	.60	0.92 (0.55-1.54)	.76
Liebowitz avoidance sum score (standardized)[h]	1.03 (0.95-1.11)	.51	1.04 (0.82-1.31)	.75	1.01 (0.79-1.30)	.94
Severity						
No. of feared social situations[i]	1.37 (1.09-1.72)	.008	1.10 (0.63-1.92)	.74	1.22 (0.73-2.02)	.45
Liebowitz anxiety sum score (standardized)[j]	1.04 (0.96-1.14)	.33	0.97 (0.74-1.27)	.81	0.94 (0.70-1.25)	.67
No. of anxiety cognitions[k]	1.29 (1.09-1.52)	.003	1.06 (0.73-1.53)	.78	1.24 (0.86-1.79)	.25
Panic						
Comorbid panic attack[l]	2.21 (1.34-3.63)	.002	1.34 (0.67-2.68)	.40	1.85 (1.08-3.18)	.03
Fear of anxiety attack in social situation[m]	1.67 (1.04-2.68)	.03	1.40 (0.78-2.52)	.26	1.23 (0.70-2.17)	.47
SCL-90–R phobic anxiety score (standardized)[n]	1.15 (1.04-1.27)	.008	0.97 (0.83-1.14)	.70	1.10 (0.99-1.23)	.09
Degree of impairment[o]	1.43 (1.01-2.04)	.04	0.82 (0.45-1.50)	.52	0.84 (0.46-1.55)	.58
Persistence, index score (standardized)[p]	1.23 (1.02-1.48)	.03	1.11 (0.83-1.47)	.49	1.03 (0.79-1.34)	.84
Duration of SAD[q]	1.01 (0.95-1.07)	.72	0.98 (0.92-1.05)	.64	1.00 (0.94-1.06)	>.99

Abbreviations: BI, behavioral inhibition; CI, confidence interval; HR, hazard ratio; MDE, major depressive episode; SAD, social anxiety disorder; SCL-90–R, Symptom Checklist-90–Revised.

[a] Data are presented as HR (95% CI) and are weighted.

[b] Data are presented as HR (95% CI) and are weighted. Includes all vulnerability and SAD characteristics as predictors.

[c] Data are presented as HR (95% CI) and are weighted. Model 1 includes all vulnerability (distal) variables as predictors; model 2 includes all SAD characteristics (proximal variables) as predictors.

[d] Includes any anxiety disorder (panic, social phobia, specific phobia, agoraphobia, generalized anxiety disorder, posttraumatic stress disorder, obsessive-compulsive disorder) or MDE based on direct family interview assessed at the first follow-up survey (T_1) or, if not available, on family history information assessed at respondents at the second (T_2) or third (T_3) follow-up survey.

[e] Indicates degree of BI, assessed with Retrospective Self-report of Inhibition (at baseline, total score; standardized, mean of 0 [SD=1] in weighted total sample).

[f] Includes specific phobia, phobia not otherwise specified, agoraphobia, panic disorder, generalized anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder.

[g] Mean across all completed waves, assessed in the Munich–Composite International Diagnostic Interview (M-CIDI) SAD section (range, 1 [never] to 4 [always]).

[h] Standardized score; adapted from Liebowitz Social Anxiety Scale (LSAS) assessed at T_2 (23 items; theoretical range, 0-49).

[i] Mean across all waves; assessed in the M-CIDI SAD section (range, 1-6).

[j] Standardized score; adapted from the LSAS, assessed at T_2 (23 items; theoretical range, 0-49).

[k] Mean across all waves; assessed in the M-CIDI SAD section (range, 1-9).

[l] Pertains to *DSM-IV* panic attack; assessed in the M-CIDI panic section.

[m] Assessed in the M-CIDI SAD section.

[n] Degree of phobic-anxiety; assessed with the SCL-90–R at baseline.

[o] Mean across completed waves; assessed in the M-CIDI SAD section (range, 1 [none] to 4 [very much]).

[p] Degree of persistence; assessed in the M-CIDI SAD section (index-score range, 0.75-24; includes degree of SAD expression at completed study waves [none, symptomatic, subthreshold, or threshold], notion of persistence of anxiety or avoidance of social situations for months or years, statement of complete avoidance of such situations, and frequency of anxiety and avoidance [none, rarely, sometimes, or always]).

[q] Time in years between age at onset and the maximum reported age at recency.

pants at the outset of the study who had developed SAD up to any of the defined ages had an increased risk for subsequent depression.

PREDICTORS OF THE PROGRESSION FROM SAD TO SUBSEQUENT DEPRESSION

To explore to what degree distal and proximal characteristics play a role in promoting the secondary depression risk in SAD, we first examined the crude associations between several putative distal risk factors and more proximal characteristics of SAD with onset of subsequent depression using Cox regressions (first column in **Table 2**). Among the distal factors, parental anxiety disorder and/or MDE, female sex, BI in childhood, and having multiple (≥3) other preceding anxiety disorders were found to be associated with increased risk for subsequent depression. Among the disorder characteristics, avoidance and duration of SAD were not associated with the risk of depression. Degree of impairment, persistence, and several indicators of greater severity of SAD were associated; a higher number of social anxiety situations and anxiety cognitions, occurrence of panic attacks, the fear of an anxiety attack in social situations, and a higher Symptom Checklist-90–Revised phobic-anxiety subscale score were all associated with second-

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ary depression among SAD cases. Although the *DSM-IV* distinction of generalized (defined as ≥3 anxiety situations) vs nongeneralized subtype of SAD (defined as 1-2 anxiety situations) did not show a significant association with subsequent depression risk (HR, 1.47 [95% CI, 0.93-2.34]), the number of feared social situations as a dimensional variable was significant (the change in hazard rate per increase by 1 anxiety situation was 1.37 [95% CI, 1.09-1.72]).

Subsequently, a series of multiple regression models were computed with all (second column in Table 2) and separate (third column in Table 2) groups of variables. Behavioral inhibition was the only variable that remained significant in the overall model for predicting subsequent depression among SAD cases (HR, 1.34 [95% CI, 1.02-1.76]). In the separate model for distal and proximal factors, BI (HR, 1.30 [95% CI, 1.04-1.62]) and the occurrence of panic attack in SAD (HR, 1.85 [95% CI, 1.08-3.18]) remained significant in the prediction of subsequent depression.

COMMENT

To our knowledge, this is the first report to describe and compare the patterns of incidence for *DSM-IV* SAD and depression among community individuals during the first 3 decades of life considered to cover the whole high-risk age period for first onset of SAD. The report is also a considerable extension of previous contributions from our group[8,22] because it covers a 10-year observation period rather than a 4-year span and demonstrates that SAD is associated with a consistently increased risk for incident depression in all ages considered.

The incidence patterns clearly support the notion of SAD as an early, adolescent-onset disorder; new-onset cases in the third decade of life, especially after 25 years of age, are rare. Although we also confirm the higher prevalence and incidence of SAD among females,[18] there is no notable sex difference in the onset distributions, with the exception of a more pronounced decrease of incidence after 20 years of age in men compared with women. For depression, a markedly different incidence function was found compared with SAD, characterized by a considerably later onset and depression incidences extending into the third and fourth decades of life. This observation is consistent with previous findings from cross-sectional retrospective studies covering a broader age range of respondents that yielded later median ages at onset in depression (20s and 30s[24,47]) compared with SAD (10s[17,24]) and similar prevalence and onset patterns.[10,48] However, according to our findings, the incidence curve of depression among cases without SAD showed continuous, high incidence rates from adolescence to the end of our observation period at 34 years of age, whereas the depression-onset curve among cases with SAD gradually plateaued after 25 years of age. This decrease in depression incidence was delayed but parallel to the decrease of SAD incidence after 21 years of age. Based on descriptive observational data, this might suggest an important role for SAD in a substantial proportion of early-onset depressions.

Our prospective analyses further provide strong support for the notion that SAD substantially increases the risk for subsequent depression. The overall effect is similar to the one reported in our previous publications[8,22] that covered only a 4-year follow-up. Because Stein et al[8] raised concerns about the nature of this relationship owing to the observation that the association between SAD and incident depression during the 4-year follow-up was found only in the older but not in the younger study cohort, we have now demonstrated with 10 years of prospective data that the risk for subsequent depression among individuals with SAD exists independent of the age at onset of SAD, as well as independent of the age of respondents. This suggests that the failure to show an association between SAD and subsequent depression in the previous reports[8,26] was most likely a result of the fact that individuals had not gone through the entire period of high risk for SAD and, particularly, depression.

The theoretical implications of this finding are that (1) the most vulnerable period for onset of SAD is limited to the adolescent years and that (2) SAD in adolescence yields a negative prognosis in terms of depression risk at any time during this period. This also lends strong support to the notion that early identification and intervention with socially anxious adolescents might therefore reduce risk for depressive disorders in adolescence and young adulthood, even more so because of previous demonstrations that SAD-comorbid depression is strongly associated with a more malignant course of depressive illness in terms of more suicidal ideation and suicide attempts, more depressive symptoms during episodes, more frequent and/or more protracted depressive episodes,[8] and poorer depression outcomes.[49] However, prevention of depression is hampered by the fact that few individuals with SAD receive adequate treatment, despite overall increased health care utilization.[9,50]

Thus, to what degree is this association mediated and/or moderated by other factors? Although this issue is beyond the scope of the present report, our exploratory multivariate regression analysis, in which a BI temperament, assessed with the Retrospective Self-report of Inhibition of Reznick et al,[34] was retained as the only significant predictor for secondary depression among all other distal and proximal variables, suggests that the depression risk seems to be particularly enhanced among vulnerable individuals with increased childhood BI. Along with Kagan's hypotheses[51] and indications that a BI temperament is also a vulnerability factor for SAD,[52-54] this finding suggests that high levels of BI might be used for defining high-risk target groups for primary prevention of SAD in childhood and adolescence and for secondary prevention of depression among individuals with SAD during adolescence and the transition to adulthood. However, this attractive speculation is tempered by data from the Dunedin Study.[55] That study did not find associations between BI and subsequent anxiety disorders, despite an association with later depression. However, other data, albeit in studies of younger subjects, suggest that BI is a risk factor for anxiety but not major depressive disorder.[54] This finding indicates that this question needs a more comprehensive analysis to identify the relevant interactions between vulnerability and risk factors in an

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attempt to identify the moderating and mediating role of a wider range of possible variables.

Furthermore, the partial failure to demonstrate a dose-response relationship between SAD severity characteristics and the risk of subsequent depression was unexpected. It seems counterintuitive, from a clinical perspective, that SAD characteristics such as severity, impairment, and persistence were not confirmed in the explorative multivariate analyses as significant predictors for subsequent depression. Only the occurrence of severe paniclike anxiety reactions remained significant in the separate multiple regression model. The core role of panic attacks is consistent with the *DSM-IV* and previous findings[22,56-58] that panic attacks are a sensible indicator for emerging severe psychopathology and depression in particular. Nevertheless, this finding needs replication and closer consideration in future studies. If this finding holds, however, it might be of substantial relevance. Given that most individuals with SAD do not get treated[1,9] on the one hand, but that the treatment of panic attacks may reduce the risk for developing major depressive disorder[59] and that approximately 10% of mood disorders may be prevented by successful early intervention in SAD[3] on the other hand, our results strongly suggest that we study the effects of early intervention programs in adolescent SAD, most importantly when panic attacks or high levels of BI co-occur.

These findings must be viewed in light of some limitations of our study. First, we did not include a psychopathological comparison group (ie, subjects with other anxiety disorders), and therefore it remains to be shown in a direct comparison whether the increased risk for subsequent depression is unique to SAD or whether the magnitude of the association is specifically pronounced in SAD—the most common form of anxiety comorbidity among depressed patients.[60,61] Previous findings suggest that the associations might not be specific to SAD.[22,26] However, it was shown that SAD without other comorbid anxiety disorders is predictive for depression onset, even when previous other disorders are controlled for.[22] Second, no causal inferences can be drawn from our observational data.[62,63] Third, we did not explore a more comprehensive range of risk factors, and in particular we did not examine whether the risk factors for subsequent depression among SAD cases are moderators or mediators of this association[64]; this will be dealt with in a follow-up report. Although we cannot rule out nonparticipation of most severely disturbed individuals, we did not find selective attrition for persons with SAD during the assessment waves. A final, more general notion of caution concerns the retrospective nature of diagnoses and age-at-onset information, despite the overall prospective-longitudinal design of our study.

To summarize, SAD is an early, adolescent-onset disorder related to a substantially and consistently increased risk for subsequent depression. Along with previous evidence that comorbid SAD is associated with a more malignant course and character of depression, these results call for testing prevention and early-intervention programs aimed at reducing the burden of SAD and its consequences. In doing so, BI and panic appear to be important indicators for targeting such programs; however, further exploration is necessary to identify their moderator or mediator role.

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