

Depression and Generalized Anxiety Disorder

Cumulative and Sequential Comorbidity in a Birth Cohort Followed Prospectively to Age 32 Years

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Context: The close association between generalized anxiety disorder (GAD) and major depressive disorder (MDD) prompts questions about how to characterize this association in future diagnostic systems. Most information about GAD-MDD comorbidity comes from patient samples and retrospective surveys.

Objective: To revisit the sequential and cumulative comorbidity between GAD and MDD using data from a prospective longitudinal cohort.

Design: Prospective longitudinal cohort study.

Setting: New Zealand.

Participants: The representative 1972-1973 Dunedin birth cohort of 1037 members was followed up to age 32 years with 96% retention.

Main Outcome Measures: Research diagnoses of anxiety and depression were made at ages 11, 13, 15, 18, 21, 26, and 32 years. Mental health services were reported on a life history calendar.

Results: Sequentially, anxiety began before or concurrently in 37% of depression cases, but depression began before or concurrently in 32% of anxiety cases. Cumulatively, 72% of lifetime anxiety cases had a history of de-

pression, but 48% of lifetime depression cases had anxiety. During adulthood, 12% of the cohort had comorbid GAD + MDD, of whom 66% had recurrent MDD, 47% had recurrent GAD, 64% reported using mental health services, 47% took psychiatric medication, 8% were hospitalized, and 11% attempted suicide. In this comorbid group, depression onset occurred first in one third of the participants, anxiety onset occurred first in one third, and depression and anxiety onset began concurrently in one third.

Conclusions: Challenging the prevailing notion that generalized anxiety usually precedes depression and eventually develops into depression, these findings show that the reverse pattern occurs almost as often. The GAD-MDD relation is strong, suggesting that the disorders could be classified in 1 category of distress disorders. Their developmental relation seems more symmetrical than heretofore presumed, suggesting that MDD is not necessarily primary over GAD in diagnostic hierarchy. This prospective study suggests that the lifetime prevalence of GAD and MDD may be underestimated by retrospective surveys and that comorbid GAD + MDD constitutes a greater mental health burden than previously thought.

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THIS ARTICLE WAS PREPARED in response to a call for research to inform how generalized anxiety disorder (GAD) should be characterized in relation to major depressive disorder (MDD) in forthcoming diagnostic systems.¹ Because the 2 disorders are closely related, key nosologic questions concern whether they ought to be classified together and whether GAD ought to be considered a subsyndrome of MDD vs an independent disorder. Substantial literature suggests that GAD ought not be viewed as independent from MDD, pointing to evidence that generalized anxiety

generally precedes MDD in sequential order and that most individuals with GAD eventually develop MDD. The present article revisits the sequential and cumulative comorbidity between GAD and MDD using data from a prospective longitudinal cohort.

Cross-sectional comorbidity for MDD and GAD is substantial; in the National Comorbidity Survey (NCS),² the odds ratio (OR) was 8.2. However, longitudinal comorbidity information can be more informative. One longitudinal question concerns "sequential comorbidity," in which 1 disorder reliably precedes the other.³ Sequential comorbidity is important be-

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cause it could suggest that treating the first disorder is a window of opportunity for preventing the second. The sequential overlap between GAD and MDD is widely believed to involve primary onset of anxiety, followed by MDD. This conclusion is supported by retrospective community surveys^{2,4-7} and studies of clinical samples.⁸⁻¹⁰ Moreover, childhood anxiety predicts later MDD, according to longitudinal studies^{4,10-13} and multigeneration family studies.¹⁴ However, not all of these studies isolated GAD for focused study; most examined anxiety broadly defined. Another potential difficulty is that virtually all studies of sequential comorbidity focused on MDD as the outcome and investigated history of anxiety, whereas balanced investigations that also ask individuals with GAD about their MDD history are lacking. A need for balanced investigations is suggested by reports that MDD antedated GAD in almost one third of comorbid cases.^{5,15}

Another longitudinal question concerns “cumulative comorbidity,” in which both disorders occur during a lifetime but not necessarily simultaneously. Cumulative comorbidity is important because cross-sections of relatively brief periods can underestimate the true extent to which individuals experience 2 disorders. Moreover, if the prevalence of the 2 disorders changes differently across age, then what seems comorbid (or not) in a study of one age group will differ from studies of groups a few years younger or older. As a result, studies of different-aged samples often disagree about comorbidity. The cumulative lifetime overlap between MDD and GAD is thought to be substantial, as documented by several retrospective epidemiologic surveys reporting ORs of 6 to 11.^{2,4,16} It has been suggested that GAD may be an early emerging prodrome indicating progression toward eventual MDD.^{13,17} Consistent with this suggestion, approximately two thirds of lifetime GAD cases retrospectively report MDD,¹⁸ implying that most individuals with GAD eventually develop MDD and that GAD may not be a separate disorder. In contrast, only one fifth of lifetime MDD cases retrospectively report GAD,¹⁸ indicating that most individuals with MDD will not have had GAD, and thus, unlike GAD, MDD is a primary disorder in its own right.

Despite the large body of literature on GAD-MDD comorbidity, decisive inferences about cumulative and sequential comorbidity have not been possible because of key methodological difficulties. First, many studies have limited their focus to adult GAD and MDD, lacking information about participants’ juvenile depression and anxiety, which could alter conclusions about sequential and cumulative comorbidity. Second, clinically ascertained samples provide biased information in comorbidity research because people with co-occurring disorders are unusually likely to attend clinics.¹⁹⁻²¹ Third, epidemiologic surveys better represent disorders in the population, but generally they must rely on participants’ retrospective recall. Retrospective ascertainment is problematic for studying sequential comorbidity because many respondents report timing of onset inaccurately,² particularly if onset occurred distantly in their teens or 20s, as is typical of GAD and MDD. Retrospective ascertainment is problematic for studying cumulative lifetime comorbidity because respondents generally

underreport past disorders.²² Although investigators performing retrospective surveys have gone to heroic lengths to promote accurate respondent recall, they acknowledge that prospective studies of representative cohorts are also needed.^{15,16,23}

We are aware of 7 longitudinal studies^{6,24-29} that used the prospective method to address anxiety-depression overlap. These studies have been highly informative; for example, they concur that comorbid cases are more severe and persistent than pure cases. However, as a group they did not report estimates of cumulative lifetime GAD-MDD comorbidity (because GAD was not diagnosed, because only 2 or 3 assessments were conducted, because the sample was followed up only during adolescence, or for other reasons). Regarding sequential comorbidity, the studies support no consensus, indicating that the predominant transition was from anxiety to MDD,^{24,28} that transitions involved MDD to anxiety about half as often as anxiety to MDD,²⁵ or that MDD strongly predicted GAD.²⁷ Thus, questions remain about prospectively measured cumulative and sequential comorbidity.

More prospective longitudinal research on onset, course, and comorbidity has been called for to fill the void of developmental information in the *DSM-IV*.³⁰ This article responds to the call, using data from a birth cohort. We present balanced analyses of cumulative and sequential comorbidity separately and simultaneously for GAD and MDD. We also examine recurrent course, service use, and suicide attempt to ascertain whether GAD + MDD comorbidity is associated with clinically consequential cases that pose a significant health burden.

METHODS

SAMPLE

Participants are members of the Dunedin Multidisciplinary Health and Development Study.³¹ Of infants born in Dunedin between April 1, 1972, and March 31, 1973, 1037 (91% of eligible births; 52% male) participated in the first follow-up at age 3 years, constituting the base sample for the longitudinal study. Participants represent the full range of socioeconomic status in the general population of New Zealand’s South Island and are primarily white. Assessments were performed at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, and 26 years and most recently at age 32 years when we assessed 972 (96%) of the 1015 study members still alive in 2004-2005. Participants attend the research unit for a full day of individual data collection. The Otago Ethics Committee approved each phase of the study. Study members gave informed consent before participating.

MEASURES

Past-year MDD at ages 11, 13, 15, 18, 21, 26, and 32 years was diagnosed as follows. At ages 11, 13, and 15 years, diagnoses followed *DSM-III* criteria³² based on structured interviews with study members using the Diagnostic Interview Schedule for Children–Child Version.³³ At older ages, interviews used the Diagnostic Interview Schedule.^{34,35} At ages 18 and 21 years, diagnoses followed the then-current *DSM-III-R*,³⁶ and at ages 26 and 32 years, diagnoses followed the then-current *DSM-IV*.³⁷ Criteria did not change from the *DSM-III-R* to *DSM-IV*; we required impairment at all ages. To allow the study of comorbidity, MDD was diagnosed regardless of the presence of other

Table. Health Burden Indicated by Recurrent Course of Disorder and Mental Health Service Use: Comorbid vs Noncomorbid Cases of Adult MDD and GAD, Defined Cumulatively From Ages 18 to 32 Years

	Diagnostic Groups, Ages 18-32 y				OR (95% CI)	
	Controls (n = 213)	Comorbid MDD + GAD (n = 117)	MDD Only (n = 212)	GAD Only (n = 18)	Comorbid MDD + GAD vs MDD Only	Comorbid MDD + GAD vs GAD Only
Birth cohort, % (N = 945)	23	12	22	2		
Female sex, %*	41	66	62	33	1.17 (0.73-1.87)	3.85 (1.34-11.02)†
Recurrent MDD (≥2 episodes), %	NA	66	33	NA	3.91 (2.42-6.30)†	
Recurrent GAD (≥2 episodes), %	NA	47	NA	11		7.79 (1.67-36.2)†
Received mental health services, ages 20-32 y, %	9	64	42	56	2.44 (1.52-3.91)†	1.10 (0.38-3.14)
Took psychiatric medication, ages 20-32 y, %	5	47	22	33	3.08 (1.88-5.05)†	1.39 (0.47-4.14)
Psychiatric hospitalization, ages 20-32 y, %	0	8	6	6	1.35 (0.56-3.27)	2.11 (0.24-18.6)
Reporting suicide attempt, ages 20-32 y, %	0	11	4	6	2.73 (1.11-6.72)†	2.72 (0.32-23.2)

Abbreviations: CI, confidence interval; GAD, generalized anxiety disorder; MDD, major depressive disorder; NA, not applicable; OR, odds ratio.

*Sex is controlled in group comparisons.

†Statistically significant.

disorders. Variable construction details, reliability and validity, and evidence of impairment for diagnoses are reported elsewhere.³⁸⁻⁴³ For example, attesting to validity, study members who were depressed at age 32 years self-reported mean ± SD impairment ratings of 3.57 ± 0.99 on a scale from 1 (some) to 5 (severe) reflecting how much MDD symptoms interfered with their lives. Of participants with MDD at age 32 years, 62% said that they received mental health services in the past year (from a general physician [53%], psychiatrist [13%], psychologist [33%], or emergency department [13%]), and 31% said that they took medication for their disorder. The past-year MDD prevalence (mean of ages 15, 18, 21, 26, and 32 years) of 14% in the Dunedin cohort is comparable with the past-year prevalence of 12% for 15- to 34-year-olds in the NCS.⁴⁴

Past-year GAD at ages 18, 21, 26, and 32 years was diagnosed as described in the previous paragraph for MDD. To allow study of comorbidity, GAD was diagnosed regardless of other disorders. The *DSM-IV* required fewer symptoms than the *DSM-III-R* but added "difficulty controlling anxiety"; we required impairment at all ages. Attesting to validity, study members who had GAD at age 32 years self-reported mean ± SD impairment ratings of 3.81 ± 0.90 on a scale from 1 (some) to 5 (severe) reflecting how much GAD symptoms interfered with their lives. Of participants with GAD at age 32 years, 55% said that they received mental health services in the past year (from a general physician [51%], psychiatrist [8%], psychologist [24%], or emergency department [8%]), and 37% said that they took medication for their disorder. The past-year GAD prevalence (mean of ages 18, 21, 26, and 32 years) of 4% in the Dunedin cohort is similar to the past-year prevalence of 3% in the NCS-R.¹⁶

Past-year anxiety disorders at ages 11, 13, and 15 years were included because although GAD was not diagnosed before adulthood in this cohort (because the *DSM-III* did not include childhood GAD), it is known that juvenile anxiety disorders often characterize individuals later diagnosed as having GAD. Thus, ignoring pre-GAD anxiety disorder would misinform about onset and recurrence. Anxiety diagnoses were made as described previously herein for juvenile MDD. Over-anxious disorder is considered the counterpart of GAD, but over-anxious disorder, separation anxiety disorder, and phobias predicted adult GAD outcome similarly well (over-anxious disorder: OR, 2.3; 95% confidence interval [CI], 1.4-3.7; separation anxiety: OR, 3.5; 95% CI, 2.0-6.1; phobias: OR, 2.7; 95% CI, 1.6-4.5). Thus, lacking empirical justification for excluding any juvenile anxiety disorders, we collapsed them together for this article.

Indicators of mental health service use were assessed using a life history calendar. This visual method (columns = time units and rows = events) has been shown to enhance recall reliability.^{45,46} As part of the assessment of life events, participants reported the years between ages 20 and 32 years in which they received mental health services (eg, from a general physician, psychiatrist, psychologist, or emergency department), took psychiatric medication, were hospitalized as an inpatient, or attempted suicide. One-month test-retest reliability of the resulting measures showed greater than 90% agreement.

STATISTICAL ANALYSES

Associations between GAD and MDD were assessed using ORs and 95% CIs. Sex differences in associations were tested. Differences between diagnostic groups were assessed in a regression framework; ORs and 95% CIs are reported (**Table**). The sexes were combined to augment statistical power for group comparisons, but sex was controlled as a covariate. Cohort members with missing diagnostic data from 2 or more of the 5 periods (ages 18, 21, 26, and 32 years and juvenile) were excluded from the analyses; 945 individuals were studied, 8.6% with 1 missing data point and 91.4% with no missing data points.

RESULTS

In this section, the term *lifetime* refers to the study period from ages 11 to 32 years. The broad term *anxiety diagnoses* is used when juvenile anxiety disorders are combined with adult GAD for cumulative analyses. The narrower term GAD is reserved for adult diagnoses of GAD at ages 18 to 32 years.

Before addressing questions of cumulative and sequential comorbidity, we describe prevalence and comorbidity at each assessment age, by sex. For MDD, prevalence in women was approximately double that in men from ages 15 to 32 years (**Figure 1**). In the juvenile period MDD was relatively rare, but both sexes showed a marked increase in prevalence at their transition to adulthood and fairly constant prevalence thereafter to age 32 years. At each successive age fewer cases of MDD were

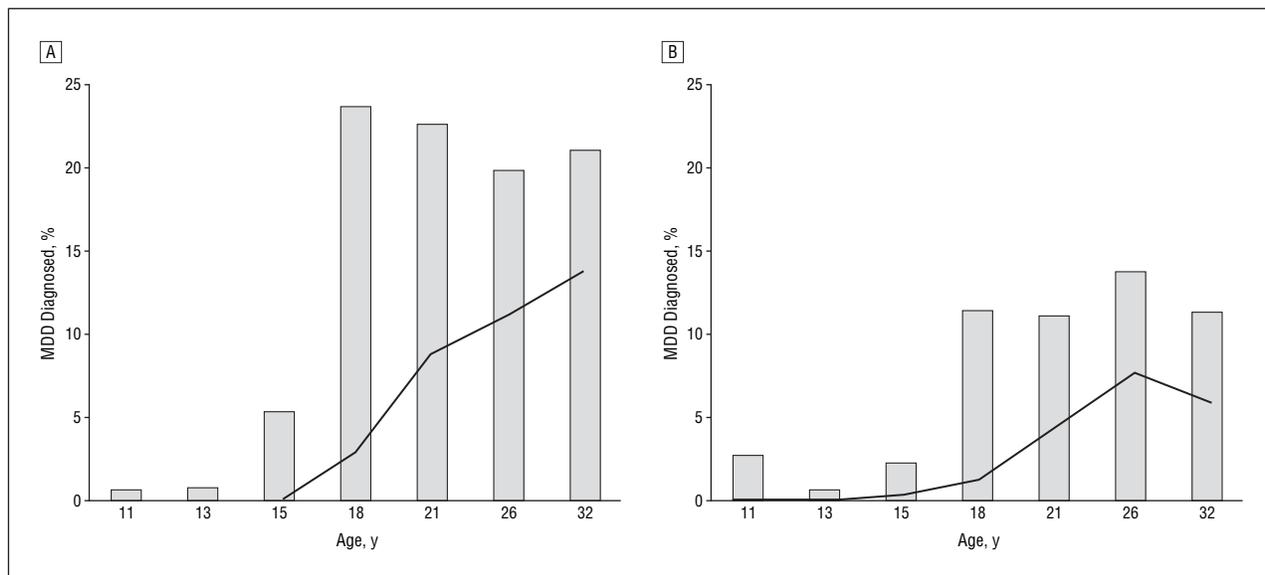


Figure 1. Prevalence of major depressive disorder (MDD) by age in the cohort of women (A) and men (B), with new-onset cases shown above the line.

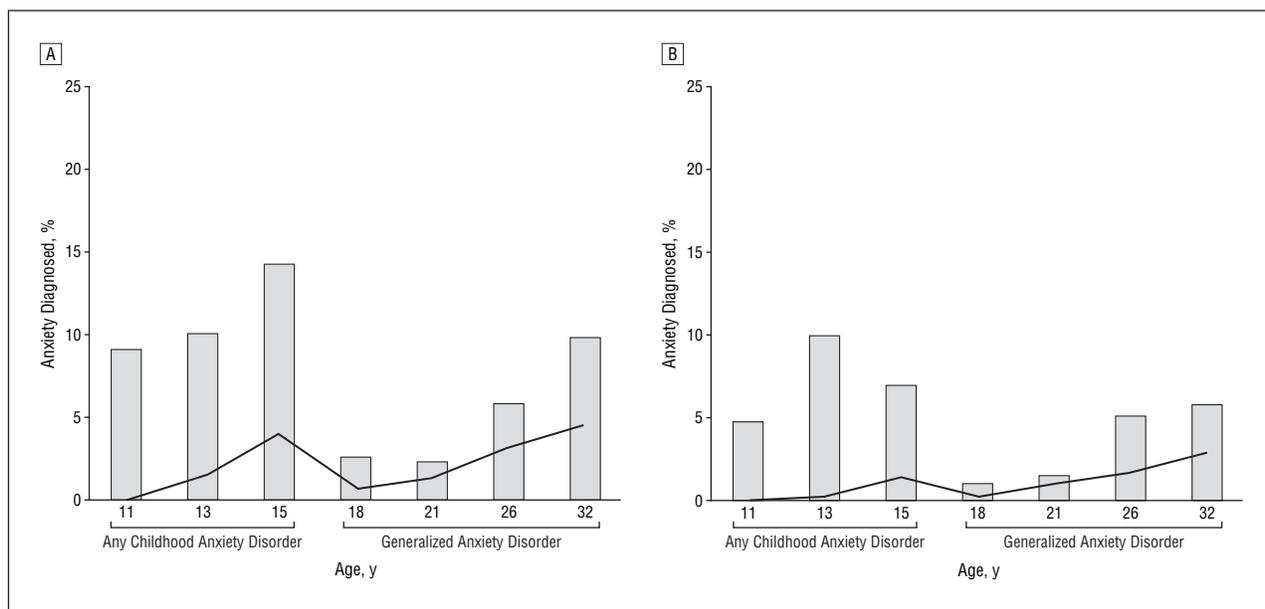


Figure 2. Prevalence of juvenile anxiety diagnoses and adult generalized anxiety disorder (GAD) by age in the cohort of women (A) and men (B), with new-onset cases shown above the line.

new onset. Thus, by age 32 years recurrent cases made up approximately two thirds of the cases in women and half of the cases in men.

For anxiety diagnoses, prevalence in women was somewhat higher than that in men at all ages (**Figure 2**). In contrast to MDD, anxiety disorders were already prevalent in the juvenile period, and thus, no marked increase in prevalence emerged at the transition to adulthood (however, note that all juvenile anxiety disorders were counted in juvenile years, whereas only GAD was counted in adult years). As with MDD, fewer cases of GAD were new onset at each successive age. Thus, by age 32 years, recurrent cases made up approximately half of the cases in women and men.

In **Figure 3** and **Figure 4**, the bars labeled “cross-sectional age” show cross-sectional comorbidity, representing the same prevalence bars for adult ages as in Figures 1 and 2 while superimposing on each prevalence bar (in black) the portion of diagnosed cases with a comorbid diagnosis that same year. These bars depict cross-sectional comorbidity for women and men separately. Collapsing across the sexes, at age 18 years, 9% of individuals with MDD had concurrent GAD, and 88% of individuals with GAD had concurrent MDD (OR, 38.6; 95% CI, 8.7-170.8). At age 21 years, 8% of individuals with MDD had GAD, and 67% with GAD had MDD (OR, 10.6; 95% CI, 3.9-28.7). At age 26 years, 21% of individuals with MDD had GAD, and 65% with GAD had

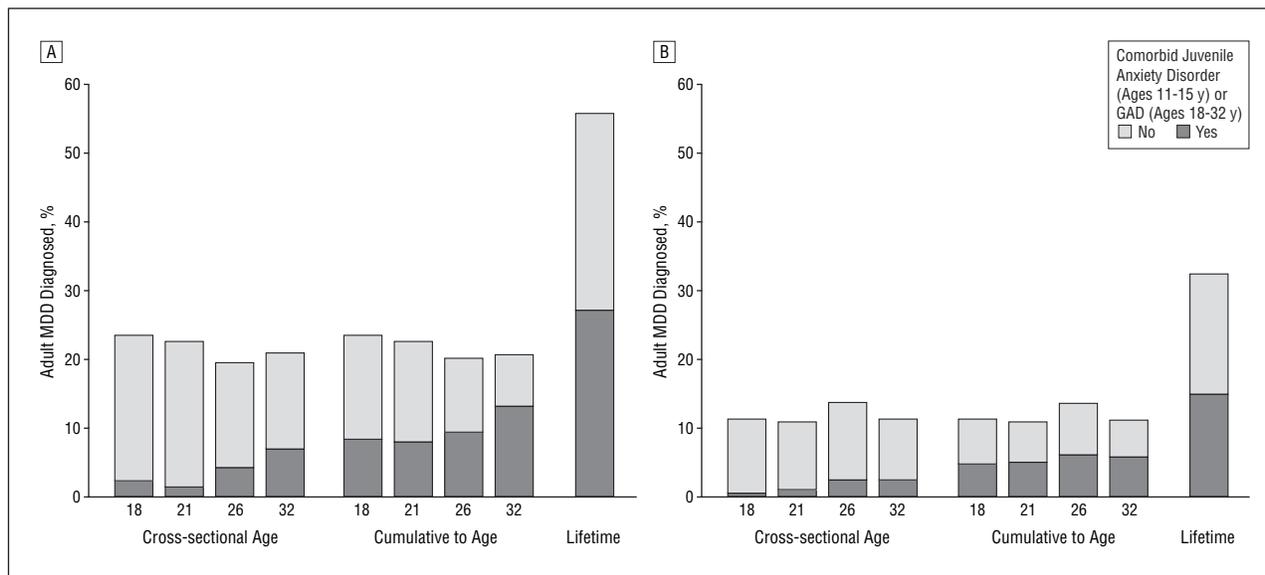


Figure 3. Adult major depressive disorder (MDD) by age in the cohort of women (A) and men (B), with and without comorbid juvenile anxiety diagnoses or generalized anxiety disorder (GAD).

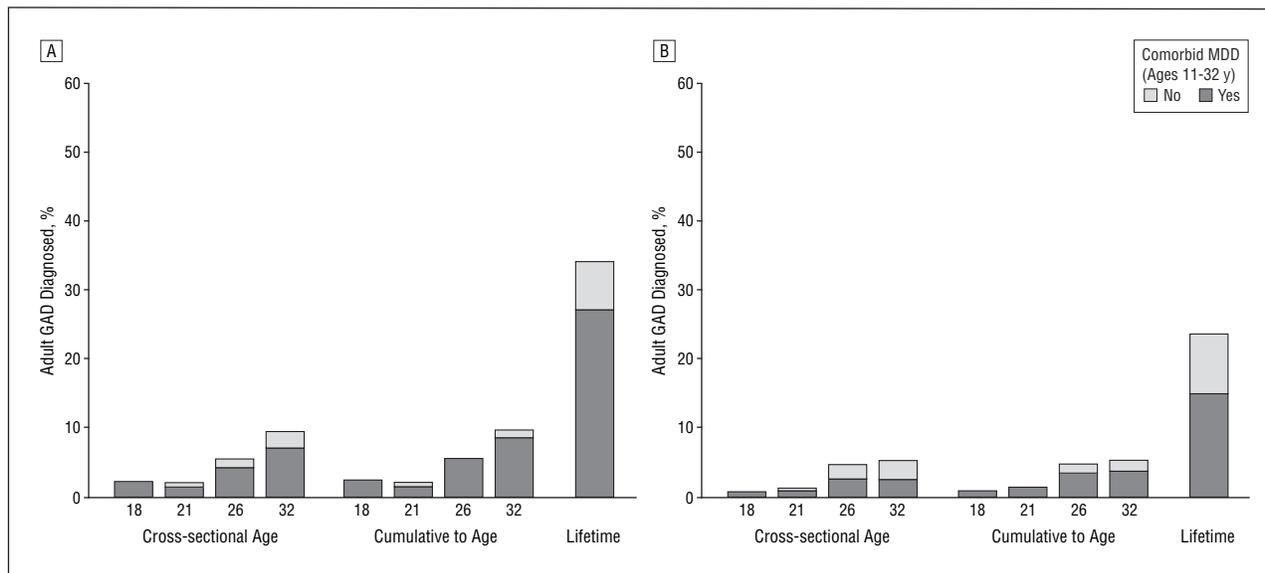


Figure 4. Adult generalized anxiety disorder (GAD) by age in the cohort of women (A) and men (B), with and without comorbid major depressive disorder (MDD).

MDD (OR, 11.2; 95% CI, 6.1-20.5). At age 32 years, 30% of individuals with MDD had GAD, and 63% with GAD had MDD (OR, 11.8; 95% CI, 7.1-19.9).

CUMULATIVE LIFETIME PREVALENCE AND COMORBIDITY TO AGE 32 YEARS

At each successive assessment, increasingly more adults with MDD had a history of anxiety (Figure 3). By age 32 years, two thirds of women and half of men with MDD diagnosed that year had previous or concurrent anxiety. Similarly, at each successive assessment, increasingly more adults with GAD had a history of MDD (Figure 4). By age 32 years, three quarters of women and half of men with GAD diagnosed that year had previous MDD.

A count of individuals ever meeting diagnostic criteria at any study assessment up to age 32 years revealed that 417 individuals (44% of the cohort) experienced at least 1 episode of MDD as a juvenile or adult and that 275 individuals (29%) experienced a juvenile anxiety disorder or adult GAD. (If juvenile anxiety was not counted, the cumulative prevalence of adult GAD from age 18 to 32 years was 15%.)

The 2 disorders had strong cumulative lifetime comorbidity from age 11 to 32 years (OR, 5.3; 95% CI, 3.9-7.2). Of lifetime MDD cases, 48% had lifetime anxiety disorder. Of lifetime anxiety cases, 72% had lifetime MDD. This pattern was similar in women (OR, 4.7; 95% CI, 3.0-7.3) and men (OR, 5.5; 95% CI, 3.5-8.7) (Figures 3 and 4, "Lifetime").

Recurrent course was defined as the presence of a disorder in multiple different assessment periods of the study

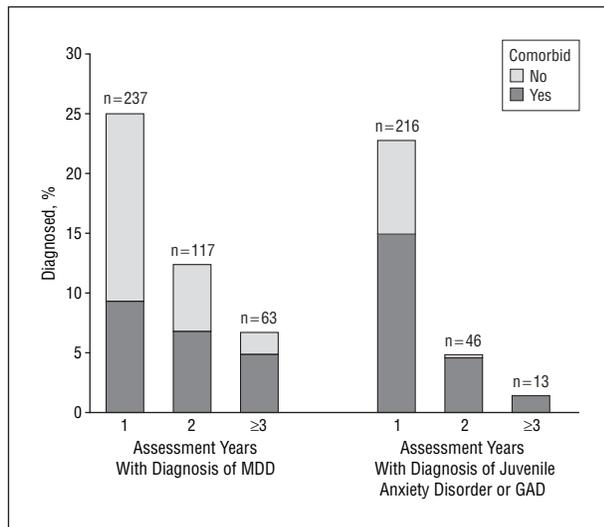


Figure 5. Lifetime comorbidity in cohort members with a single episode of disorder vs recurrent diagnoses at ages 11 to 32 years. GAD indicates generalized anxiety disorder; MDD, major depressive disorder.

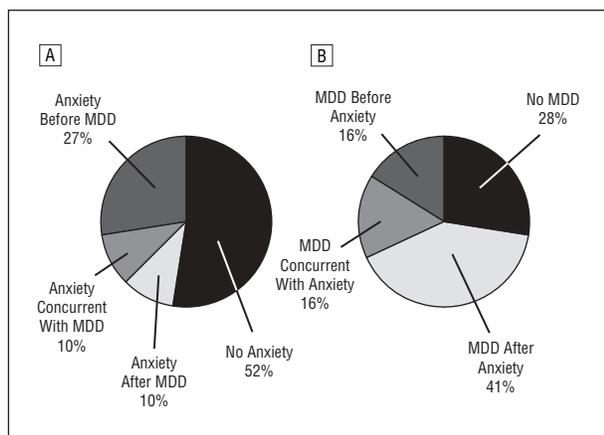


Figure 6. Sequential order of onset of major depressive disorder (MDD) (n=417) (A) and juvenile anxiety diagnosis or generalized anxiety disorder (n=275) (B) in cohort members at ages 11 to 32 years.

(ages 18, 21, 26, and 32 years or juvenile); 6.2% of cohort members evidenced recurrent GAD, and 19% evidenced recurrent MDD, so defined. Increasing recurrence of MDD was associated with greater cumulative anxiety comorbidity ($\chi^2=29.1$; $P<.001$) (Figure 5A). This pattern was similar in women ($\chi^2=20.7$; $P<.001$) and men ($\chi^2=8.4$; $P<.01$). Of cohort members who had MDD at 3 or more assessment ages, 73% had an anxiety diagnosis. Similarly, increasing recurrence of anxiety diagnosis was associated with greater cumulative MDD comorbidity ($\chi^2=22.7$; $P<.001$) (Figure 5B). This pattern was similar in women ($\chi^2=13.0$; $P<.01$) and men ($\chi^2=9.6$; $P<.01$). Of cohort members who had anxiety diagnoses at 3 or more ages, 100% experienced MDD.

SEQUENTIAL COMORBIDITY

Among cohort members ever diagnosed as having MDD from ages 11 to 32 years, anxiety began before or concurrently in 37% (Figure 6A). However, for the other

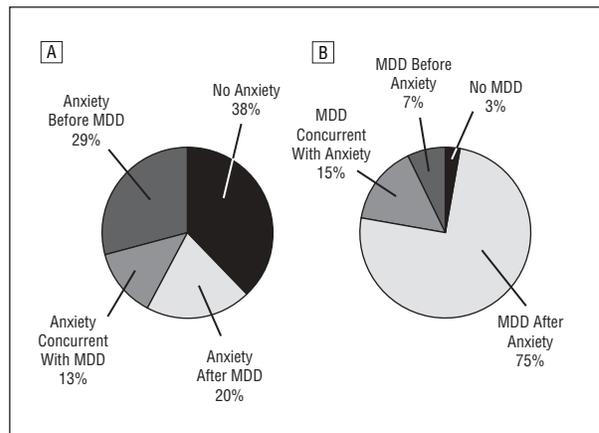


Figure 7. Sequential order of onset of major depressive disorder (MDD) (n=180) (A) and juvenile anxiety diagnosis or generalized anxiety disorder (n=59) (B) in recurrent cases (≥ 2 episodes) at ages 11 to 32 years.

62% of MDD cohort members, anxiety began after MDD or did not occur by the end of the study period at age 32 years. This pattern was similar in women (28% had an anxiety diagnosis before MDD, 9% in the same year, 11% after, and 52% never) and men (25% before, 12% in the same year, 9% after, and 54% never).

Among cohort members ever diagnosed as having juvenile anxiety or GAD from ages 11 to 32 years, MDD began before or concurrently in 32% (Figure 6B). For the other 69% of cohort members with anxiety, MDD began after anxiety or did not occur by the end of the study period at age 32 years. This pattern was similar in women (18% had MDD before anxiety diagnosis, 15% in the same year, 46% after, and 21% never) and men (12% before, 17% in the same year, 34% after, and 37% never).

Because cumulative comorbidity between GAD and MDD was most marked in cohort members who experienced recurrent disorder (Figure 5), we repeated the analyses of sequential order, limiting the cases to those having diagnoses at 2 or more assessments (Figure 7). Among cohort members with recurrent MDD, anxiety began before or concurrently in 42%. Among cohort members with recurrent anxiety, MDD began before or concurrently in 22%.

In the subset of 117 study members with adult GAD + MDD comorbidity, juvenile anxiety or GAD was diagnosed first in 42%, but MDD was diagnosed first in 32% (the remaining 26% were first diagnosed as having GAD and MDD concurrently) (Figure 8A). This article reports GAD diagnosed with at least a 6-month duration, following the current DSM-IV. However, some researchers argue for returning to the 1-month duration criterion for GAD in DSM-III.¹⁶ Moreover, the DSM-IV's 6-month duration criterion for GAD is stricter than its 2-week criterion for MDD, a difference that can undermine comparisons between the 2 disorders. Analyzing 1-month GAD also reveals balance in onset order between the disorders (Figure 8B).

PREVALENCE AND HEALTH BURDEN OF ADULTHOOD MDD + GAD COMORBIDITY

An adult MDD + GAD group was defined as all cohort members diagnosed as having both disorders during the

adult study period (ages 18, 21, 26, and 32 years). This group comprised 12% of the cohort (n=117; 66% female) and was compared with 2 noncomorbid groups (Table). The MDD-only group comprised cohort members diagnosed as having MDD in adulthood but never GAD and never juvenile anxiety (n=212). The GAD-only group comprised cohort members diagnosed as having GAD in adulthood but never MDD as a juvenile or an adult (n=18). The Table also shows no-diagnosis controls, who never had any diagnosis of Axis I mental or substance abuse disorder (n=213). The comorbid MDD + GAD group's rates of recurrent course and mental health service use indicators were elevated compared with lower rates for the MDD-only and GAD-only groups (although for the GAD-only group the differences were not statistically significant, in part owing to small sample size).

COMMENT

Debate about whether GAD ought to be classified as independent of MDD in diagnostic systems has been prompted by a prevailing notion that the generalized anxiety syndrome generally precedes and eventually develops into MDD. This prospective longitudinal cohort study questions that prevailing notion by showing that sequential and cumulative comorbidity between GAD and MDD may be more balanced than previously thought, at least in the first 3 decades of life. Four findings are notable.

First, the sequential comorbidity findings were only somewhat and not completely consistent with the prevailing notion that anxiety disorder usually precedes depression. Up to 37% of depression cases were preceded by anxiety disorder, but at least 63% were not. In addition, the balanced look revealed that up to 32% of anxiety disorder cases were preceded by depression (or emerged concurrent with it). This balance in sequential comorbidity applied whether GAD was diagnosed using the 6-month or the 1-month duration criterion (Figure 8). This and other prospective studies^{25,27} must question the notion that most individuals with juvenile anxiety disorder or GAD eventually develop MDD in a predictable and unidirectional life course progression. As a caveat, we did not rule out that some MDD cases might be preceded by an adult anxiety disorder (eg, panic) that first emerged in adulthood in study members having no GAD and no previous childhood anxiety. However, the main debate about sequence has focused on early-onset generalized syndromes of anxiety, such as we studied herein.

Second, we found strong cumulative overlap regardless of target disorder: 72% of lifetime GAD cases also had MDD, and 48% of lifetime MDD cases also had GAD or juvenile anxiety. Retrospective studies concur closely with the first finding^{18,20} but not the second, as they report that fewer than 20% of lifetime MDD cases ever have GAD.^{2,18} There is some evidence to suggest that a memory bias toward recalling negative information from the past characterizes depression but not anxiety¹⁷; if this is true, retrospective underreporting could reduce the prevalence of GAD more than that of MDD. However, this study had the advantage of juvenile diagnoses made prospectively. Note that

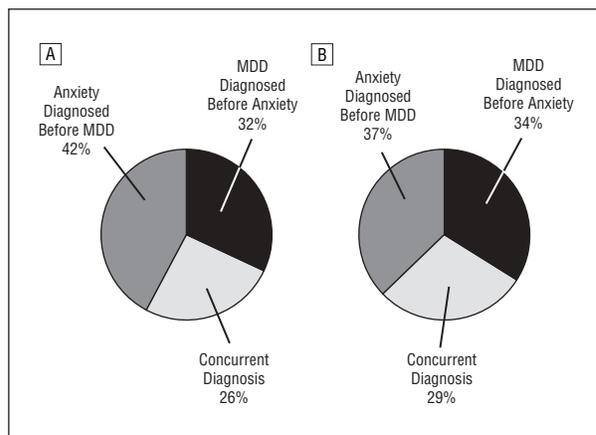


Figure 8. Generalized anxiety disorder (GAD) with a 6-month duration (n=117) (A) vs a 1-month duration (n=189) (B) showing sequential order of onset among cases with comorbid major depressive disorder (MDD) and GAD in adults aged 18 to 32 years.

we included all juvenile anxiety disorders because they showed equivalent continuity to adult GAD. However, some researchers would prefer it if we included only overanxious disorder; if we did so, 39% of MDD cases ever had GAD or overanxious disorder, a rate still much higher than the 20% from retrospective surveys.

Third, recurrence was virtually synonymous with comorbidity in this cohort. Almost all of the study members diagnosed as having either anxiety or depression at 3 or more of the study assessments experienced the other disorder. The balanced relation between GAD and MDD revealed herein applied somewhat less to recurrent cases; depression preceded up to 22% of recurrent anxiety cases, whereas anxiety preceded up to 42% of recurrent depression cases. If recurrent cases make up a greater proportion of clinic-based samples, this could explain why clinic-based studies have emphasized that anxiety precedes MDD. However, if recurrence is considered a sign of severity and clinical significance, our finding suggests that MDD precedes GAD in a notable portion of cases of a clinically consequential nature.⁴⁷

Fourth, the cumulative prevalence of adult comorbid MDD + GAD was 12% of the cohort. This prevalence seemed high, particularly because the cohort was followed up only to age 32 years (and juvenile disorders were not counted in the 12%). However, this comorbidity seemed to be associated with a nontrivial health burden, as indicated by recurrent course, mental health service use, and suicide attempt. This new finding of 12% MDD + GAD prevalence illustrates how prospective longitudinal studies can complement retrospective surveys: prospective studies provide unique information, specifically about cumulative prevalence. A count of individuals ever meeting diagnostic criteria at any study assessment revealed that 44% of the present cohort experienced at least 1 episode of MDD by age 32 years. By comparison, cumulative lifetime prevalence of MDD was 25% in the NCS-Replication for the 18- to 29-year-old group.⁴⁸ The discrepancy for GAD was also wide; 15% experienced adult GAD in the Dunedin cohort. In contrast, the prevalence of lifetime GAD was 6% in the NCS⁴⁹ and the NCS-R.¹⁶

We are obliged to offer an explanation for this discrepancy between prospective and retrospective cumulative prevalence estimates. Several factors may contribute to the Dunedin study's high prevalence. We diagnose GAD and MDD regardless of the presence of other disorders, eschewing the exclusionary criteria used in most studies. Also, the cohort's 96% participation rate lets us count individuals with disorders who are overlooked by most studies. Moreover, after more than 30 years of participation with no confidentiality violation, longitudinal study members are more forthcoming about psychiatric symptoms than participants in single-wave surveys. Finally, the Dunedin cohort diagnoses are based on concurrent symptom reports; lifetime cases are not undercounted owing to failure to recall criterion symptoms from years past, as occurs in retrospective surveys. The possibility that the Dunedin data are in error can probably be ruled out for 2 reasons. First, virtually identical high cumulative prevalence rates have been reported by others who followed up adolescent cohorts to adulthood while conducting repeated diagnostic assessments (using different interview instruments) in North Carolina, New York, and Oregon.^{29,50,51} Second, although prospective and retrospective studies disagree markedly about cumulative prevalence, they agree strongly about past-year prevalence. For example, past-year MDD prevalence was 14% across ages 15 to 32 years in the Dunedin cohort, similar to the 12% past-year prevalence for the age group 15 to 34 years in the NCS.⁴⁴ Past-year 6-month GAD prevalence averaged across assessments was 4% in the Dunedin cohort, similar to 3% in the NCS¹⁸ and 3% in the NCS-R.¹⁶ Thus, when data collection does not involve long-term retrospective recall, the NCS and Dunedin study interview procedures ascertain cases equally well in past-year assessments. Dunedin study lifetime rates reflect a cumulative count of cases, each of which was ascertained in a past-year assessment. If the Dunedin study data are not in error, the alternate explanation is that retrospective surveys underestimate lifetime disorder, a suspicion voiced previously.^{15,22,52} In retrospective surveys the prevalence of lifetime disorder seems low relative to the prevalence of past-year disorder,¹⁵ suggesting implausibly that most people who ever in their lives had an episode of disorder also happened to have an episode during the year they were interviewed for the survey. This implausible ratio from retrospective surveys could be explained if currently healthy respondents underreport past disorder in their lifetimes.²² Regarding the research questions of this article, retrospective surveys may have markedly underestimated the proportion of adults in the population who experience both GAD and MDD during their lifetimes, and thus also underestimated the health burden.

This study's findings should be considered in light of several design limitations. First, the data are from 1 country. However, the findings generally mirror those from longitudinal research in Switzerland, Germany, Canada, the United States, and Sweden. Second, we reported diagnostic groups to answer the call for DSM-relevant information about diagnosable GAD and MDD. Future studies should model latent correlational structures at the symptom level to determine whether these conclusions

transcend ascertainment method^{53,54} and apply to other anxiety syndromes.^{55,56} Third, the gaps between Dunedin assessment windows may have led us to undercount cases. We suspect that case undercounting is trivial; only 8 cohort members who reported on the life history calendar that they received mental health services for anxiety or depression between assessments had not been diagnosed by the study. The gaps probably led us to undercount episodes and consequently to underidentify recurrence, but there is no reason to expect that missed episodes between assessments would be less comorbid or would differ in order of onset. Fourth, our diagnoses covered a 1-year reporting period, and for a few cases whose first onset of MDD and GAD co-occurred in the same year, we did not establish onset sequence. Prospective longitudinal studies that can resolve onset timing month-to-month during the life course would allow better temporal resolution, but none exist. Fifth and most important among the limitations, the present study data are right-hand censored at age 32 years. How many new cases should be expected after age 32 years? Retrospective surveys suggest that new GAD and MDD cases emerge after age 30 years,^{16,48} but midlife incidence may be overestimated because retrospective survey respondents often recall their onset age as older than it was (forward telescoping) and underreport early-life episodes. One analysis³⁷ showed that if prospective information is available, onset before age 18 years will be revealed for 75% of adult psychiatric patients, suggesting that prospective studies will add fewer new cases across adulthood than retrospective surveys anticipate. With the cumulative prevalence in the Dunedin study already near 40% by age 32 years, it is difficult to envisage an influx of new cases. However, future follow-up can reveal how much the comorbidity picture might change with age.

Similar to previous studies, we found that the GAD-MDD relation is strong. Lifetime cumulative comorbidity ORs were similar across studies: 6.0 in the NCS,² 6.4 in the NCS-R,¹⁶ and 5.3 in the Dunedin cohort (ages 11-32 years). Together these associations support proposals to group GAD and MDD together in nosologic systems, perhaps in a "distress" category.⁵⁸ However, this study challenged the prevailing notion of a predominant pattern in which generalized anxiety usually develops into depression by showing that depression develops into generalized anxiety almost as often. These findings seem consistent with the idea that GAD can be viewed as a consequential disorder in and of itself.⁵⁹ In addition, GAD-MDD comorbidity may affect more of the adult population and constitute a greater health burden than previously thought.

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