Longitudinal Trajectories of Depression and Anxiety in a Prospective Community Study

The Zurich Cohort Study

Kathleen Ries Merikangas, PhD; Heping Zhang, PhD; Shelli Avenevoli, PhD; Suddhasatta Acharyya, PhD; Martin Neuenschwander, PhD; Jules Angst, MD

Background: The dearth of long-term follow-up studies of community-based samples and differences in methodology in existing studies highlight the need for research designed to examine the stability, comorbidity, and diagnostic thresholds of depression and anxiety in the community.

Methods: Prospective study of a community-based cohort aged 19 and 20 years from the canton of Zurich, Switzerland. Semistructured diagnostic interviews were administered by clinically experienced interviewers at 5 assessment points during a 15-year period. The format of the interview permitted assessment of major mental disorders at both the diagnostic and subthreshold levels.

Results: Comorbid anxiety and depression tended to be far more persistent than either syndrome alone. Individuals with anxiety states alone tended to develop either depression alone or comorbid anxiety and depression as they progressed through adulthood. In contrast, depression alone and depression comorbid with anxiety tended to be more stable than anxiety alone over time. The patterns of stability were similar for subthreshold- and threshold-level disorders.

Conclusions: These findings have important implications for classification and treatment of affective disorders. The greater stability of comorbid anxiety and depression than either disorder alone illustrates the importance of further investigation of comorbid states compared with noncomorbid states in etiologic and treatment research. The persistence of subthreshold-level depression and anxiety from early to mid adulthood also suggests the importance of characterizing the continuum of expression of depression and anxiety rather than adhering to strict diagnostic thresholds.

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even incorporates a specific category for mixed anxiety-depression based on concurrent expression of subthreshold-old-level anxiety and depression.16

There are several issues that complicate the longitudinal evaluation of the course and stability of depression. The first issue concerns the lack of inclusion of comorbid anxiety and depression in the characterization of the course of each of these disorders alone. A second issue is the classification of subjects who continue to manifest symptoms but fail to meet full criteria for depression at follow-up.17,18 The third problem is the consideration of methodologic effects such as missing observations, age distribution of the sample, and varying observation periods.

The dearth of long-term follow-up studies of community-based samples and differences in methodology across existing studies highlights the need for additional research designed to examine the stability of depression and anxiety in the community that systematically incorporates comorbid and noncomorbid subtypes and threshold and subthreshold levels of pathologic manifestation. The present study uses data from a prospective study of a cohort of young adults followed up for 15 years. The major goals of this article are (1) to examine the stability of anxiety and depression over time; (2) to investigate the role of comorbidity in the stability of and transitions between anxiety and depression; and (3) to examine whether inclusion of subthreshold manifestations of anxiety and depression increases the stability of depression and anxiety.

Table 1. Sample and Design of Zurich Cohort Study

<table>
<thead>
<tr>
<th>Year</th>
<th>Male</th>
<th>Female</th>
<th>Total No.</th>
<th>Age, y</th>
<th>Assessment</th>
</tr>
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<tbody>
<tr>
<td>1978</td>
<td>2201</td>
<td>2346</td>
<td>4547</td>
<td>19-20</td>
<td>Screen</td>
</tr>
<tr>
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<td>292</td>
<td>299</td>
<td>591</td>
<td>20-21</td>
<td>Interview</td>
</tr>
<tr>
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<td>270</td>
<td>504</td>
<td>21-22</td>
<td>Questionnaire</td>
</tr>
<tr>
<td>1981</td>
<td>220</td>
<td>238</td>
<td>456</td>
<td>22-23</td>
<td>Interview</td>
</tr>
<tr>
<td>1986</td>
<td>225</td>
<td>232</td>
<td>457</td>
<td>27-28</td>
<td>Interview</td>
</tr>
<tr>
<td>1988</td>
<td>200</td>
<td>224</td>
<td>424</td>
<td>29-30</td>
<td>Interview</td>
</tr>
<tr>
<td>1993</td>
<td>192</td>
<td>215</td>
<td>407</td>
<td>34-35</td>
<td>Interview</td>
</tr>
</tbody>
</table>

The Zurich Cohort Study was composed of a subset of a cohort of 4547 subjects (2201 men and 2346 women), representative of the canton of Zurich in Switzerland, who were screened at the age of 19 years (men) and 20 years (women) in 1978 with the Symptom Checklist 90-R (SCL-90R).19 A 2-stage sampling of 591 subjects (292 men and 299 women) was used to enhance the probability of cases in a general population sample consisting of two thirds of high scorers (defined by ≥85th percentile on the SCL-90R) and the remainder selected from a random sample of those who had scores below the 85th percentile.20,21

All subjects provided written informed consent after receiving a complete description of the study and having an opportunity to ask questions. Table 1 displays the sample size, age, and sex at the 5 interviews of the study.

Ninety percent of the sample participated in 2 or more interviews, and 6% of the original sample remained in the cohort across the 15 years of the study. Those who dropped out did not differ significantly in their baseline measures in terms of demographic characteristics or risk status at study entry. Data are weighted to yield estimates of the population rates with the use of coefficients that reflect the representation of the subjects with respect to the entire population assessed.

DIAGNOSTIC ASSESSMENT

The diagnostic instrument used in the Zurich Cohort Study was the Structured Diagnostic Interview for Psychopathologic and Somatic Syndromes (SPIKE), a semistructured instrument that was developed for epidemiologic studies.22 The SPIKE was designed for administration by trained psychiatric residents and clinical psychologists. Information was collected on childhood characteristics, treatment history, psychiatric and somatic syndromes, and use and abuse of various substances.

Screening probes based solely on the major phenomenologic features of each syndrome were administered for each diagnostic category. Positive endorsement of the entry probe was followed first by queries about specific symptoms and second by their duration, frequency, and severity, and treatment history and impairment. The core phenomenologic probe and treatment for all of the syndromes was asked about each of the interim years between interviews to cover the entire assessment period. At the first 2 interviews, the criteria for generalized anxiety disorder and panic were assessed in a single section of the interview. Fewer symptoms were collected in these sections than in later interviews, which included separate diagnostic sections as the DSM criteria for these 2 syndromes evolved. The interrater reliability of the SPIKE was found to be very high, with k of 0.89 and 0.91 for the symptoms of depression and anxiety (generalized anxiety disorder) and of 0.90 for the corresponding syndromal diagnoses.23 The validity of the SPIKE has also been assessed by comparing physician ratings and medical records with the SPIKE administered by another clinician among 140 patients drawn from psychiatric clinics or social-psychiatric services in the canton of Zurich24-26 and from a local hospital.27 The SPIKE rating of the diagnostic level of depression was found to have high sensitivity and specificity (0.95 and 0.99, respectively, for major depression and 0.83 and 0.63, respectively, for minor depression). Likewise, the SPIKE had high sensitivity for detecting subthreshold depression, anxiety, and mania (ie, respective k of 0.90, 0.83, and 0.67), confirming its ability to capture subclinical and medical and psychiatric complaints.

DIAGNOSTIC DEFINITIONS

The diagnoses from the 1979 to 1993 interviews were made according to the DSM-III or DSM-III-R criteria for most of the major categories. Because the SPIKE sections did not restrict collection of information based on specific diagnostic thresholds, we were also able to examine subthreshold manifestations of diagnostic categories.28 The definitions of these new syndromes were based on classic psychopathologic criteria: number of symptoms, duration, and frequency of episodes. Evidence of the existence of an anxiety spectrum and depressive spectrum has been previously presented.1,28-36

For the present analyses, the sample was classified into 4 levels of anxiety and depression disorder: threshold, subthreshold, symptoms present, and no symptoms.30,36-38 The diagnostic level of depression was based on DSM-III-R major depression or dysthymia. Subthreshold depression included “minor depression,” which required 3 or 4 symptoms of depression with a minimum duration of 2 weeks, and “recurrent brief depres-
Anxiety disorders included symptoms of either panic or generalized anxiety disorder. Threshold-level panic was defined according to DSM-III-R (ie, 4 or more panic symptoms and 3 attacks in 3 weeks). Subthreshold panic was defined as 4 or more panic symptoms plus at least 2 attacks in 1 year. The symptom level of panic was defined as a panic attack with at least 1 of the concomitant panic symptoms.

The diagnostic level of generalized anxiety was defined according to the DSM-III-R criteria. Subthreshold anxiety included subthreshold generalized anxiety disorder and brief and recurrent generalized anxiety. Subthreshold generalized anxiety required excessive worrying, 1 to 3 symptoms plus duration of 4 or more weeks; subthreshold brief anxiety required excessive worrying plus 1 or more anxiety symptoms and a duration of 2 to 3 weeks; and recurrent brief anxiety required excessive worrying, 3 or more anxiety symptoms, duration less than 2 weeks, and more than 1 episode per month.

### STATISTICAL ANALYSIS

Our analysis applied log-linear models with the use of SAS PROC CATMOD software (SAS Institute Inc, Cary, NC). The model estimation procedure first requires preparation of observed cell counts, which is used as the response variable in PROC CATMOD. Odds ratios were estimated on the basis of observed cell counts, which is used as the response variable in PROC CATMOD. The diagnostic level of generalized anxiety was defined according to the DSM-III-R criteria. Subthreshold anxiety included subthreshold generalized anxiety disorder and brief and recurrent generalized anxiety. Subthreshold generalized anxiety required excessive worrying, 1 to 3 symptoms plus duration of 4 or more weeks; subthreshold brief anxiety required excessive worrying plus 1 or more anxiety symptoms and a duration of 2 to 3 weeks; and recurrent brief anxiety required excessive worrying, 3 or more anxiety symptoms, duration less than 2 weeks, and more than 1 episode per month.

### RESULTS

The 1-year frequencies of comorbid and noncomorbid anxiety and depression by level of diagnostic threshold are presented in Table 2. The rates of threshold-level comorbid anxiety and depression and anxiety alone tended to increase over time, whereas the rates of depression alone tended to stabilize over time. When stratified by sex, there was an approximate 1 1/2- to 2-fold female preponderance for both combined and pure forms of anxiety and depression. When subthreshold and symptom levels were considered, the patterns varied for comorbid anxiety and depression. Subthreshold levels of anxiety alone tended to be higher at later assessments, whereas subthreshold levels of depression alone tended to be lower at later assessments.

**Figure 1** displays the stability, the concurrent co-morbidity, and the predictive association across subsequent waves of interviews between symptom level and higher anxiety and depression compared with those with or without symptoms alone. The stability estimates of anxiety across successive waves are generally 2-fold or greater (range, 1.8-3.8); however, the estimates and sig-

<table>
<thead>
<tr>
<th>Year</th>
<th>Anxiety + Depression</th>
<th>Anxiety Only</th>
<th>Depression Only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dx Sub Sx</td>
<td>Dx† Sub‡ Sx†</td>
<td>Dx§ Sub</td>
</tr>
<tr>
<td>1979</td>
<td>0.2 1.1 9.3</td>
<td>0.5 1.9</td>
<td>2.8 8.7 47.0</td>
</tr>
<tr>
<td>1981</td>
<td>1.4 1.7 5.2</td>
<td>0.9 4.6</td>
<td>3.4 7.9 35.1</td>
</tr>
<tr>
<td>1988</td>
<td>0.5 1.4 2.6</td>
<td>2.3 3.9</td>
<td>6.6 12.8 34.2</td>
</tr>
<tr>
<td>1993</td>
<td>1.6 2.4 7.5</td>
<td>6.0 13.6</td>
<td>5.9 7.5 20.6</td>
</tr>
</tbody>
</table>

Abbreviations: Dx, threshold level for diagnosis; Sub, subthreshold level; Sx, symptom level.

*Repeated panic attacks or generalized anxiety disorder.
†Recurrent brief anxiety or Dx.
‡Anxiety symptoms or Sub or Dx.
§Major depression or dysthymia, with impairment.
¶Minor or recurrent brief depression or Dx.
‖Depressive symptoms or Sub or Dx.

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**Figure 1** displays the stability, the concurrent co-morbidity, and the predictive association across subsequent waves of interviews between symptom level and higher anxiety and depression compared with those with or without symptoms alone. The stability estimates of anxiety across successive waves are generally 2-fold or greater (range, 1.8-3.8); however, the estimates and sig-
Hedeker. Despite the reduction in sample size in the 2 in 1 log-linear model, as recommended by Gibbons and ing observations by including all 5 waves of assessment were lowered. higher and confidence intervals smaller as thresholds similar; however, estimates of stability were generally aculations in the diagnostic threshold levels were remarkably across nearly all waves of assessment. The effects of alter-

The estimates of stability and comorbidity for the inter-
da morbidity between anxiety and depression was also highly significant throughout the study (range, 3.0-6.0). The effects of alterations in the diagnostic threshold levels were remarkably similar. Despite significant concurrent comorbid-

By contrast, the magnitude of noncomorbid depression (range, 2.1-3.6) was quite stable over time, but, with the exception of the last interview, the estimates across all interviews were highly significant. Again, inclusion of higher thresholds yielded somewhat lower estimates and levels of significance but similar patterns of effects across waves of assessment.

Figure 3 depicts the patterns of transitions be-
timates reported in Figure 1 are not strongly influenced by missing observations.

Figure 2 presents the stability of anxiety only, de-
pression only, and comorbid depression and anxiety with the use of the lower threshold of symptoms and higher. There was substantial stability of the comorbid syndromes across all waves of assessment (range, 7.1-20.7), suggesting that comorbid anxiety and depression is much more stable than noncomorbid anxiety or depression. Although the stability odds ratios were elevated for noncomorbid anxiety (range, 1.8-4.6), the only significant finding emerged for stability between 1986 and 1988. The lack of statistical significance for the earlier indexes was attributable in part to the small numbers in these categories.

Not shown here, we also assessed the impact of missing observations by including all 5 waves of assessment in 1 log-linear model, as recommended by Gibbons and Hedeker. Despite the reduction in sample size in the 2 models, there was remarkable consistency in both the magnitude and significance of the associations. Thus, es-
erate probability of developing depression only (range of odds ratios, 1.5-7.8), whereas those with depression only did not develop anxiety only at any of the interviews over time (odds ratio range, 0.3-1.8). In contrast, there were substantial transitions from both pure anxiety and pure depression to comorbid anxiety and depression across all of the interviews, with odds ratios ranging from 1.5 to 10.0. Figure 3B presents the transitions from the comorbid cases to pure cases of anxiety and depression. This figure shows that there was also fluctuation between comorbid and pure conditions of both anxiety and depression.

The empirical probabilities of transition are presented in Table 3 to demonstrate the magnitude of the findings described above. The rows and columns present the 1-year rates of the mutually exclusive cross-classification of anxiety and depression at adjacent pairs of interview. Both anxiety alone and depression alone were strongly associated with the development of comorbid anxiety and depression at subsequent interviews. Across all interviews, an average of 21% (range, 0.14-0.22) of those with depression alone and 24% (range, 0.17-0.31) of those with anxiety alone developed comorbid anxiety and depression at follow-up. Transitions from anxiety alone to depression alone were also quite common, particularly across earlier interviews (range, 0.05-0.29). Collectively, nearly half of those with anxiety alone developed depression either alone or comorbid with anxiety at subsequent interviews.

By contrast, the transition from depression to anxiety alone was quite rare; an average of only 9% (range, 0.04-0.13) of those with depression alone reported anxiety alone. The transition from the comorbid syndrome to anxiety alone was also uncommon; an average of only 11% (range, 0.07-0.14) developed anxiety alone at subsequent interviews. Transitions to depression occurred more frequently, with 24% (range, 0.18-0.31) of the comorbid cases manifesting depression alone at a subsequent interview.

We also examined the potential sex difference in the longitudinal trajectories of anxiety and depression by fitting separate log-linear models for men and women. Although there were no statistical differences between men and women on estimates of stability or comorbidity, men tended to exhibit somewhat greater concurrent comorbidity whereas women tended to manifest greater predictive comorbidity. That is, women were more likely than men to exhibit transitions from pure anxiety or depression to comorbid conditions at follow-up. Sex differences in patterns of transitions between comorbid and noncomorbid anxiety and depression could not be assessed because of reduced power when stratifying by sex.

Lewis noted that anxiety is an integral part of the depressive reaction. Although the observations of Lewis and others were based on clinical samples, subsequent studies of inpatients, outpatients, and community samples converge in verifying this astute clinical observation. There has been a surfeit of research on comorbidity during the past 2 decades since the term was first applied in psychiatry. The results of large community studies in the United States and elsewhere show that comorbidity is pervasive for most Axis I psychiatric disorders. Reviews of potential explanations for comorbidity in adults were presented by Kessler and Price, Merikangas, Kendler

Table 3. Probability of Transitions Between Noncomorbid and Comorbid Anxiety and Depression by Year of Interview

<table>
<thead>
<tr>
<th></th>
<th>Anx Only</th>
<th>Dep Only</th>
<th>Anx + Dep</th>
<th>No Anx or Dep</th>
</tr>
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<tr>
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<td>0.28</td>
<td>0.09</td>
<td>0.62</td>
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<tr>
<td>1981</td>
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<td></td>
</tr>
<tr>
<td>Anx only</td>
<td>0.16</td>
<td>0.05</td>
<td>0.32</td>
<td>0.47</td>
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<tr>
<td>Dep only</td>
<td>0.10</td>
<td>0.41</td>
<td>0.18</td>
<td>0.31</td>
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<tr>
<td>Anx + Dep</td>
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<td>0.28</td>
<td>0.43</td>
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<td>0.21</td>
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<tr>
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<tr>
<td>No Anx or Dep</td>
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<td>0.20</td>
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<td>0.63</td>
</tr>
</tbody>
</table>

Abbreviations: Anx, anxiety; Dep, depression.
much more likely to predict the subsequent onset of and retrospective studies suggesting that anxiety is methods. These findings are consistent with prospective differences in the diagnostic criteria and assessment subtypes.

examined the specificity of comorbid and noncomorbid syndromes in general may be more persistent in women may not be more chronic in women, the course of these anxiety as individuals progress through adulthood. Retrospective and prospective studies of youth drawn from both clinics and the community have also shown stability of anxiety and depression; however, few have examined the specificity of comorbid and noncomorbid subtypes.

SEX DIFFERENCES

Although not a major goal of these analyses, inspection of sex differences in the stability and transitions between anxiety and depression disclosed few differences in the longitudinal patterns of stability between men and women. Although both men and women exhibited comorbidity between anxiety and depression, men exhibited somewhat higher concurrent comorbidity, suggesting greater severity of anxiety or depression in men at the time of the actual episode. By contrast, women with anxiety tended to develop subsequent depression and women with depression tended to develop subsequent anxiety, more so than men with anxiety or depression. Thus, although the course of anxiety or depression alone may not be more chronic in women, the course of these syndromes in general may be more persistent in women than men. These patterns require further evaluation, especially since not all findings were significant and findings from previous studies suggest few sex differences in the course of anxiety and depression.

The finding that the associations between sex and risk group (SCL-90) and anxiety were significant at early waves but not at later waves suggests that these factors may be associated with the onset, but not the maintenance, of anxiety. In contrast, stronger associations between these factors and depression at the most recent interview suggest they may be important factors in the course of depression later in adulthood. Additional research is necessary to evaluate these explanations.

DIAGNOSTIC THRESHOLDS FOR DEPRESSION AND ANXIETY

Previous work on this community sample has demonstrated that contemporary diagnostic systems fail to cover depressive and anxiety states among those who do not meet duration or impairment criteria yet exhibit recurrence and subjective distress and have a history of treatment. This conclusion is substantiated by accumulating evidence of the importance of subthreshold syndromes manifested in clinical, primary care, and community samples, as well as by the emergence of similar patterns of longitudinal stability and comorbidity in the current study. Wittchen et al found similar results in a short-term follow-up (19.7 months) of those with threshold-level anxiety and depression at baseline. This suggests that there are fluctuations across threshold and subthreshold levels over time among those who experience anxiety and depression. Therefore, classification of stability by means of only threshold-level diagnostic criteria at each cross-sectional evaluation will fail to capture the majority of cases with persistent anxiety and depression across the life span. This conclusion is particularly important because we found that very few persons experience time-limited symptoms; individuals who meet subthreshold diagnostic criteria at an early age continue to manifest symptoms with impairment throughout adult life. This indicates that mood and anxiety disorders are chronic diseases rather than transient perturbations in response to stressful life events.

COMORBIDITY

The major finding of the present study is the remarkable longitudinal stability of comorbid anxiety and depression. Once comorbidity develops, the probability of recurrence of either disorder alone, and particularly anxiety, is far lower than that of comorbidity. These findings were generally consistent across differential diagnostic cutoff points. When taken together with the results of family and twin studies demonstrating common etiologic factors underlying anxiety and depression with age-specific (or development-specific) manifestations across the life span that are in part attributable to invalid diagnostic thresholds and boundaries for these syndromes, the results of this study suggest that the term comorbidity may be a misnomer. That is, anxiety and depression may be manifestations of the same underlying diathesis, perhaps with age-dependent expression, rather than comprising independent disorders. Despite the stability of comorbid anxiety and depression in the present study, there may also be specific anxiety and depression subtypes without a shared diathesis. For example, Sartorious et al noted that the more severe the anxiety and
depression, the better the 2 syndromes could be discriminated in a primary care study of 15 international sites.

Comorbidity has been linked to the chronicity and course of both anxiety and depression. Treatment studies suggest a poor prognosis for comorbid depression, and community studies suggest that comorbid major depression is more persistent and severe than pure or primary depression. Moreover, primary anxiety is associated with a more persistent course of depression and with self-perceived interference with life and activities, suicide attempts, hospitalization for depression, and overall treatment rates. Similarly, comorbidity with depression confers a substantially negative impact on the outcome of anxiety disorders. Since these findings suggest that comorbid depression is both more common and more stable than either anxiety or depression alone in the community, far more effort should be devoted to studying the etiologic pathways and treatment strategies for comorbid anxiety-depression. Further research on the stability, familial specificity, treatment response, and biological markers of comorbid anxiety and depression, as well as of specific subtypes of these disorders, is therefore indicated.

STRENGTHS AND LIMITATIONS OF THE ZURICH COHORT STUDY

The major strengths of this study are the prospective design, the long-term follow-up period of 15 years, and the community-based sample. The evaluation of a single age cohort also eliminates the potential confounding influence of age in the association between the order of onset and stability of anxiety and depression. Additional features including the nonhierarchical approach to diagnosis, the collection of data on symptoms and subthreshold manifestations of anxiety and depression, and the data analytic method enable advancement of our understanding of the association between anxiety and depression over time. To our knowledge, this is the first long-term prospective study of the patterns of comorbidity of anxiety and depression using contemporary diagnostic nomenclature.

Limitations of the study include the following: (1) differences in diagnostic information available across waves, since the clinical interview was expanded over time to capture the evolution of more extensive diagnostic systems; (2) the 15-year attrition rate of 30%; and (3) the relatively small sample size of this cohort. Finally, these analyses are based on aggregate anxiety and depressive disorders and may not apply to specific diagnostic subtypes of these syndromes (eg, panic, social phobia, dysthymia).

IMPLICATIONS OF FINDINGS

Findings of stability and comorbidity of anxiety and depression have important implications for treatment. In their classic articles, Feinstein and Kaplan and Feinstein argued that comorbidity must be integrated into the design of clinical trials, since its neglect can seriously bias conclusions regarding treatment efficacy. Contemporary clinical trials often exclude comorbid cases despite the overwhelming evidence shown here and elsewhere that comorbidity is more common than depression or anxiety alone.

There are also major implications of these findings for the diagnostic nomenclature and etiologic research. Advances in the tools that tap central nervous system function and structure have far surpassed our ability to define the clinical entities for investigation. Longitudinal studies such as the one described herein are critical to validate current diagnostic concepts that will inform future research on the pathogenesis of affective disorders. Developmental neurobiological approaches should examine the primarily unidirectional association between anxiety disorders and depression as well as the factors underlying the age-dependent expression of anxiety and depression. Likewise, the greater stability of depression alone and comorbid anxiety and depression suggests further investigation of the etiologic factors underlying comorbid states. Although both labor- and time-intensive, studies such as the Zurich Cohort Study are invaluable in informing diagnostic classification, clinical course, and etiologic pathways in psychiatry.

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