# Antecedents to Panic Disorder in Nonreferred Adults

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***Objective:*** Previous work has shown that childhood anxiety disorders are unique antecedents for panic disorder. The current study examined both childhood and adult comorbid disorders as potential antecedent disorders to panic disorder in a large sample of nonreferred adults.

***Methods:*** Subjects were 1018 adults with (N = 58) and without (N = 960) panic disorder who were derived from a sample originally ascertained through family studies of probands with and without attention-deficit/hyperactivity disorder (ADHD); data were obtained from 1988 to 1996. Classification and regression trees (CART) analysis was used to examine anxiety and nonanxiety disorders antecedent to panic disorder.

***Results:*** CART analysis showed that separation anxiety disorder, social phobia, and simple phobia were unique predictors of subsequent panic disorder.

***Conclusion:*** These results support and expand previously reported findings in referred samples documenting that comorbid anxiety disorders are unique antecedent risk factors for panic disorder.

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It has long been hypothesized that childhood anxiety disorders may reflect an underlying vulnerability for the development of panic disorder in adults.[1] Although early findings suggested a specific link between childhood separation anxiety disorder and panic disorder in adulthood,[1,2] some investigators have challenged the uniqueness of this association.[3–6] Otto et al.[4] reported that the most prevalent childhood anxiety disorders in a sample of 100 subjects with panic disorder were social phobia (36%) and overanxious disorder (31%), followed by avoidant disorder (20%) and separation anxiety disorder (19%). Similarly, in a 7-year prospective follow-up study of children and adolescents diagnosed with separation anxiety disorder, generalized anxiety disorder, or social phobia,[7] children with separation anxiety disorder did not show elevated rates of panic disorder but did show higher rates of specific phobia, obsessive-compulsive disorder (OCD), and posttraumatic stress disorder. Most of the extant literature has relied on referred clinical samples of adults and children with anxiety disorders. It is possible that predictors of panic will differ in nonreferred samples.

The extant literature examining antecedents to panic disorder relied largely on analyses of age at onset. The advent of empirical approaches to examining complex patterns of risk factors in psychiatric disorder offers the possibility of gaining new insights into antecedent risk factors for panic disorders. These data-mining methods are capable of handling data sets with a complex structure (e.g., panic disorder and multiple antecedent disorders such as anxiety and nonanxiety disorders) and are able to detect context-dependent effects that a standard statistical model would not.

In a previous report,[8] we used recursive partitioning to examine childhood disorders that were antecedent to panic disorder. This work showed that childhood anxiety disorders are unique antecedent disorders to panic disorder in both referred and nonreferred samples. But, because this study examined only childhood disorders, uncertainties remain as to whether other adult anxiety and nonanxiety disorders may also be important antecedent risk factors for panic disorder.

The purpose of this study was to reevaluate antecedents to panic disorder in a large sample of nonreferred adults

using an empirical analytic approach and considering a wide range of anxiety and nonanxiety disorders emerging across the life cycle. On the basis of the literature, we hypothesized that childhood anxiety disorders would be the most predictive antecedent disorders to subsequent panic disorder.

## METHOD

### Subjects

The nonreferred group was derived from an opportunistic sample originally ascertained through family studies of probands with and without attention-deficit/hyperactivity disorder (ADHD); data were obtained from 1988 to 1996.[9] As previously described, these ADHD studies assessed probands of both genders, aged 6–18 years, with (N = 280) and without (N = 242) DSM-III-R ADHD and their biological first-degree relatives.[9] Probands were ascertained from psychiatric and pediatric sources. The biological first-degree relatives (N = 1608; 1031 parents, 577 siblings) of these probands who were assessed yielded 58 parents with and 960 parents without panic disorder (13 were missing the diagnosis).

### Procedures

The Institutional Review Board approved all study procedures, and all participants signed written informed consent. Direct psychiatric assessments were conducted with the referred and nonreferred adults using the Structured Clinical Interview for DSM-III-R (SCID) for lifetime adult diagnoses[10] and supplements from the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version (K-SADS-E)[11] modules for childhood disorders (disruptive behavior disorders and childhood anxiety disorders). We documented the degree of impairment associated with each diagnosis as well as the age at onset and the type of treatment obtained. We assessed socioeconomic status (SES) with the Hollingshead Four-Factor Index,[12] which includes information about subjects' educational and occupational levels. The scale ranges from 1 (the highest SES) to 5 (the lowest SES).

Interviews were conducted by raters with a bachelor's degree in psychology, under the supervision of senior investigators. Raters underwent a comprehensive training program in which they were required to (1) master the diagnostic instruments, (2) learn about DSM-III-R criteria, (3) watch training tapes, (4) participate in interviews performed by experienced raters, and (5) rate several subjects under the supervision of the experienced raters. Raters received ongoing supervision of their assessments from senior project staff, and all interviews were audiotaped and randomly checked for reliability. Kappa coefficients of agreement were computed between the interviewers and board-certified psychiatrists who listened to the audiotape interviews. Based on 500 assessments from interviews of children and adults, the median kappa coefficient was 0.98. Kappa coefficients for individual diagnoses included the following: ADHD (0.88), conduct disorder (CD; 1.0), oppositional defiant disorder (ODD; 0.90), major depression (1.0), mania (0.95), separation anxiety (1.0), agoraphobia (1.0), panic (0.95), OCD (1.0), generalized anxiety disorder (GAD; 0.95), specific phobia (0.95), and social phobia (1.0). These measures indicated excellent reliability between ratings made by the nonclinician raters and experienced clinicians. In addition, to estimate the reliability of the diagnostic review process, we computed kappa coefficients of agreement between clinician reviewers. For these clinical diagnoses, the median reliability between individual clinicians and the diagnoses assigned by the review committee was 0.87. Kappa coefficients for individual diagnoses included the following: ADHD (1.0), CD (1.0), ODD (0.90), major depression (1.0), mania (0.78), separation anxiety (0.89), agoraphobia (0.80), panic (0.77), OCD (0.73), GAD (0.90), specific phobia (0.85), and social phobia (0.90). Ambrosini[13] reported kappa values between 0.51 and 0.77 for audiotaped reliability tests of the K-SADS-E. Diagnoses for all subjects were made on the basis of a consensus judgment by the senior investigators.

### Statistical Analyses

All statistical tests controlled for the case-control ADHD status of the family. In addition, because we are analyzing spouses, the assumption that each observation is independent of all other observations is violated in these data. To account for this, we used robust estimates of variance so that p values would be valid when analyzing data that are not statistically independent. The classification and regression trees (CART) method[14] does not require the assumption of statistical independence because it does not estimate variances. All tests were 2-tailed with alpha set at 0.01 to protect against type I error.

The CART method was used to determine which antecedent psychiatric disorders best predict a subsequent diagnosis of panic disorder. An antecedent disorder was defined as a disorder for which the age at onset was prior to the age at onset of panic disorder.

CART uses binary recursive partitioning to select the best predictors (in this case, antecedent disorder) of the outcome (in this case, panic disorder). CART does this by considering all possible binary splits given the number of subjects and number of predictor variables (e.g., 1018 subjects × 17 variables = 17,306 splits) and rank orders each of these splits using a goodness-of-fit criterion, which measures how well the split separates positive and negative diagnoses.[14] When the best splitting predictor is found, CART splits the sample into 2 "child nodes" or strata, 1 for each value of the predictor variable.

The 2 resulting child nodes continue to be split using the best predictor variable until a "maximal tree" (i.e., no

**Table 1. Demographic Characteristics of Subjects With and Without Panic Disorder**

| Variable | Panic (N = 58) | Non-Panic (N = 960) | Test Statistic | p Value |
|---|---|---|---|---|
| Age, mean ± SD, y | 40.5 ± 6.4 | 42.0 ± 6.0 | F = 2.80, df = 1,521 | p = .10 |
| Male subjects, N (%) | 23 (40) | 475 (49) | $\chi^2$ = 2.29, df = 1 | p = .13 |
| Socioeconomic status,[a] mean ± SD | 1.9 ± 1.1 | 1.7 ± 0.9 | $\chi^2$ = 0.14, df = 1 | p = .71 |

[a]Socioeconomic status was assessed with the Hollingshead Four-Factor Index and was scored from 1 (highest) to 5 (lowest).

**Table 2. Rates of Lifetime Disorders in Subjects With and Without Panic Disorder**

| Psychiatric Disorder[a] | Panic Disorder (N = 58) | No Panic Disorder (N = 960) | z | p Value |
|---|---|---|---|---|
| Total lifetime disorders, mean ± SD | 3.5 ± 2.4 | 1.7 ± 1.9 | 7.31 | < .001 |
| Disruptive Behavior Disorders | | | | |
| Attention-deficit/hyperactivity disorder | 8 (14) | 103 (11) | 0.13 | .90 |
| Oppositional defiant disorder | 2 (4) | 65 (7) | –1.21 | .22 |
| Conduct disorder | 2 (4) | 72 (8) | –1.26 | .21 |
| Antisocial personality disorder | 2 (4) | 69 (7) | –1.21 | .23 |
| Anxiety Disorders | | | | |
| Separation anxiety disorder | 9 (16) | 32 (3) | 3.63 | < .001 |
| Overanxious disorder | 12 (21) | 104 (11) | 1.93 | .05 |
| Simple phobia | 17 (29) | 107 (11) | 3.82 | < .001 |
| Social phobia | 20 (34) | 123 (13) | 3.97 | < .001 |
| Agoraphobia | 20 (34) | 26 (3) | 7.93 | < .001 |
| Obsessive-compulsive disorder | 5 (9) | 10 (1) | 3.46 | .001 |
| Generalized anxiety disorder | 20 (36) | 72 (8) | 5.67 | < .001 |
| Mood Disorders | | | | |
| Major depressive disorder | 35 (60) | 271 (28) | 4.51 | < .001 |
| Bipolar disorder | 6 (10) | 34 (4) | 2.31 | .02 |
| Psychoactive Substance Use Disorders | | | | |
| Alcohol abuse | 11 (19) | 122 (13) | 1.45 | .15 |
| Alcohol dependence | 12 (21) | 184 (19) | –0.05 | .96 |
| Substance abuse | 13 (22) | 125 (13) | 1.89 | .06 |
| Substance dependence | 10 (18) | 90 (9) | 1.65 | .10 |

[a]Values shown as N (%) unless otherwise noted.

further splits are possible) is created. This tree is then pruned to an "optimal tree" by procedures that weigh the cost of the complexity of the tree versus the benefit of additional correct classifications. In addition, CART incorporates a cross-validation algorithm by splitting the sample into 10 equal parts with similar distributions of the outcome variable. Essentially, each of 10 maximal trees is created using 9 parts of the sample. The remaining 10th is used as a test sample to estimate error rates of pruned trees. The process therefore allows each observation to be used in a test sample that does not influence the growth of the tree it is testing. Error rates for each sub-tree of the full-sample maximal tree are computed by combining results from the 10 test samples' summed error counts and are used to select the best tree. CART is advantageous for our analysis primarily because it is a nonparametric procedure that can accommodate a large number of predictor variables. Mueser et al.[15] demonstrated the use of classification tree analysis by predicting alcohol, cannabis, and cocaine use disorders in order to identify specific patient subgroups that might require varying service needs. Geller[16] supplemented his findings of the predictive validity of the Child Behavior Checklist obsessive-compulsive scale with CART. He found that CART's cutoff scores provided better sensitivity and specificity than a method using factor analysis.

## RESULTS

### Demographics

Panic disorder and non–panic disorder adults were compared on demographic variables of age, gender, and SES. The 2 groups did not show significant differences in any of the demographic variables assessed (Table 1).

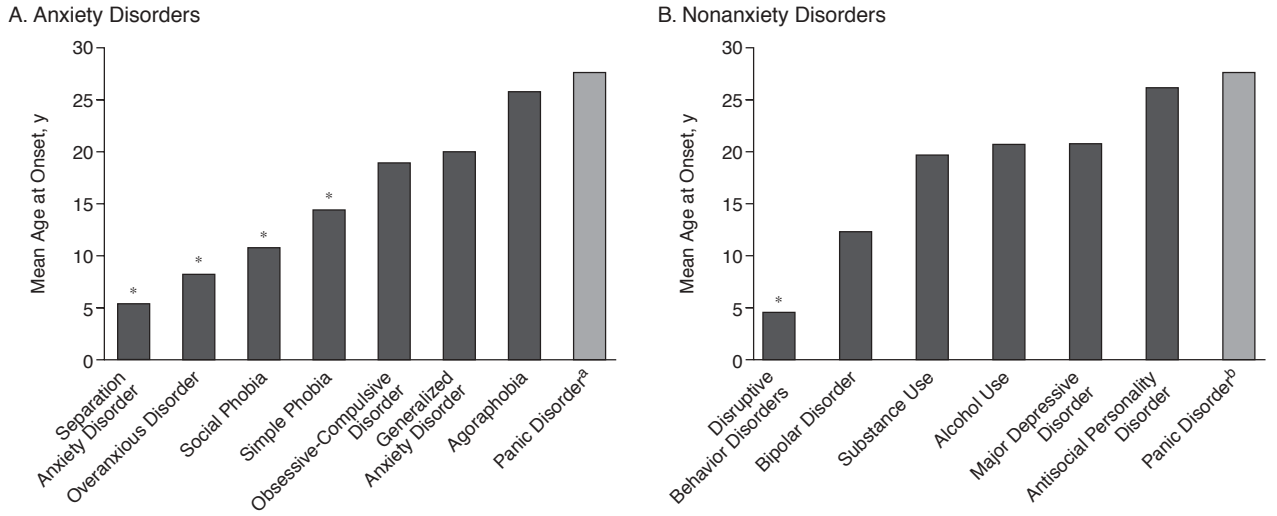
### Rates of Comorbid Disorders

Panic disorder adults had a significantly higher total number of disorders compared with the non–panic disorder adults (Table 2). Compared with all others, adults with panic disorder had significantly higher rates of separation anxiety disorder, simple phobia, social phobia, agoraphobia, OCD, GAD, and major depression (Table 2).

### Developmental Sequence

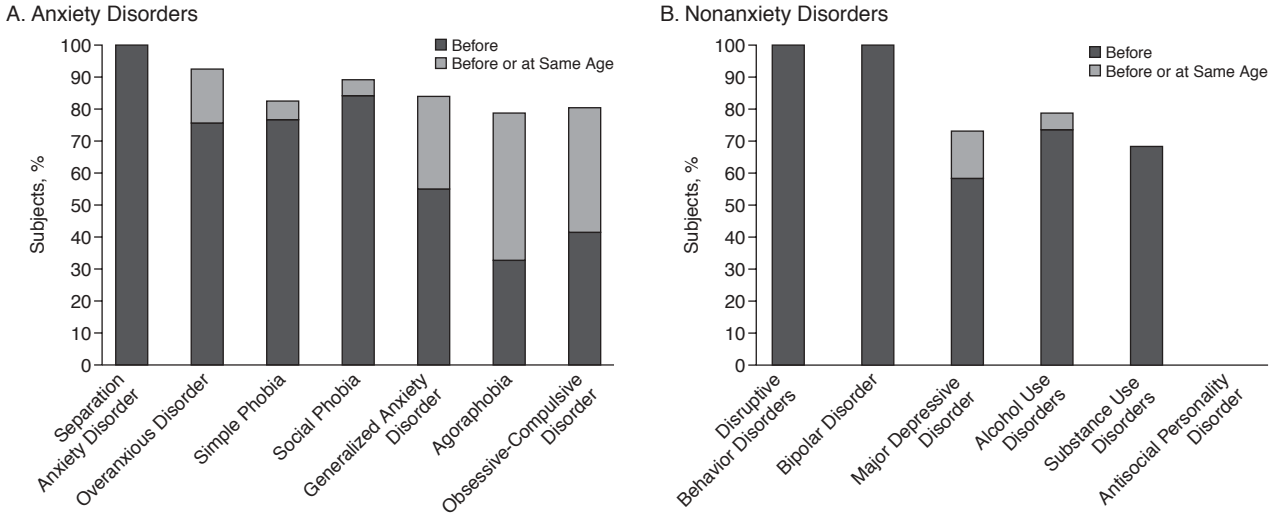
The mean age at onset of panic disorder was older than the mean age at onset of any comorbid disorder (Figures

**Figure 1. Mean Ages at Onset of Panic Disorder and Comorbid Disorders**



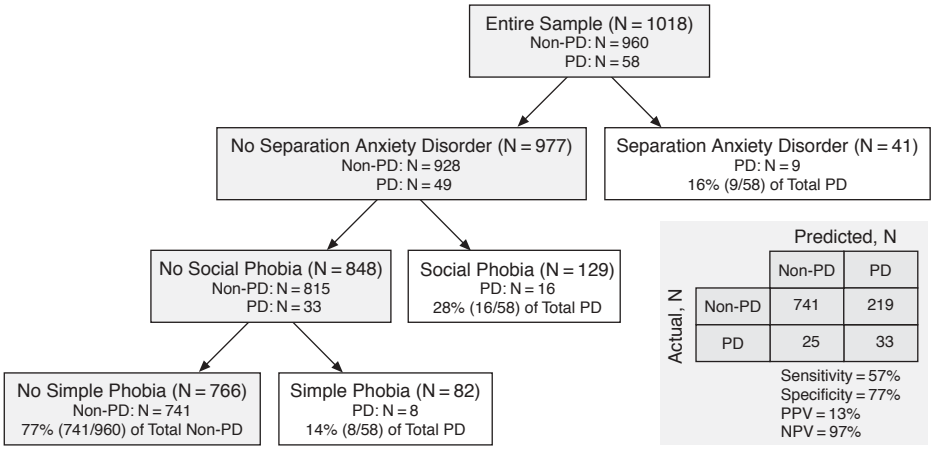

[a]Mean age at onset among all patients with panic disorder and a comorbid anxiety disorder.
[b]Mean age at onset among all patients with panic disorder and a comorbid nonanxiety disorder.
*Significantly lower vs. panic disorder, $p < .01$.

**Figure 2. Percentage of Subjects With Onset of Comorbid Disorder Before Onset of Panic Disorder**




1A and 1B). The mean ± SD age at onset of panic disorder (reported here as the onset age among subjects with panic disorder and each respective comorbid disorder) was significantly later than the onsets of comorbid disruptive behavior disorder (25.4 ± 9.9 vs. 4.6 ± 3.1 years, $p < .001$), separation anxiety disorder (20.9 ± 7.5 vs. 5.5 ± 2.3 years, $p < .001$), overanxious disorder (22.2 ± 7.4 vs. 8.2 ± 5.7 years, $p < .001$), social phobia (26.4 ± 9.7 vs. 10.8 ± 8.6 years, $p < .001$), and simple phobia (28.9 ±11.6 vs. 14.4 ± 11.2 years, $p = .003$). Figures 2A and 2B show the percentage of panic disorder subjects whose comorbid disorder onset before or at the same age as the onset of panic disorder (and by deduction, the percentage of onsets after panic disorder). For example, 100% of panic disorder subjects with bipolar disorder had an age at onset of panic disorder that occurred after the age at onset of bipolar disorder, whereas 58% of subjects with panic disorder and major depression had major depression onset

Figure 3. Classification Tree[a]




[a]The entire sample in the top box is split into 2 groups, those with (to the right) and without (to the left) separation anxiety disorder. Subjects without separation anxiety disorder are further split into those with and without social phobia. Finally, subjects without separation anxiety disorder and without social phobia are split into those with and without simple phobia. Subjects without any of the 3 splitting disorders are in the non-PD predicting group, while subjects with any of the 3 disorders are in the PD predicting groups.
Abbreviations: NPV = negative predictive value, PD = panic disorder, PPV = positive predictive value.

prior to panic disorder, 14% had the same age at onset of panic disorder and major depression, and 28% had major depression onset after panic disorder (Figure 2B).

Panic disorder subjects with bipolar disorder had a younger age at onset of panic disorder than panic disorder subjects without bipolar disorder (18.8 ± 2.3 vs. 28.3 ± 1.3 years, p = .003). Aside from bipolar disorder, there were no significant relationships between the age at onset of panic disorder and any other comorbid disorder.

## CART Analysis

A classification tree was created using panic disorder as the dependent variable and the following as predictor variables: separation anxiety disorder, overanxious disorder, simple phobia, social phobia, agoraphobia, GAD, OCD, ADHD, ODD, CD, antisocial personality disorder, major depression, bipolar disorder, alcohol abuse, alcohol dependence, substance abuse, and substance dependence. Because we were interested in predicting antecedents of panic disorder, adults with panic disorder were given a positive diagnosis of each comorbid disorder only if its onset occurred prior to the onset of panic disorder. Eighty-eight percent of panic disorder subjects (51/58) had at least 1 antecedent comorbid disorder (the median was 2 antecedent disorders and the maximum was 8 antecedent disorders). Sixty-five percent of subjects without panic disorder (625/960) had at least 1 of the disorders (the median was 1 antecedent disorder and the maximum was 11 antecedent disorders).

As shown in Figure 3, the classification tree showed 3 disorders to be predictive of subsequent panic disorder: separation anxiety disorder, social phobia, and simple phobia, in that order. Adults who had a disorder before the onset of panic disorder were grouped in the "positive node" (on the right), and those who did not have the disorder or whose onset occurred after or at the same time as the onset of panic disorder were grouped in the "negative node" (on the left). These positive nodes, also called "terminal" nodes, represent subjects with a positive diagnosis for an antecedent disorder that predicts panic disorder. The final terminal node, defined by the absence of any "splitter" disorders, predicts no panic disorder. Each terminal node displays the number of subjects in its predicted group as well as the percentage of the total number of subjects in this predicted group. For example, the third terminal node contains all subjects who do not have separation anxiety disorder and do not have social phobia disorder but do have simple phobia, consisting of 8 panic disorder subjects (14% of the total 58) and 82 total subjects (therefore, this node contains 74 non–panic disorder subjects). The table of actual versus predicted panic disorder was used to determine the tree's sensitivity (57%), specificity (77%), positive predictive value (13%), and negative predictive value (97%).

The tree suggests that the 3 splitters were important and independent predictors of panic disorder and that other disorders did not improve predictive accuracy. Because a positive node formed by a particular disorder does not continue to split past the positive diagnostic group, each of the 3 splitters can be viewed as a diagnosis for which the ability to predict panic disorder is not improved by the presence or absence of any other disorder in the model.

## DISCUSSION

We used recursive partitioning to examine the association between antecedent anxiety and nonanxiety disorders and panic disorder in a sample of nonreferred adults. A majority (88%) of adults with panic disorder had at least 1 antecedent disorder. CART analysis showed that separation anxiety disorder, social phobia, and simple phobia were independent predictors of subsequent panic disorder. These results underscore the importance of childhood anxiety disorders as predictors of panic disorder and indicate that previous findings in the literature showing that childhood anxiety disorders are antecedent risk factors for panic disorder are not attributable to antecedent mood or other anxiety disorders.

Ideally, predictors of adult panic disorder would be useful for identifying children for whom preventive interventions might be warranted. Our conditional probability analysis suggests that more work is needed to develop clinically useful predictors of subsequent panic disorder in nonreferred samples. Although the CART model correctly classifies with 97% accuracy those who will not develop panic disorder, 87% of subjects predicted to have panic disorder will not have the condition. This high false-positive rate is consistent with the low base rate of panic disorder in these nonreferred adults and the known sensitivity of conditional probability statistics to the base rate of the disorder being predicted.[17] Studies in clinically referred samples, which would have a higher base rate of panic disorder, would likely show a lower false-positive rate.

Despite a high false-positive rate, our findings suggest that children and adolescents with separation anxiety disorder, social phobia, or simple phobia are at a significantly higher risk for developing subsequent panic disorder compared with children and adolescents without these anxiety disorders. Specifically, the risk for panic disorder in our sample increased nearly 6-fold (odds ratio = 5.6, $p < .001$) if a subject had antecedent separation anxiety disorder, social phobia, or simple phobia. Clinically, this finding suggests that when such individuals (in particular, children) present clinically with separation anxiety disorder, social phobia, or simple phobia, they should be monitored for signs of onset of panic disorder. This finding also raises the hypothesis that individuals presenting clinically with these disorders might benefit from treatment approaches (e.g., cognitive-behavioral work on anxiety management strategies) that might, in addition to alleviating their presenting symptoms, generalize in ways that might reduce their risk of developing subsequent panic disorder.

Compared with traditional statistical analyses, CART's main advantage is its ability to simultaneously assess the predictive qualities of a large number of antecedent disorders, making it particularly applicable to many classification problems in medicine.[18–22] The 2 possible combinations[17] of antecedent comorbidities in our study make it difficult to discover context-dependent effects or interactions when using standard statistical procedures. This problem is accentuated if there is multicollinearity among the predictors. In contrast, we can include predictors in CART even if they are highly collinear. For example, if all panic disorder subjects with separation anxiety disorder also had social phobia, CART would not have selected social phobia as the second splitter. Because social phobia predicted panic disorder in the group of subjects who did not have separation anxiety disorder, we can conclude that social phobia is an important predictor of panic disorder independent of separation anxiety disorder. On the other hand, our classification tree was very simple given the possible combinations of antecedent disorders. For example, we did not find any context-dependent effects (e.g., substance use only a risk factor in the context of social phobia). Therefore, the use of more standard statistical models would likely find similar results.

The independent contributions of separation anxiety disorder, social phobia, and simple phobia to the prediction of adult panic disorder challenge previous claims that separation anxiety disorder is a unique predictor of subsequent panic disorder.[23] Consistent with our findings, the relationship between separation anxiety disorder and panic disorder has been challenged by several investigators because high rates of separation anxiety disorder in childhood have been found in most anxiety and mood disorders.[5,24–29] For example, Lipsitz et al.[27] found a significantly higher prevalence of childhood separation anxiety disorder in adults with 2 or more anxiety disorders, suggesting that separation anxiety disorder may be a risk factor for multiple anxiety syndromes in adulthood. We were unable to replicate previous findings[8,30] that separation anxiety disorder was associated with early-onset panic disorder.

Irrespective of specificity, as Otto et al.[31] suggested, the presence of childhood anxiety disorders may be a marker for greater anxiety and avoidance and a broader range of anxiety disorders in adulthood. Such findings support the idea that childhood anxiety disorders are due to an underlying anxiety diathesis that increases susceptibility to a range of adult anxiety disorders. Alternatively, early anxiety experiences in childhood may influence learned responses to anxiety and tendencies toward avoidance.[31] Either hypothesis is consistent with studies that indicate that earlier onset of a disorder is linked with greater familiality, severity, and comorbidity.[32–34]

Overanxious disorder was not found to be an antecedent of panic disorder, despite a rate of overanxious disorder twice as high in the panic versus nonpanic subjects and a significantly younger onset of overanxious disorder compared with comorbid panic disorder. Overanxious disorder was previously found to be an antecedent disorder in our CART analyses using only childhood anteced-

ents to panic disorder.[8] These different findings may be explained by the collinearity of overanxious disorder and social phobia (not used in the previous analyses), whereby panic disorder is better predicted by antecedent social phobia than by overanxious disorder. This explanation also lends further support to the hypothesis that nonspecific antecedent anxiety disorders put individuals at risk for panic disorder.

Although we found significant differences in lifetime rates of agoraphobia, GAD, OCD, and major depression between subjects with and without panic disorder, none of these disorders emerged as an antecedent predictor of panic disorder. This is explained by the large percentage of panic disorder subjects whose onsets of these comorbid disorders occurred at the same age or after their onset of panic disorder. Fifty-eight percent of our subjects with panic disorder and MDD had an onset of MDD prior to panic disorder, similar to the report by Kessler et al.[35] of 48% from the National Comorbidity Survey. Kessler et al.[35] also found that antecedent major depressive disorder did not predict subsequent onset of panic disorder but did predict the first onset of panic attacks. In a sample consecutively admitted to a psychiatric clinic, Savino et al.[36] found that only 28% of patients had major depressive disorder precede their onset of panic disorder, suggesting a possible difference between nonreferred and referred samples.

We found that OCD had a primary onset in 40% of individuals with comorbid OCD and panic disorder, but we cannot say with any confidence that this result is representative, because it is based on 5 subjects. Starcevic[37] reported that OCD had an earlier onset in 83% of subjects with panic disorder and OCD, but the sample size was 6 subjects. Larger samples are needed to clarify these discrepant findings. On the other hand, Starcevic[37] found that GAD had an onset subsequent to that of comorbid panic disorder in 14% of subjects with both disorders, similar to our rate of 15%. Likewise, agoraphobia had a secondary onset in 21% of our subjects with both agoraphobia and panic disorder compared with 20% reported by Thompson et al.[38] from a community sample.

Alcohol use disorders preceded panic disorder in 73% of our subjects, the same percentage found in a referred sample by Marquez et al.[39] and similar to the 75% found in Starcevic's[37] referred sample and 63% from Katerndahl and Realini's[40] community-based sample. Likewise, we found substance use disorders to precede panic disorder in 67% of subjects, a rate between the 59% found by Katerndahl and Realini[40] and the 82% found by Starcevic.[37] Even though the majority of alcohol and substance use disorders occurred before the onset of panic disorder, these disorders were not found to be antecedent predictors of subsequent panic disorder.

We found a significant relationship between age at onset of panic disorder and comorbidity with bipolar disorder, consistent with Goodwin and Hoven's[41] finding that co-occurring bipolar disorder was associated with earlier onset of panic attacks. Interestingly, Schürhoff et al.[42] found the converse, that early onset bipolar disorder was associated with greater comorbidity of panic disorder. This is also consistent with our sample, where the onset of bipolar disorder ranged from 8 to 15 years of age and always preceded comorbid panic disorder. Despite this, bipolar disorder was not identified as an antecedent to panic disorder. Again, this could be explained by collinearity with other antecedent anxiety disorders; in the present study, 5 of the 6 subjects with panic disorder and bipolar disorder also had separation anxiety disorder, social phobia, and/or simple phobia.

Our findings should be interpreted in the context of some limitations. Because diagnoses were based on retrospective reports by adults, they could have been influenced by recall biases. Prospective longitudinal studies are needed to confirm our findings. CART's method of exploring many variables to discover predictive relationships in complex data sets raises the possibility that we have discovered false-positive associations. However, CART's built-in cross-validation method and the similar results from previous work suggest that this is not the case. Because CART does not estimate variances, the classification tree would most likely be the same regardless of the sample size or rate of panic disorder in the sample. However, it is possible that comorbid disorders with low rates (e.g., OCD) might appear as antecedent disorders if the sample was sufficiently large. More work is needed to confirm these findings. Due to the unique nature of this sample, our findings may not generalize to the general or other populations. However, recent analysis of antecedents to panic disorder showed similar results between this sample and a clinically referred sample.[8] Despite these limitations, our findings indicate that a majority of subjects with panic disorder have antecedent anxiety disorders and that separation anxiety disorder, social phobia, and simple phobia are independent predictors of subsequent panic disorder. These results confirm and extend previous findings in the literature indicating that childhood anxiety disorders are important antecedent risk factors for panic disorder.

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