A Comprehensive Model of Predictors of Recurrence or Persistence in Individuals With Panic Disorder:
Results From a National 3-Year Prospective Study

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ABSTRACT

Objective: Multiple factors may influence the risk of recurrence or persistence of panic disorder, suggesting the need to combine them into an integrative model to develop more effective prevention strategies. In this report, we sought to build a comprehensive model of the 3-year risk of recurrence or persistence in individuals with panic disorder using a longitudinal, nationally representative study, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; Wave 1, 2001–2002; Wave 2, 2004–2005).

Methods: We used structural equation modeling to simultaneously examine the effects of 5 broad groups of clinical factors previously identified as potential predictors of recurrence or persistence in adults with a past-year *DSM-IV* diagnosis of panic disorder (n = 775): (1) severity of panic disorder, (2) severity of comorbidity, (3) family history of psychiatric disorders, (4) sociodemographic characteristics, and (5) treatment-seeking behavior.

Results: The 3-year rates of persistence and recurrence were 13.0% and 27.6%, respectively. A general psychopathology factor, representing the shared effect of all comorbid psychiatric disorders, panic disorder liability, a lower physical health–related quality of life, a greater number of stressful life events, and the absence of treatment-seeking behavior at baseline, significantly and independently predicted recurrence or persistence of symptoms between the two waves (all *P* < .05).

Conclusions: This integrative model could help clinicians to identify individuals at high risk of recurrence or persistence of panic disorder and provide content for future research.

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Panic disorder is a common anxiety disorder with a lifetime prevalence of 5.1%.[1] This disorder is associated with psychiatric (eg, major depressive disorder, anxiety disorders) and medical comorbidity[2,3] and deleterious consequences on quality of life[2–4] and functioning.[5,6] It has a chronic course in many patients, with an average duration of illness of 8.4 years,[5,7–10] and the recurrence rate ranges from 25% to 50%.[10–12] Previous studies estimated a remission rate between 30% and 60% at 1 to 11 years of follow-up.[4,5,13,14]

Because of the heterogeneous course of panic disorder,[3,8] there is a need to develop a comprehensive predictive model of recurrence or persistence for these patients, which could help practitioners adapt therapeutic strategies and develop prevention strategies in high-risk individuals.

Prior research suggests risk factors for both recurrence and persistence in panic disorder, including specific panic symptoms[10,15]; overall disorder severity[16]; early age at onset[17–19]; a greater number of panic attacks[10,20]; psychiatric comorbidity[10] such as mood,[9,21] anxiety,[16,22] personality,[13,23,24] and substance use disorders[15,20]; and sociodemographic and environmental characteristics, including female sex,[15,22] exposure to stressful life events,[20,25,26] younger age,[15,22] and treatment-seeking behavior.[15,21] Potential recurrence risk factors further comprise functional impairment and disability at work and home.[12,27] Finally, persistence risk factors include the duration of illness, panic attack frequency, family history of psychiatric disorders, low physical health, being African American, low socioeconomic status, being divorced/separated, and low educational attainment (detailed in Supplementary Table 1).

However, most prior studies relied on clinical samples, limited sample sizes that reduced their statistical power, and cross-sectional designs. Besides, each risk factor, when considered individually, accounts for a small proportion of the variance in risk.[10,28] Finally, these potential risk factors' frequent co-occurrence suggests the need to combine them into a broad multivariable model. Yet, few integrative models have been proposed to identify independent predictors and mitigate the influence of confounding

Clinical Points

- Panic disorder is a disabling illness; multiple individual risk factors increase its persistence or recurrence, but there is a need for an integrative model.

- Clinicians should look for psychiatric comorbidities in patients with panic disorder and should inquire about quality of life and stressful events to reduce risk factors for the disorder.

- Encouraging treatment-seeking in this population could help prevent chronicity.

variables.[15,21,22] To our knowledge, no study has used structural equation modeling to take into account multiple correlations across predictors, such as across panic disorder symptoms and comorbid psychiatric disorders.

In this report, we sought to build a comprehensive model of the 3-year risk of recurrence or persistence in individuals with panic disorder using the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Since transdiagnostic factors may account for links between psychiatric disorders and risk of recurrence or persistence,[29–38] we used a latent variable approach to examine simultaneously the effects of 5 groups of clinical factors previously identified as potential predictors of recurrence or persistence: (1) severity of panic disorder, (2) severity of comorbidity, (3) family history of psychiatric disorders, (4) sociodemographic characteristics, and (5) treatment-seeking behavior (Figure 1). Because risk factors may partially differ for recurrence or persistence, we distinguished these two risks separately. Using a large, nationally representative sample, we hoped to obtain stable estimates that could be generalized beyond clinical samples.

MATERIALS AND METHODS

Sample

Data were drawn from Waves 1 and 2 of NESARC, a nationally representative face-to-face survey of the US adult population conducted in 2001–2002 (Wave 1) and 2004–2005 (Wave 2) by the National Institute on Alcoholism and Alcohol Abuse.[39] The sample included the civilian non-institutionalized US population, aged 18 years and older. The overall response rate at Wave 1 was 81%, resulting in 43,093 interviews. The cumulative response rate at Wave 2 was 70.2%, resulting in 34,653 interviews.[39] We used participants who completed both waves of interviews to analyze the 3-year period between Waves 1 and 2. The NESARC research protocol, including written informed consent procedures, received full human subjects review and approval from the US Census Bureau and the Office of Management and Budget.

For this study, the sample consisted of all participants diagnosed with panic disorder according to the Alcohol Use Disorder and Associated Disabilities Interview Schedule–DSM-IV (AUDADIS-IV).

Assessments of *DSM-IV* Past-Year Axis I and Lifetime Axis II Diagnoses in Wave 1

Psychiatric disorders were assessed using the AUDADIS-IV, a structured diagnostic instrument administered by trained lay interviewers.[39] Following *DSM-IV* criteria, a diagnosis of panic disorder required meeting clinical significance criteria (ie, distress or impairment) and having a primary panic disorder (ie, excluding substance-induced or general medical conditions). Other Axis I diagnoses included substance use disorders (alcohol or drug disorder and nicotine dependence), mood disorders (major depressive disorder, dysthymic disorder, and mania/hypomania), anxiety disorders (social anxiety, specific phobia, generalized anxiety disorder, and agoraphobia without panic disorder). For panic disorder and all Axis I disorders, diagnoses were made in the 12 months before Wave 1. Axis II disorders (including avoidant, dependent, obsessive-compulsive, histrionic, paranoid, schizoid, and antisocial personality disorders) were assessed on a lifetime basis. The baseline duration of panic disorder and the number of lifetime panic attacks were retrospectively estimated in Wave 1 with the AUDADIS-IV. The test-retest reliability and validity of AUDADIS-IV measures of *DSM-IV* psychiatric disorders are good to excellent for substance use disorders and fair to good for panic disorder and other psychiatric disorders.[40,41]

Sociodemographic Characteristics in Wave 1

Sociodemographic characteristics included age, sex (men vs women), marital status (married vs non-married), race-ethnicity (White vs non-White), education (college or higher vs high school graduate or less), and poverty (household income < $20,000). Participants were asked whether they had experienced 1 or more of about 12 stressful life events concerning various occupational, familial, financial, and legal issues in the past year of Wave 1.[39] This variable was dichotomized at the median (ie, over vs equal or lower than the median, ie, 3).

### Family History of Psychiatric Disorders in Wave 1

A family history of psychiatric disorders was considered met if the participant reported that any first-degree relative had any of the following conditions: a history of depression, alcohol or drug use disorder, and antisocial personality disorder, ascertained in separate modules of the AUDADIS-IV.[41] The test-retest reliability of AUDADIS-IV measures of family history of psychiatric disorders is very good.[41] Family history of panic disorder was not assessed in the NESARC.

Psychiatric and Other Physical Health Related Quality of Life in Wave 1

Participants completed Version 2 of the Short Form 12-item Health Survey (SF-12v2),[42] which assesses the quality of life (over the last 4 weeks). This resulted in a norm-based mental component summary score (MCS) and a norm-based physical component summary score (PCS). All standardized scale scores range from 0 to 100 with a

Figure 1. A Conceptual Comprehensive Model of the 3-Year Occurrence of Recurrence or Persistence in Individuals With a Past-Year *DSM-IV* Diagnosis of Panic Disorder (n = 775)
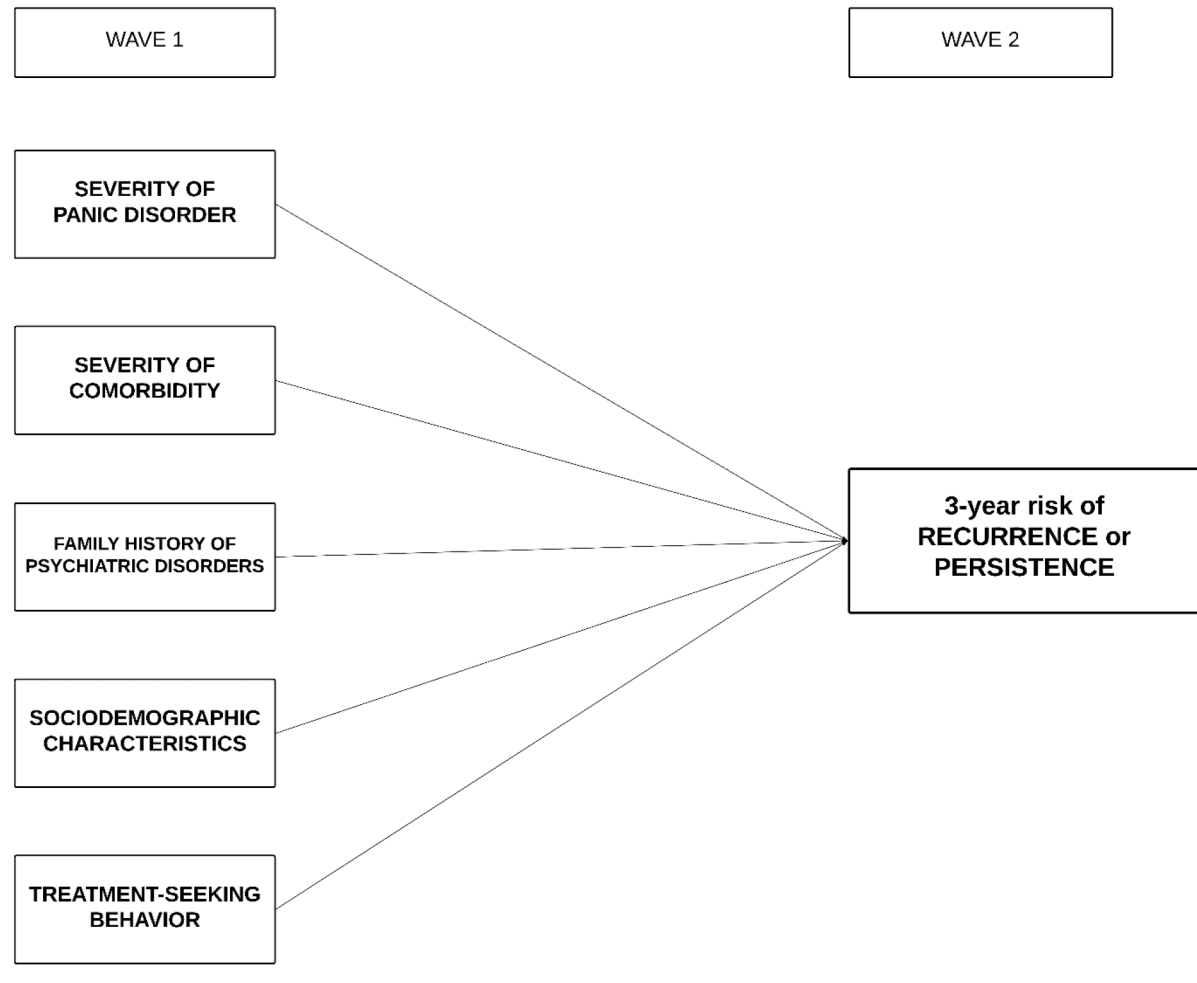
mean of 50 (standard deviation = 10); higher scores signify better functioning. Studies support the reliability and convergent validity of SF-12v2 scores in both community and clinical samples.[42–44] The MCS and PCS variables were dichotomized as follows: equal to or over the theoretical mean (ie, 50) versus under the mean.

**Treatment-Seeking Behavior
for Panic Disorder in Wave 1**

Participants with a past-year *DSM-IV* diagnosis of panic disorder who declared going to a hospital or emergency department or having consulted a mental health professional to receive help for anxiety during the year preceding the Wave 1 interview were considered to have sought treatment for panic disorder.

**Assessment of Recurrence or
Persistence of Panic Disorder in Wave 2**

Persistence was defined as meeting full criteria for current panic disorder at Wave 1 and throughout the entire 3-year follow-up period (ie, the times when they had panic attacks in the last 12 months was the continuation of a period beginning before Wave 1). Recurrence was defined as meeting full criteria for current panic disorder at Wave 1 and since Wave 1 but not before the 12 months immediately preceding Wave 2. Three-year incidence of panic disorder was assessed at Wave 2, using the AUDADIS-IV.

Statistical Analysis

Among participants with a past-year *DSM-IV* diagnosis of panic disorder at Wave 1, we first performed a set of binary logistic regressions of associations of each categorical or continuous putative factor assessed at Wave 1 with the 3-year risks of persistence and recurrence assessed at Wave 2.

Next, we used confirmatory factor analyses (CFAs) to identify the latent structures underlying individual comorbid psychiatric disorders and panic disorder symptoms. Specifically, on the basis of previous models used to examine the relationship of psychiatric disorders with recurrence or persistence in these data,[15,22] we built on the internalizing-externalizing CFA model and performed a bifactor model[31,45,46] to determine whether a general psychopathology factor measured by

all psychiatric disorders in addition to disorder-specific factors (ie, internalizing and externalizing dimensions) fit the underlying structure of psychiatric disorders assessed at Wave 1. To assess our results' robustness, we conducted a sensitivity analysis using an alternative approach to modeling psychiatric disorder comorbidity and built on the distress-fear-externalizing CFA model[30,47] that includes antisocial personality disorder, but not other personality disorders. Following prior research,[48–50] we included agoraphobia in these bifactor models as an indicator of the fear factor and the internalizing factor, respectively.

We also built on the CFA model fit by Drenckhan et al,[51] who generated a 3-factor respiratory-cardiac-vestibular structure underlying the 10 *DSM-IV* symptoms of panic disorder. We performed a bifactor CFA model to determine whether a panic disorder liability factor measured by all panic symptoms in addition to the 3 symptom-specific factors fit the underlying structure of panic disorder symptoms. To assess robustness, we conducted a sensitivity analysis using an alternative approach to modeling panic symptom co-occurrence and built on the CFA model fit in these data by Rappaport et al,[52] who generated a 4-factor structure underlying 13 *DSM-IV* symptoms of panic disorder, and performed a bifactor CFA model.

We examined measures of goodness-of-fit, including the comparative fit index (CFI), the Tucker-Lewis index (TLI), and the root mean squared error of approximation (RMSEA). CFI and TLI values greater than 0.95 and RMSEA values less than 0.06 indicate good model fit.[53]

Finally, following our a priori conceptual model (Figure 1), we used a structural equation model (SEM) to examine simultaneously the effects of potential predictors assessed at Wave 1 on the 3-year risks of persistence or recurrence assessed at Wave 2 while taking into account multiple associations across predictors. As indicated in Figure 1, our conceptual model included 5 groups of predictors, comprising 15 predictors in all. Severity of panic disorder measures included severity of panic disorder, which was measured by 3 latent dimensions including 10 panic symptoms (in the respiratory-cardiac-vestibular structure; see Supplementary Table 2), age at onset of panic disorder, and number of lifetime panic attacks. To determine if specific disorders/symptoms or disorder/symptom-specific dimensions were associated with persistence or recurrence above and beyond the effects of other factors, we calculated modification indices (ie, χ^2 tests with 1 degree of freedom) to test if any residuals were correlated with recurrence. Because our model was semi-exploratory and defined a priori, statistical significance was evaluated using a 2-sided design with α set a priori at .05. To reduce the risk of including significant direct effects related to multiple testing, we considered significant direct effects of items with modification index greater or equal to 10.

All analyses were conducted in Mplus Version 7.2[54] to account for the NESARC's complex design. The default estimator for the analysis was the variance-adjusted weighted least squares (WLSMV), a robust estimator appropriate for ordered categorical observed variables such as those used in this study.[54]

RESULTS

Bivariate Associations Between Baseline Clinical Characteristics and 3-Year Risk of Recurrence or Persistence

Among the 775 participants with a 12-month diagnosis of panic disorder at Wave 1, 13.0% (SE = 0.3, n = 101) had a persistent panic disorder and 27.6% (SE = 0.4, n = 214) had a recurrence of panic disorder during the 3-year follow-up period. The mean (SE) duration of illness was 9.5 (0.4) years. Binary logistic models showed that a greater number of lifetime panic attacks and the presence of any Axis I or II comorbid disorder and any Axis I disorder, and particularly social anxiety disorder, were significantly associated with the 3-year risk of both recurrence and persistence. The specific symptoms "sweating," "feelings of choking," and "paresthesias"; the comorbid disorders mania/hypomania, general anxiety disorder, and nicotine dependence; lower mental and physical component summary scores of quality of life; and exposure to a greater number of stressful life events in the past year were significantly associated with the 3-year risk of recurrence only (Table 1).

In addition, there was no significant difference concerning baseline variables when comparing the two outcomes, except for the number of lifetime panic attacks, which was significantly greater among participants who had a persistent rather than a recurrent disorder (Supplementary Table 3).

Structure of Comorbid Psychiatric Disorders and Symptoms of Panic Disorder

The bifactor models of the structures "distress-fear-externalizing" and "internalizing-externalizing" underlying comorbid psychiatric disorders provided a good fit to the data (CFI ≥ 0.987, TLI ≥ 0.983, RMSEA ≤ 0.033) (Supplementary Tables 4 and 5), as did the bifactor models of the structures "respiratory-cardiac-vestibular" and "beta adrenergic–alpha adrenergic–cognitive-respiratory" underlying symptoms of panic disorder (CFI ≥ 0.982, TLI ≥ 0.977, RMSEA ≤ 0.031) (Supplementary Tables 2 and 6).

Structural Equation Model of the 3-Year Risk of Recurrence or Persistence

We found that the general psychopathology factor significantly increased the 3-year risk of both recurrence and persistence of panic disorder. Panic disorder liability factor measured by all panic symptoms, exposure to a greater number of stressful life events in the past year, lower physical component summary score, and the absence of treatment-seeking behavior significantly and independently increased the 3-year risk of recurrence only. There were no additional direct effects from any other factor or individual panic symptom or psychiatric disorder or any sociodemographic characteristics on these risks (Figure 2 and Supplementary Figures 1–3).

Table 1. Associations of Baseline Indicators of Panic Disorder Severity, Psychiatric Comorbidity, Quality of Life, Sociodemographic Characteristics, and Treatment-Seeking Behavior at Wave 1 in Individuals With a Past-Year *DSM-IV* Diagnosis of Panic Disorder (n = 775) According to the 3-Year Occurrence of Recurrence or Persistence
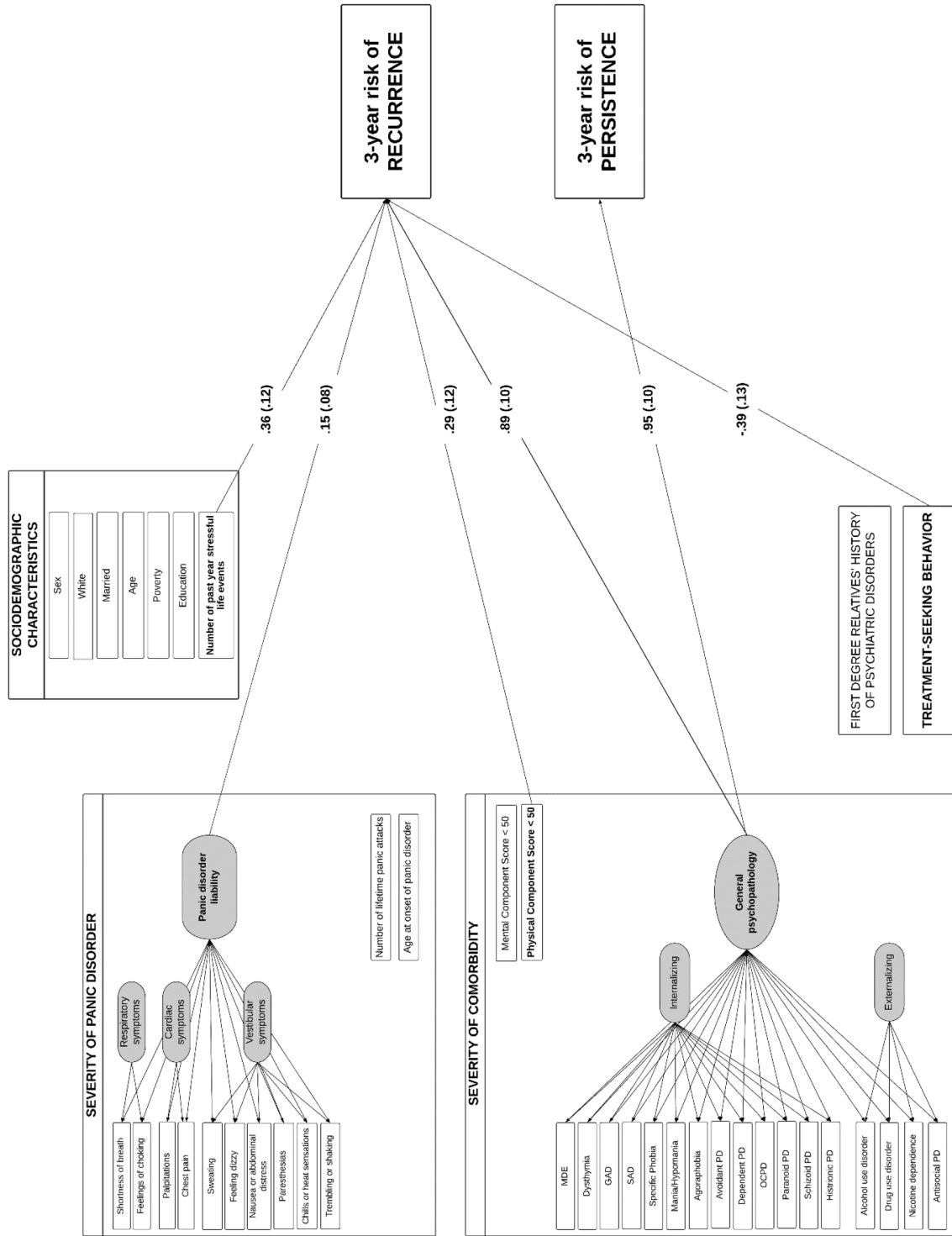
Variable	Recurrence (n = 214)[a]	Persistence (n = 101)[a]	Remission (n = 557)[a]	Recurrence vs Remission, OR (95% CI)/Wald F[b]	Persistence vs Remission, OR (95% CI)/Wald F[b]
Severity of Panic Disorder					
Individual symptoms					
Palpitations	96.2 (1.7)	98.2 (1.0)	95.0 (1.0)	1.3 (0.5–3.6)	2.8 (0.9–8.9)
Sweating	82.6 (3.6)	82.0 (5.8)	72.1 (2.3)	**1.8 (1.1–3.2)***	1.8 (0.8–3.9)
Trembling or shaking	76.5 (4.3)	71.4 (6.8)	76.8 (2.2)	1.0 (0.6–1.6)	0.8 (0.4–1.5)
Sensations of shortness of breath	90.6 (2.5)	88.0 (3.4)	86.5 (1.8)	1.5 (0.8–2.9)	1.1 (0.5–2.4)
Feelings of choking	49.1 (4.2)	45.8 (5.8)	39.0 (2.5)	**1.5 (1.0–2.2)***	1.3 (0.8–2.2)
Chest pain or discomfort	70.0 (3.9)	66.4 (6.6)	60.2 (2.6)	1.5 (1.0–2.4)	1.3 (0.7–2.4)
Nausea or abdominal distress	64.3 (3.9)	60.9 (6.2)	59.1 (2.5)	1.3 (0.8–1.9)	1.1 (0.6–1.9)
Feeling dizzy	75.5 (4.3)	74.6 (5.7)	72.7 (2.3)	1.2 (0.7–1.9)	1.1 (0.6–2.1)
Chills or heat sensations	77.5 (3.6)	77.5 (5.6)	70.1 (2.6)	1.5 (0.9–3.4)	1.5 (0.7–3.0)
Paresthesias	64.4 (4.1)	64.4 (5.8)	51.5 (2.8)	**1.7 (1.1–2.6)***	1.7 (1.0–3.0)
Derealization or depersonalization	69.6 (4.6)	75.4 (5.9)	62.5 (2.4)	1.4 (0.9–2.2)	1.8 (1.0–3.6)
Fear of losing control or going crazy	64.1 (4.4)	60.4 (6.9)	63.9 (2.5)	1.0 (0.6–1.6)	0.9 (0.5–1.6)
Fear of dying	57.4 (4.1)	52.7 (6.6)	52.2 (2.5)	1.2 (0.8–1.8)	1.0 (0.6–1.8)
No. of lifetime panic attacks, mean (SE)	14.9 (3.17)	23.0 (6.2)	9.0 (0.9)	**5.4***	**14.36***
Duration of illness, mean (SE), y	9.2 (1.0)	11.2 (1.6)	9.9 (0.6)	0.14	1.38
Age at onset of panic disorder, mean (SE), y	30.8 (3.17)	28.8 (1.5)	31.3 (0.7)	0.14	2.39
First-degree relatives' history of psychiatric disorders	84.0 (2.9)	82.5 (4.4)	80.3 (2.0)	1.3 (0.8–2.1)	1.2 (0.6–2.2)
Psychiatric Comorbidity[c]					
Any Axis I or II disorder	91.9 (2.0)	94.6 (2.2)	83.0 (2.0)	**2.3 (1.3–4.2)****	**3.6 (1.5–8.6)*****
Any Axis I disorder	86.9 (2.3)	85.9 (4.1)	74.9 (2.3)	**2.2 (1.3–3.8)*****	**2.0 (1.0–4.1)***
Any Axis II disorder	65.7 (4.0)	70.3 (5.6)	48.6 (2.5)	1.4 (0.9–2.0)	1.8 (1.0–3.1)
MDE	45.5 (4.1)	48.8 (7.0)	39.8 (2.6)	1.3 (0.9–1.9)	1.4 (0.8–2.6)
Dysthymia	6.8 (1.8)	6.4 (2.3)	7.7 (1.2)	0.9 (0.5–1.6)	0.8 (0.4–1.8)
Mania/hypomania	28.6 (3.9)	24.5 (5.2)	19.2 (2.0)	**1.7 (1.1–2.7)***	1.4 (0.8–2.5)
GAD	27.6 (3.9)	26.6 (5.0)	19.1 (1.8)	**1.6 (1.0–2.6)***	1.5 (0.9–2.7)
Social anxiety disorder	28.8 (3.8)	34.9 (6.4)	17.5 (1.9)	**1.9 (1.2–3.0)****	**2.5 (1.4–4.7)*****
Specific phobia	37.6 (3.9)	43.0 (6.5)	30.1 (2.4)	1.4 (0.9–2.2)	1.8 (1.0–3.1)
Agoraphobia	26.9 (3.2)	28.8 (5.4)	26.4 (2.4)	1.0 (0.7–1.5)	1.1 (0.7–2.0)
Alcohol use disorder	21.4 (3.7)	19.8 (4.7)	14.5 (1.8)	1.6 (1.0–2.6)	1.5 (0.8–2.8)
Drug use disorder	8.7 (2.3)	13.1 (3.4)	6.9 (1.3)	1.3 (0.6–2.6)	2.0 (1.0–4.3)
Nicotine dependence	43.0 (4.8)	42.4 (6.2)	32.4 (2.2)	**1.6 (1.0–2.4)***	1.5 (0.9–2.6)
Histrionic PD	10.1 (2.7)	11.1 (4.0)	8.0 (1.3)	1.3 (0.7–2.5)	1.4 (0.6–3.4)
Schizoid PD	15.3 (3.1)	16.5 (4.9)	15.7 (1.6)	1.0 (0.6–1.7)	1.1 (0.5–2.2)
Paranoid PD	25.4 (4.0)	27.2 (6.1)	22.7 (2.1)	1.2 (0.7–1.8)	1.3 (0.7–2.4)
OCPD	32.0 (4.3)	34.1 (7.0)	25.2 (2.1)	1.4 (0.9–2.2)	1.5 (0.8–2.9)
Dependent PD	6.3 (1.9)	7.7 (3.6)	4.4 (1.0)	1.5 (0.7–3.3)	1.8 (0.6–5.5)
Avoidant PD	17.4 (3.0)	19.0 (4.7)	15.4 (1.8)	1.2 (0.7–1.9)	1.3 (0.7–2.6)
Antisocial PD	14.1 (2.8)	13.7 (4.2)	12.3 (1.9)	1.2 (0.7–2.1)	1.1 (0.5–2.5)
Quality of Life					
Mental component score (MCS)					
50+	25.5 (3.8)	23.0 (5.4)	35.7 (2.7)	1.0	1.0
< 50	74.5 (3.8)	77.0 (5.4)	64.3 (2.7)	**1.6 (1.0–2.6)***	1.9 (1.0–3.5)
Physical component score (PCS)					
50+	42.9 (4.2)	45.0 (6.2)	56.7	1.0	1.0
< 50	57.1 (2.0)	55.0 (6.2)	43.4	**1.7 (1.2–2.6)****	1.6 (0.9–2.7)
Sociodemographic Characteristics					
Sex					
Men	34.1 (4.3)	29.3 (5.3)	27.1 (2.2)	1.0	1.0
Women	65.9 (4.3)	70.7 (5.3)	73.0 (2.2)	1.4 (0.9–2.1)	1.1 (0.6–2.0)
Race/ethnicity					
White	82.1 (3.2)	83.4 (4.3)	75.2 (2.3)	1.0	1.0
Non-White	17.9 (3.2)	16.7 (4.3)	24.8 (2.3)	1.5 (1.0–2.3)	1.7 (0.9–3.0)
Marital status					
Married or as if married	57.6 (4.4)	58.1 (6.3)	57.9 (2.5)	1.0	1.0
Not married	42.4 (4.4)	42.0 (6.3)	42.1 (2.5)	1.0 (0.6–1.5)	1.0 (0.6–1.8)
Age, mean (SE), y	40.5 (1.0)	40.2 (0.4)	40.9 (0.8)	0.12	0.18
Poverty (household income < $20,000)	30.5 (4.0)	29.3 (6.0)	28.3 (2.1)	1.1 (0.7–1.7)	1.1 (0.6–1.9)
No. of past-year stressful life events					
≤ 3	54.1 (4.1)	59.4 (6.9)	68.7 (2.2)	1.0	1.0
> 3	45.9 (4.1)	40.7 (6.9)	31.4 (2.2)	**1.9 (1.3–2.8)*****	1.5 (0.8–2.8)
Education					
College or higher	38.4 (4.0)	38.7 (5.6)	46.1 (2.7)	0.7 (0.5–1.1)	0.7 (0.4–1.2)
High school graduate or less	61.6 (4.0)	61.4 (5.6)	54.0 (2.7)	1.0	1.0
Seeking treatment for panic symptoms	79.9 (4.6)	76.0 (7.2)	70.2 (3.0)	1.7 (0.9–3.2)	1.4 (0.6–3.0)

[a]Values are reported as % (SE) unless designated as mean (SE). Percentages and means are weighted. The n values for recurrence and persistence overlap.
[b]Crude ORs and Wald F (df = 1) indicate measures of association for binary and continuous variables, respectively, and were estimated using logistic regression models; ORs and Wald F tests in bold are statistically significant with α set a priori fixed at .05.
[c]Axis I disorders were past-year diagnoses while Axis II disorders were assessed on a lifetime basis.
*P < .05. ** P < .01. *** P < .005. **** 2-Sided P value < .001.
Abbreviations: GAD = generalized anxiety disorder, MDE = major depressive episode, NA = not applicable, OCPD = obsessive-compulsive personality disorder, OR = odds ratio, PD = personality disorder, SE = standard error.

Figure 2. Structural Equation Model of the 3-Year Risk of Recurrence or Persistence in a General Population Sample of Adults With a Past-Year *DSM-IV* Diagnosis of Panic Disorder (n = 775), Including the Bifactor Models of the Structures "Internalizing-Externalizing" and "Respiratory-Cardiac-Vestibular" Underlying Comorbid Psychiatric Disorders and Panic Disorder Symptoms, Respectively[a]

[a]Ellipses are used to denote latent constructs; rectangles are used to denote the observed variables. Regression coefficients shown are standardized. Values in brackets indicate their standard errors. Only significant effects (2-sided *P* < .05) are represented in the model. Axis I disorders were past-year diagnoses, whereas Axis II disorders were assessed on a lifetime basis.
Abbreviations: GAD = generalized anxiety disorder, MDE = major depressive episode, OCPD = obsessive-compulsive personality disorder, PD = personality disorder, SAD = social anxiety disorder.

DISCUSSION

In a large nationally representative sample, the 3-year persistence and recurrence rates were 13.0% and 27.6%, respectively. The general psychopathology factor, panic disorder liability, lower physical health–related quality of life, a greater number of stressful life events in the past year, and the absence of treatment-seeking behavior were independently associated with increased risk of persistence or recurrence. The general psychopathology factor was the only factor associated with both outcomes. No sociodemographic characteristics had an independent effect on this risk. These findings held when using different approaches to modeling psychiatric comorbidity and symptoms of panic disorder.

To our knowledge, this population-based epidemiologic study is the first to show that treatment-seeking behavior may be a protective factor against the risk of recurrence, contrasting with prior studies.[15,28] Our use of a sample representative of the general population and our ability to adjust for the severity of psychopathology, which is likely to be associated with both treatment-seeking behavior and poor outcomes, may explain this discrepancy. Because individuals with panic disorder often consult for a non-psychiatric reason,[55] our findings suggest that early psychiatric care for panic disorder might reduce the number of visits in emergency units after psychiatric treatment.[56]

Prior research indicates that most comorbid psychiatric disorders are independently associated with increased risk of recurrence or persistence of panic disorder (see Supplementary Table 1). Our findings suggest that this risk is not related to a specific comorbid disorder but rather to a factor accounting for the shared effect of all comorbid psychiatric disorders (ie, the general psychopathology factor). This result is in line with prior findings that showed that the general psychopathology factor may account for the links between psychiatric comorbidity and negative outcomes[31,57,58] and that the number and severity of disorders[59,60] may predict the risk of recurrence or persistence. Thus, interventions directed at more global psychopathologic processes are likely to have greater effect.[61–63]

We found that the panic disorder liability factor was associated with an increased risk of recurrence, suggesting that the severity of the disorder rather than specific individual symptoms increased this risk.[10,15] This finding is in line with prior work[51,52] indicating many panic disorder symptoms may be underpinned by shared mechanisms, including impaired cardiac β-adrenergic tone, cerebral blood flow,[63,64] and increased sympathetic activity.[65]

Lower physical health–related quality of life was independently associated with increased risk of persistence or recurrence. This result is in line with prior research showing that patients with panic disorder are more likely to have a greater number of physical conditions such as cardiovascular, gastrointestinal, neurologic, and respiratory diseases[66] and physical impairment,[12,27,67] which could have an essential role in the etiology,[68] incidence,[69] and recurrence.[70] They also may have hypersensitivity to physical stimuli[71] or a subclinical autonomic hyperactivity,[72,73] resulting in diminished adaptability to changes.[72,73]

No sociodemographic factor was independently associated with the risk of recurrence or persistence. Because the effects of psychiatric illness and psychosocial adversity are bidirectional, separating their effects on those risk can be difficult. Thus, it seems crucial to look for and develop more specific panic disorder markers, whether biological,[24] physiologic (eg, CO_2 challenge, cardiac examination),[64,67] topological (eg, cerebral changes),[62,63] or genetic.[1]

Limitations

Our study has several limitations. First, although this study examined a wide range of psychiatric disorders, several disorders (eg, insomnia, borderline personality disorder) known to be linked to recurrence or persistence risk[24,74] were not assessed at Wave 1. Second, our study used a 3-year period, and results might be different for other follow-up periods.[5,8–10,75] Third, despite its prospective design, we cannot conclude causal relationships between baseline risk factors and the 3-year occurrence of persistence or recurrence, limiting generalizability of the results to the clinical setting. Fourth, the interviews were conducted by lay interviewers, so the results may differ from those of an assessment by expert psychiatrists. Furthermore, the retrospective assessment may lead to approximations in the evaluation of disorder histories, such as the number of panic attacks or the duration of the disorder. Fifth, our definitions of recurrence and persistence may differ from those in other studies, and a consensual definition would allow better patient management. Sixth, panic symptoms were measured as binary variables in NESARC; a measure of the severity of each symptom may have helped refine the dimensional structure of panic disorder. Finally, our results may not be generalizable to other countries.

CONCLUSION

On the basis of a longitudinal, nationally representative and prospective sample, we propose a comprehensive model of recurrence or persistence in individuals with panic disorder. The severity and the number of comorbid psychiatric disorders, the severity and the number of panic disorder symptoms, current stressful life events, and physical health–related quality of life are indicators that may help clinicians identify individuals with panic disorder at high risk of recurrence or persistence. Early treatment-seeking behavior should be promoted, as it may reduce the risk of recurrence.

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Supplementary Material

List of Supplementary Material for the article

the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Risk factors reported by prior studies of increased recurrence or persistence risk in individuals with panic disorder.

Factors	Overall	Recurrence	Persistence
Specific symptoms of panic disorder		Ehlers et al., (1995) ; Liu et al., (2015)	
Panic disorder severity	Heldt et al., (2010)		Batelaan et al., (2009) ; Faravelli et al., (1987) ; Noyes et al., (1989) ; Toni et al., (2000)
Other associated features			
Duration of illness			Katschnig et al., (1995) ; Noyes et al., (1993) ; Pollack et al., (1992)
Frequency of panic attacks			Batelaan et al., (2010) ; Ehlers et al., (1995)
Phobic avoidance		Katschnig et al., (1995)	
Early age at onset		Ramsawh et al., (2011)	Segui et al., (1999) ; Warshaw et al., (1997)
Greater number of panic attacks		Ehlers et al., (1995)	Aronson et al., (1987)
Insomnia			Aronson et al., (1987)
Psychiatric comorbidity			
Greater number of comorbidities		Ehlers et al., (1995)	Brown et al., (1995) ; Cowley et al., (1996)
Major depressive disorder	Bruce et al., (2005) ; Roy-Byrne et al., (1994)	Nay et al., (2013)	Albus et al., (1993) ; Benitez et al., (2009) ; Coryell et al., (1988) ; Cowley et al., (1996) ; Francis et al., (2007) ; Reich et al., (1988)
Dysthymic disorder		Liu et al., (2015)	Heldt et al., (2006)

Alcohol and other substance use disorders		Liu et al., (2015) ; Nay et al., (2013)	Batelaan et al., (2009)
Anxiety disorders			Batelaan et al., (2009) ; Benitez et al., (2009) ; Faravelli et al., (1987)
Agoraphobia	Bruce et al., (2005) ; Roy-Byrne et al., (1994)	Weisberg et al., (2002)	Andersch et al., (2003) ; Batelaan et al., (2009) ; Carpiniello et al., (2002) ; Cowley et al., (1996) ; Faravelli et al., (1987) ; Francis et al., (2007) ; Warshaw et al., (1997)
Generalized anxiety disorder	Nay et al., (2013)	Mavissakalian et al., (2004) ; Rodriguez et al., (2005)	Heldt et al., (2006)
Social anxiety disorder			Heldt et al., (2006) ; Nay et al., (2013) ; Warshaw et al., (1997)
Personality disorders	Roy-Byrne et al., (1994) ; Svanborg et al., (2008)	Pollack et al., (1992)	Faravelli et al., (1987) : O'Rourke et al., (1996)
Histrionic			Cowley et al., (1996) ; Reich et al., (1988)
Antisocial			Reich et al., (1988)
Schizotypal			Cowley et al., (1996)
Borderline		Ansell et al., (2011)	
Paranoid			Faravelli et al., (1987)
Family history of psychiatric disorders			Faravelli et al., (1987)
Childhood trauma		Liu et al., (2015)	
Stressful life events	Heldt et al., (2010) ; Roy-Byrne et al., (1986)	Nay et al., (2013)	Aronson et al., (1987) ; Batelaan et al., (2009) ; Faravelli et al., (1987) ; Moitra et al., (2011)
Functional impairment		Mavissakalian et al., (2004) ; Rodriguez et al., (2005)	

Low physical health			Benitez et al., (2009) ; Bringager et al., (2008) ; Warshaw et al., (1997)
Sociodemographic characteristics			
Younger age		Liu et al., (2015) ; Nay et al., (2013)	Francis et al., (2007)
Female sex		Liu et al., (2015) ; Nay et al., (2013) ; Yonkers et al., (2003)	Maier et al., (1988)
Being divorced or separated or widowed			Wade et al., (1993)
Poverty and low socioeconomic			Warshaw et al., (1997)
Low education			Aronson et al., (1987) ; Faravelli et al., (1987)
African-American			Sibrava et al., (2013)
Treatment-seeking behavior		Liu et al., (2015)	Aronson et al., (1987)

Supplementary Table 2. Confirmatory factor analysis model of the structure "Respiratory-Cardiac-Vestibular" underlying the 10 disaggregated DSM-IV criteria for Panic Disorder in individuals with a past year DSM-IV diagnosis of Panic Disorder (N=775) in Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

	Panic disorder liability	Respiratory	Cardiac	Vestibular
CFI	**0.991**			
TLI	**0.988**			
RMSEA	**0.029**			
Shortness of breath	0.58****	0.58****		
Feeling of choking	0.57****	0.50****		
Palpitations	0.54****		0.59****	
Chest pain or discomfort	0.81****		-0.38	
Sweating	0.26***			0.68****
Feeling dizzy	0.35****			0.38***
Nausea or abdominal distress	0.23***			0.40****
Paresthesias	0.59****			0.32***
Chills or heat sensations	0.35****			0.62****
Trembling or shaking	0.39****			0.22*
Factor correlation				
Panic disorder liability	1.00			
Respiratory	0.00	1.00		
Cardiac	0.00	0.00	1.00	
Vestibular	0.00	0.00	0.00	1.00

Abbreviations: CFI, Comparative Fit Index; TLI, Tucker-Lewis Index; RMSEA, Root Mean Square Error of Approximation.

**** p<.001; *** p<.005; ** p<.01; * p<.05.

Supplementary Table 3. Comparison of baseline indicators of panic disorder severity, psychiatric comorbidity, quality of life, sociodemographic characteristics and treatment-seeking behavior at Wave 1 in individuals with a past-year DSM-IV diagnosis of panic disorder (n=775) according to the 3-year occurrence of recurrence or persistence.

	Persistence vs Recurrence
	OR [95%CI] / Wald F[c]
Severity of panic disorder	
Palpitations	0.3 [0.1-1.6]
Sweating	1.2 [0.5-3.0]
Trembling or shaking	1.9 [0.7-4.7]
Sensations of shortness of breath	1.9 [0.6-6.4]
Feelings of choking	1.4 [0.8-2.6]
Chest pain or discomfort	1.4 [0.7-3.0]
Nausea or abdominal distress	1.4 [0.7-2.7]
Feeling dizzy	1.1 [0.4-2.9]
Chills or heat sensations	1.1 [0.5-2.3]
Paresthesias	1.1 [0.5-2.1]
Derealization or depersonalization	0.6 [0.3-1.5]
Fear of losing control or going crazy	1.5 [0.7-3.1]
Fear of dying	1.5 [0.8-3.0]
Number of lifetime panic attacks	**16.9******
Duration of illness	3.9
Age at onset of panic disorder	3.0
First degree relatives' history of psychiatric disorders	1.3 [0.5-3.3]
Psychiatric comorbidity [a]	
Any Axis I or II disorder	0.5 [0.2-1.4]
Any Axis I disorder	1.2 [0.5-2.9]

Any Axis II disorder	0.7 [0.4-1.3]
MDE	0.9 [0.4-1.7]
Dysthymia	1.2 [0.4-3.6]
Mania/hypomania	1.6 [0.8-3.2]
GAD	1.2 [0.7-2.3]
Social anxiety disorder	0.7 [0.3-1.4]
Specific phobia	0.7 [0.4-1.4]
Agoraphobia	1.0 [0.5-2.0]
Alcohol use disorder	1.1 [0.5-2.5]
Drug use disorder	0.4 [0.1-1.2]
Nicotine dependence	1.1 [0.6-2.2]
Histrionic PD	0.8 [0.2-2.5]
Schizoid PD	0.9 [0.4-2.0]
Paranoid PD	1.0 [0.4-2.1]
OCPD	0.9 [0.4-2.0]
Dependent PD	1.1 [0.3-4.2]
Avoidant PD	1.0 [0.4-2.3]
Antisocial PD	1.2 [0.4-3.0]
Quality of life	
Mental component score (MCS)	
≥50	0.8 [0.4-1.8]
<50	
Physical component score (PCS)	
≥50	1.3 [0.7-2.4]
<50	
Sociodemographic characteristics	
Sex	
Men	
Women	1.4 [0.7-2.7]
Race/Ethnicity	
White	
Non-White	0.9 [0.4-1.8]

Marital Status	
Married or as if married	
Not married	1.0 [0.5-2.1]
Age	0.1
Poverty (household income<$20,000)	1.1 [0.6-2.2]
Number of past year stressful life events	
≤3	
>3	1.3 [0.7-2.8]
Education	
College or higher	1.1 [0.6-2.2]
High school graduate or less	
Seeking treatment for panic symptoms	1.7 [0.6-4.8]

[a]Axis I disorders were past year diagnoses while Axis II disorders were assessed on a lifetime basis. Abbreviations: MDE, major depressive episode; GAD, generalized anxiety disorder; SE, standard error; PD, personality disorder; OCPD, obsessive-compulsive personality disorder; NA, not applicable.

[c] Crude ORs/Wald F (d.f.=1) indicate measures of association for binary/continuous variables and were estimated using logistic regression models; ORs and Wald F tests in bold are statistically significant with alpha set *a priori* fixed at 0.05.

**** two-sided p-value (p) <.001; *** p<.005; ** p<.01; * p<.05.

Supplementary Table 4. Bifactor model of the structure "Distress-Fear-Externalizing" underlying past-year Axis I disorders and antisocial personality disorder in individuals with a past-year DSM-IV diagnosis of Panic Disorder (N=775) in Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

CFI	0.990			
TLI	0.986			
RMSEA	0.033			
Disorder	General psychopathology factor	Externalizing	Fear	Distress
MDE	0.50****			0.71****
Dysthymia	0.31*			0.58****
GAD	0.52****			0.27***
Social Anxiety Disorder	0.59****		0.57****	
Specific phobia	0.45****		0.45****	
Agoraphobia	0.23***		0.92****	
Alcohol use disorder	0.14	0.67****		
Drug use disorder	0.36***	0.77****		
Nicotine dependence	0.37****	0.50****		
Antisocial PD	0.36****	0.66****		
Factor loading of the factor Internalizing			-0.11	0.71****
Factor correlation				
General psychopathology factor	1.00			
Externalizing	0.00	1.00		
Fear	0.00	0.00	1.00	
Distress	0.00	0.00	0.00	1.00

Abbreviations: CFI, Comparative Fit Index; TLI, Tucker-Lewis Index; RMSEA, Root Mean Square Error of Approximation; MDE, major depressive episode; GAD, generalized anxiety disorder; PD, personality disorder.
**** $p<.001$; *** $p<.005$; ** $p<.01$; * $p<.05$.

Supplementary Table 5. Bifactor model of the structure "Internalizing-Externalizing" underlying past-year Axis I disorders and lifetime Axis II disorders in individuals with a past year DSM-IV diagnosis of Panic Disorder (N=775) in Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

CFI	**0.987**		
TLI	**0.983**		
RMSEA	**0.023**		
Disorder	**General psychopathology factor**	**Internalizing**	**Externalizing**
MDE	0.65****	-0.14	
Dysthymia	0.45****	-0.28	
GAD	0.48****	0.15*	
Social Anxiety Disorder	0.53****	0.68****	
Specific phobia	0.35****	0.47****	
Agoraphobia	0.23**	0.77****	
Mania/Hypomania	0.71****	-0.04	
Avoidant PD	0.69****	0.39****	
Dependent PD	0.78****	0.35***	
OCPD	0.52****	0.22*	
Paranoid PD	0.63****	0.29***	
Schizoid PD	0.56****	-0.06	
Histrionic PD	0.62****	-0.09	
Antisocial PD	0.48****		0.51****
Alcohol use disorder	0.14		0.71****
Drug use disorder	0.41****		0.77****
Nicotine dependence	0.36****		0.49****
Factor correlation			
General psychopathology factor	1.00		
Internalizing	0.00	1.00	
Externalizing	0.00	0.00	1.00

Abbreviations: CFI, Comparative Fit Index; TLI, Tucker-Lewis Index; RMSEA, Root Mean Square Error of Approximation; MDE, major depressive episode; GAD, generalized anxiety disorder; PD, personality disorder; OCPD, obsessive-compulsive personality disorder
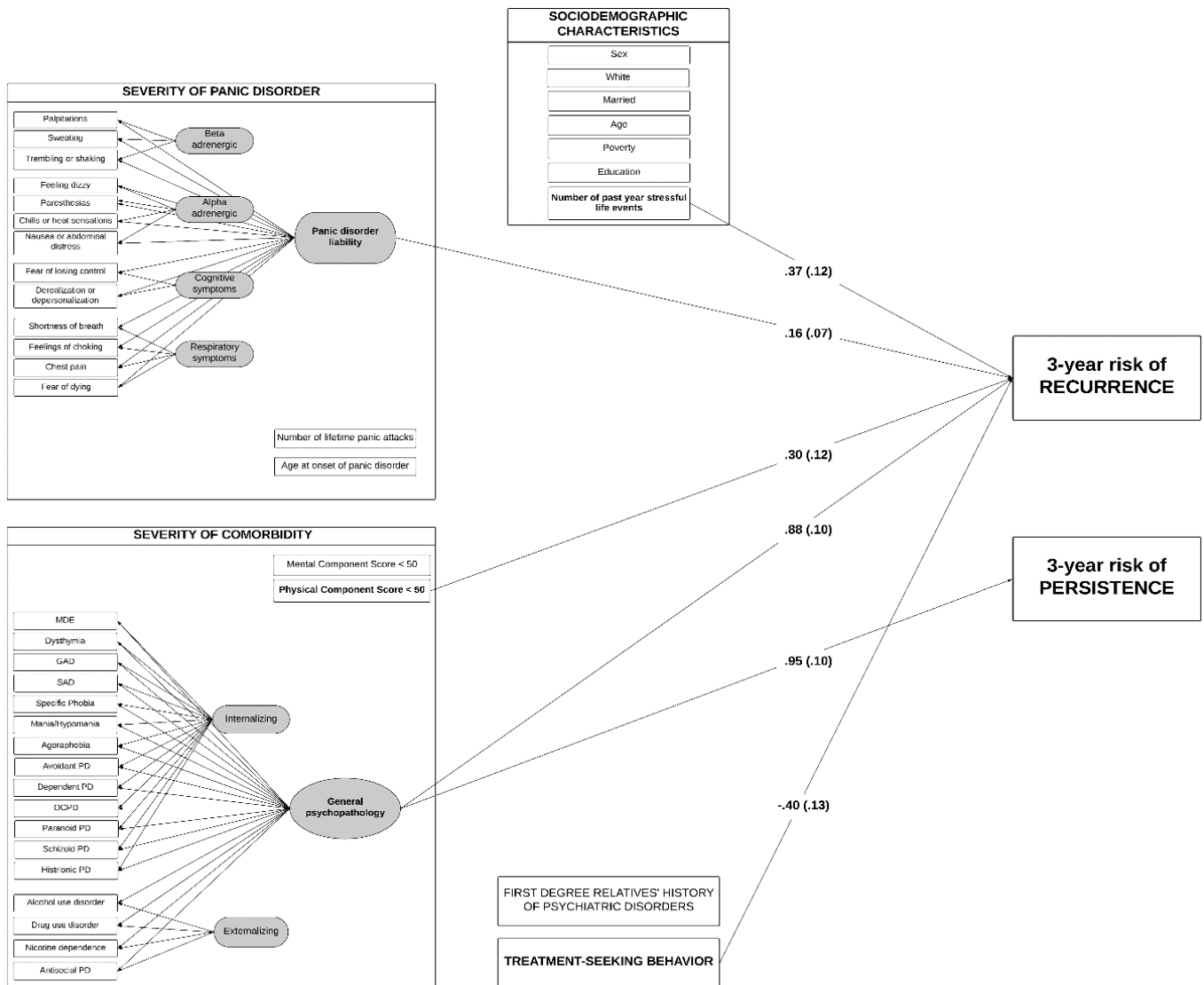**** p<.001; *** p<.005; ** p<.01; * p<.05.

Supplementary Table 6. Confirmatory factor analysis model of the structure "Beta adrenergic-Alpha adrenergic-Cognitive-Respiratory" underlying the 13 disaggregated DSM-IV criteria for Panic Disorder in individuals with a past year DSM-IV diagnosis of Panic Disorder (N=775) in Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

CFI	**0.982**				
TLI	**0.977**				
RMSEA	**0.031**				
	Panic disorder liability	**Beta-adrenergic**	**Alpha-adrenergic**	**Cognitive**	**Respiratory**
Palpitations	0.45****	0.63****			
Trembling or shaking	0.46****	0.13			
Sweating	0.45****	0.19			
Feeling dizzy	0.40****		0.65****		
Paresthesias	0.65****		0.29***		
Chills or heat sensations	0.46****		0.43****		
Nausea or abdominal distress	0.36****		0.24*		
Derealization or depersonalization	0.43****			0.64****	
Fear of losing control	0.51****			0.25*	
Shortness of breath	0.58****				0.58****
Feeling of choking	0.47****				0.61****
Chest pain or discomfort	0.61****				0.33***
Fear of dying	0.45****				-0.01
Factor correlation					
Panic disorder liability	1.00				
Beta adrenergic	0.00	1.00			
Alpha adrenergic	0.00	0.00	1.00		
Cognitive	0.00	0.00	0.00	1.00	
Respiratory	0.00	0.00	0.00	0.00	1.00

Abbreviations: CFI, Comparative Fit Index; TLI, Tucker-Lewis Index; RMSEA, Root Mean Square Error of Approximation.

**** $p < .001$; *** $p < .005$; ** $p < .01$; * $p < .05$.

Supplementary Figure 1. Structural equation model of the 3-year risk of recurrence or persistence in a general population sample of adults with a past-year DSM-IV diagnosis of panic disorder (n=775), including the bifactor models of the structures "Internalizing-Externalizing" and "Beta adrenergic-Alpha adrenergic-Cognitive-Respiratory" underlying comorbid psychiatric disorders and panic disorder symptoms, respectively.[a]
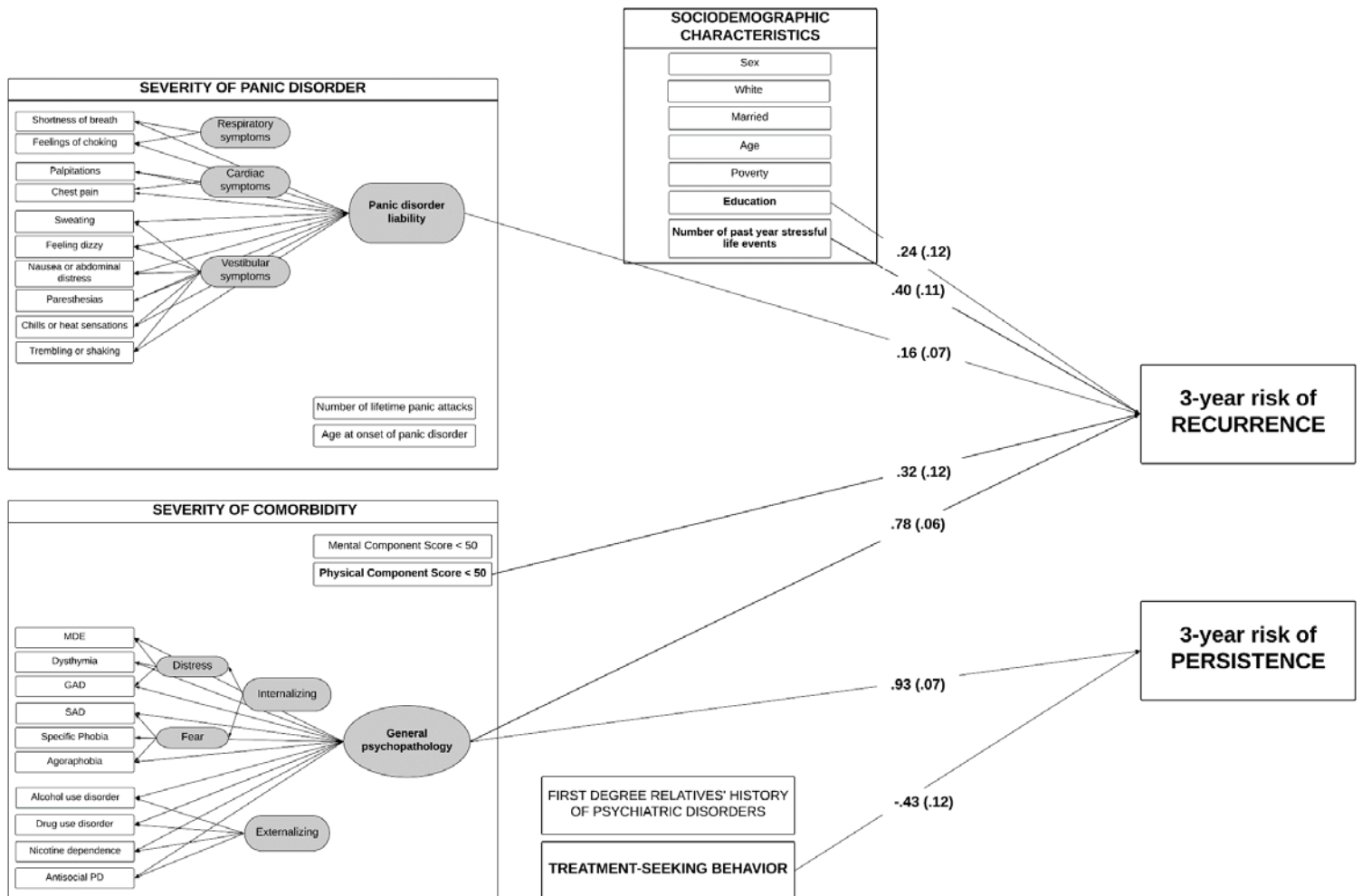

[a] Ellipses are used to denote latent constructs, rectangles are used to denote the observed variables. Regression coefficients shown are standardized. Values in brackets indicate their standard errors. Only significant effects (two-sided $p<.05$) are represented in the model.

Axis I disorders were past year diagnoses while Axis II disorders were assessed on a lifetime basis.
Abbreviations: MDE, major depressive episode; GAD, generalized anxiety disorder; SAD, social anxiety disorder; PD, personality disorder; OCPD, obsessive-compulsive personality disorder.
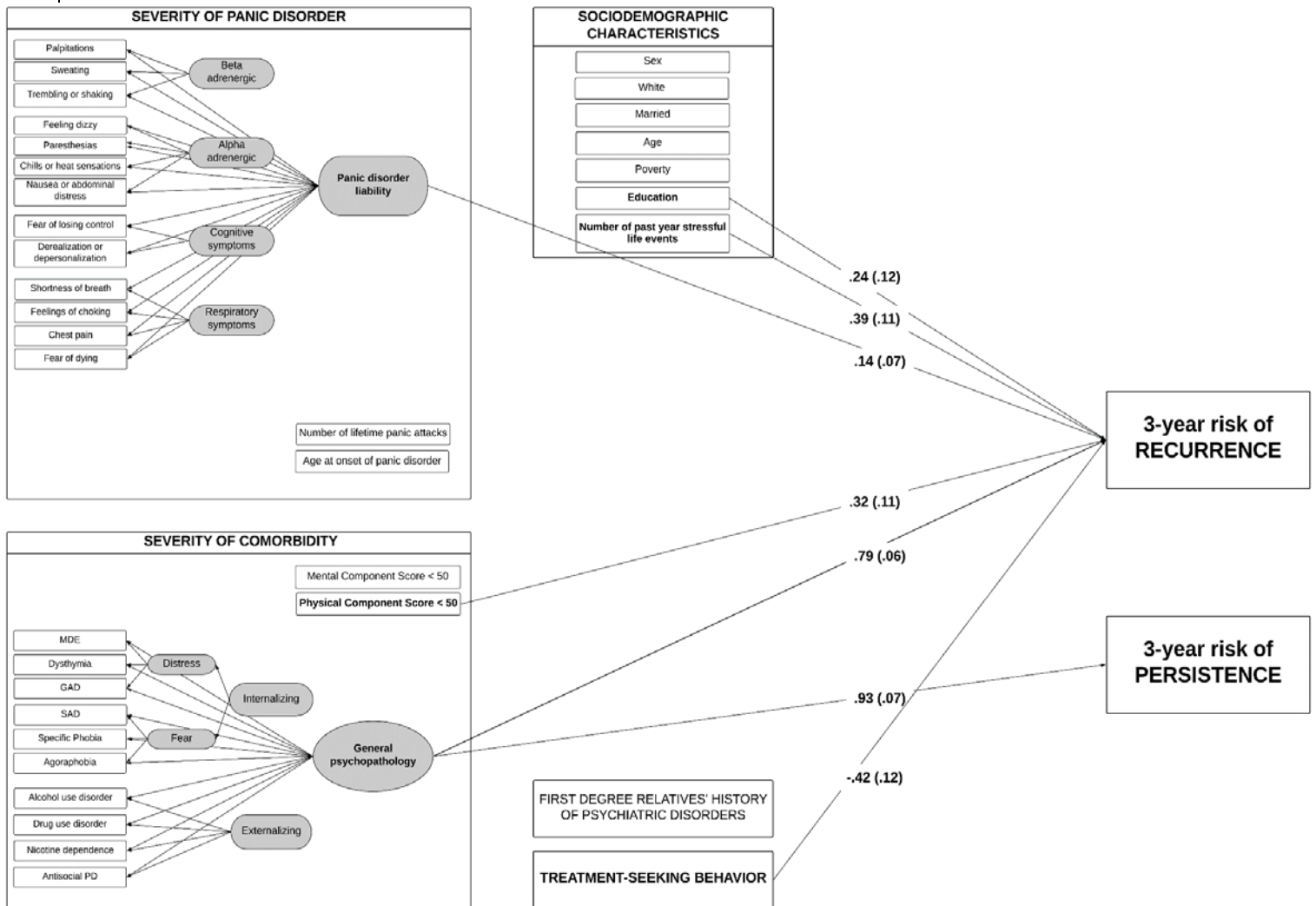
Supplementary Figure 2. Structural equation model of the 3-year risk of recurrence or persistence in a general population sample of adults with a past-year DSM-IV diagnosis of panic disorder (n=775), including the bifactor models of the structures "Distress-Fear-Externalizing" and "Respiratory-Cardiac-Vestibular" underlying comorbid psychiatric disorders and panic disorder symptoms, respectively. [a]

[a] Ellipses are used to denote latent constructs, rectangles are used to denote the observed variables. Regression coefficients shown are standardized. Values in brackets indicate their standard errors. Only significant effects (two-sided $p<.05$) are represented in the model.

Axis I disorders were past year diagnoses while Axis II disorders were assessed on a lifetime basis. Abbreviations: MDE, major depressive episode; GAD, generalized anxiety disorder; SAD, social anxiety disorder; PD, personality disorder

Supplementary Figure 3. Structural equation model of the 3-year risk of recurrence or persistence in a general population sample of adults with a past-year DSM-IV diagnosis of panic disorder (n=775), including the bifactor models of the structures "Distress-Fear-Externalizing" and "Beta adrenergic-Alpha adrenergic-Cognitive-Respiratory" underlying comorbid mental disorders and panic disorder symptoms, respectively.

[a] Ellipses are used to denote latent constructs, rectangles are used to denote the observed variables. Regression coefficients shown are standardized. Values in brackets indicate their standard errors. Only significant effects (two-sided $p<.05$) are represented in the model.
Axis I disorders were past year diagnoses while Axis II disorders were assessed on a lifetime basis.
Abbreviations: MDE, major depressive episode; GAD, generalized anxiety disorder; SAD, social anxiety disorder; PD, personality disorder.