

# Smoking and Panic Attacks

## An Epidemiologic Investigation

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**Background:** Epidemiologic studies have reported a lifetime association between smoking and panic disorder. In this study, we examine potential explanations for this association.

**Methods:** Analysis was conducted on data from 2 epidemiologic studies, the Epidemiologic Study of Young Adults in southeast Michigan (N = 1007) and the National Comorbidity Survey Tobacco Supplement (n = 4411). Cox proportional hazards models with time-dependent covariates were used to estimate the risk for onset of panic attacks associated with prior smoking and vice versa, controlling for history of major depression. The role of lung disease in the smoking–panic attacks association was explored.

**Results:** Daily smoking signaled an increased risk for

first occurrence of panic attack and disorder; the risk was higher in active than past smokers. No significant risk was detected for onset of daily smoking in persons with prior panic attacks or disorder. Exploratory analyses suggest that lung disease might be one of the mechanisms linking smoking to panic attacks.

**Conclusions:** The evidence that the association between smoking and panic disorder might result primarily from an influence in one direction (ie, from prior smoking to first panic attack) and the possibility of a higher risk in active than past smokers suggest a causal hypothesis for the smoking–panic attacks relationship.

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**E**PIDEMIOLOGIC studies have reported positive associations between smoking and psychiatric disorders,<sup>1-4</sup> confirming previous reports that the rate of smoking is higher in patients with psychiatric disorders, including depressive and anxiety disorders.<sup>5</sup> The relationship between smoking and major depression has been the focus of considerable research.<sup>6-13</sup> In contrast, little is known about the relationship of smoking with panic disorder, beyond the observation of positive associations. Clinical studies suggest that in patients with panic disorder smoking preceded the onset of panic disorder.<sup>14,15</sup>

We examine the lifetime association between daily smoking and panic attacks in 2 community-based data sets, the Epidemiologic Study of Young Adults in southeast Michigan<sup>1,2</sup> and the National Comorbidity Survey (NCS) Tobacco Supplement,<sup>16</sup> and examine potential explanations for the observed association.

A lifetime association between daily smoking and panic attacks might reflect causal and noncausal mechanisms. Daily smoking might cause panic attacks; con-

versely, panic attacks might increase the risk for daily smoking. Alternatively, the association might be noncausal: smoking and panic attacks might be linked by shared etiologies. Although observational studies cannot definitively test causal hypotheses, they can dampen the plausibility of some hypotheses and suggest the plausibility of others. Evidence that daily smoking is associated with an increased risk for first panic attack but no increased risk in the reverse direction (ie, from panic attacks to onset of daily smoking) would dampen the plausibility that panic increases the risk for smoking. It would suggest the hypothesis that daily smoking causes panic attacks, although the plausibility of shared causes could not be ruled out. Furthermore, evidence of a greater risk for panic attacks in active smokers than in those who have quit would dampen the plausibility of the shared causes explanation. In contrast, evidence of influences in both directions and evidence of an equally increased risk for panic attacks in smokers who quit and those who continued to smoke would suggest the hypothesis that the observed association reflects common causes.

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## SUBJECTS, MATERIALS, AND METHODS

### SAMPLES AND DATA

#### Epidemiologic Study of Young Adults

A sample of 1200 persons was randomly selected from all 21- to 30-year-old members of a large health maintenance organization in southeast Michigan. Personal interviews were conducted in 1989 with 1007 subjects (84%) and follow-up interviews were conducted in 1990, 1992, and 1994. Complete follow-up data are available for 974 persons (97%). At baseline the sample was 62% female, 80% white, 45% married, and 29% college educated. Detailed information on the sample has been previously reported.<sup>1,2</sup>

The National Institute of Mental Health Diagnostic Interview Schedule,<sup>23</sup> revised according to the *DSM-III-R*, was used. *Panic attack* is defined in the *DSM-III-R* as an attack in which at least 4 of the following 13 symptoms are experienced: shortness of breath, dizziness, palpitation, trembling, sweating, choking, nausea, depersonalization, numbness, flushes or chills, chest pain, fear of dying, and fear of going crazy. *Panic disorder* is defined as the occurrence of either 4 attacks within a 4-week period or 1 or more attacks followed by a period of at least 1 month of persistent fear of having another attack. The Diagnostic Interview Schedule elicits information on the age at which the first *DSM-III-R* panic attack occurred. Age at first panic attack is also used to define age of onset of panic disorder in the subset meeting the *DSM-III-R* criteria for the disorder. The onset of daily smoking is defined as the age at which the respondent first smoked daily for 1 month or longer. Lifetime history of panic attacks, psychiatric disorders, and smoking was measured at baseline, and interval history, covering the period since the last assessment, was gathered at each follow-up interview. Data from baseline and follow-up interviews were combined, providing

lifetime data up to age 35 years, the upper age limit of the respondents at the last interview.

#### NCS Tobacco Supplement

The NCS is based on a stratified, multistage area probability sample of persons aged 15 to 54 years in the United States.<sup>16</sup> The diagnostic interview was a modified version of the Composite International Diagnostic Interview, which also yields *DSM-III-R* diagnoses.<sup>24</sup> The Composite International Diagnostic Interview is modeled on the National Institute of Mental Health Diagnostic Interview Schedule. The Tobacco Supplement was administered in the second half of the survey. Data are available on 4411 respondents of the total NCS sample of 8098. Because the NCS fieldwork was conducted in replicate samples, the subset with data from the Tobacco Supplement is also representative of the US population.<sup>16</sup>

#### STATISTICAL ANALYSIS

Cox proportional hazards models for censored survival data, with daily smoking as a time-dependent covariate,<sup>25-27</sup> were used to calculate the hazard ratio (HR) of first occurrence of panic attack associated with prior daily smoking (research question 1). The HR estimates the risk for first panic attack in persons who smoked daily compared with persons who had not. Time was defined as chronological age. Persons who had not experienced a panic attack by the time of the last interview were censored.

The advantage of the Cox proportional hazards model, compared with logistic regression, is that it permits taking into account differences across individuals in the period of risk for the outcome. The added advantage of models with time-dependent covariates is that they allow consideration of independent variables that vary over time. The parameter estimate ( $\beta$ ) in the Cox proportional hazards

We address 3 questions: (1) Does daily smoking signal an increased risk for first-time occurrence of a panic attack? (2) Is the risk for first panic attack greater in persons who continue to smoke than in those who have quit? (3) Does a history of panic attacks signal an increased risk for daily smoking? To each data set, we apply the same statistical methods that take advantage of information on the timing of onset of daily smoking and first occurrence of panic attack. Results are presented on *DSM-III-R* panic attacks and panic disorder. Previous reports suggest an association between pulmonary dysfunction and panic disorder.<sup>17-22</sup> In view of this evidence and the established causal role of smoking in lung disease, we explore the potential mediating role of lung disease in the smoking-panic attack relationship.

## RESULTS

### THE EPIDEMIOLOGIC STUDY OF YOUNG ADULTS

**Table 1** presents the lifetime prevalence of the major variables in the analysis and the lifetime prevalence of panic attacks in subsets stratified according to the cross-

classification of daily smoking and major depression. The lifetime association between panic attacks and daily smoking was similar in men and women; odds ratios (ORs) were 3.13 (95% CI, 1.30-7.50) and 2.61 (95% CI, 1.66-4.09), respectively.

Estimated in a Cox proportional hazards model with daily smoking as a time-dependent covariate and adjusting for sex and major depression, the HR of panic attack associated with prior daily smoking was 3.96 (95% CI, 2.28-6.89). This estimate compares daily smokers with no history of major depression with persons who neither smoked daily nor experienced major depression. The HR of panic attacks associated with prior major depression alone was 12.98 (95% CI, 6.70-25.18), and with major depression plus daily smoking, 12.77 (95% CI, 6.73-24.26). In another model, history of major depression plus daily smoking was coded as 2 covariates according to their temporal order: first major depression and then daily smoking and vice versa. The results suggest an added effect of subsequent daily smoking in persons with preexisting major depression compared with persons with major depression alone (HR, 16.28; 95% CI, 7.35-36.05). This was not the case if daily smoking preceded the onset of major depression (HR, 10.64; 95% CI, 4.93-22.98).

model is a regression coefficient from which the HR can be obtained by taking the antilogarithm of the parameter estimate. Hazard ratios with 95% confidence intervals (CIs) that do not include the null value of 1 are significant at  $\alpha < .05$  (2 tailed).

We controlled for the potential influence of major depression, which is associated with both panic attacks (or disorder) and smoking. Three time-dependent covariates were used, representing the 4 strata of the independent variable: daily smoking alone, major depression alone, and daily smoking plus major depression, with neither daily smoking nor major depression as the reference. This model yields an estimate of the HR for panic attacks in daily smokers who have never experienced major depression, compared with persons who have neither smoked daily nor experienced major depression. We used the SAS procedure for proportional hazards regression, with the logit link to address the interval-censored data.<sup>28</sup> The proportionality assumption was tested for each model, using graphic techniques.<sup>29</sup>

The proportional hazards model with the 3 time-dependent covariates is as follows:

$$h_i(t) = e^{\beta z_i(t) + \gamma y_i(t) + \alpha x_i(t)} h_0(t)$$

where  $z_i(t)$  is 1 if the respondent smoked daily (but had no history of major depression) before time  $t$  and 0 if not;  $y_i(t)$  is 1 if the respondent experienced major depression (but not daily smoking) before time  $t$  and 0 if not;  $x_i(t)$  is 1 if the respondent experienced major depression plus daily smoking before time  $t$  and 0 if not; and  $\beta$ ,  $\gamma$ , and  $\alpha$  are the coefficients of risk for panic attacks associated with daily smoking alone, major depression alone, and daily smoking plus major depression, respectively.

To estimate the HR for panic attacks associated with continued as opposed to discontinued smoking (research question 2), daily smoking was defined as a time-dependent covariate that can change twice: first from nondaily smoking to daily smoking, and then from daily

smoking to quitting. It yields an estimate of the HR of panic attack in daily smokers who continued to smoke and the HR in those who quit, using nondaily smokers as a reference. History of major depression was controlled, as described above. To estimate the HR of daily smoking associated with prior panic attacks (research question 3), we employed Cox proportional hazards models with time-dependent covariates like those described above for research question 1. Interactions between sex and independent variables of interest were tested. No significant interactions were detected at  $\alpha < .15$ . Sex was included in these models as a covariate.

We also tested the influence of heavy drinking on these models, given the evidence of its potential role in panic attacks<sup>30</sup> and its association with smoking.<sup>1-4,31,32</sup> Heavy drinking was significantly associated with an increased risk for panic disorder, but its inclusion in the model did not alter the estimates of the relationships between daily smoking and panic disorder. Analysis is available upon request from the authors.

We explored the role of lung disease in the smoking-panic attack association. The Epidemiologic Study of Young Adults elicited information on a list of diseases, among them "chronic bronchitis or emphysema." The NCS included an item that encompasses "severe asthma, bronchitis, emphysema, TB, or other lung problems." Because information on the age of onset of lung disease is not available in either study, the temporal order between smoking, lung disease, and panic attacks cannot be determined. Using the lifetime retrospective data in each study, we estimated the odds for panic attacks associated with smoking and lung disease with logistic regressions, using respondents who neither smoked nor reported lung disease as a reference.

To take into account the complex sampling design of the NCS, we also present estimates of the lifetime prevalence of the major variables in the analysis and results of the exploratory logistic regression based on weighted data, using SUDAAN.<sup>33</sup>

Cox proportional hazards models with time-dependent covariates were used to estimate the HRs of the first occurrence of panic attacks in daily smokers who continued to smoke and in smokers who quit. Compared with persons who neither smoked daily nor experienced major depression, the HR of first panic attack in smokers who continued to smoke was 4.71 (95% CI, 2.70-8.21), but in smokers who quit it was 0.21 (95% CI, 0.05-0.88). The contrast between continued and discontinued smoking was statistically significant ( $P = .002$ ).

### Onset of Daily Smoking After Panic Attacks

The sex-adjusted HR of daily smoking associated with prior panic attacks was 2.13 (95% CI, 1.24-3.67). However, adjusting additionally for major depression obliterated any evidence of an increased risk of daily smoking associated with panic attacks (HR, 1.00; 95% CI, 0.40-2.48).

### Panic Disorder

Of the 121 persons who experienced panic attacks, 52 met the criteria for *DSM-III-R* panic disorder (Table

1). The sex-adjusted OR that estimates the lifetime association between daily smoking and panic disorder was 4.24 (95% CI, 2.23-8.06). Calculated in a Cox proportional hazards model with time-dependent covariates, the sex-adjusted HR of onset of panic disorder (ie, first panic attack in persons meeting criteria for panic disorder) in daily smokers compared with nondaily smokers was 4.73 (95% CI, 2.36-9.49). When history of major depression was controlled, the HR of panic disorder in daily smokers was 13.13 (95% CI, 4.41-39.10) compared with persons who neither smoked daily nor experienced major depression. The HR of panic disorder in daily smokers who continued to smoke was 14.46 (95% CI, 4.81-43.50), but in smokers who quit, 0.51 (95% CI, 0.12-2.28), using persons who neither smoked daily nor experienced major depression as a reference. The contrast because of quitting was significant ( $P = .001$ ).

Looking at the relationship in the reverse direction (ie, from prior panic disorder to onset of daily smoking), the sex-adjusted HR was 2.20 (95% CI, 1.10-4.42). However, controlling also for prior major depression, the HR of daily smoking after the onset of panic disorder fell to 0.82 (95% CI, 0.20-3.39).

**Table 1. Lifetime Prevalence of Daily Smoking, Smoking Cessation, Major Depression, Panic Attacks, Panic Disorder, and Panic Attacks in Subsets Classified by History of Smoking and Major Depression\***

	Epidemiologic Study of Young Adults (N = 1007), No. (%)	NCS Tobacco Supplement (N = 4411), No. (Unweighted %) [Weighted %]
<b>Lifetime Prevalence</b>		
Daily smoking	431 (42.8)	2088 (47.3) [47.1]
Smoking cessation†	162 (37.6)	671 (32.4) [32.6]
Major depression	211 (21.0)	805 (18.2) [16.9]
Panic attack	121 (12.0)	302 (6.8) [6.5]
With major depression	72 (7.2)	148 (3.4) [3.2]
Without major depression	49 (4.9)	154 (3.5) [3.3]
Panic disorder	52 (5.2)	149 (3.4) [3.4]
With major depression	37 (3.7)	85 (1.9) [1.9]
Without major depression	15 (1.5)	64 (1.5) [1.5]
<b>Proportions With Panic Attacks by Smoking and Major Depression</b>		
No smoking/no depression	492 (4.5)	1989 (3.6) [3.2]
Daily smoking only	304 (8.9)	1602 (5.1) [5.0]
Major depression only	84 (25.0)	334 (16.2) [16.1]
Daily smoking/depression	127 (40.2)	469 (20.0) [20.5]

\*NCS indicates National Comorbidity Survey.

†Percentage of daily smokers.

## THE NCS TOBACCO SUPPLEMENT

Unweighted and weighted prevalence estimates of the major variables in the NCS appear in Table 1. The lifetime association of panic attacks with daily smoking in men was 1.64 (95% CI, 1.10-2.50) and in women, 1.69 (95% CI, 1.26-2.25).

Applying the same Cox proportional hazards models with time-dependent covariates, the HR of first panic attack in daily smokers was 2.02 (95% CI, 1.47-2.77), adjusted for sex and major depression. The HR of first panic attack in daily smokers who continued to smoke was 2.07 (95% CI, 1.49-2.87) and in those who had quit, 1.85 (95% CI, 0.98-3.50), using persons who neither smoked daily nor experienced major depression as a reference. The difference in the HRs was not significant ( $P = .73$ ). Analysis of the relationship in the reverse direction showed that the HR of daily smoking associated with prior panic attacks was 1.37 (95% CI, 0.99-1.88).

Of the 301 persons with a history of panic attacks, 149 met the criteria for panic disorder (Table 1). The sex-adjusted OR measuring the lifetime association between daily smoking and panic disorder was 1.60 (95% CI, 1.27-2.18). Calculated in a Cox proportional hazards model with time-dependent covariates, the HR of onset of panic disorder associated with prior daily smoking was 2.93 (95% CI, 1.84-4.66), adjusted for sex and major depression. In persistent smokers it was 3.18 (95% CI, 1.99-5.10) and in smokers who had quit, 1.82 (95% CI, 0.69-4.28). The difference between the estimates was not significant ( $P = .24$ ). The HR of daily smoking associated with prior panic disorder was only 1.06 (95% CI, 0.54-2.08), controlling for sex and major depression.

**Table 2** presents a summary of the results from the 2 data sets. Although estimates from the NCS of the HRs of

**Table 2. Hazard Ratio (HR) Estimates of the Relationship of Smoking With Panic Attack and Disorder From the Epidemiologic Study of Young Adults and the NCS Tobacco Supplement\***

Hazard Models†	Study of Young Adults (N = 997), HR (95% CI)	NCS Tobacco Supplement (N = 4394), HR (95% CI)
Daily smoking to panic attack‡	3.96 (2.28-6.89)	2.02 (1.47-2.77)
Panic attack to daily smoking§	1.00 (0.40-2.48)	1.37 (0.99-1.88)
Daily smoking to panic disorder‡	13.13 (4.41-39.10)	2.93 (1.84-4.66)
Panic disorder to daily smoking§	0.82 (0.20-3.39)	1.06 (0.54-2.08)
Continued smoking to panic attack	4.71 (2.70-8.21)	2.07 (1.49-2.87)
Quit smoking to panic attack	0.21 (0.05-0.88)	1.85 (0.98-3.50)
Continued smoking to panic disorder	14.46 (4.81-43.50)	3.18 (1.99-5.10)
Quit smoking to panic disorder	0.51 (0.12-2.28)	1.82 (0.69-4.28)

\*CI indicates confidence interval; NCS, National Comorbidity Survey.

†Results from the 6 Cox proportional hazards models with time-dependent covariates, controlling for sex and major depression; each estimate represents the HR for the first-time occurrence of the outcome. Numbers are reduced because of incomplete data on age of onset.

‡Hazard ratio for first panic attack (or disorder) in daily smokers is estimated relative to persons with neither smoking nor major depression.

§Hazard ratio for daily smoking associated with prior panic attack (or disorder) is estimated relative to those with neither prior panic attack (or disorder) nor major depression.

||Hazard ratios for first panic attack (or disorder) associated with continued and discontinued smoking are estimated in single models, using those with neither daily smoking nor major depression as reference.

panic attack and disorder associated with prior daily smoking are lower than corresponding estimates from the Epidemiologic Study of Young Adults, the results follow the same pattern, showing an influence primarily from daily smoking to panic attacks. Also, the effect of smoking cessation on diminishing the risk for panic attack or disorder is suggested by both studies, although the differences between active and past smoking were not significant in the NCS.

## EXPLORATORY ANALYSIS OF THE POTENTIAL ROLE OF LUNG DISEASE

The sex-adjusted ORs for panic attacks associated with lung disease, alone and with daily smoking, were higher than for daily smoking alone (**Table 3**). However, in both data sets, daily smokers with no history of lung disease had higher odds for panic attacks than the reference group with neither daily smoking nor lung disease: sex-adjusted OR of panic attacks in daily smokers with no history of lung disease in the Epidemiologic Study of Young Adults was 3.0 (95% CI, 1.76-5.28) and in the NCS, 1.9 (95% CI, 1.29-2.72).

Taking advantage of the prospective data in the Epidemiologic Study of Young Adults, we estimated the relative risk for first occurrence of panic attack during the 5-year follow-up interval according to smoking and lung disease status at baseline (**Table 4**). The OR of first panic attack associated with lung disease alone was 9.2 (95% CI, 2.26-37.24) and for current daily smoking, 1.7 (95% CI, 0.92-3.08). Although the OR for first panic attack associated with daily smoking alone did not reach significance ( $P = .09$ ), the direction of the estimate and the

**Table 3. Lifetime Prevalence of Panic Attacks by History of Daily Smoking and Lung Disease in the Study of Young Adults and the National Comorbidity Survey (NCS): Exploratory Analysis\***

	Epidemiologic Study of Young Adults (N = 1007)		NCS Tobacco Supplement (N = 3132)†			
			Unweighted		Weighted	
	Panic Attack, No. (%)	OR‡ (95% CI)	Panic Attack, No. (%)	OR‡ (95% CI)	Panic Attack, %	OR‡ (95% CI)
Neither	600 (3.5)	1.0	1513 (7.1)	1.0	6.0	1.0
Daily smoking	378 (10.0)	3.0 (1.76-5.28)	1428 (10.2)	1.6 (1.19-2.01)	10.5	1.9 (1.29-2.72)
Lung disease only	13 (23.1)	7.7 (1.95-30.12)	79 (15.2)	2.2 (1.14-4.19)	9.3	1.5 (0.78-3.07)
Both	16 (25.0)	8.1 (2.39-27.40)	103 (22.3)	3.5 (2.09-5.79)	23.8	4.3 (1.92-9.48)

\*OR indicates odds ratio; CI, confidence interval.

†Data on chronic diseases were gathered on a subset who were administered the risk factors interview.

‡Sex-adjusted odds ratios from a logistic regression.

**Table 4. Prospective Data on First Occurrence of Panic Attacks During a 5-Year Interval Since Baseline From the Study of Young Adults (n = 941)\***

Baseline Status	First Attack, No. (%)	OR (95% CI)
Neither	672 (4.5)	1.0
Daily smoking	247 (7.3)	1.7 (0.92-3.08)
Lung disease	12 (33.3)	9.2 (2.26-37.24)
Both	10 (30.0)	10.7 (3.05-37.53)

\*Persons with a history of panic attacks at baseline were excluded. OR indicates odds ratio; CI, confidence interval.

upper limit of its CI are consistent with the retrospective data.

#### COMMENT

Parallel analyses of 2 epidemiologic data sets revealed that daily smoking was associated with an increased risk for first-time occurrence of panic attack; the risk for first panic attack was higher in active than in past smokers; there was no evidence that prior panic attacks were associated with a significant increased risk for daily smoking when co-occurring major depression was taken into account; analysis of the subset with panic disorder also supports an asymmetry in the relationship, in that an increased risk was observed from smoking to first onset of panic disorder but not in the reverse direction; these relationships held in both men and women, with no evidence of sex interactions; and exploratory analysis suggests that lung disease might be one of the mechanisms linking smoking to panic attacks.

The prevalence estimates of *DSM-III-R* panic attack and disorder were higher in the Epidemiologic Study of Young Adults than in the NCS. This was caused primarily by the longitudinal design of the Epidemiologic Study of Young Adults—multiple follow-up assessments added incidence cases that occurred during successive intervals. At baseline, the prevalence estimates were similar to those in the NCS. Despite these and other differences between the 2 studies, both lead to similar inferences with respect to the relationship between daily smoking and panic attacks or disorder.

In this study, we examined the relationship of daily smoking with panic attack and panic disorder. While history of panic attack defines a heterogeneous category that includes those with a history of a single isolated attack, panic disorder defines a more distinct clinical phenomenon. Time of onset of panic disorder was defined as first occurrence of panic attack in persons meeting the *DSM-III-R* criteria for the disorder. The age at which the full criteria were first met is not ascertained in the Diagnostic Interview Schedule or the Composite International Diagnostic Interview. However, first panic attack might be the most reliably recalled by persons with panic disorder.

The results suggest the possibility that the relationship between smoking and panic attack or disorder might flow primarily in one direction (ie, from smoking to subsequent onset of panic attacks or disorder). Evidence suggesting an influence in the reverse direction (ie, an increased risk for daily smoking in persons with panic attacks), was suggested in the NCS, but the risk was smaller and not significant. Results from the Epidemiologic Study of Young Adults show increased risk for panic attack and disorder in active smokers but not in past smokers. Corresponding results from the NCS, although consistent with this pattern, were less clear-cut. The evidence that smoking cessation diminished the risk for panic attacks and disorder should be interpreted with caution.

Alternative hypotheses that link smoking to panic attacks have been suggested.<sup>14</sup> One potential mechanism explored in this study is lung disease. The data on this issue have important limitations, including reliance on self-reports of lung disease and lack of information on the time of onset of lung disease relative to first panic attack. The results from both data sets show an increased lifetime prevalence of panic attacks in smokers who reported lung disease compared with smokers who did not. Among nonsmokers, lung disease was associated with an increased risk of panic attacks, confirming previous reports.<sup>20-22</sup> By increasing the risk for lung disease, smoking might indirectly increase the risk for panic attacks. However, the fact that only a small proportion of smokers reported lung disease and the increased incidence of panic attacks/disorder in smokers with no history of lung disease suggest the possibility of other pathways from smoking to panic.

Klein<sup>34,35</sup> proposed that panic attacks represent a suffocation false alarm and that a subset of the general population is predisposed to overreact to suffocation signals. Cigarette smoking leads to chronic bronchitis and emphysema as well as to subclinical respiratory impairment. Smokers with pulmonary problems who are predisposed to overreact to suffocation signals might manifest panic attacks. Alternatively, carbon monoxide in cigarette smoke might affect the suffocation alarm threshold. It has been suggested<sup>36</sup> that one asphyxiation monitor for the suffocation alarm system may be the carotid body, which is inhibited by carbon monoxide.<sup>37</sup> Such a direct effect would decrease the alarm reaction in smokers; however, rebound receptor sensitization effects caused by smoking pauses may also occur. Other causal mechanisms in the smoking-panic relationship, including a role for smoking and nicotine in anxiety, also should be considered.<sup>38-40</sup>

Experimental research that could provide definitive evidence for ruling out noncausal explanations of the association between smoking and panic and for establishing the role of compromised lung function as a mechanism is not feasible in humans. However, it seems clear that longitudinal epidemiological investigations can go beyond cross-sectional associations in influencing the plausibility of competing hypotheses. Clinical research in panic disorder has benefited from experiments in which patients have been perturbed by both psychological and physiological stimuli. Further clarification might be gained if stimuli such as carbon dioxide or intravenous sodium lactate were applied to subjects with and without panic attacks, who also varied with regard to smoking status. Also, longitudinal studies with repeated administration of such stimuli in subjects at high risk for progression to heavy smoking could test if smoking induces panic by stimulating a preexisting hypersensitive suffocation alarm system or may actually induce such hypersensitivity.

A comment on the statistical analysis of the NCS data is in order. Prevalence estimates and measures of lifetime associations, the latter calculated in logistic regression models, were based on weighted data to adjust for the complex sampling design (Tables 1 and 3). To estimate the risk for first occurrence of panic attack associated with prior daily smoking and to address other questions that concern temporal relationships between variables, Cox proportional hazards models with time-dependent covariates were applied to unweighted data. To our knowledge, there is no software for the analysis of weighted data in the Cox proportional hazards model with time-dependent covariates. The discrete-time logistic model, for which software procedures for weighted data are available, has been used to address similar questions.<sup>41,42</sup> This application of the discrete-time logistic model to interval censored data, such as those produced by the Diagnostic Interview Schedule or the Composite International Diagnostic Interview (which date events by year of occurrence), has been questioned recently by Hosmer and Lemeshow.<sup>43</sup> We evaluated the effects of weighting by applying the discrete-time logistic models to the unweighted and the weighted data. A com-

parison of the results with those that appear in Table 2 shows only a few differences. Specifically, the relative risk estimate for panic disorder associated with prior daily smoking was higher in the discrete-time logistic model (OR, 3.9; 95% CI, 2.3-6.7, based on the weighted data). The estimate of the relative risk for daily smoking associated with prior panic attack in the discrete-time logistic model was slightly higher and significant (OR, 1.63; 95% CI, 1.02-2.61, based on the weighted data). The discrepancies in both instances occurred in the shift to the discrete-time logistic model, whereas the use of weights had little added effect. It is therefore unlikely that any bias in our estimates from the Cox proportional hazards models calculated on the unweighted data would be more than minimal.

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