

Smoking Increases the Risk of Panic

Findings From a Prospective Community Study

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Background: We examined prospectively determined bidirectional associations between smoking and panic and other anxiety disorders and their temporal ordering of onset in a representative community sample of adolescents and young adults.

Methods: Baseline and 4-year follow-up data were used from the Early Developmental Stages of Psychopathology Study, a prospective longitudinal study of adolescents and young adults in Munich, Germany. We assessed smoking (occasional and regular), nicotine dependence, panic attacks, panic disorder, other anxiety disorders, and other mental disorders using the Munich-Composite International Diagnostic Interview.

Results: At baseline, panic attacks and panic disorder were strongly associated with occasional and regular smoking and nicotine dependence (odds ratio [OR] range, 3.0-28.0). In the prospective analyses, we found increased risk for new onset of panic attacks with prior regular smoking (OR, 2.9; 95% confidence interval [CI], 1.0-8.4) and nicotine

dependence (OR, 3.6; 95% CI, 1.2-10.5). Prior nicotine dependence increased also the risk for onset of panic disorder (OR, 3.3; 95% CI, 1.0-10.5), whereas preexisting panic was not associated with subsequent smoking or nicotine dependence. When using Cox regression with time-dependent covariates, prior nicotine dependence was confirmed to be related to subsequent panic attacks (hazard ratio, 2.7; 95% CI, 1.7-4.2), but not panic disorder (hazard ratio, 1.7; 95% CI, 0.7-3.9). Rather, we found indications that prior panic attacks/disorder might also have an effect on secondary development of nicotine dependence.

Conclusions: In young adults, prospective analyses revealed a fairly unique and specific, unidirectional relationship between prior smoking and increased risk for subsequent panic attacks/disorder. However, we could not exclude the existence of a second, less frequent, reverse pathway of prior panic and secondary nicotine dependence.

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EPIDEMIOLOGICAL AND clinical studies have reported positive associations between smoking and mental disorders in general, and anxiety disorders in particular.¹⁻¹³ There are several reasons to examine the relationship between anxiety disorders and smoking. Nicotine is postulated to be a potentially effective substance for self-medication to ameliorate symptoms of anxiety. This reduction in anxiety with smoking could be a direct pharmacological effect of nicotine, or could be mediated by the reduction in peer pressure that can accompany the initiation of cigarette use. In this regard, using a prospective longitudinal design, our group has already shown that adolescents and young adults with preexisting social fears have a higher risk for the subsequent onset of nicotine dependence when compared with subjects without social fears.¹⁰

However, nicotine might also trigger and increase anxiety symptoms. This anxiogenic effect is hypothesized to be more important in the etiology of some cases of panic disorder. In etiologic models like the false suffocation alarm theory,^{14,15} impairment of the respiratory system, which can be induced by smoking, is hypothesized to be the underlying cause for panic. This mechanism should be especially important for panic and less relevant for other anxiety disorders. Several studies have focused specifically on smoking and panic disorder, and, with a single exception,⁶ they have consistently confirmed a positive relationship between these 2 conditions.^{11,12,16,17}

Moving from the demonstration of association to the possibility of addressing temporal ordering, 2 studies evaluated the temporal priorities between smoking and panic disorder. In the first study, in which data from the National Comorbidity Sur-

vey Tobacco Supplement and the Epidemiologic Study of Young Adults in southeast Michigan were analyzed, Breslau and Klein¹⁶ found that daily smoking increases the risk for later onset of panic attacks or disorder. As they did not find such an association in the opposite direction, their results suggest that the association between smoking and panic disorder might proceed mainly in 1 direction, ie, from preexisting smoking to subsequent panic. Comparable results were also reported by Johnson et al¹⁷ from a prospective longitudinal investigation during approximately 6 years. Their results suggest that heavy smoking (ie, >20 cigarettes per day) during adolescence increases the risk for the development of panic disorder during early adulthood. An association between the occurrence of any anxiety disorder at baseline and the onset of smoking during follow-up was not found. These temporal patterns in the association between panic and smoking could be explained by the following 2 plausible models: (1) Smoking could cause panic attacks by resulting in impaired lung function or through the pharmacological effects of nicotine on mood and/or noradrenergic hyperactivity,^{1,16,18} or (2) The association between smoking and panic could be noncausal, resulting from factors that increase vulnerability to smoking and panic (eg, genetic factors comparable to the association between smoking and depression⁸). Another explanation, however, is that respondents with panic might have biased recall about the extent and/or timing of their cigarette use in relation to the onset of their symptoms of mental disorder. This possibility can probably be strongly reduced by using a strict prospective design assessing subjects in the period of risk for the onset of smoking and panic.

The goal of this report is to further increase our understanding of the longitudinal association between smoking behavior and panic and other anxiety disorders by examining data from the prospective longitudinal Early Developmental Stages of Psychopathology (EDSP) Study.^{19,20} In a representative population sample of 3021 adolescents and young adults aged 14 to 24 years at baseline (2548 respondents at follow-up), and using a prospective longitudinal design, this report explores (1) to what degree *DSM-IV* panic attacks and *DSM-IV* panic disorder are associated with occasional smoking, regular smoking, and *DSM-IV* nicotine dependence in adolescents and young adults; (2) how temporally primary smoking affects the onset of panic attack and disorder; (3) how temporally primary panic attacks and disorder affect the onset of occasional and regular smoking and the onset of nicotine dependence; (4) whether these associations can be proven as well for other anxiety disorders or whether they are specific for panic attacks and panic disorder; and (5) potentially different associations between specific features of smoking, such as duration or number of daily smoked cigarettes and the occurrence of panic.

METHODS

DESIGN

Data were collected as part of the EDSP Study, a prospective longitudinal study designed to collect data on the prevalence,

incidence, familial and other risk factors, comorbidity, and course of substance use and other mental disorders in a representative sample of 3021 subjects aged 14 to 24 years at baseline. The study consists of a baseline survey, 2 follow-up surveys, and a family history component that includes direct parent interviews. Detailed descriptions of the EDSP design and field procedures are reported elsewhere.^{19,20}

SAMPLE

The EDSP sample was drawn randomly from the 1994 government population registers of residents in metropolitan Munich and the surrounding counties, with an expected age range for the sampled subjects of 14 to 24 years at the time of the baseline interview in 1995. Details about the sampling and representativeness of the entire EDSP sample and its sociodemographic characteristics have been presented elsewhere.^{19,20} A total of 3021 interviews were completed at baseline (T0; response rate, 71%). The first follow-up study (T1) was conducted only for subjects aged 14 to 17 years at baseline, whereas the second follow-up study (T2) was conducted for all subjects. A total of 1228 completed the T1 interviews, an average of 20 months after baseline (response rate, 88%). From the 3021 subjects of the baseline study, a total of 2548 interviews were completed at the T2 interview, an average of 42 months after baseline (response rate, 84%).

The baseline results reported herein are based on 3021 respondents, whereas the prospective analyses and Cox regressions with time-dependent covariates were performed using the 2548 respondents who completed the whole study.

DIAGNOSTIC ASSESSMENT

Diagnostic assessments were based on the computer-assisted version of the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI),²¹ an updated version of the World Health Organization's CIDI version 1.2.²² Reliability and validity of the M-CIDI have been reported.²³⁻²⁶ One-week test-retest reliability, investigated in a general population sample of 60 adolescents and young adults aged 14 to 24 years, was excellent for panic disorder ($\kappa=1.0$), and acceptable for *DSM-IV* panic attacks ($\kappa=0.57$) and nicotine dependence ($\kappa=0.64$). For other anxiety disorders, good to excellent reliability was proved, with the exception of generalized anxiety disorder ($\kappa=0.45$).²⁴

Diagnostic findings were obtained by using the M-CIDI/*DSM-IV* diagnostic algorithms. In all assessments, interviews were administered by highly trained clinical interviewers, most of whom were clinical psychologists. Most interviews were performed in the home of the respondents.

At T0 assessment, the lifetime version of the interview was used. At each of the follow-up assessments, the M-CIDI interval version, which refers to the time period of assessment from the last interview until the present, was applied. For those respondents aged 14 to 17 years at baseline, the complete follow-up status was assessed from the aggregation of information obtained from the T1 and T2 interviews. For respondents older than 17 years at baseline, the follow-up status was assessed from the second follow-up questions, which refer to the time from the T0 to the T2 interviews.

DEFINITION OF PANIC ATTACK AND PANIC DISORDER

Panic attack and panic disorder are defined according to *DSM-IV* criteria.²⁷ On the basis of information provided by the subject for the M-CIDI panic disorder section (a more detailed description of the panic disorder section of the M-CIDI is provided elsewhere²⁸), we divided the sample into the following 3 mu-

Table 1. Lifetime Prevalence of Smoking, Nicotine Dependence, and Panic at Baseline in 3021 Subjects*

	Lifetime Prevalence at Baseline	
	No. (%)	95% CI
Total		
Nicotine/tobacco		
Nonusers	799 (23.7)	22.1 to 25.5
Occasional users†	1272 (40.4)	38.4 to 42.4
Nondependent regular smokers†	468 (17.1)	15.6 to 18.7
Dependent regular smokers†	482 (18.8)	17.2 to 20.5
Panic		
DSM-IV panic attack without panic disorder	80 (2.7)	2.1 to 3.5
DSM-IV panic disorder	42 (1.6)	1.1 to 2.3
Men		
Nicotine/tobacco		
Nonusers	358 (20.1)	18.0 to 22.4
Occasional users	691 (43.4)‡	40.5 to 46.2
Nondependent regular smokers	239 (17.5)	15.3 to 19.8
Dependent regular smokers	245 (19.1)	16.8 to 21.6
Panic		
DSM-IV panic attack without panic disorder	28 (2.1)	1.4 to 3.2
DSM-IV panic disorder	10 (0.8)	0.4 to 1.6
Women		
Nicotine/tobacco		
Nonusers	441 (27.3)	24.8 to 29.9
Occasional users	581 (37.5)	34.8 to 40.4
Nondependent regular smokers	229 (16.7)	14.6 to 19.0
Dependent regular smokers	237 (18.5)	16.3 to 21.0
Panic		
DSM-IV panic attack without panic disorder	52 (3.3)	2.4 to 4.5
DSM-IV panic disorder	32 (2.4)‡	1.6 to 3.6

Abbreviations: CI, confidence interval; OR, odds ratio.

*The categories of tobacco users are described in the "Definition of Smoking and Nicotine Dependence" subsection of the "Methods" section. Percentages have been weighted.

†Among the respondents with at least occasional use (n = 2222), 7 exclusively used tobacco products other than cigarettes.

‡Indicates the group with the higher rate for those with a significant sex difference ($P < .05$). For male vs female subjects, ORs are 1.6 (95% CI, 0.9 to 2.7) for panic attack without panic disorder, 3.2 (95% CI, 1.4 to 6.9) for DSM-IV panic disorder, 0.6 (95% CI, 0.5 to 0.8) for occasional smoking, 0.9 (95% CI, 0.7 to 1.2) for nondependent regular smoking, and 0.9 (95% CI, 0.7 to 1.2) for dependent regular smoking.

tually exclusive groups: (1) no DSM-IV panic attack was reported in the M-CIDI stem question; (2) the subject fulfilled criteria for at least 1 DSM-IV panic attack, but failed to meet diagnostic criteria for DSM-IV panic disorder; and (3) the subject fulfilled criteria for DSM-IV panic disorder with or without agoraphobia. Other anxiety disorders that are assessed with the M-CIDI covering DSM-IV criteria include social phobia, specific phobia, generalized anxiety disorder (GAD), agoraphobia without panic disorder, phobia not otherwise specified, post-traumatic stress disorder, and obsessive-compulsive disorder. Detailed descriptions of the assessment of these respective disorders have been presented elsewhere.²⁹⁻³¹

DEFINITION OF SMOKING AND NICOTINE DEPENDENCE

Although the CIDI defines tobacco products as cigarettes, cigars, pipes, snuff, or chewing tobacco, 99% of tobacco users at baseline reported cigarettes as the only tobacco product used.

Therefore, we used the terms *smoking* and *tobacco use* synonymously. In Germany, the legal age for the purchase of tobacco products is 16 years, although this age limit is rarely enforced because vending machines are present in most public places.

The following categories were created to operationalize the consumption status for smoking (these can be compared with Sonntag et al¹⁰): (1) nonsmokers stated that they had never used any tobacco product in their lifetime; (2) occasional users used at least 1 tobacco product at least once in their lifetime, but never used it on a daily basis for a period of at least 4 weeks (ie, including experimental as well as occasional use); (3) nondependent regular smokers smoked cigarettes daily for a period of 4 weeks or more at least once in their lifetime, but never met DSM-IV criteria for nicotine dependence; and (4) dependent regular smokers smoked cigarettes daily for a period of 4 weeks or more at least once in their lifetime and met DSM-IV criteria for nicotine dependence.²⁷

STATISTICAL ANALYSES

We performed statistical analyses using Stata software, version 7.0,³² and applying the Hubert-White sandwich estimator for accurate assessment of precision of estimated measures in the case of weighted data.³³ For binary outcomes, we quantified associations with odds ratios (ORs) from logistic regressions³⁴ while adjusting for other disorders. In the case of counting variables as outcomes (eg, the number of cigarettes smoked) with considerable positive skewness, differences were quantified with mean ratios (MRs; the factor by which the mean differs between 2 groups) from negative binomial regressions.³⁵ For other quantitative outcomes, associations were quantified with mean differences (MDs; the difference in means between 2 groups) from linear regressions. We also analyzed directed associations between panic and smoking using the aggregated information from all 3 assessments and age-of-onset data. Together, these provide the information for the whole lifetime period until the T2 interview. This was performed with Cox regressions with time-dependent covariates.³⁶ For example, when evaluating panic attacks as a risk factor for nicotine dependence, the time-dependent covariate at age t was defined as having ever had a panic attack up to the age of $t - 1$.

Because of the different sampling probabilities (for different age groups), we used relative weights inversely proportional to the sampling fraction. In addition, these weights also accounted for nonresponse according to age, sex, and geographic distribution (urban vs rural) of the respondents.¹⁹

RESULTS

LIFETIME PREVALENCE OF SMOKING, NICOTINE DEPENDENCE, AND PANIC ATTACKS AND DISORDER AT BASELINE

Table 1 shows the EDSP baseline prevalence findings for lifetime smoking, nicotine dependence, and panic attacks and disorder. These have been reported in previous publications.^{29,37,38} At baseline, approximately three quarters of the sample had ever used a tobacco product at least once in their life, with nearly equal proportions fulfilling lifetime criteria for occasional (40.4%) and regular (35.9%) use. Among regular users, approximately one in two fulfilled criteria for nicotine dependence, resulting in a lifetime prevalence for nicotine dependence of 18.8%. Although men reported a higher rate of occasional smoking, rates for nondependent and dependent regular smoking were comparable for male and female

Table 2. Baseline Associations Between Smoking Status and Panic and Other Anxiety Disorders in 3021 Subjects*

Anxiety	Smoking Status at Baseline						
	Nonusers, No. (%) (n = 799)	Occasional Users (n = 1272)		Nondependent Regular Smokers (n = 468)		Dependent Regular Smokers (n = 482)	
		No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Panic status at baseline							
No panic attack or disorder (n = 2899)	790 (99.1)	1233 (96.8)	1.0	447 (96.0)	1.0	429 (88.7)	1.0
<i>DSM-IV</i> panic attack (n = 80)	8 (0.7)	24 (2.0)	3.0† (1.2 to 7.1)	12 (1.9)	3.0† (1.1 to 8.0)‡	36 (7.6)	12.8† (5.6 to 28.9)
<i>DSM-IV</i> panic disorder (n = 42)	1 (0.2)	15 (1.3)	9.8† (1.2 to 74.7)	9 (2.1)	13.8† (1.7 to 108.6)	17 (3.8)	28.0† (3.7 to 208.4)
Other anxiety disorders at baseline							
Agoraphobia (n = 69)	15 (2.2)	21 (1.6)	0.8 (0.3 to 1.8)	9 (1.5)	0.8 (0.3 to 2.1)	24 (4.9)	2.8† (1.3 to 5.8)‡
Social phobia (n = 201)	48 (6.4)	70 (5.9)	0.9 (0.6 to 1.5)	27 (6.2)	0.9 (0.5 to 1.6)	56 (12.3)	1.9† (1.2 to 3.1)‡
Specific phobia (n = 479)	109 (14.8)	188 (14.7)	1.0 (0.7 to 1.4)	62 (12.2)	0.8 (0.5 to 1.3)	120 (25.0)	2.0† (1.4 to 2.8)‡
Phobia NOS (n = 164)	52 (6.0)	58 (4.5)	0.8 (0.5 to 1.3)	20 (4.5)	0.8 (0.4 to 1.5)	34 (6.2)	1.2 (0.6 to 2.0)
GAD (n = 51)	6 (0.7)	10 (0.9)	1.4 (0.4 to 4.1)	12 (3.2)	4.2† (1.5 to 11.5)‡	23 (5.5)	7.4† (2.9 to 19.0)
Obsessive-compulsive disorder (n = 20)	6 (0.8)	6 (0.5)	0.7 (0.1 to 2.3)	4 (1.0)	1.3 (0.3 to 4.9)	4 (0.9)	1.1 (0.3 to 4.1)
Posttraumatic stress disorder (n = 32)	5 (0.8)	5 (0.6)	0.8 (0.2 to 3.0)	3 (0.5)	0.7 (0.1 to 3.1)	19 (4.4)	6.4† (2.3 to 17.4)‡

Abbreviations: CI, confidence interval; GAD, generalized anxiety disorder; NOS, not otherwise specified; OR, odds ratio.

*The categories of tobacco users are described in the "Definition of Smoking and Nicotine Dependence" subsection of the "Methods" section. Percentages have been weighted. All ORs are controlled for age and sex.

†Significant at $P < .05$.

‡Association failed to reach significance when controlled for comorbidity at baseline (ie, depressive disorders, panic attacks, other anxiety disorders, alcohol and illicit drug disorders, and eating disorders).

subjects. At baseline, 2.7% of the respondents reported having experienced a *DSM-IV* panic attack (without fulfilling the criteria for panic disorder) at least once in their lifetime, and 1.6% fulfilled lifetime criteria for *DSM-IV* panic disorder. For panic disorder, rates were significantly higher for female than male subjects.

BASELINE ASSOCIATIONS BETWEEN SMOKING BEHAVIOR AND PANIC

Table 2 reports the lifetime associations between the respondents' smoking status and panic status, based on the retrospective data collected at the T0 assessment. The rates for panic attacks and panic disorder increased with higher tobacco consumption status. Although only 0.7% of nonsmokers reported panic attacks, this rate was about 10-fold higher among regular smokers with nicotine dependence (7.6%; OR, 12.8; 95% CI, 5.6-28.9). Occasional and nondependent regular smokers fell in between, with panic attack rates of 2.0% (OR, 3.0; 95% CI, 1.2-7.1) and 1.9% (OR, 3.0; 95% CI, 1.1-8.0), respectively.

A similar pattern was found for panic disorder. Although only 0.2% of the nonsmokers fulfilled criteria for *DSM-IV* panic disorder, rates were significantly higher among occasional smokers (1.3%; OR, 9.8; 95% CI, 1.2-74.7), nondependent regular smokers (2.1%; OR, 13.8; 95% CI, 1.7-108.6), and subjects with nicotine dependence (3.8%; OR, 28.0; 95% CI, 3.7-208.4). Among 42 subjects with panic disorder, all but 1 were at least occasional smokers.

To exclude the hypothesis that the associations could be explained by comorbid mental disorders, we reran the analyses controlling for comorbid lifetime disorders. These additional analyses resulted in an almost identical pattern of significant associations.

Associations were significantly higher in subjects with nicotine dependence than those with occasional

smoking for panic attack (OR, 4.3; 95% CI, 2.3-7.8) and panic disorder (OR, 9.3; 95% CI, 1.0-82.2) and in subjects with nondependent regular smoking for panic attack (OR, 4.3; 95% CI, 2.0-9.0) and panic disorder (OR, 9.4; 95% CI, 1.0-87.5). No statistically significant differences in associations were found between regular and occasional smokers or between male and female subjects (data not shown). The examination of interaction with cohort showed only that among occasional smokers the risk for panic attacks was increased in the older cohort (OR for interaction, 10.7; 95% CI, 1.3-83.1).

To explore to what extent these associations are unique and specific for panic attacks and panic disorder or whether they can also be found for other anxiety disorders, we also evaluated associations between smoking behavior and all other assessed *DSM-IV* anxiety disorders (Table 2). We found no association between occasional smoking and the other anxiety disorders under study and only 1 association between nondependent regular smoking and GAD. Although associations were found between dependent regular smoking and most of the anxiety disorders, after controlling for comorbid disorders, all but one association then failed to reach significance. The only association that remained stable was that between dependent regular smoking and GAD (OR, 3.6; 95% CI, 1.2-10.2).

Few associations were found between panic attacks or panic disorder status and smoking features such as the number of years of regular smoking, the current number of cigarettes smoked per day, or the number of cigarettes smoked per day during the period of peak use (**Table 3**). The only significant association was between the occurrence of panic attacks and the number of cigarettes smoked per day during the period of peak use. This association, however, was smaller (MR, 0.9; 95% CI, 0.7-1.3) and no longer statistically significant when controlling for comorbid mental disorders. After con-

Table 3. Baseline Associations Between Smoking Features and Panic in 950 Subjects

Smoking Features at Baseline Among Regular Smokers	Panic Status at Baseline				
	No Panic Attacks or Disorder, Mean (SE)* (n = 876)	DSM-IV Panic Attack (n = 48)		DSM-IV Panic Disorder (n = 26)	
		Mean (SE)	MR/MD (95% CI)	Mean (SE)	MR/MD (95% CI)
No. of years of regular smoking	3.9 (0.10)	3.7 (0.43)	-0.06 (-1.0 to 0.8)	3.45 (0.54)	-0.68† (-1.8 to 0.4)
No. of cigarettes per day					
During the last 4 weeks	12.6 (0.28)	15.1 (1.56)	1.23 (0.9 to 1.6)	13.50 (1.85)	1.08 (0.8 to 1.5)
During the period of peak use	19.3 (0.46)	23.2 (1.73)	1.25‡ (1.0 to 1.5)§	22.40 (3.44)	1.18 (0.8 to 1.7)

Abbreviations: CI, confidence interval; MD, mean difference (difference in mean number of years of regular smoking from linear regression, controlled for age and sex); MR, mean ratio (ratio of truncated number of cigarettes [number of cigarettes - 1] from negative binomial regression, controlled for age and sex).

*Indicates reference group.

†Association is significant when controlling for comorbidity at baseline (ie, depressive disorders, anxiety disorders, alcohol and illicit drug disorders, and eating disorders) (MD, -1.1; 95% CI, -2.1 to 0.9).

‡Significant at $P < .05$.

§Failed to reach significance when controlling for comorbidity at baseline (MR, 0.94; 95% CI, 0.7 to 1.3).

Table 4. Association Between Smoking Status Baseline and New Onset of Panic Attacks/Disorder and Other Anxiety Disorders in 2548 Subjects During the 4-Year Follow-up Period*

Onset of DSM-IV Anxiety Disorders During Follow-up	Smoking Status at Baseline						
	Nonusers, No. (%) (n = 696)	Occasional Users (n = 1092)		Nondependent Regular Smokers (n = 380)		Dependent Regular Smokers (n = 380)	
		No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Cumulative follow-up (T1+T2) panic status							
Neither onset of panic attack nor disorder (n = 2366)	673 (97.8)	1031 (97.7)	1.0	345 (95.7)	1.0	317 (93.5)	1.0
Onset of panic attack (n = 62)	9 (1.4)	23 (2.0)	1.6 (0.5 to 4.1)†	16 (3.6)	2.9‡ (1.0 to 8.4)	14 (4.4)	3.6‡ (1.2 to 10.5)
Onset of panic disorder (n = 21)	7 (0.9)	4 (0.2)	0.3 (0.0 to 1.3)	2 (0.7)	1.1 (0.2 to 5.7)	8 (2.1)	3.3‡ (1.0 to 10.5)§
Other anxiety disorders (T1+T2)							
Agoraphobia (n = 28)	5 (0.6)	10 (1.0)	2.0 (0.6 to 6.5)	4 (1.3)	2.6 (0.7 to 9.9)	9 (1.8)	3.7‡ (1.1 to 12.1)§
Social phobia (n = 71)	16 (2.9)	25 (2.0)	0.7 (0.3 to 1.6)	13 (3.1)	1.3 (0.5 to 3.1)	17 (5.1)	2.5‡ (1.1 to 5.4)§
Specific phobia (n = 158)	34 (5.7)	65 (5.8)	1.2 (0.7 to 2.0)	30 (8.6)	2.0‡ (1.1 to 3.7)	29 (10.5)	2.5‡ (1.3 to 4.5)§
Phobia NOS (n = 73)	18 (2.6)	31 (2.3)	1.1 (0.5 to 2.1)	7 (1.9)	1.0 (0.3 to 2.6)	17 (4.6)	2.4‡ (1.1 to 5.1)§
GAD (n = 20)	4 (0.9)	5 (0.3)	0.4 (0.0 to 1.8)	1 (0.0)	0.1‡ (0.0 to 0.5)	10 (3.3)	3.6 (0.9 to 13.3)
Obsessive-compulsive disorder (n = 15)	2 (0.5)	4 (0.2)	0.4 (0.0 to 3.5)	1 (0.1)	0.2 (0.0 to 3.7)	8 (2.1)	4.2 (0.6 to 29.1)
Posttraumatic stress disorder (n = 21)	3 (0.3)	10 (0.9)	3.0 (0.7 to 11.6)	2 (0.6)	2.2 (0.3 to 13.3)	6 (1.4)	5.1‡ (1.2 to 21.5)§

Abbreviations: CI, confidence interval; GAD, generalized anxiety disorder; NOS, not otherwise specified; OR, odds ratio; T1, first follow-up study conducted only for subjects aged 14 to 17 years at baseline; T2, second follow-up study conducted for all subjects.

*The categories of tobacco users are described in the "Definition of Smoking and Nicotine Dependence" subsection of the "Methods" section. Percentages have been weighted. Respondents with the respective anxiety disorders were excluded from the analysis. All ORs are controlled for age and sex.

†Significant interaction effect (OR, 10.1; 95% CI, 1.6 to 36.4) was found for sex. The OR for female subjects was 5.1 (95% CI, 1.3 to 19.2); for male subjects, 0.5 (95% CI, 0.1 to 1.8).

‡Significant at $P < .05$.

§Failed to reach significance when controlling for comorbidity (ie, depressive disorders, anxiety disorders, panic attacks, alcohol and illicit drug disorders, and eating disorders).

trolling for comorbid disorders, the negative association between number of years of regular smoking and panic disorder became stronger and reached significance (MD, -1.1; 95% CI, -2.1 to -0.9). This result suggests a shorter duration of smoking in respondents with panic disorder compared with respondents who never experienced a panic attack.

We also checked possible associations between the other anxiety disorders and the different smoking features (data not shown). We found only the association that subjects with a lifetime specific phobia smoked more cigarettes in the peak period of consumption than did subjects without a specific phobia (MR 1.2; 95% CI, 1.0-1.4, controlled for comorbidity).

PREEXISTING SMOKING AND INCREASED RISK FOR ONSET OF PANIC ATTACKS AND DISORDERS

Table 4 examines whether respondents with lifetime occasional, regular, or dependent smoking at baseline have an increased risk for the first onset of panic attacks or panic disorder during the 4-year follow-up. To guarantee the temporal preexistence of smoking, all cases of lifetime panic attack or panic disorder at baseline were excluded from these analyses.

Overall, the rate of incident panic attacks increased with a higher smoking status at baseline. When compared with baseline nonsmokers, the rate of new on-

Table 5. Associations Between Panic Attack/Disorder and Other Anxiety Disorder Status at Baseline and Incident Smoking in 1788 Subjects During the 4-Year Follow-up*

Anxiety Status at Baseline	Cumulative Follow-up (T1+T2) Smoking Status				
	No Onset of Regular Smoking, No. (%) (n = 1341)	Onset of Nondependent Regular Smoking (n = 311)		Onset of Dependent Regular Smoking (n = 136)	
		No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Panic status at baseline					
No panic attack or disorder (n = 1747)	1310 (80.4)	305 (14.3)	1.0	132 (5.3)	1.0
Panic attack (n = 27)	19 (72.3)	5 (17.4)	1.6 (0.5 to 4.7)	3 (10.3)	2.6 (0.4 to 13.8)
Panic disorder (n = 14)	12 (93.0)	1 (3.7)	0.3 (0.0 to 2.3)	1 (3.3)	0.7 (0.0 to 6.0)
Other anxiety disorders					
Agoraphobia (n = 29)	22 (85.9)	3 (7.2)	0.5 (0.1 to 1.7)	4 (6.9)	1.2 (0.4 to 3.5)
Social phobia (n = 101)	77 (80.8)	14 (12.0)	1.1 (0.5 to 2.0)	10 (7.2)	2 (0.8 to 4.4)
Specific phobia (n = 247)	184 (80.8)	41 (13.2)	1 (0.6 to 1.6)	22 (6.0)	1.3 (0.7 to 2.4)
Phobia NOS (n = 94)	69 (79.2)	15 (13.0)	0.9 (0.4 to 1.7)	10 (7.8)	1.4 (0.6 to 3.1)
GAD (n = 13)	10 (85.2)	3 (14.8)	1.1 (0.2 to 4.1)	0	NE
Obsessive-compulsive disorder (n = 10)	9 (92.5)	0	NE	1 (7.5)	1.2 (0.1 to 10.0)
Posttraumatic stress disorder (n = 8)	8 (100.0)	0	NE	0	NE

Abbreviations: CI, confidence interval; GAD, generalized anxiety disorder; NE, not estimable (ORs were considered not estimable when the 2x2 table contained an empty cell); NOS, not otherwise specified; OR, odds ratio.

*The categories of tobacco users are described in the "Definition of Smoking and Nicotine Dependence" subsection of the "Methods" section. Percentages have been weighted. Respondents with regular smoking at baseline were excluded from the analyses. All ORs are controlled for age and sex.

set of panic attacks was significantly elevated among baseline nondependent regular (3.6% vs 1.4%; OR, 2.9; 95% CI, 1.0-8.4) and dependent (4.4% vs 1.4%; OR, 3.6; 95% CI, 1.2-10.5) smokers. Dependent smokers at baseline also had a higher risk for development of incident panic attacks compared with baseline occasional smokers (4.4% vs 2.0%; OR, 2.4; 95% CI, 1.0-5.2). The risk for new onset of DSM-IV panic disorder was elevated only among baseline dependent smokers compared with nonsmokers (2.1% vs 0.9%; OR, 3.3; 95% CI, 1.0-10.5); no significant differences in risks were found among baseline nonsmokers and occasional and regular smokers. Controlling for comorbid mental disorders at baseline yielded similar results, with the exception that the association between dependent smoking and incident panic disorder then failed to reach significance, although the point estimate did not change considerably (OR, 2.7; 95% CI, 0.8-9.0). Detailed subanalyses revealed that depressive disorders, social and specific phobia, GAD, eating disorders, and alcohol dependence were able to remove this association when controlling for each item separately.

Occasional smoking at baseline was related to a higher rate of incident panic attacks during follow-up for female subjects only (OR, 5.1; 95% CI, 1.3-19.2) compared with male subjects (OR, 0.5; 95% CI, 0.1-1.8; interaction effect for sex OR, 10.1; 95% CI, 1.6-36.4). No other interaction effects were found for sex or cohort.

Cox regressions with time-dependent covariates confirmed that nicotine dependence increased the risk for subsequent onset of panic attack(s) (HR, 2.7; 95% CI, 1.7-4.2), whereas this directed association could not be established with the same clarity for panic disorder (HR, 1.7; 95% CI, 0.7-3.9).

To reexamine the question of specificity, Table 4 also reports the prospective data for other incident anxiety disorders. Similar to Table 2, the risk for new onset of

most anxiety disorders was higher among baseline dependent smokers compared with baseline nonusers, whereas only 2 significant associations were found for nondependent regular smokers (specific phobia and GAD). After taking other comorbid mental disorders into account, almost all of these associations lost statistical significance. Exceptions included specific phobia (OR, 1.8; 95% CI, 1.0-3.5) and the lower risk for development of GAD (OR, 0.3; 95% CI, 0.0-0.4). The association found for incident GAD is based on only very few cases, and therefore should be interpreted with caution.

INFLUENCE OF PREEXISTING PANIC ON THE RISK FOR ONSET OF SMOKING

Using the prospective data, logistic regression analyses provided no evidence that respondents with preexisting baseline panic attacks or panic disorder have an increased risk for first onset of occasional, regular, or dependent smoking during the 4-year follow-up interval (**Table 5**). Likewise, there was no interaction effect for sex or for cohort. These results remained stable when controlling for comorbid mental disorders at baseline.

However, when we used Cox regressions with time-dependent covariates, we found significant associations between panic and the subsequent onset of nicotine dependence (panic attack HR, 3.3; 95% CI, 2.5-4.5; panic disorder HR, 3.3; 95% CI, 2.1-5.1). A closer inspection suggests that this discrepancy might be explained by the broader age range that is covered by the Cox regression and by the fact that it also takes into account the retrospective age-of-onset information before the baseline interview. We found no association between prior other (ie, other than panic) anxiety disorders and subsequent onset of smoking.

The goal of this report was to examine the bidirectional associations between panic attacks and panic disorder and smoking behavior among adolescents and young adults. Specifically, we investigated whether prior smoking and nicotine dependence increase the risk for the development of panic attacks and panic disorder, and vice versa. Another issue under study was the specificity of these associations. Could they be shown only for panic or also for other anxiety disorders?

Notable features of the EDSP Study that were of relevance to this study are (1) the large representative community sample aged 14 to 24 years at baseline; (2) inclusion of a sample of adolescents who were young enough at baseline that the outcomes under consideration had not yet developed in most, thereby permitting a strict prospective investigation of the associations between panic and smoking; (3) standardized symptom and diagnostic assessments of smoking behavior, *DSM-IV* nicotine dependence, *DSM-IV* panic attacks and panic disorder, and other mental disorders along with information about first onset of symptoms and diagnoses; and (4) availability of 2 follow-up assessments after baseline that covered a period of about 4 years, allowing a strict prospective longitudinal evaluation of the temporal ordering between panic and smoking.

Before discussing the results in detail, we must consider a major limitation of our study. Because of the constrained age range and the limited follow-up period, we do not know what happens in later adulthood. Our sample covers the period assumed to be associated with a very high risk for onset of smoking and panic. However, the generalizability of our findings to other age groups is unknown. Furthermore, since only a small number of subjects with panic attacks or panic disorder had not already smoked at baseline, the question whether prior panic increases the risk for subsequent smoking could be explored only on the basis of a very low sample size in the prospective analyses.

ASSOCIATIONS BETWEEN SMOKING AND PANIC

Using the retrospective baseline data, we first demonstrated associations between smoking and panic already on the level of occasional and regular nondependent smoking, and even higher associations for dependent smoking. Therefore, although the associations were higher for nicotine dependence, we demonstrated a heightened risk for all categories of smoking and, in contrast to the results reported by Breslau et al,¹ not only for nicotine dependence. In terms of a dose-response relationship, we found an association between the number of cigarettes smoked per day during peak use at baseline and incident panic attacks during follow-up. However, this relationship was much weaker and no longer statistically significant when adjusted for the presence of comorbid mental disorders. By using this cross-sectional data set, even occasional smoking, ie, rather low doses of nicotine, could be shown to be associated with panic.

Therefore, with the use of the strictly prospectively collected data for the evaluation of the temporal order-

ing between first onset of smoking and panic, only unidirectional associations from prior smoking to the subsequent onset of panic attack and disorder could be shown. Specifically, we found that prior regular and dependent smoking increased the risk for new onset of panic, whereas preexisting panic did not show any association with later onset of smoking or nicotine dependence. However, the analyses of potential associations between prior panic and subsequent smoking are based on very low sample sizes and, thus, poor statistical power.

The results gained by using the prospective data set are in line with those of previous epidemiological studies,^{16,17} which also failed to support reciprocal influences of smoking and panic but showed unidirectional associations. Nevertheless, regarding the small group numbers and broad CIs, one cannot rule out that even strong associations in the opposite direction might also exist. When relying on age-of-onset data in Cox regressions with time-dependent covariates, panic could indeed be shown to be a risk factor for nicotine dependence. These seemingly conflicting results might be explained by differences in power, by the broader age range that is covered by the regression analyses (including subjects with early onset of smoking and panic before the baseline examination), and by potential recall bias in the retrospective data on the relative age of onset. Furthermore, because of the earlier onset of smoking, the association of prior panic with subsequent smoking concerns a much smaller number of individuals. Nevertheless, the existence of this potential second alternative pathway remains an open issue that should be clarified by further studies that cover a broader age range prospectively than the present study, which is limited to adolescents and young adults aged 14 to 24 years at baseline.

We were able to demonstrate that almost all of these associations (baseline and prospective analyses) remained relatively stable and significant after controlling for the presence of a broad range of comorbid *DSM-IV* mental disorders. Therefore, these associations between panic and smoking cannot be explained by comorbidity with other disorders like depressive or substance use disorders, and they seem to be unique for panic.

CAUSAL RELATIONSHIP BETWEEN SMOKING AND PANIC

Various models are available to explain associations between 2 mental disorders. First, causal models suggest that for the association between panic and smoking, panic causes smoking or smoking causes panic. The first model, which implies an anxiolytic effect of nicotine and subsumes theories like self-medication, does not seem to be supported entirely by our strict prospective data with all its limitations (eg, the many subjects who already smoked at baseline), but, nevertheless, it is supported by the results of the Cox regression analyses. The second model posits an anxiogenic effect of nicotine consumption and conceptualizes smoking as a risk factor for panic. This model is more consistent with our results from the strict test of temporality using prospective data, which showed that regular and dependent smoking increases the risk for subsequent onset of panic attacks and panic disorder.

Several causal mechanisms are suggested to explain this temporal relationship. Biological models are based on the influence of nicotine on several neurochemical systems that may play an etiologic role in panic. One possible link is the noradrenergic system, which is dysregulated in panic disorder and is influenced by nicotine consumption. Nicotine causes the release of norepinephrine and epinephrine, resulting phenomenologically in an increase of heart rate and blood pressure. At high concentrations, nicotine can produce physiological effects characteristic of panic attacks.¹⁸ Furthermore, following the cognitive perspective of panic attacks,^{39,40} these cardiovascular changes induced by nicotine can be misinterpreted as signs of danger and trigger panic attacks. Smokers, who would therefore be exposed to panic triggers more often than nonsmokers, would be predicted to have an increased risk for panic. Moreover, the intermittent, recurrent occurrence of nicotine withdrawal associated with symptoms such as distractibility, anxious mood, or nervousness is an additional source of these misinterpretations. Another possible causal mechanism explaining this relationship between smoking and panic is suggested by Klein,^{14,15} ie, that impaired lung function caused by cigarette smoking triggers panic attacks, which result from the false interpretation of respiratory restrictions as suffocation. This explanation is also consistent with the pattern of temporality in the results of the prospective analyses. The relevance of lung function linking smoking to panic was also supported by exploratory analyses by Breslau and Klein,¹⁶ who found an especially high risk for panic attacks in smokers with lung disease (assessed by self-report). Longitudinal assessment of lung function (and perceptions thereof) would be required to further test this hypothesis. These future studies should consider sex effects, since there is evidence that rates for dyspneic symptoms are higher in female subjects.⁴¹ With our data, we could show only occasional use at baseline being associated with a higher risk for onset of panic attack during follow-up in female subjects.

Models of shared vulnerability may also explain the relationship between 2 mental disorders. In these models, a third variable or set of variables is assumed to predispose to both smoking and panic. In line with this idea, it is plausible (although not necessary) to expect reciprocal influences between the 2 disorders. We did not find these reciprocal effects using the prospectively assessed data. To test the model of shared vulnerability, future studies should include comparisons of active and past smokers. This would be worthwhile because, if the risk for panic attacks is higher in active smokers than in past smokers, this would dampen the plausibility of a shared etiology explanation. An equally increased risk in past and active smokers would suggest that the observed association reflects shared etiology.¹⁶

INVESTIGATION OF SPECIFICITY

Another issue of interest was whether the associations with smoking could be proved also for other anxiety disorders or whether the risk is specifically increased for panic. For other anxiety disorders, we found in the base-

line and prospective analyses no associations on the level of occasional smoking, very few for regular smoking, and several for dependent smoking. These results suggest (1) a remarkable specificity for associations between panic and occasional and regular smoking and (2) nonspecificity for associations with nicotine dependence. In the same way as for panic, the associations between other anxiety disorders and smoking through nicotine dependence were temporally unidirectional in the prospective analyses. Prior nicotine dependence increases the risk for the later onset of other anxiety disorders, but no higher incidence of smoking among cases with preexisting anxiety disorders could be proved (the CIs in Table 4 do not rule out much). Johnson et al¹⁷ also found that prior smoking increased the risk for later onset of a range of several anxiety disorders, suggesting a nonspecific relationship. This nonspecificity would challenge causal theories to explain the panic-smoking relationship, which focus on lung disease and its special relationship to dyspneic symptoms of panic attacks. However, when comorbid disorders were controlled for in our data, almost all associations with other anxiety disorders were much smaller. These findings suggest that the relationship between other anxiety disorders and nicotine dependence seems to be driven to a large extent by other comorbid disorders, whereas smoking-panic associations are independent of and not explained by comorbidity. Therefore, our results suggest a substantial specificity in associations between smoking and panic, ie, that smoking and nicotine dependence increase the risk for panic attacks and disorder but not for most other anxiety disorders. If replicated in other samples, these results would strengthen some of the etiologic hypotheses discussed herein.

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