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Daily smoking and the subsequent onset of psychiatric disorders

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ABSTRACT

Background. Recent research has demonstrated that smokers are at an elevated risk for psychiatric disorders. This study extends the enquiry by examining: (1) the specificity of the psychiatric sequelae of smoking; and (2) the variability in the likelihood of these sequelae by proximity and intensity of smoking.

Method. Data come from the National Comorbidity Survey (NCS), a representative sample of the US population 15–54 years of age. The Smoking Supplement was administered to a representative subset of 4414 respondents. A modified World Health Organization – Composite International Diagnostic Interview was used to measure DSM-III-R disorders. Survival analysis with smoking variables as time-dependent covariates was used to predict the subsequent onset of specific psychiatric disorders.

Results. The estimated effects of daily smoking varied across disorders. In the case of mood disorders, daily smoking predicted subsequent onset, with no variation between current *versus* past smokers or by smoking intensity. In the case of panic disorder and agoraphobia, current but not past smoking predicted subsequent onset; furthermore, the risk of these disorders in past smokers decreased with increasing time since quitting. In the case of substance use disorders, current but not past smoking predicted subsequent onset, with no variation by time since quitting or smoking intensity.

Conclusions. The data suggest that smoking cessation programmes would not prevent the onset of mood disorder, as ex-smokers do not differ from current smokers in their risk for these disorders. In comparison, daily smoking might be a causal factor in panic disorder and agoraphobia, conditions that might be preventable by smoking cessation. Additionally, current smoking might serve as a marker for targeting interventions to prevent alcohol and drug disorders.

INTRODUCTION

Associations between smoking and psychiatric disorders have been reported in both clinical (Hughes *et al.* 1986; Glassman *et al.* 1988; Pohl *et al.* 1992; Glassman, 1993; Amering *et al.* 1999) and epidemiological (Glassman *et al.* 1990; Breslau *et al.* 1991; Covey *et al.* 1994; Lasser *et al.* 2000) studies. Recent research has shown that these associations are due, at least in part, to the role of smoking in predicting the subsequent onset of psychiatric disorders. Specifically, there is an elevated risk of first onset major depression in smokers (Kendler *et al.* 1993; Brown *et al.* 1996; Breslau *et al.* 1998) and a subsequent increase in depressive symptoms in persons who have smoked in adolescence (Kandel *et al.* 1986;

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Wu & Anthony, 1999; Goodman & Capitman, 2000). Recent advances in neuroscience suggest linkages between smoking and depression that might be mediated by common neurochemical mechanisms. Neuropharmacological studies show nicotine activity on dopaminergic systems that are closely tied to the reinforcing functions served by the administration of drugs, such as cocaine and nicotine (Pontierl *et al*. 1996). Separate lines of research link these systems to depressed mood and mood disorders. Recent brain imaging studies link smoking to decreased levels of monoamine oxidase B, probably through smoke substances other than nicotine (Fowler *et al*. 1996). In addition, the possibility that the association of smoking and major depression results from genetic factors that influence the liability to both has been suggested by twin studies (Kendler *et al*. 1993).

Breslau & Klein (1999) reported results based on prospective data from an epidemiological study of young adults that showed that smoking predicted the subsequent first onset of panic disorder. Johnson *et al*. (2000) replicated these findings and also reported that smoking predicted agoraphobia and generalized anxiety disorder. Pulmonary disease induced by smoking might be one of the mechanisms that link smoking to the onset of panic disorder (Breslau & Klein, 1999). Another possible mechanism in the smoking–anxiety disorders connection is an anxiogenic effect of smoking and nicotine (Cohen & Lichtenstein, 1990; Jarvis, 1994; West & Hajek, 1997; Parrott, 1999). With respect to the association of smoking with drug disorders, Kandel (1975, 1978) has documented that illicit drug use typically follows the initiation of smoking, drinking or both. The progression of substance use from 'gateway' drugs to hard drugs has been confirmed in numerous studies (e.g. Donovan & Jessor, 1983; Fleming *et al*. 1989; Kandel *et al*. 1992). However, a recent study has reported that this sequence does not hold across birth cohorts and is non-causal (Golub & Johnson, 2001).

This report uses data from the National Comorbidity Survey (NCS) and survival analysis with time-dependent variables to extend the investigation of the psychiatric consequences of smoking in two important directions. (The role of pre-existing psychiatric disorders in predicting smoking and nicotine dependence is a topic of a separate report by Breslau *et al*. 2003.) First, we examine the role of daily smoking in predicting a wide range of psychiatric disorders and test the specificity of the smoking effects. Previous studies have focused primarily on a single disorder (e.g. major depression) or a class of disorders (e.g. anxiety or drug-use disorders) and have not examined the specificity question. Secondly, we examine variations in the effects of smoking according to indicators of the temporal proximity and intensity of daily smoking. We consider whether the respondent is a current *versus* a past smoker and whether time since quitting among past smokers is a relevant factor in predicting the onset of psychiatric disorders. We also consider whether the smoker or the ex-smoker was nicotine dependent and examine whether level of cigarette consumption and early onset of daily smoking predict the subsequent onset of psychiatric disorders.

Evidence that daily smoking does not predict the subsequent onset of a psychiatric disorder would rule out daily smoking as a causal risk factor. However, evidence that daily smoking does predict the subsequent onset of a disorder would be consistent with both a causal effect of smoking as well as an influence of a third factor on both conditions. Data on variations in smokers' risk of a psychiatric disorder according to the temporal proximity and the intensity of smoking can serve to evaluate further the plausibility of the causal *versus* non-causal alternative interpretations. Evidence that smokers' increased risk of a psychiatric disorder does not vary by indicators of temporal proximity (e.g. current *versus* past smoking, or number of years since quitting) and intensity of smoking (e.g. total consumption) would be inconsistent with a causal explanation and would suggest instead that both conditions result from common factors. On the other hand, evidence that smokers' risk of a psychiatric disorder varies by whether they currently smoke or have quit smoking or by other measures of the temporal proximity and the intensity of smoking would be consistent with a causal explanation.

METHOD

Sample

The sampling scheme of the National Comorbidity Survey (NCS) has been described

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in detail previously (Kessler, 1995). Briefly, the NCS is a stratified multi-stage area probability sample of 8098 persons 15–54 years of age, selected from the non-institutionalized population of the United States. Data were gathered between September 1990 and March 1992. The Tobacco Supplement, which elicits information on daily smoking and nicotine dependence, was administered in the second half of the survey to 4414 NCS respondents. Because the NCS fieldwork was conducted in replicates, each designed to be a representative national sample, data from the Tobacco Supplement subsample are representative of the United States population.

Assessment

A modified version of the World Health Organization's Composite International Diagnostic Interview (CIDI) (WHO, 1990) was used to ascertain psychiatric disorders according to DSM-III-R. The WHO-CIDI is a structured interview designed to be used by trained interviewers who are not clinicians. In this report, we focus on 10 psychiatric disorders: major depression, dysthymia, panic disorder, agoraphobia, simple phobia, social phobia, generalized anxiety disorder, post-traumatic stress disorder, and alcohol and drug abuse/dependence (A/D). These CIDI-DSM-III-R diagnoses have good reliability and validity (Kessler *et al.* 1998). Mania and non-affective psychosis are not included in this analysis, because of their low reliability and validity (Kessler *et al.* 1998) Antisocial personality was not included, because information on age of onset is unavailable.

The section on nicotine dependence inquires first whether the respondents have ever smoked daily for a month or more. The onset of daily smoking is defined by the age (in years) at which daily smoking for a month or more first occurred. Persons who have ever smoked daily are asked about the DSM-III-R defining symptoms of nicotine dependence. The DSM-III-R adopted a unitary definition of dependence across all psychoactive substances. The definition requires the lifetime occurrence of three or more criterion symptoms of dependence, with some symptoms persisting for a month or more. Age of onset of nicotine dependence is defined by the age (in years) at which symptoms of dependence first occurred among daily smokers who have ever met DSM-III-R criteria for nicotine dependence. The CIDI does not enquire about the age of onset of each individual symptom of dependence. Instead, it enquires about the respondent's age 'at which symptoms like that first occurred', referring to criterion symptoms of dependence endorsed by the respondent. Thus, the onset of nicotine dependence refers to the age at which multiple symptoms occurred, as opposed to the age at the earliest symptom. As previously reported (Breslau *et al.* 2001), in 95% of dependent smokers, the age of onset of nicotine dependence lagged by at least 1 year after the onset of daily smoking. Information on smoking initiation, i.e. whether the respondent ever smoked a cigarette and age at first cigarette, was not obtained in the NCS.

Definition of smoking variables in the survival analysis

The focus of this analysis is on the role of pre-existing daily smoking and smoking characteristics in predicting the subsequent onset of specific psychiatric disorders. Daily smoking was defined as 'pre-existing' if it first occurred 1 year or more before the year of onset of the psychiatric disorder defined as the outcome. Pre-existing daily smoking was classified as current *versus* past according to the year in which the respondent last smoked, relative to the year of onset of the disorder. Smokers were classified as 'past smokers' if they last smoked 1 year or more before the onset of the disorder and as 'current smokers' if they continued to smoke in the year of onset of the disorder. In addition, current and past daily smokers were classified as 'nicotine dependent *versus* non-dependent'. In the absence of a detailed year-by-year assessment of smoking behaviour, we assumed that daily smoking continued in all the intervening years from the year in which it began until the last year in which it occurred. We also assumed that nicotine dependence among daily smokers continued from the year of onset of dependence until the last year in which daily smoking occurred. 'Early onset of daily smoking' was defined as onset falling in the earliest 10% of the age of onset distribution of all same sex members of the smoker's birth cohort who smoked daily. Early onset of daily smoking was included as a proxy for an underlying risk taking propensity. We previously reported that the

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10% cumulative incidence of daily smoking occurred at 14–15 years of age across all four cohorts of the NCS (see Breslau *et al*. 2001, Fig. 2). Lifetime 'consumption of tobacco' was measured by pack-years of cigarettes, a time-dependent and standardized measure (*z* scores) of the number of packs of cigarettes smoked daily multiplied by the number of years of smoking. Estimates of daily tobacco consumption were based on respondents' reports of the average number of cigarettes smoked daily when the respondent smoked the most. In the absence of year-by-year smoking history, it is assumed that tobacco consumption continued at a constant level from the year of onset of daily smoking to the year that daily smoking last occurred. Similar measures have been used in research on smoking and cancer (e.g. Lotufo *et al*. 2000; Lee *et al*. 2001; Semenza *et al*. 2001). 'Time since quitting' among past daily smokers was a standardized measure (*z* scores) of the number of years beginning the year after they last smoked daily.

Statistical analysis

The data were weighted to adjust for variation in the probabilities of selection and non-response and to approximate the data to the United States population on key sociodemographic characteristics (Kessler, 1995). Discrete-time survival models (Efron, 1988), with person-year as the unit of analysis and smoking variables as time-dependent, were used to predict the subsequent first onset of 10 psychiatric disorders: major depression, dysthymia, six specific anxiety disorders, alcohol A/D and drug A/D. Logistic regression was applied to the person-year files to predict a dichotomous measure of the onset of the outcome disorder (coded 1 for the year of onset and 0 for prior years). The logistic regression coefficients can be interpreted as survival coefficients and can be exponentiated to generate odds ratios. Separate models were estimated for each disorder. Time was defined as chronological age in years. Cases in which the onset of the psychiatric disorder occurred in the same year as the onset of daily smoking were represented by a separate term in the models. The estimates of these terms are not presented, because of the indeterminate temporal relationship between the onset of the disorder and the onset of daily smoking in these cases.

The advantage of survival analysis for addressing our stated research questions is that it permits taking into account differences in the period of risk for an outcome across respondents of varying age at assessment. The added advantage of survival analysis with time-dependent covariates is that it allows consideration of independent variables whose value for any given person may change over time. A person's smoking status (an independent variable) can change from never smoking daily to daily smoking at any time until the onset of the psychiatric disorder of interest or age at interview (whichever comes first). In analyses of the risk for the subsequent onset of specific psychiatric disorders by smoking status, presented in Table 2, respondents may change from never smoking daily to daily smoking and then from daily smoking to past smoking or instead to dependent smoking and then, if they were nicotine dependent, to past dependent smoking (defined by last year of daily smoking) at any time until the onset of the psychiatric disorder or age at interview. The models in Table 2 yield estimates of the risk for a specific psychiatric disorder in four subgroups of smokers, relative to persons who never smoked daily. Models presented in Table 3 include early onset of smoking, total consumption of cigarette pack-years in current and past daily smokers, and number of years since quitting in past smokers. Models in all tables were adjusted for race, sex, age cohort and education. Models in Tables 2 and 3 were adjusted additionally for other pre-existing psychiatric disorders. Interactions between daily smoking, on the one hand, and age cohort, sex and history of pre-existing disorders, on the other, were tested but none was detected.

To take into account the complex survey design of the NCS, the 95% confidence intervals (CI) of odd ratios and Wald χ^2 tests were computed using Jacknife Repeated Replications (JRR) method, implemented in user developed SAS macros (Kish & Frankel, 1974). The number of person-years in survival models used for estimating the odds for specific psychiatric disorders ranged from 102 767 (alcohol A/D) to 137 040 (PTSD). Within disorders, the proportions of person-years in current daily smokers were far higher than in past daily smokers. Information on person years across disorders is presented in the Appendix.

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Table 1. *Odds ratio for onset of specific psychiatric disorders associated with pre-existing daily smoking*

Subsequent disorder	OR (95% CI)
Major depression	3·2* (1·6, 6·5)
Dysthymia	3·6* (1·8, 7·5)
Panic disorder	2·6* (1·2, 5·4)
Agoraphobia	4·4* (2·3, 8·2)
Simple phobia	1·4 (0·7, 2·8)
Social phobia	1·1 (0·5, 2·4)
GAD	2·7 (0·9, 8·1)
PTSD	1·3 (0·6, 2·9)
Alcohol A/D	3·0* (2·1, 4·4)
Drug A/D	3·4* (2·1, 5·4)

Odds ratio (OR) and 95% confidence interval (CI) from a series of 10 survival models for first onset of specific disorders associated with prior daily smoking as time dependent, adjusted for race, sex, age, education and same year onset.

GAD, Generalized anxiety disorder; PTSD, post-traumatic stress disorder; A/D, abuse or dependence.

* $P<0{\cdot}05$.

RESULTS

Lifetime prevalence of smoking and nicotine dependence

The lifetime prevalence of daily smoking for $\geqslant 1$ month in the Tobacco Supplement subset of the NCS ($N=4\,414$) was 49·4%. Of those who ever smoked daily for $\geqslant 1$ month, 48·0% met DSM-III-R criteria for nicotine dependence. The demographic characteristics of the Tobacco Supplement subsample and the prevalence proportions of psychiatric disorders are approximately the same as in the total NCS sample, as reported in Kessler *et al.* (1994).

History of daily smoking and the subsequent onset of psychiatric disorders

The odds ratios for the first onset of psychiatric disorders in persons with pre-existing daily smoking are presented in Table 1. These models predict the subsequent onset of specific disorders in all daily smokers, without controlling for other psychiatric disorders that preceded the onset of daily smoking and without taking into account the proximity and intensity of smoking. (These variables are included in models presented in Tables 2 and 3.) Results in Table 1 are adjusted for race, sex, age cohort and education (as time varying). Significant odds ratios associated with pre-existing daily smoking were found for the onset of major depression, dysthymia, panic disorder, agoraphobia, alcohol A/D and drug A/D. Significant odds ratios for the effects of prior daily smoking range from 2·6 (panic disorder) to 4·4 (agoraphobia).

Current *versus* past and dependent *versus* nondependent daily smoking

Odds ratios of the subsequent first onset of psychiatric disorders across four subgroups of daily smokers, defined by current *versus* past and dependent *versus* non-dependent, are presented in Table 2. These odds ratios are adjusted also for pre-existing psychiatric disorders (relative to onset of daily smoking) in addition to sociodemographic variables. The odds for the subsequent onset of four anxiety disorders, alcohol A/D and drug A/D varied significantly across the four groups. Furthermore, in panic disorder, agoraphobia and substance use disorders, there were significantly higher odds ratios in current than past daily smokers, independent of nicotine dependence (Table 2). In contrast, major depression and dysthymia were found to be at a significantly increased risk in all four groups of daily smokers, with no significant differences between the current *versus* past and the nicotine dependent *versus* non-dependent groups (Table 2). Nicotine dependence did not predict an increased likelihood of the subsequent first onset of psychiatric disorders in daily smokers. In the case of PTSD, we found a significantly lower odds ratio in non-dependent past smokers, an isolated finding that accounts for the significant differences in the comparisons between the current *versus* past and the nicotine dependent *versus* non-dependent groups.

Early onset of daily smoking and cumulative tobacco consumption

Early onset of daily smoking did not predict the first onset of any of the 10 psychiatric disorders examined in this study (Table 3). Cumulative tobacco consumption was generally unrelated to the risk of subsequent onset of psychiatric disorders in current or past daily smokers (Table 3). Exceptions to this pattern were observed in relation to: (1) panic disorder and PTSD, for which slightly decreasing risks were associated with increases in tobacco consumption in current smokers; and (2) alcohol A/D, for which a slightly increasing risk was associated with an increase in tobacco consumption in past daily

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Table 2. *Odds ratios for psychiatric disorders associated with current* v. *past daily smoking and nicotine dependence*

	Current smoking		Past smoking		Wald χ^2	
	Dependent OR (95% CI)	Non-dependent OR (95% CI)	Dependent OR (95% CI)	Non-dependent OR (95% CI)	Current *v.* Past	Dependence *v.* No dependence
Major depression	2·9* (1·2, 6·5)	2·3* (1·2, 4·4)	3·0* (1·2, 7·6)	2·8* (1·2, 6·4)	0·3	0·3
Dysthymia	2·8* (1·3, 5·9)	2·3* (1·2, 4·4)	4·2* (1·1, 16·8)	4·4* (1·8, 11·1)	2·2	0·1
Panic disorder	2·7* (1·2, 6·0)	1·8 (0·9, 3·6)	0·4* (0·2, 0·9)	0·7 (0·3, 1·8)	34·1*	0·3
Agoraphobia	2·8* (1·5, 5·3)	3·4* (1·9, 5·9)	2·6 (0·8, 8·0)	1·0 (0·5, 2·2)	4·0*	0·3
Simple phobia	0·6 (0·2, 2·2)	1·4 (0·7, 2·9)	0·6 (0·2, 1·7)	0·5 (0·2, 1·1)	3·4	0·6
Social phobia	0·4 (0·1, 1·1)	0·8 (0·4, 1·6)	2·7 (0·7, 9·9)	3·0 (0·8, 11·2)	0·5	1·1
GAD	1·5 (0·6, 4·3)	3·4 (0·9, 12·1)	1·5 (0·4, 5·8)	0·8 (0·2, 3·0)	3·8	0·1
PTSD	1·1 (0·3, 3·3)	0·9 (0·4, 1·9)	0·9 (0·3, 2·6)	0·2* (0·1, 0·5)	7·1*	6·7*
Alcohol A/D	2·3* (1·3, 3·9)	2·8* (1·9, 4·0)	1·2 (0·5, 2·8)	0·9 (0·4, 2·2)	10·3*	0·1
Drug A/D	3·4* (2·0, 5·8)	2·9* (1·8, 4·5)	0·8 (0·3, 2·0)	1·1 (0·4, 2·7)	16·2*	0·1

Odds ratio (OR) and 95% confidence interval (CI) from a series of 10 survival models with four time dependent smoking variables, with non-daily smokers as reference, adjusted for sociodemographic characteristics and other pre-existing psychiatric disorders.

Current *v.* past Wald χ^2 (df = 1) compares ORs between two current *v.* two past groups; dependent *v.* non-dependent Wald χ^2 (df = 1) compares ORs between two dependent *v.* two non-dependent groups.

Wald χ^2 (df = 3) from tests comparing ORs in the four smoking groups were significant ($P < 0{\cdot}05$) for panic disorder, agoraphobia, simple phobia, PTSD, Alcohol A/D and Drug A/D (not displayed).

* $P < 0{\cdot}05$.

Table 3. *Characteristics of daily smoking and subsequent onset of psychiatric disorders*

	Early smoking onset OR (95% CI)	Pack-years in current smokers OR (95% CI)	Pack-years in past smokers OR (95% CI)	Years since quitting OR (95% CI)
Major depression	1·7 (0·8, 3·7)	1·0 (0·8, 1·2)	1·2 (1·0, 1·5)	0·9 (0·6, 1·1)
Dysthymia	1·2 (0·4, 3·6)	1·1 (0·9, 1·4)	1·3 (1·0, 1·7)	1·3 (1·0, 1·7)
Panic disorder	1·2 (0·5, 3·0)	0·8* (0·6, 0·9)	1·4 (1·0, 2·0)	0·5* (0·4, 0·7)
Agoraphobia	1·5 (0·6, 3·3)	1·0 (0·8, 1·2)	1·1 (0·8, 1·4)	0·5* (0·5, 0·8)
Simple phobia	1·2 (0·4, 3·4)	1·0 (0·8, 1·3)	0·9 (0·4, 1·9)	0·9 (0·6, 1·3)
Social phobia	2·4 (0·9, 6·1)	0·8 (0·6, 1·2)	0·8 (0·5, 1·2)	0·6* (0·4, 0·8)
GAD	1·1 (0·4, 3·1)	1·3 (1·0, 1·6)	1·4 (1·0, 1·8)	1·2 (0·9, 1·6)
PTSD	1·8 (0·9, 3·8)	0·7* (0·6, 0·8)	1·1 (0·8, 1·6)	1·0 (0·8, 1·2)
Alcohol A/D	1·2 (0·5, 2·9)	1·1 (0·7, 1·7)	1·4* (1·1, 1·7)	1·2 (0·7, 1·9)
Drug A/D	2·4 (0·8, 8·1)	1·0 (0·7, 1·4)	1·4 (0·9, 2·1)	1·4 (0·8, 2·4)

Odds ratio (OR) and 95% confidence interval (CI) from a series of 10 survival models with four smoking variables, adjusted for ever smoking, sociodemographic characteristics and other pre-existing psychiatric disorders.

* $P < 0{\cdot}05$.

smokers. These exceptions do not form discernable patterns of a dose–response relationship in these disorders.

Number of years since quitting in past daily smokers

We tested the relationship between time since quitting and the risk of the first onset of psychiatric disorders in past daily smokers, using a standardized variable that counts the number of years passed beginning with the year after quitting (Table 3). The likelihood of two anxiety disorders – panic disorder and agoraphobia – was reduced in half (OR = 0·50) ($P < 0{\cdot}05$) with each standard deviation unit of time since quitting. The odds ratios of other disorders for which daily smokers were at an increased risk, as displayed in Tables 1 and 2, did not vary significantly with the passage of time since quitting. In the case of social phobia, a disorder for which there was no evidence of a relationship with daily smoking, we found a significant inverse relationship of time since quitting in past daily smokers.

DISCUSSION

The findings of this study should be interpreted in light of the following limitations. First, the data on age of onset of psychiatric disorders,

daily smoking, nicotine dependence and smoking cessation are based on retrospective reports that cover the lifetime of the respondents and are thus subject to recall error. To some extent, the evidence that the associations between daily smoking and psychiatric disorders did not vary across age groups of the NCS, despite differences in the length of recall, argues against a bias associated with respondents' age at interview. To overcome the limitations inherent in these retrospective data, longitudinal studies with frequent assessments, beginning in early adolescence and continuing into adulthood, are needed.

Secondly, in the absence of a detailed year-by-year assessment of smoking in the NCS, intermittent years of abstinence (if they occurred) could not be identified. We assumed that daily smoking continued from the year of onset until the year in which daily smoking last occurred. Accordingly, persons who have ever smoked daily for at least 1 month were coded as current smokers in all the intervening years from the year of onset until the last year in which daily smoking occurred. However, any errors due to coding years of intermittent abstinence as years of current smoking, instead of past smoking, would have rendered the estimates of risk for psychiatric disorders associated with current smoking more conservative. In the case of a disorder for which the risk in current smokers was higher than in past smokers (e.g. panic disorder), such miscoding would have inflated the person-year pool of current smokers on which the estimates are based, resulting in understating the true risk for the disorder among current smokers. In the case of disorders for which the risk in current and past smokers was similar (e.g. major depression), inflating the person-year pool of current smokers would have had no consequence. A related limitation is the absence of year-by-year information on the level of tobacco consumption. Following the approach applied in research on cancer, we assumed that tobacco consumption was constant from the year of onset of daily smoking until the last year in which daily smoking occurred. The effect of this limitation on the results is unclear.

Thirdly, because the NCS did not enquire about smoking initiation, we cannot estimate the risk of psychiatric disorders associated with occasional smoking either during the period preceding the transition to daily smoking or in persons who have never smoked daily. Consequently, the results of this study cannot be generalized to all persons who have ever smoked a cigarette. If there were an elevated risk of a psychiatric disorder associated with occasional smoking (prior to the progression to daily smoking or in persons who never smoked daily), our results would have underestimated the total effect of smoking in predicting that disorder. Furthermore, in the absence of information on smoking initiation, our results on the role of nicotine dependence in predicting psychiatric disorders apply only to daily smokers. In the small number of cases ($<5{\cdot}0\,\%$) in which the onset of nicotine dependence did not lag behind daily smoking (Breslau *et al.* 2001), the onset of nicotine dependence was set at the year in which daily smoking began. The potential role of nicotine dependence in predicting psychiatric disorders among persons who smoked occasionally but never daily could not be estimated. However, we examined this issue in data from the Detroit area study of young adults (Breslau *et al.* 1991, 1998; Breslau & Klein, 1999), in which nicotine dependence was ascertained in all persons who have ever smoked a cigarette. In that study, only $0{\cdot}5\,\%$ of dependent smokers have never smoked daily (unpublished data), suggesting that the effect of this limitation in the NCS cannot be more than trivial.

Fourthly, the impact of daily smoking on antisocial personality disorder (ASPD) was not examined in this study, because data on age of onset were not available. In addition, the potential effect of pre-existing ASPD was not controlled in models that estimated the effects of daily smoking in predicting the subsequent onset of specific disorders. The absence of information on ASPD and other unmeasured factors that might have influenced the association between smoking and subsequent disorders, e.g. early stress or personality traits that predispose to both smoking and psychiatric disorders, should be taken into account in interpreting the results.

The results show that the estimated effects of pre-existing daily smoking varied across disorders: (1) in the case of major depression and dysthymia, daily smoking predicted the subsequent first onset, with no variation according to current *versus* past smoking or other

measures of temporal proximity and intensity of smoking; (2) in the case of panic disorder and agoraphobia, current daily smoking, but not past daily smoking, predicted the subsequent first onset (furthermore, the risk of panic disorder and agoraphobia in past daily smokers decreased with the increase in the number of years since quitting); (3) in the case of substance use disorders, current daily smoking, but not past daily smoking, predicted the subsequent first onset, with no evidence that the risk varied by smoking intensity or time since quitting.

There were a few exceptions to the observed patterns in the data. First, while the analysis show that there was no increased risk of PTSD associated with daily smoking, it yielded a significantly lower odds ratio for PTSD in past non-dependent daily smokers, compared to persons who never smoked daily. Secondly, while cumulative tobacco consumption, as a rule, was unrelated to the risk of subsequent disorders, there was a significant inverse relationship between tobacco consumption and panic disorder and PTSD in active daily smokers and a positive relationship between tobacco consumption and alcohol A/D in past daily smokers. Thirdly, while the analysis shows no increased risk of social phobia in current or past daily smokers, time since quitting in past daily smokers was found to be inversely related to onset of social phobia. These findings do not form discernable patterns of relationship between disorders and proximity or intensity of smoking and are difficult to interpret. The most parsimonious explanation is that they are chance findings.

We found that smokers' risk for the subsequent onset of psychiatric disorders (including alcohol and drug disorders) did not vary by whether or not they were nicotine dependent or began to smoke daily at an earlier age than most daily smokers in their birth cohort. Although the relationship of psychiatric disorders with nicotine dependence and early smoking has been previously examined, our results cannot be directly compared with previous reports. Previous studies reported cross-sectional associations between nicotine dependence and psychiatric disorders among smokers; the risk for the subsequent onset of disorders associated with nicotine dependence has not been evaluated. In a prospective study, Breslau *et al.* (1993) observed an increased risk for major depression in persons with history of nicotine dependence. However, that study did not control for other pre-existing psychiatric disorders. Previous studies have reported that early smoking initiation (i.e. age at first use in preteens and early teens) predicts the progression to illicit drug use (Kandel, 1978; Yamaguchi & Kandel, 1984; Golub & Johnson, 2001). In this study, we focused on early onset of daily smoking, which occurs at an older age (Breslau *et al.* 1993). This factor has not been previously examined.

While our findings that history of daily smoking, as a single indicator, predicts the first onset of mood disorders, panic disorder, agoraphobia and substance use disorders replicate results from previous research (Kandel *et al.* 1986; Kendler *et al.* 1993; Brown *et al.* 1996; Breslau *et al.* 1998; Breslau & Klein, 1999; Wu & Anthony, 1999; Goodman & Capitman, 2000; Johnson *et al.* 2000), the additional findings on the proximity and intensity of smoking provide new evidence relevant to the evaluation of potential causal pathways. The results on major depression and dysthymia show moderate increases in the risk of first onset not only in current daily smokers but also in smokers who have quit, regardless of whether they have recently quit or have been ex-smokers for any number of years, and regardless of smoking intensity. The failure to find evidence of any of these relationships argues against a direct causal effect of daily smoking on the onset of mood disorders and is consistent with the explanation that common factors, hereditary or acquired, influence both smoking and mood disorders.

The results on panic disorder and agoraphobia show a moderately elevated risk of first onset in current daily smokers and a decrease in past smokers' risk as the number of years since quitting increases. These findings suggest that the elevated risk of panic disorder and agoraphobia observed in current daily smokers does not disappear upon quitting but dissipates gradually, a pattern consistent with a causal effect of smoking that reverses as time since quitting increases. Previous reports that show no evidence of an increased risk in the reverse direction, i.e. from pre-existing panic disorder and agoraphobia to daily smoking (Breslau & Klein, 1999; Johnson *et al.* 2000), lend further

support for a causal influence of daily smoking on these disorders. Previous research has suggested that lung disease might be one of the mechanisms linking smoking to the onset of panic attacks (Breslau & Klein, 1999). The finding of no dose–response relationship with cumulative tobacco consumption, measured by pack-years, suggests that even minor respiratory problems caused by relatively low levels (or short duration) of smoking could trigger panic attacks in susceptible persons. A model of an underlying susceptibility to panic attacks that involves a heightened sensitivity to suffocation signals in subsets of the population has been proposed by Klein (1993, 1994). The finding that daily smokers were not at an elevated risk for anxiety disorders other than panic disorder and agoraphobia argues against a generalized anxiety-inducing effect of smoking on the genesis of anxiety disorders.

With respect to alcohol A/D and drug A/D, current daily smokers were at an increased risk of first onset, a risk that was not observed in past daily smokers. This finding *per se* might suggest that active smokers, in contrast with persons who had previously smoked but quit $\geqslant 1$ year earlier, are persistent smokers who are more likely to be predisposed to addiction to a variety of psychoactive substances (Bierut *et al*. 1998; True *et al*. 1999). However, the failure to find differences in the risk of substance use disorders between dependent *versus* non-dependent smokers or by cumulative tobacco consumption suggests that current smoking might be a marker of life-style – the usual ways in which individuals spend their vocation and leisure time – that is conducive to the use of psychoactive drugs.

The data suggest that smoking cessation programs would not prevent the onset of mood disorders in smokers, as ex-smokers do not differ from current smokers with respect to their elevated risk for the onset of these disorders. However, the data suggest the possibility that smoking cessation programmes, apart from reducing mortality and morbidity due to physical disease, might reduce societal burden due to severe anxiety disorders. The data also show that active smokers are at an elevated risk for alcohol and drug use disorders, thus active smoking might serve as a marker for targeting interventions to prevent alcohol and drug use disorders.

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APPENDIX: DESCRIPTIVE DATA FOR TIME VARYING EFFECTS OF DAILY SMOKING ON PSYCHIATRIC OUTCOMES

Psychiatric outcomes	Total npy	Non-smoker		Current				Past			
				Non-dependent		Dependent		Non-dependent		Dependent	
		%	npy	%	npy	%	npy	%	npy	%	npy
Major depression (years with onset)	807	56·8	458	28·5	230	8·2	66	4·1	33	2·5	20
Years with no disorder	126 668	72·5	91 852	18·6	23 562	4·4	5605	3·2	3995	1·3	1654
Dysthymia (years with onset)	342	50·3	172	29·5	101	12·6	43	5·0	17	2·6	9
Years with no disorder	135 885	72·4	98 419	18·3	24 812	4·9	6598	3·1	4150	1·4	1906
Panic disorder (years with onset)	149	55·0	82	28·2	42	13·4	20	2·0	3	1·3	2
Years with no disorder	122 364	69·5	85 068	20·2	24 742	5·4	6668	3·3	4070	1·5	1816
Agoraphobia (years with onset)	245	64·5	158	24·9	61	6·9	17	2·0	5	1·6	4
Years with no disorder	133 272	72·9	97 138	18·1	24 071	4·8	6351	3·0	3990	1·3	1722
Simple phobia (years with onset)	464	84·7	393	11·6	54	1·5	7	1·1	5	1·1	5
Years with no disorder	136 186	75·0	102 194	16·7	22 682	4·3	5805	2·9	3883	1·2	1622
Social phobia (years with onset)	549	83·2	457	12·4	68	1·8	10	1·5	8	1·1	6
Years with no disorder	127 374	73·3	93 426	17·9	22 846	4·5	5742	2·9	3738	1·3	1622
GAD (years with onset)	227	49·8	113	26·0	59	15·4	35	5·7	13	3·1	7
Years with no disorder	133 176	71·1	94 729	19·0	25 366	5·1	6753	3·3	4387	1·5	1941
PTSD (years with onset)	329	68·1	224	23·1	76	6·4	21	1·2	4	1·2	4
Years with no disorder	136 711	74·0	101 186	17·4	23 723	4·5	6102	2·9	3943	1·3	1757
Alcohol A/D (years with onset)	1015	51·4	522	40·7	413	6·0	61	1·3	13	0·6	6
Years with no disorder	101 752	71·8	73 082	19·5	19 792	4·2	4236	3·4	3417	1·2	1225
Drug A/D (years with onset)	515	49·1	253	41·7	215	7·6	39	1·2	6	0·4	2
Years with no disorder	103 894	68·1	70 724	21·7	22 572	5·1	5332	3·6	3732	1·5	1534

npy, Number of person years.

The 'Total' column represents the denominators (100%) on which the row percents are calculated.

For each specific disorder, the total npy is presented in two rows: 'years with onset' and 'years with no disorder'. The rows of 'years with onset' provide the numbers of persons with the disorder in the total sample and their distribution across non-smokers and the four smokers groups classified by current *v.* past and dependent *v.* non-dependent. For example, for major depression, the total number of cases (100%) was 807, 56·8% (or 458) occurred in persons with no history of daily smoking, 28·5% (or 230) occurred in current/non-dependent smokers, 8·2% (or 66) occurred in current dependent, etc.

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