

Major Depression and Stages of Smoking

A Longitudinal Investigation

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Background: Epidemiologic studies have reported an association between major depression and smoking. This prospective study examines the role of depression in smoking progression and cessation, and the role of smoking in first-onset major depression.

Methods: Data are from a 5-year longitudinal epidemiologic study of 1007 young adults. Incidence and odds ratios (ORs) are based on the prospective data. Hazards ratios are based on the combined lifetime data and estimated in Cox proportional hazards models with time-dependent covariates.

Results: Based on the prospective data, history of major depression at baseline increased significantly the risk for progression to daily smoking (OR, 3.0; 95% confidence interval, 1.1-8.2), but did not decrease significantly smokers' rate of quitting (OR, 0.8; 95% confi-

dence interval, 0.4-1.6). History of daily smoking at baseline increased significantly the risk for major depression (OR, 1.9; 95% confidence interval, 1.1-3.4). These estimates were reduced somewhat when history of early (ie, before age 15 years) conduct problems was controlled. Estimates based on lifetime data were consistent with these results.

Conclusions: The observed influences from major depression to subsequent daily smoking and smoking to major depression support the plausibility of shared etiologies. Separate causal mechanisms in each direction might also operate, including self-medication of depressed mood as a factor in smoking progression and neuropharmacologic effects of nicotine and other smoke substances on neurotransmitter systems linked to depression.

Arch Gen Psychiatry. 1998;55:161-166

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RECENT epidemiologic studies have reported an association between smoking and major depression,¹⁻³ replicating earlier observations from clinical samples^{4,5} and studies linking smoking to depressive symptoms.⁶⁻⁸ Several alternative explanations for the association have been proposed. It has been suggested that major depression plays a causal role in smoking—increasing the risk for smoking initiation and the progression to regular and heavy smoking and decreasing the potential for smoking cessation.^{3,9-11} At the core of this causal explanation is the notion of self-medication, ie, that smokers use nicotine to medicate their depressed mood and that the reinforcing effects of nicotine's mood-altering characteristic are especially powerful in depressed smokers. Contending explanations include (1) a causal influence of smoking on major depression, based on the possible effects of long-term nicotine exposure on neurobiologic systems that are implicated in the etiology of depression³; and (2) the effects

of shared environmental or genetic factors that predispose to both smoking and major depression.^{3,9}

Information bearing on these explanations is sparse. The available data do not support a role for major depression in smoking initiation.¹¹ With the exception of observations on short-term outcomes in some smoking cessation trials, there is little evidence that history of major depression decreases smokers' potential for quitting.^{5,12-16} We have previously reported on the relationship between major depression and nicotine dependence, based on prospective data from an epidemiologic study of young adults.¹⁷ The relatively short interval period, approximately 1 year, yielded a small number of new daily smokers, precluding analysis of the link between prior major depression and progression to daily smoking. We used the *DSM-III-R*¹⁸ definition of level of severity of dependence and estimated the odds of progression across levels of nicotine dependence, from nondependence to mild and moderate dependence. History

SUBJECTS AND METHODS

SAMPLE AND DATA

A random sample of 1200 persons was selected from all 21- to 30-year-old members of a large health maintenance organization in southeastern Michigan. Personal interviews were conducted in 1989 with 1007 individuals (84%) and follow-up interviews were conducted in 1990, 1992, and 1994. Complete follow-up data are available on 974 persons (97%). The sample was 62% female, 80% white, 45% married, and 29% college educated. (Detailed information on the population and the sample has been described previously.^{2,17})

Smoking initiation was defined as ever smoking a cigarette, and daily smoking was defined as smoking daily for 1 or more months. Progression was defined as the onset of daily smoking among persons who have ever smoked a cigarette. Smoking cessation was defined as abstinence for 1 or more years for persons who had smoked daily. Major depression and other psychiatric and substance use disorders were measured by the NIMH [National Institute of Mental Health]-Diagnostic Interview Schedule,²³ (NIMH-DIS) revised according to *DSM-III-R*.¹⁸ Alcohol use disorder included dependence or abuse. Early conduct problems were measured by 8 items from the NIMH-DIS inventory of conduct problems before age 15 years that constitutes a part of the antisocial personality module.²³ The items inquire whether the respondent had frequent encounters with teachers or principals because of misbehavior, was truant, repeated a grade, was suspended or expelled from school, ran away from home, told a lot of lies, started fights, and had early sexual experiences. Lifetime history of major depression and smoking was measured at baseline, and interval

history, which covered the interval period since the last assessment, was measured in each of the follow-up interviews. Prospective data on the entire 5-year follow-up period were constructed by combining information from the 3 follow-up interviews.

STATISTICAL ANALYSIS

The prospective analysis was conducted on 974 subjects with complete data from all assessments. Relative risks for smoking progression and cessation in persons with prior major depression and for first-onset major depression in daily smokers were estimated by sex-adjusted odds ratios (ORs), calculated in logistic regression analyses. Relative risks were estimated also in multivariable models that controlled for sex, early conduct problems, and history of alcohol use disorder at baseline.

To evaluate the extent to which the associations observed in the prospective data apply more broadly to respondents' life span, we used the combined data from the baseline and the follow-up interviews. Cox proportional hazards models for censored survival data with time-dependent covariates²⁴⁻²⁶ were used to estimate the hazards ratios (HRs) of (1) progression to daily smoking associated with preexisting major depression, (2) smoking cessation associated with preexisting major depression, and (3) onset of major depression associated with prior daily smoking. Hazards ratios with 95% confidence intervals (CIs) that do not include the null value of 1 are statistically significant ($P < .05$). The SAS statistical software for proportional hazards regression was used.²⁷ The proportionality assumption of the HRs was tested for each model, using graphic techniques.²⁸ All models included sex as a fixed covariate. Expanded models with early conduct problems and prior alcohol use disorder also were estimated.

Table 1. Baseline History of Smoking and Major Depression (MD) (N=974)

	No. (%) of Total	No. (%) With MD in Smoking Subset
Ever smoking a cigarette*	728 (74.7)	102 (14.0)
Ever smoking daily ≥ 1 mo	381 (39.1)	76 (19.9)
Ever smoking a cigarette/never daily	347 (35.6)	26 (7.5)
Current daily smoking	281 (28.9)	63 (22.4)
MD	131 (13.4)	...

*"Ever smoking a cigarette" includes both "ever smoking daily ≥ 1 mo" and "ever smoking a cigarette/never daily."

of major depression at baseline increased the risk for progression to nicotine dependence and more severe levels of dependence, measured according to *DSM-III-R* criteria. We also reported an increased risk for first-onset major depression associated with preexisting nicotine dependence.¹⁷

In this report, we present prospective data from a 5-year follow-up assessment of the sample. We address the following questions: (1) Does history of major depression at baseline increase the risk for progression to daily smoking among persons who have ever smoked a cigarette? (2) Does history of major depression at baseline de-

crease smokers' rate of quitting? (3) Does daily smoking increase the risk for first-onset major depression? The role of major depression in smoking initiation cannot be evaluated in these prospective data that cover a period of 5 years in early adulthood, past the age at which the initiation of smoking occurs.¹¹ The inquiry of the relationship between major depression and stages of smoking took into account other key factors that have been linked to smoking stages, chiefly, early conduct problems (ie, before age 15 years) and alcohol use disorder.¹⁹⁻²²

RESULTS

MAJOR DEPRESSION AND PROGRESSION TO DAILY SMOKING

Table 1 shows the baseline history of smoking and major depression and history of major depression at baseline in subsets of smokers, based on 974 subjects for whom complete data from all assessments were available. Of the 728 individuals who had ever smoked a cigarette, 347 had never smoked daily for 1 or more months up to the time of the baseline interview. During the 5-year follow-up interval, 36 progressed to daily smoking. The rate of progression in persons with history of major depression at baseline was 23.0%, compared with 9.3% in persons with no history of major depression at baseline. No

interaction with sex was detected. The sex-adjusted OR for progression to daily smoking associated with history of major depression was 3.00 (95% CI, 1.10-8.19) ($P=.01$). Estimated in a model that controlled for early conduct problems and baseline history of alcohol use disorder, the OR for progression was 2.69 (95% CI, 0.97-7.47) ($P=.06$).

MAJOR DEPRESSION AND SMOKING CESSATION

Of the 281 daily smokers who had smoked within 1 year of the baseline interview, 60 had quit for 1 year or more during the 5-year follow-up. The rates of 5-year smoking cessation in daily smokers with history of major depression vs no major depression were 19.0% and 21.6%, respectively. No interaction with sex was detected. The sex-adjusted OR of smoking cessation associated with history of major depression was 0.81 (95% CI, 0.44-1.64) ($P=.55$). This estimate remained unchanged when early conduct problems and baseline history of alcohol use disorder were controlled.

DAILY SMOKING AND RISK FOR MAJOR DEPRESSION

Of the 843 persons who had never experienced major depression up to the time of the baseline interview, 76 met criteria for major depression during the follow-up interview. The incidence of first-onset major depression in daily smokers was 12.1%, compared with 6.5% in persons who had ever smoked a cigarette but never smoked daily for 1 month or more up to the time of the baseline interview. The sex-adjusted OR for major depression associated with daily smoking was 1.91 (95% CI, 1.10-3.36) ($P=.02$). No sex interaction was detected. Controlling for early conduct problems and baseline history of alcohol use disorder reduced the relative risk for major depression to 1.50 (95% CI, 0.82-2.73).

RESULTS FROM LIFETIME DATA

Calculated in a Cox proportional hazards model, with major depression as a time-dependent covariate and using the combined lifetime data up to age 35 years, the HR for progression to daily smoking associated with prior major depression was 2.06 (95% CI, 1.36-3.13). No sex interaction was detected. **Figure 1** displays the cumulative incidence curves of daily smoking from age 10 to 35 years. These curves differ from the standard Kaplan-Meier curves in that major depression is not treated as a fixed variable, but instead can change from “no major depression” to “major depression” over time, reflecting its status as a time-dependent covariate in the model. Beginning in early adolescence, the cumulative percentage of daily smoking was higher in smokers with preexisting major depression. When early conduct problems and prior alcohol use disorder were controlled, the HR for progression to daily smoking associated with prior depression was 1.57 (95% CI, 1.02-2.37).

The HR of smoking cessation in persons with prior major depression vs those without prior major depression, estimated from the time at onset of daily

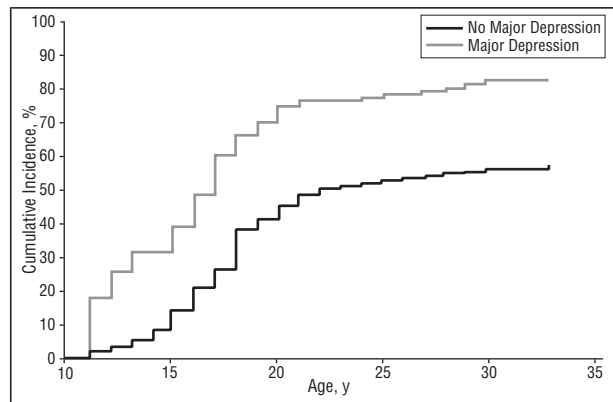


Figure 1. Cumulative incidence of daily smoking in persons who ever smoked a cigarette by preexisting major depression ($n=746$).

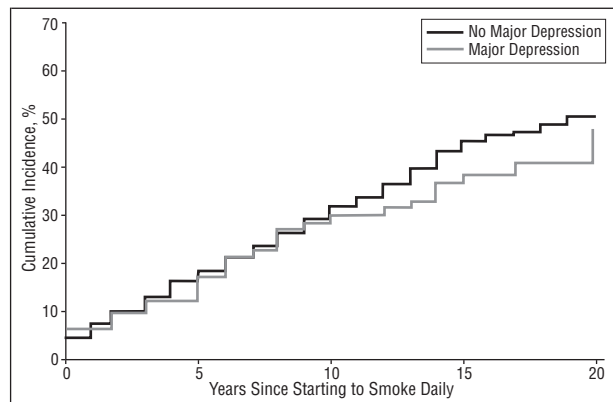


Figure 2. Cumulative incidence of smoking cessation in daily smokers by preexisting major depression ($n=429$).

smoking, was 0.78 (95% CI, 0.51-1.21). **Figure 2** displays the cumulative incidence curves of smoking cessation by prior status of major depression. The curves do not diverge during the 12-year period in which most of the cessation events occurred. The divergence after 12 years is based on a small sample size and is not statistically significant. The expanded model yielded similar results.

The HR for major depression associated with prior daily smoking was 1.96 (95% CI, 1.37-2.80). No sex interaction was detected. As shown in **Figure 3**, beginning at age 19 years, the cumulative incidence of major depression was higher in persons with prior daily smoking than in those with no prior daily smoking. (Note that the crossover of the curves before age 19 years involves only few cases and does not represent a material violation of the proportionality assumption of the HRs, as our diagnostic evaluation revealed.) The estimate of the HR for major depression, controlling for early conduct problems and alcohol use disorder, was 1.62 (95% CI, 1.10-2.36).

Early conduct problems were significantly associated with increased risk for progression to daily smoking, decreased smokers' potential for cessation, and increased risk for first-onset major depression. With each additional early conduct problem, the HR for progression to daily smoking was 1.28 (95% CI, 1.18-1.37); for smoking cessation, 0.87 (95% CI, 0.78-

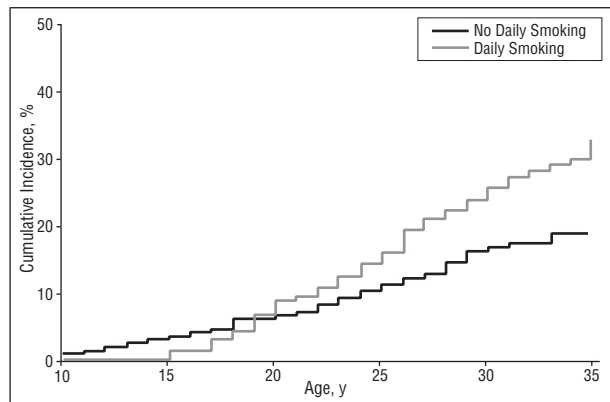


Figure 3. Cumulative incidence of major depression in ever-smokers by preexisting daily smoking (n=746).

0.96); and for major depression, 1.15 (95% CI, 1.02-1.30). Prior alcohol use disorder was not significant in any of these models. Models that included race and education did not alter the estimates of the associations between major depression and the smoking variables or between early conduct problems and progression to daily smoking, quitting smoking, and major depression.

A summary of the results from the combined lifetime data and the prospective data is shown in **Table 2**. Both sets of findings support the role of major depression in the progression to daily smoking and the role of daily smoking in first-onset major depression; neither supports the hypothesis that major depression decreases the potential for smoking cessation.

COMMENT

Analysis of the 5-year prospective data indicates that (1) history of major depression at baseline was associated with a 3-fold increase in the risk for progression to daily smoking, (2) history of major depression at baseline did not decrease significantly smokers' rate of quitting during the ensuing 5 years, (3) history of daily smoking at baseline increased significantly the risk for major depression, and (4) analysis of the combined lifetime data yielded consistent results.

The generalizability of the results is limited by the age range of the sample and the characteristics of the health maintenance organization sample, which does not represent the extremes of the socioeconomic range, especially the uninsured poor. The average annual incidence of major depression during the 5-year follow-up, approximately 1.7%, is similar to that estimated previously,²⁹ taking into account the young age of the sample.

With the exception of our earlier report on the progression to *DSM-III-R* nicotine dependence and more severe levels of dependence, we are aware of no previous reports on the influence of major depression on the progression of smoking among persons who have ever smoked. This report strengthens our previous findings in an important respect. The longer follow-up period permitted the estimation of progression to daily smoking, a clearer and more distinct transition than onset of nico-

tine dependence, which is defined according to nosologic systems that are in flux and requires a far more complex operationalization.

The prospective data included incidence cases occurring during a 5-year period in persons 22 to 35 years of age. The combined lifetime data permit inferences to a broader age range that encompasses childhood and adolescence. They offer a view of the relationship between major depression and the progression to daily smoking across respondents' life span and suggest that the influence of major depression on the progression to daily smoking begins in adolescence.

We did not estimate the effect of major depression on smoking initiation in the prospective data because smoking initiation rarely occurs after age 18 years. A previous longitudinal study by Kandel and Davies⁶ reported that depressive symptoms at age 15 years predicted daily smoking in early adulthood. Their report falls short of supporting a role for depressive symptoms in the initiation of smoking, because smoking status in adolescence was not controlled. When calculated in the subset who had never smoked in adolescence, initiation rates in those who had been highly depressed in adolescence vs not highly depressed were nearly equal, 53.0% vs 52.2%, respectively (Denise Kandel, PhD, written communication of unpublished data, August 2, 1996). Reports of a cross-sectional (lifetime) association between major depression and ever smoking do not inform on the temporal order between major depression and smoking initiation.⁵ A recent study of adolescents reported that history of major depression at baseline was associated with smoking 3 or more times a week during the subsequent 12 months.³⁰ However, it is unclear whether the excess in smoking associated with prior major depression represents progression from occasional smoking.³⁰

This study, taken together with previous studies, suggests that major depression predicts the progression to daily smoking but might not predict smoking initiation. A similar pattern has been suggested in regard to illicit drug use.³¹ Although the mechanisms that drive the progression of substance use and abuse in adolescence from one stage to the next are not known, it is recognized that each stage might be preceded by unique conditions. There is evidence to suggest that initiation of drug use is likely to result chiefly from social influences, whereas progression to regular use is more closely tied to internal processes, such as depressed mood.³¹

There is no support in these data for an influence of major depression on smoking cessation. Two earlier prospective studies examined the effects of depressive symptoms (as distinct from major depression) on smoking cessation in the general population. Anda et al⁷ reported a lower rate of smoking cessation during a 9-year follow-up in smokers who scored higher on depressive symptoms at baseline compared with those who scored lower. Salive and Blazer³² reported on the 3-year incidence of quitting among smokers 65 years and older by high and low depressive symptoms score. In women smokers, high depression scores predicted a 2-fold increase in quitting, and in men, depression was not significantly related to subsequent quitting. Three cross-sectional studies reported significantly lower proportions

Table 2. Comparison of Estimates From Prospective Data and Combined Lifetime Data for Major Depression (MD) and Smoking (N=1007)*

	Prospective Data, OR (95% CI)		Combined Lifetime Data, HR (95% CI)	
	Sex-Adjusted†	Multivariable‡	Sex-Adjusted†	Multivariable‡
Daily smoking following MD	3.00 (1.10-8.19)	2.69 (0.97-7.47)	2.06 (1.36-3.13)	1.57 (1.01-2.37)
Smoking cessation following MD	0.81 (0.44-1.64)	0.81 (0.40-1.66)	0.78 (0.51-1.21)	0.81 (0.53-1.25)
MD following daily smoking	1.91 (1.10-3.36)	1.50 (0.82-2.73)	1.96 (1.37-2.80)	1.62 (1.10-2.36)

*OR indicates odds ratio from logistic regressions; CI, confidence interval; and HR, hazards ratios from Cox proportional hazards model.

†Results from models that controlled for sex.

‡Results from models that included also early conduct problems and alcohol use disorder; alcohol disorder was defined at baseline in the prospective analyses and as a time-dependent covariate in the combined lifetime data.

of former smokers among ever-smokers who were depressed than among ever-smokers who were not depressed,^{1,2,7} whereas 1 study reported an association only in women with recurrent major depression.³³ Because age at onset of depression in relation to quitting was not taken into account, these studies are ambiguous with respect to the potential effect of depression on subsequent quitting.

Adverse effects of history of major depression on cessation were reported in several randomized trials of smoking cessation.^{5,12,14,15} However, only short-term effects were observed. Also, in 2 of these studies, the findings did not reach statistical significance^{12,15} and in 1 study adverse effects were noted only for women with a history of recurrent major depression.¹⁴ None of the studies that evaluated long-term effects supports a role for history of major depression in smoking cessation.^{13,15,16}

Our finding that daily smoking increased the risk for first-onset major depression is consistent with earlier reports of increases in depressive symptoms and greater risk for episodes of major depression associated with prior smoking.^{3,6,30,34}

The observed influences from smoking to major depression and from major depression to subsequent daily smoking support the plausibility of shared etiologies. A population-based genetic study suggested that the smoking-major depression relationship results solely from genes that predispose to both conditions.³ Other potential shared etiologies are factors in the social environment, personality, and coping styles. Our results suggest that history of early conduct problems was an influential antecedent factor in both smoking and major depression, and that history of early conduct problems accounted in part for the observed associations of major depression with smoking stages. The potential role of neuroticism, self-esteem, and social skills in the depression-smoking association is an important topic for future research.

More complex explanations should be considered as well, namely, that there might be separate causal mechanisms that lead from major depression to the progression of smoking and from smoking to major depression. Attempts to self-medicate depressed mood might explain the progression to daily smoking. As to the potential influence of smoking on major depression, recent advances in neuropharmacology offer new leads. Relevant findings come from studies that show nicotine activity on dopaminergic systems in the shell

of the nucleus accumbens, systems that are closely tied to the reinforcing functions served by the administration of drugs such as cocaine and nicotine.³⁵ 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.³⁶ Further developments in neuroscience might clarify the nature of the associations of major depression with stages of smoking observed in longitudinal epidemiologic studies.

Accepted for publication April 8, 1997.

This work was supported by research grant MH-48802 from the National Institute of Mental Health, Bethesda, Md.

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