

# Smoking and the Risk of Suicidal Behavior

## A Prospective Study of a Community Sample

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**Background:** A link between cigarette smoking and suicidal behavior has been reported in clinical and epidemiological studies.

**Objective:** To examine the association between smoking and suicidal thoughts or attempt in a longitudinal study, in which proximate status of smoking and psychiatric disorders in relation to timing of suicidal behaviors is taken into account.

**Design:** A longitudinal study of young adults interviewed initially in 1989, with repeated assessments over a 10-year follow-up.

**Setting and Participants:** The sample was selected from a large health maintenance organization representing the geographic area, except for the extremes of the socioeconomic range. The response rate at each follow-up (3, 5, and 10 years after baseline) exceeded 91%.

**Main Outcome Measures:** Relative risk of occurrence of suicidal behaviors during follow-up intervals by status of smoking and psychiatric disorders at the start of the interval, estimated by generalized estimating equa-

tions with repeated measures. The National Institute of Mental Health Diagnostic Interview Schedule was used at baseline and at each reassessment.

**Results:** Current daily smoking, but not past smoking, predicted the subsequent occurrence of suicidal thoughts or attempt, independent of prior depression and substance use disorders (adjusted odds ratio, 1.82; 95% confidence interval, 1.22-2.69). Additionally, current daily smoking, but not past smoking, predicted the subsequent occurrence of suicidal thoughts or attempt, adjusting for suicidal predisposition, indicated by prior suicidality, and controlling for prior psychiatric disorders (adjusted odds ratio, 1.74; 95% confidence interval, 1.17-2.54).

**Conclusions:** The biological explanation of the finding that current smoking is associated with subsequent suicidal behavior is unclear. Recent observations of lower monoamine oxidase activity (which may play a role in central nervous system serotonin metabolism) in current smokers but not ex-smokers might provide clues, but interpretations should proceed cautiously.

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**A** LINK BETWEEN CIGARETTE smoking and suicide has been reported in epidemiological investigations since the 1970s.<sup>1-6</sup> These associations were observed in studies that controlled for potential confounders, that is, features shared by smokers and by persons who commit suicide, such as income, race, and history of serious physical illness and alcohol abuse. Bolstering the evidence were the findings of a dose-response relationship between the level of smoking and the risk of suicide.<sup>1,2,6</sup> The interpretation of these epidemiological observations has been a subject of controversy, however.<sup>7</sup>

Two large-scale studies published in 2000 replicated the smoking-suicide association. A prospective study of 50000

US men found a dose-response relationship between smoking and suicide, ranging from a relative risk of 1.4 (in former smokers) to 4.3 (in smokers of >15 cigarettes daily), controlling for age, marital status, body mass index, physical activity, alcohol intake, coffee consumption, and history of cancer.<sup>8</sup> A prospective study of 300000 US Army male personnel also demonstrated a dose-response relationship between smoking and suicide, controlling for education, race, alcohol consumption, marital status, level of physical exercise, and military rank.<sup>9</sup>

Previous studies have not obtained data on major depression, an established risk factor of suicide.<sup>10-18</sup> It might be argued that, because major depression may in part result from smoking, either via nicotine or

smoke substances other than nicotine,<sup>19,20</sup> it should not be controlled in analysis of the smoking-suicide association. However, the evidence that depressive symptoms in adolescence predict subsequent smoking onset<sup>21-23</sup> and that major depression leads to increased risk for progression to regular smoking and nicotine dependence<sup>19</sup> indicates the need to consider history of depression in evaluating the possibility of an increased risk of suicide in smokers.

Although it did not control for major depression per se, a study of 49323 Swedish men, evaluated at 18 to 21 years of age when conscripted for military service, included several psychological measures. The study showed a significant dose-response relationship between smoking and the risk of suicide over a 26-year period, with those smoking more than 20 cigarettes per day having a greater than 2-fold risk for suicide than nonsmokers.<sup>24</sup> This relationship dissipated and was no longer significant when the authors adjusted for a wide range of potential confounders, among them indicators of conduct problems, alcoholism, and having a psychiatric diagnosis and "low emotional control" (a summary assessment of mental stability, emotional maturity, and tolerance for stress and frustration), measured at time of conscription, when smoking status was ascertained. It should be noted that the interpretation of the negative results (when adjusted for these potential confounders) must take into account the lack of information on the temporal order between the onset of smoking and the risk factors controlled in the analysis, which precludes the possibility of separating factors that had preceded the onset of smoking (potential confounders) from those that followed it (which should not be considered potential confounders). Adjusting for the latter might mask a true relationship.

A link between drug use, including tobacco, and suicidal thoughts or attempt has been reported in clinical and community studies.<sup>25-27</sup> In a community sample of adolescents, more than 7% reported suicide attempts.<sup>28</sup> Associations between smoking and a variety of suicidal behaviors were observed.<sup>28</sup> Prior suicidal thoughts are predictors of suicide attempts,<sup>29</sup> and the 2 are predictors of completed suicide<sup>11-13,30,31</sup> and are therefore important intermediate points in understanding the etiology of suicide.

Biological plausibility of the role of smoking in suicidality comes from recent research linking smoking to monoamine oxidase (MAO),<sup>20,32</sup> which has long been investigated as a biological marker for psychopathology.<sup>33</sup> Monoamine oxidase is central to a number of neurotransmitter functions and plays an important role in serotonin metabolism and in modulating serotonergic transmission. Low platelet MAO activity has been associated with violence and suicide and with lower cerebrospinal fluid 5-hydroxyindoleacetic acid (5-HIAA).<sup>34</sup> Low platelet MAO has been linked to a variety of mental disorders, including depression, alcoholism, and schizophrenia,<sup>32</sup> all disorders in which the rate of smoking is high.<sup>35-38</sup>

Using the Australian Twin Registry, Whitfield et al<sup>39</sup> report low platelet MAO activity in current smokers but not in ex-smokers, suggesting a direct effect of smoking. Further support for the hypothesis that smoking

might have played a causal role in smokers' low platelet MAO (rather than low MAO representing a genetic factor predisposing individuals to smoking) came from Whitfield and colleagues<sup>39</sup> findings that (1) nonsmoking monozygotic twins had significantly higher MAO activity than their smoking co-twins and (2) there were no significant differences in MAO activity between nonsmoking subjects with and without smoking co-twins (in either the monozygotic or the dizygotic pairs). With respect to suicidality, the authors report that subjects with history of serious suicide attempts had significantly lower platelet MAO than subjects with no suicidal thoughts or attempt. (Potential links between low MAO activity, violence and suicide, lower 5-HIAA, and the possibility of impaired central nervous system serotonin metabolism are outlined by Whitfield and colleagues.<sup>39</sup>)

A recent study of psychiatric inpatients found an inverse association between the number of cigarettes smoked daily and serotonin function, measured by cerebrospinal fluid 5-HIAA.<sup>40</sup> The authors suggest that lower serotonergic function may be related to cigarette smoking, as well as to suicidal and aggressive behaviors.<sup>40</sup> Evidence of low cerebrospinal fluid 5-HIAA concentration in suicidal subjects is consistent with low MAO activity.<sup>34</sup> The possibility of neurobiological links between smoking and suicide provides a rationale for re-examining the smoking-suicide association in longitudinal studies, in which data on smoking and psychiatric disorders are available.

In this study, we examine the relationship between smoking and suicidal behavior in a longitudinal epidemiological study in which major depression and other psychiatric disorders were also measured. Prospective data from repeated assessments over a 10-year period were used to estimate the association between smoking and subsequent suicidal behavior (suicidal thoughts and attempt), controlling for potential confounders, including major depression.

## METHODS

### SAMPLE

A sample of 1200 persons was randomly selected in 1998 from all 21- to 30-year-old members of a large health maintenance organization in southeast Michigan. The health maintenance organization's membership represented the population of the geographic area, with the exception of the extremes of the socioeconomic range, at the time of the 1990 US census. Personal interviews were conducted in 1989 with 1007 persons, 83.9% of the sample. Follow-up interviews were conducted in 1992, 1994, and 1999-2001, at 3, 5, and 10 years after baseline, respectively. Complete data from all 4 assessments are available on 899 persons, and 990 persons (98.3%) had at least 1 follow-up interview (detailed information of the sample and the population was reported previously).<sup>41</sup>

### ASSESSMENT

The National Institute of Mental Health Diagnostic Interview Schedule<sup>42</sup> for *DSM-III-R* was used to measure psychiatric disorders. The baseline interview inquired about lifetime history of psychiatric disorders and daily smoking, and each fol-

low-up assessment inquired about disorders and smoking occurring during the interval since the previous assessment. The tobacco section of the interview inquired whether the respondent had smoked daily for 1 month or longer. Substance use disorder is defined by the presence of 3 or more criterion symptoms, that is, cognitive, behavioral, or physiological problems that characterize compulsive use of any psychoactive substance. The National Institute of Mental Health Diagnostic Interview Schedule questions on suicidal thoughts and suicide attempt are as follows: "Have you ever felt so low that you thought about committing suicide?" and "Have you ever attempted suicide?" At each assessment, the occurrence of episodes of disorders, daily smoking, and the occurrence of suicidal thoughts and attempt since the last assessment were ascertained. Age at onset of suicidal behaviors within the interval covered in each re-assessment was not ascertained. Consequently, information is available on whether suicidal thoughts and attempts occurred during the interval covered in each follow-up assessment, not the specific year within the interval.

We combine suicidal thoughts and attempt into a single outcome. The number of persons who reported suicide attempts during the 10-year follow-up was small ( $n=19$ ), limiting our ability to calculate reliable estimates of associations in multivariable analysis. The validity of a composite variable—suicidal thoughts and/or attempt—has received empirical support in a recent twin study by Fu et al.<sup>43</sup> The authors report that, controlling for known risk factors, the same genes affect risk of suicidal ideation and suicide attempt.

## STATISTICAL ANALYSIS

To examine the risk of suicidal behavior prospectively, we used logistic regression analysis with repeated measures, applying generalized estimating equations (GEE) with an unstructured correlation matrix.<sup>44,45</sup> In these models, the occurrence of suicidal behavior is set in a clear temporal sequence in relation to daily smoking (as well as psychiatric disorders of interest) across the follow-up assessments. Smoking and psychiatric disorders measured at baseline and at the 3- and 5-year follow-up assessments are the repeated measures used to predict suicidal behavior during the respective subsequent periods: from baseline to the 3-year assessment, from the 3- to the 5-year assessment, and from the 5- to the 10-year assessment. The advantage of this approach over standard regression is that it uses all the prospectively gathered information relevant to the temporal order between suicidal behavior, as the outcome, and the time-varying predictors (ie, smoking and psychiatric disorders), taking into account changes in these predictors that occurred between each re-assessment and the preceding one. This is a critical advantage for the etiologic interpretation of the results, compared with standard logistic regression, in which baseline history of daily smoking and psychiatric disorders as fixed variables are used to predict the cumulative incidence of suicidal behavior during the entire 10-year follow-up period. Generalized estimating equations take into account correlations within persons across multiple measures and use all persons in the sample, including those with incomplete follow-up data. The GEE regression, as the standard logistic regression, yields estimates of the odds ratios for subsequent suicidal behavior associated with daily smoking, adjusted for other variables in the model. The GENMOD procedure in SAS<sup>46</sup> was used.

For each of the first 3 assessments, daily smoking and the psychiatric disorders used as covariates were coded as mutually exclusive categories: current, past, or never. This classification represents a person's proximate smoking and psychiatric status (current, past, or never) at the start of each successive follow-up period (reflecting also any changes across the re-

peated assessments). Current is defined as occurrence *within* the 12-month period preceding the time of assessment. Past is defined as occurrence *at any time before* the 12-month period that preceded the time of assessment but not within that 12-month period. For example, for the 3-year follow-up assessment, the definition of major depression (or smoking) as current, past, or never refers to a person's status ascertained in the preceding interview (which in this case is at baseline), specifically, whether it occurred during the 12 months preceding the baseline interview (current), at any earlier time only (past), or never. By the same rule, for the 10-year follow-up assessment, the coding of major depression (or smoking) as current means occurrence in the 12-month period before the start of the period (which in this case is the 12 months preceding the time of the 5-year assessment), whereas past major depression (or smoking) means that it occurred at any time before that 12-month period. Additionally, the category coded past in each follow-up assessment also includes occurrence in previous assessments carried forward. For example, past smoking at the 5-year assessment includes current and past smokers in the previous assessments who were not current smokers in the 5-year assessment. For each disorder and for daily smoking, the category never served as a reference. It should be noted that psychiatric disorders, past or current, include disorders with onset that preceded the uptake of daily smoking.

Because the relationship between time and suicidal behavior did not appear to be linear in the log odds, we used 2 binary terms to represent the 3 follow-up assessments. We examined whether differences in the duration between interviews influenced the estimates by testing the interactions between each of the 2 time terms and daily smoking. The results of these tests showed that the relationship between suicidal behavior and daily smoking did not vary significantly across the 3 follow-up assessments.

The final model is illustrated in the equation  $y = \alpha + \beta_1$  (current smoking) +  $\beta_2$  (past smoking) +  $\beta_3$  (current depression) +  $\beta_4$  (past depression) +  $\beta_5$  (current alcohol/drug disorder) +  $\beta_6$  (past alcohol/drug disorder) +  $\beta_7$  (assessment 2) +  $\beta_8$  (assessment 3), where suicidal behavior at 3-, 5-, and 10-year assessments is the outcome ( $y$ ).

In an additional model, we included prior suicidal thoughts or attempt as a time-varying covariate, using the same GEE approach. This model estimates the relative risk of subsequent suicidal behavior associated with smoking, adjusting for persons' propensity for suicidal behavior, as indicated by their past experience.

The effect of history of panic disorder, which has been found to be associated with increased risk of suicidality,<sup>47</sup> was examined. However, no significant association with subsequent suicidal behavior was detected in the multivariable models that included major depression and substance use disorders. Sex, race, and education were tested as covariates in alternative models but were not significant in multivariable models. The final GEE models presented here do not include these variables.

## RESULTS

The follow-up sample on which the GEE analysis was conducted comprised 990 persons. Of this sample, 63% were female, 80% were white, 3.5% did not complete high school, 29% completed college, and 46% were married. These distributions reflect the characteristics of the total sample of 1007 respondents interviewed at baseline, as would be expected given the high follow-up rate.<sup>41</sup> The number of persons with suicidal thoughts during the entire 10-year follow-up period was 130. The number with

**Table 1. Percentages of Suicidal Thoughts/Attempt by Sample Characteristics Across 3 Follow-Up Assessments After the 1989 Baseline Interview: Detroit Metropolitan Area Sample\***

Predictor	1992 Reassessment	1994 Reassessment	1999-2001 Reassessment
Overall	8.2 (80/979)	4.6 (45/974)	8.0 (73/913)
Female	9.4 (57/608)	5.3 (32/607)	9.0 (52/575)
Male	6.2 (23/371)	3.5 (13/367)	6.2 (21/338)
White	8.2 (65/789)	5.1 (40/786)	8.8 (65/740)
Black	7.9 (15/190)	2.7 (5/188)	4.6 (8/173)
College education	4.2 (12/286)	2.5 (7/282)	5.6 (15/269)
Less than college education	9.8 (68/693)	5.5 (38/692)	9.0 (58/644)
Daily smoking			
Current	12.0 (34/284)	7.9 (21/266)	16.0 (38/238)
Past	8.9 (9/101)	5.6 (8/144)	5.8 (9/154)
Never	6.2 (37/594)	2.9 (16/556)	5.0 (26/518)
Major depression			
Current	30.2 (19/63)	21.6 (11/51)	28.9 (15/52)
Past	18.8 (13/69)	11.8 (16/136)	20.7 (30/145)
Never	5.7 (48/846)	2.3 (18/776)	3.9 (28/710)
Alcohol/drug use disorders			
Current	10.1 (14/139)	13.0 (12/92)	20.0 (18/89)
Past	14.2 (17/120)	4.5 (9/199)	8.5 (16/188)
Never	6.8 (49/720)	3.6 (24/672)	6.1 (39/636)
History of suicidality			
Prior	26.3 (54/205)	13.0 (30/231)	24.5 (56/229)
Never	3.4 (26/774)	2.0 (15/734)	2.5 (17/680)

\*Data are presented as percentages of suicidality (number of suicide thoughts or attempts/number of individuals at risk). At each reassessment, classifications of smoking, major depression, and alcohol/drug use disorders represent respondents' status in the preceding assessment. For the first reassessment (1992), the preceding assessment (1989) was at baseline and covered lifetime history; for the second reassessment (1994), the preceding assessment was in 1992; and for the third reassessment (1999-2001), the preceding assessment was in 1994.

suicide attempts during that interval was 19, of whom 17 also reported suicidal thoughts. The total cumulative number with suicidal thoughts or attempt was 132.

**Table 1** presents descriptive data on the prevalence proportions of suicidal thoughts or attempt during each of the 3 follow-up interval periods after the 1989 baseline interview (in 1992, 1994, and 1999-2001), with each subsequent assessment covering an interval period since the previous one, ie, 3-year, 2-year, and 5-year periods, respectively. These data show that the prevalence of suicidal thoughts or attempt in each assessment period was highest in persons who were current daily smokers at the start of the interval period. (Formal statistical analyses appear in **Table 2** and **Table 3**.) **Table 1** also indicates the well-established association of major depression with subsequent suicidal behaviors. Further, the percentage of persons with suicidal behaviors during each period differed by the temporal proximity of major depression: those with current major depression at the start of the period had higher rates than those with past major depression or with no history of major depression. History of alcohol or drug use disorders also was associated with excess rates of subsequent occurrence of suicidal behavior. Sex and education were related to suicidal behavior

**Table 2. Adjusted Odds Ratios (OR) and 95% Confidence Intervals (CI) of Suicidality From Successive Generalized Estimating Equations Models With Repeated Assessments: Detroit Metropolitan Area Sample, 1989-2000 (n = 990)\***

Predictor	Model 1	Model 2	Model 3
Daily smoking†			
Current	2.48 (1.71-3.59)‡	2.04 (1.40-2.97)‡	1.82 (1.22-2.69)‡
Past	1.41 (0.84-2.39)	1.20 (0.70-2.08)	1.09 (0.62-1.91)
Major depression			
Current	NA	4.82 (2.91-7.85)‡	4.61 (2.78-7.63)‡
Past	NA	3.76 (2.40-5.91)‡	3.68 (2.35-5.78)‡
Alcohol/drug abuse or dependence			
Current	NA	NA	1.74 (1.07-2.82)‡
Past	NA	NA	1.31 (0.85-2.04)

Abbreviation: NA, not applicable.

\*All models also include 2 terms representing the 3 time intervals (suppressed). Current indicates occurrence during the 12 months preceding the time of each interview. Past indicates occurrence more than 12 months preceding the time of each interview. For each variable, never is the reference category.

†Differences in OR of current vs past smoking are significant ( $P < .05$ ) in all models.

‡ $P < .05$ .

**Table 3. Adjusted Odds Ratios (OR) and 95% Confidence Intervals (CI) of the Occurrence of Suicidal Behavior in Smokers Estimated in Generalized Estimating Equations Models With Repeated Assessments: Detroit Metropolitan Area Sample, 1989-2000 (n = 990)\***

Predictor	OR (95% CI)
Daily smoking†	
Current	1.74 (1.17-2.54)‡
Past	1.14 (0.67-1.94)
Major depression	
Current	3.14 (1.93-5.12)‡
Past	2.02 (1.28-3.21)‡
Alcohol/drug abuse or dependence	
Current	1.48 (0.92-2.37)
Past	0.95 (0.60-1.49)
Prior suicidal behavior§	5.37 (3.51-8.21)‡

\*Model includes 2 terms representing the 3 time intervals (suppressed). Current indicates occurrence during the 12 months preceding the time of each interview. Past indicates occurrence more than 12 months preceding the time of each interview. For each variable, never is the reference category.

†Difference in OR of current vs past smoking is significant ( $P < .05$ ).

‡ $P < .05$ .

§Defined as occurrence preceding the beginning of the subsequent follow-up period.

across the follow-up assessments, with women exceeding men and those with less than college education exceeding college graduates. Race did not show a consistent association with suicidal behavior across the reassessment.

#### DAILY SMOKING AND SUBSEQUENT SUICIDAL BEHAVIOR: GEE RESULTS

**Table 2** displays results from 3 successive GEE models used to estimate the association of daily smoking with the risk for subsequent suicidal thoughts or attempt. The

first model estimates the relationship of current and past daily smoking (vs never daily smoking) with subsequent suicidal thoughts or attempts, unadjusted for psychiatric disorders. The second model introduces history of major depression, and the third model additionally introduces history of alcohol and drug use disorders. All models include 2 terms representing the 3 follow-up intervals (not displayed in the table). Because panic disorder, race, sex, and education were not significant in these multivariable models, they are not included in the final models displayed in Table 2.

Model 1 of Table 2 shows an increased risk for subsequent suicidal thoughts or attempt associated with current daily smoking (odds ratio, 2.48; 95% confidence interval [CI], 1.71-3.59). History of past daily smoking did not significantly predict subsequent suicidal thoughts or attempt. The difference between the odds ratios associated with current vs past daily smoking was significant ( $P=.02$ ). The estimated risk for subsequent suicidal thoughts or attempt associated with current daily smoking was reduced somewhat when it was adjusted for major depression in model 2 but remained significant ( $P<.005$ ). It was further reduced when adjusted additionally for alcohol and drug use disorders in model 3 (odds ratio, 1.82; 95% CI, 1.22-2.69) but remained significant ( $P<.005$ ). The adjusted estimates of suicidal thoughts and attempt associated with current daily smoking in models 2 and 3 were significantly higher than the estimates associated with past daily smoking ( $P<.05$ ), as they were in model 1. Interactions between assessment time (first, second, and third) and daily smoking were not significant ( $P=.11$  for model 1,  $P=.16$  for model 2, and  $P=.18$  for model 3).

The results in Table 2 show that major depression, current and past, predicted subsequent suicidal thoughts and attempt. The difference between current and past major depression was not significant ( $P>.05$ ). Current (but not past) alcohol and drug use disorders also predicted subsequent suicidal thoughts and attempt.

#### THE RISK OF SUBSEQUENT SUICIDAL BEHAVIOR IN SMOKERS, ADJUSTED FOR PRIOR SUICIDAL BEHAVIOR

In additional GEE analyses, we repeated the models in Table 2, including also prior occurrence of suicidal thoughts and attempt during the preceding periods (Table 3). The estimates of the risk for subsequent occurrence of suicidal thoughts and attempt associated with daily smoking in these models are similar in magnitude to those presented in Table 2. Specifically, the odds ratio of current daily smoking adjusted for prior suicidality was reduced from 2.48 (95% CI, 1.71-3.59) in model 1, Table 2, to 2.02 (95% CI, 1.39-2.95), when prior suicidality was controlled. It was reduced from 2.04 (95% CI, 1.40-2.98) in model 2, Table 2, to 1.82 (95% CI, 1.25-2.66), when prior suicidality was controlled (not displayed). Finally, it was reduced from 1.82 (95% CI, 1.22-2.69) in model 3, Table 2, to 1.74 (95% CI, 1.17-2.54), when prior suicidality was controlled (Table 3). The estimated risk for recurrence of suicidal thoughts or attempt in persons with prior suicidal thoughts and at-

tempt was 5.37 (95% CI, 3.51-8.21). Current and past major depression predicted the occurrence of suicidal behavior, adjusted for prior suicidal behavior. However, neither current nor past alcohol and/or drug abuse/dependence predicted an increased risk for the subsequent occurrence of suicidal behavior when prior suicidal behavior was controlled.

#### ADDITIONAL ANALYSIS: SMOKING AT BASELINE AND 10-YEAR CUMULATIVE INCIDENCE OF SUICIDAL BEHAVIOR

We compared the GEE results, which incorporate information on change over time, with those in which baseline smoking status is used to predict the cumulative occurrence of suicidal behavior during the 10-year follow-up period. Standard logistic regression analysis that estimated the association of daily smoking at baseline with the 10-year cumulative occurrence of suicidal thoughts or attempt yielded similar results. Adjusted odds ratio for suicidal behavior associated with current smoking at baseline was 1.71 (95% CI, 1.12-2.63) and with past smoking, 1.15 (95% CI, 0.59-2.26), estimated in models that included major depression and substance use disorder as covariates.

#### COMMENT

Key findings of this prospective study are as follows. Compared with never daily smokers, current daily smokers had an increased risk of subsequent suicidal thoughts or attempt. In contrast, past daily smokers were not at increased risk for subsequent occurrence of suicidal thoughts or attempt. A significant association between current daily smoking and the subsequent occurrence of suicidal thoughts or attempt was independent of major depression and alcohol or drug use disorders. Prior suicidal behavior was the strongest predictor of the occurrence of suicidal behavior in subsequent 2- to 5-year follow-up periods; the risk of recurrence was more than 5-fold. Nonetheless, current smoking was associated with an increased risk of the subsequent occurrence of suicidal thoughts or attempt, adjusting for the predisposition to experience suicidality, as indicated by prior history of suicidal thoughts or attempt.

Limitations of the study are that we have no data on completed suicide and that the number of suicide attempts was small and therefore was combined with suicidal thoughts. To analyze these rare outcomes, a much larger sample and longer follow-up period are needed. Whether the results can be extrapolated to attempted or completed suicide is uncertain. However, suicidal behaviors are established predictors of completed suicide. These antecedents and their potential etiologies are therefore of scientific and public health interest. A note about the information on the temporal sequence of events in this analysis is in order. In estimating the risk of suicidality during each follow-up interval conditional on smoking status (current, past, and never) at the start of the interval, we do not allow for changes in smoking status during the interval. For example, a nonsmoker could have

started to smoke daily during the interval and then become suicidal, a positive finding that would have been missed, lowering the chance to detect a reliable risk for suicidality associated with current smoking. Any bias due to this type of error would have rendered the estimate more conservative. Alternatively, a daily smoker could have stopped during the interval and become suicidal anyway. This is less probable, given our overall finding of no increased risk of suicidality in past smokers.

In this analysis, we adjusted for history of major depression and substance use disorders at baseline and at the first and second follow-up assessments. We adjusted for disorders that preceded as well as those that followed the onset of daily smoking. Consequently, our estimates of the risk for suicidal behavior associated with smoking are likely to be conservative. This is because disorders that began after the onset of daily smoking might in part have been caused by smoking. Our analysis yields an estimate of the current smoking-suicidality risk that is not attributable either to preexisting depression and substance use disorders or to the potential mediating role of these disorders.

There remains the possibility that we did not consider the entire range of potential confounders, such as severe or disabling physical illness (which would be rare in this young sample) or adverse life experiences that might cause the uptake of smoking as well as the subsequent occurrence of suicidal behavior directly, without also increasing the risk for the psychiatric disorders controlled in this analysis.

This epidemiologic study extends the previous findings on the association between smoking and the risk of suicidality in several important ways. First, major depression, an established risk factor for suicide-related behavior, was controlled in this analysis. Our results show that prior major depression accounted in part for smokers' increased risk for suicidal behavior. However, the estimated association was reduced by only 20%, from an odds ratio of 2.48 to 2.04 (Table 2). Second, the prospective design, with repeated assessments, allowed us to align the temporal sequence between daily smoking, the exposure variable, and the subsequent occurrence of suicidal behavior, the postulated outcome, taking into account change in exposure over time. For example, persons who had never smoked daily up to the time of the baseline interview could have become daily smokers later on but before suicidal behavior occurred. These design features have allowed us to achieve the same alignment with respect to critical variables that are associated with both smoking and suicidal behavior, namely, major depression and alcohol or drug abuse and dependence, variables that also vary over time. Third, data from the periodic reassessments regarding daily smoking and psychiatric disorders of interest allowed us to separate current exposure (ie, in the preceding 12 months) from past exposure (ie, ever in lifetime but not in the preceding 12 months), in relation to the risk of subsequent suicidal behavior. These features provide a finer-grained evaluation of the smoking-suicidality relationship than in previous studies (eg, Hemmingsson and Kriebel<sup>24</sup>). In those studies, smoking status, psychiatric or emotional

status, and alcohol or drug use disorders were measured at baseline as fixed variables and were assumed to have remained stable over subsequent decades in which suicide occurred. Moreover, our final model (Table 3) shows that the association survived the ordeal of adjusting additionally for prior suicidal behavior.

The finding of an increased suicidal behavior associated with current but not past smoking parallels the observation reported by Whitfield et al<sup>39</sup> of a lower MAO activity in current smokers but not in ex-smokers. Previous reports of low platelet MAO in current as well as remitted alcoholics were interpreted as evidence supporting a trait (rather than a state) feature in alcoholism. The finding of low platelet MAO in current smokers led Whitfield et al<sup>39</sup> to question whether the trait-like feature in alcoholism (supported by the similarly low MAO findings in remitted as in current alcoholics) might be explained by the continuation of smoking in remitted alcoholics. The function of MAO in relation to neurotransmitters implicated in suicidality has been confirmed in recent work, strengthening the biological plausibility of an effect of smoking on suicidality. Future research on suicidality in persons with history of alcohol abuse or dependence adjusted for smoking status would illuminate this question.

The finding of an association between smoking and homicidal death, which parallels the smoking-suicide association, has been put forward as an analogy in arguing against the biological plausibility of a causal interpretation of the smoking-suicide association: if homicidal death, which is also elevated in smokers, could not conceivably be caused by smoking, how could suicidal death?<sup>7,48</sup> However, the association between smoking and homicidal death might be explained by the fact that these neurobiological activities also have been found to be implicated in aggression and impulsivity. Further, there is evidence that homicidal deaths and assaultive victimization are not randomly distributed in the population<sup>49,50</sup> and that predisposition to impulsivity might increase the risk for assaultive victimization.<sup>51</sup> It also should be noted that the recent analysis by Hemmingsson and Kriebel,<sup>24</sup> which concluded that the smoking-suicide association is due to shared predispositions, is likely to be overcontrolled, in that events that have occurred after the onset of smoking (and might have been influenced by it) were controlled. The question as to whether smoking per se is an independent cause of suicidal behavior cannot be definitively answered here. Replications that ascertain proximate sequencing of suicidality with exposure to smoking and other suspected risk factors and further developments in neuroscience might bring a better resolution.

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