Smoking and Major Depression

A Causal Analysis

Kenneth S. Kendler, MD; Michael C. Neale, PhD; Charles J. MacLean, PhD; Andrew C. Heath, DPhil; Lindon J. Eaves, PhD, DSc; Ronald C. Kessler, PhD

Among 1566 personally evaluated female twins from a population-based register, average lifetime daily cigarette consumption was strongly related to lifetime prevalence and to prospectively assessed 1-year prevalence of major depression (MD). Using the cotwin control method, we evaluated whether the association between smoking and lifetime MD was causal or noncausal. While the relative risk (95% confidence interval) for ever smoking given a lifetime history of MD was 1.48 (1.30 to 1.65) in the entire sample, it was 1.18 (0.88 to 1.47) and 0.98 (0.71 to 1.26), respectively, in dizygotic and monozygotic twin pairs discordant for a history of MD. The relative risk for a history of MD given ever smoking was 1.60 (1.39 to 1.83) in the entire sample, while in dizygotic and monozygotic twins discordant for smoking, it was 1.29 (0.87 to 1.74) and 0.96 (0.59 to 1.42), respectively. Controlling for personal smoking history, family history of smoking predicted risk for MD; controlling for the personal history of MD, family history of MD predicted smoking. The best-fitting bivariate twin model suggested that the relationship between lifetime smoking and lifetime MD resulted solely from genes that predispose to both conditions. These results suggest that the association between smoking and MD in women is not a causal one but arises largely from familial factors, which are probably genetic, that predispose to both smoking and MD.

(Arch Gen Psychiatry. 1993;50:36-43)

A substantial body of research suggests that smoking and depression co-occur more frequently than would be expected by chance. General population surveys in adults and adolescents have, with rare exception, demonstrated a significant association between current smoking and depressive symptoms. Rates of smoking in depressed psychiatric patients substantially exceed those observed in the general population. In two epidemiologic samples, smokers had a substantially higher lifetime prevalence rate for major depression (MD) than did nonsmokers.

THE NATURE OF THE ASSOCIATION BETWEEN SMOKING AND DEPRESSION

Three plausible hypotheses can explain the association between smoking and MD. First, MD could cause smoking. Because smoking can produce an elevation in mood and sense of well-being, depressed individuals may self-medicate with cigarettes. Second, smoking could cause MD. Nicotine use or withdrawal may increase vulnerability to MD, as nicotine influences several neurochemical systems that may play an etiologic role in MD. Third, the association between them could be noncausal, resulting from a third set of traits that predispose to both smoking and MD.

If the noncausal hypothesis is correct, it is important to identify the predisposing traits shared by smoking and MD. Because familial factors are etiologically important in both MD and smoking, the observed association could result from familial environmental and/or genetic factors that predispose to both conditions.

THE GOALS OF THIS REPORT

This report has the following goals: (1) to document, in a large, population-based sample, the association between cigarette consumption and MD; (2) to evaluate the plausibility of the three hypotheses for the association between smoking and MD; and (3) to determine, if the noncausal hypothesis is supported, whether the association between smoking and MD can be explained by genetic or familial environmental factors.

SUBJECTS AND METHODS

Sample

As outlined in detail previously, data for this report come from a study of genetic and environmental risk factors for common psychiatric disorders in white female same-sex twin pairs from the population-based Virginia Twin Registry. Herein, we examine results from the subset of this sample, consisting of 1566 twins (727 complete pairs and 112 unpaired individuals), who completed, an average of 2 years before personal interview, the smoking section of a self-report survey. Zygosity was determined on the basis of self-report information, photographs, and, in
uncertain cases, DNA-based genotyping.\textsuperscript{10,25} Final zygotics assignment for this sample was 415 monozygotic (MZ) pairs, 310 dizygotic (DZ) pairs, and two pairs of unknown zygotics.

**Measures and Interviewers**

Lifetime history of MD and history of MD during the preceding year were assessed with use of an adapted version of the Structured Clinical Interview for DSM-III-R diagnosis,\textsuperscript{26} conducted by interviewers who had at least a master's degree in social work or a bachelor's degree and 2 years of clinical experience. Each member of a twin pair was always interviewed by a different interviewer. The presence or absence of a history of MD in the twins' parents was assessed with use of the Family History Research Diagnostic Criteria.\textsuperscript{27} The similarity of childhood and adult environments of our twin pairs was assessed via standard questions.\textsuperscript{28,29}

The self-report survey assessed, with the following item, average lifetime cigarette consumption: “Write in the number which expresses your best estimate of the DAILY cigarette consumption (or equivalence in pipefuls or cigars) for each of the following during his/her lifetime.”

The twins rated themselves, their cotwins, and their mothers and fathers on a six-point scale, as follows: (1) never smoked, (2) smoked one to five per day, (3) smoked five to 10 per day, (4) smoked 11 to 20 per day, (5) smoked 21 to 40 per day, and (6) smoked more than 40 per day. These results are termed cigarette smoking because the proportion of pipe and cigar smoking in women is negligible.\textsuperscript{30} Because of the small number of twins in the heaviest smoking category, they were, for most analyses, combined with those of the next highest group. For certain analyses, we divided the sample into never-smokers and ever-smokers or into never-smokers, “chippers” (who, by regularly smoking five or fewer cigarettes per day, usually avoid nicotine dependence\textsuperscript{31}), and “regular” smokers.

The preceding year and lifetime diagnoses of MD were assigned by one of us (K.S.K., an experienced diagnostician), using DSM-III-R criteria after a blind review of the entire interview protocol.

**Reliability**

Reliability of the assessment of smoking was obtained by comparing, in twin pairs, the report of twin 1 about her own smoking and twin 2's report of twin 1's smoking and vice-versa. The polychoric correlation between these two ratings (n=1415) was high (r=+.92, \(P=.000\)). The polychoric correlation between twins in their ratings of father's and mother's smoking was similar (\(r=+.82\) and \(+.90\), respectively, both \(P=.000\)). Interrater reliability of psychiatric diagnoses was assessed in 53 jointly conducted interviews, and the chance-corrected agreement for the DSM-III-R diagnosis of MD was +.96±.04 (\(P=.000\)). Chance-corrected agreement for the family history diagnoses of MD, from these same 53 twins, was unity in both mothers and fathers.
Regression Analyses

The association between average lifetime smoking and MD was assessed by logistic regression. Because both age and years of education were significantly related to smoking and MD in these data, all regression analyses were conducted controlling for their effects. In these analyses, nonindependence of observations from members of a twin pair, which does not influence the accuracy of the regression coefficients but produces spuriously low SEs, must be considered. The SEs in these analyses were therefore corrected upward as a function of the proportion of the sample that were complete twin pairs and the magnitude of the correlation of the dependent variable in those twin pairs. All tests of significance reported herein are based on these corrected SEs. All relative risks (RRs) were calculated with logistic regression, controlling for age and years of education.

The Cotwin Control Method

The cotwin control method attempts to discriminate causal from noncausal relationships between a putative risk factor and a disorder or trait by comparing rates for the disorder in MZ and DZ twin pairs discordant for exposure to the risk factor. By causal, we mean that the risk factor directly causes the disorder. By noncausal, we mean that the association between the risk factor and the disorder is due to another factor that influences both exposure to the risk factor and development of the disorder. If the risk factor causes the disorder (Fig 1, top, leftmost three bars), then the chances of having the disorder if exposed to the risk factor will be similarly increased in the general population and in MZ and DZ twins discordant for risk factor exposure. That is, in MZ twins discordant for risk factor exposure, the exposed twin will have a high risk for the disorder and the unexposed twin will have a low risk.

If the relationship between the risk factor and the disorder is not causal, but is due to shared family environment (eg, low social class of rearing predisposing both to the disorder and to the risk factor), then the risk factor and the disorder will still be strongly associated in the general population. However, within discordant twin pairs, there will be no association between risk factor exposure and the disorder (Fig 1, top, middle three bars). That is, the RR for the disorder given the risk factor is unity. This will occur because the unexposed member of the discordant MZ or DZ twin pairs would, along with the exposed member, have experienced the same family environment that predisposes to the disorder.

Alternatively, the relationship between the risk factor and the disorder may not be causal but may be due to genetic factors that predispose to both the disorder and the risk factor. In this situation, a different pattern of result would be expected (Fig 1, top, rightmost three bars). Again, the RR for the disorder given the risk factor would be substantially in the general population. However, in MZ twin pairs discordant for risk factor exposure, the RR would be unity. This is because the unexposed member of a discordant MZ twin pair would share completely with the exposed member the genetic predisposition to the disorder. In DZ twins discordant for risk factor exposure, by contrast, the RR for the disorder given the risk factor would be intermediate between that found in the general population and that found in discordant MZ twin pairs. This is because DZ twins share, on average, 50% of their genes identical by descent. Therefore, the unexposed member of the DZ twin pairs discordant for risk factor exposure will share some, but not all, of the genetic predisposition to the disorder with the exposed member of that pair.

Of course, it is possible that the relationship between the risk factor and the disorder is partly causal and partly noncausal. In that case, for example, the family environment model would predict that the RR for the disorder given the risk factor would be greater than 1 in MZ and DZ twin pairs discordant for risk factor exposure but still much less than the RR observed in the general population.

While RRs are reported because they are easy to interpret, the statistical assessment of the models employs three logistic regression coefficients (of ever smoking predicting MD or MD predicting ever smoking): (1) $\beta_1$ from the entire sample minus discordant MZ and DZ twins; (2) $\beta_2$ from discordant DZ twins, and (3) $\beta_3$ from discordant MZ twins. The three models depicted in Fig 1, top, are fitted by weighted least-square maximum likelihood, with use of the computer program MLX.29 to these regression coefficients and their corrected SEs, with the models parameterized as follows: causal: $\beta_1=\beta_2=\beta_3=0$; noncausal family environment: $\beta_2=\beta_3=0$, and noncausal genetic: $\beta_1=\beta_2=0$. The assumption of the third model that $\beta_3=0$ is only an approximation that might vary as a function of the nature of genetic effects (eg, additive vs nonadditive). The best-fitting model was chosen by using Akaike's28 information criterion (AIC), in which the most negative value reflects the model with the best combination of goodness of fit and parsimony.

The Risk Factor Family History Method

This method tests for the presence of a familial predisposing trait that influences the association between a risk factor and a disorder. As illustrated in Fig 2, individuals are classified as a function of both their personal and their family history of risk factor exposure. If the association between the risk factor and the disorder is causal, then, taking into account an individual's personal history of risk factor exposure, their probability of having the disorder will be unrelated to their family history of risk factor exposure (Fig 2, top left). However, this would not be the expected pattern if the association between the risk factor and the disorder were not entirely causal, but in part results from a trait that both runs in families and predisposes to both the disorder and to the risk factor. If this noncausal hypothesis is correct, then an individual's family history of risk factor exposure should influence their probability of succumbing to the disorder even after taking into account an individual's own personal history of exposure to the risk factor (Fig 2, top right).

If, for example, an individual has a strong family history but no personal history of MD, he or she should have a relatively low probability of being a smoker if MD causes smoking. However, if the association between smoking and MD is largely the result of a familial predisposing trait that influences the risk for both smoking and MD, then this individual should be at a relatively high risk for smoking.

A limitation of this method is that it assumes that the level of risk factor exposure is the same in those with and without a family history of risk factor exposure. This may not be true. However, this can be controlled for in a regression analysis, testing whether a family history of risk factor exposure predicts risk for the disorder after controlling for the level of an individual's risk factor exposure.

As a measure of family history of MD and smoking herein, we created a variable ranging from 0 to 3, where one point is given for a positive history of MD or ever smoking, respectively, in the mother, father, or cotwin. In the cotwin, when available, the history of smoking and MD were directly assessed. In the parents, we relied on the reporting of the twins. In graphically presenting these data, we collapsed categories where necessary to maintain a minimum of 50 twins in each cell.

Twin Model Fitting

While the cotwin control method has the important advantage of conceptual clarity, it uses only a subset of the available data: twins discordant for smoking or MD. To test more definitively the sources of resemblance between smoking and MD in these data, we also applied bivariate association models, which have been outlined previously in this journal. In brief, these analyses are based on a liability-threshold model, which assumes that underlying the observed polytomous distribution of variables of interest, there is a continuous, normally distributed latent liability.

These models are fit to correlations in liability estimated from the contingency table cross-classifying twin 1 and twin 2 on the relevant variables by the method of maximum likelihood by the
The association between smoking and MD is highly significant ($\chi^2=54.07, df=1, P=\ldots$). The relationship between smoking and MD is a result of higher rates of MD in ever-smokers vs non-smokers ($\chi^2=35.97, df=1, P=\ldots$) and among ever-smokers, a positive association between the lifetime prevalence of MD and the average number of cigarettes smoked ($\chi^2=19.93, df=1, P=\ldots$). Controlling for education and age, the RR and 95% confidence intervals (CI) for MD given a history of ever smoking is 1.60 (1.39 to 1.83) and for ever smoking given a lifetime history of MD is 1.48 (1.30 to 1.65).

We examined the extent to which the relationship between ever smoking and MD might be mediated by other psychiatric disorders. Controlling for education, age, and history of alcohol dependence, as defined by DSM-III-R, the RR and 95% CI for MD given a history of ever smoking is 1.50 (1.30 to 1.71). Controlling also for similarly for a lifetime history of generalized anxiety or panic disorder, defined by DSM-III-R, the RR and 95% CI was 1.45 (1.23 to 1.68).

The Association Between Ever Smoking and Future Episodes of MD

The relationship between average lifetime smoking and the 1-year prevalence of MD, assessed 2 years after smoking behavior was measured, is shown in Fig 5. As shown in Fig 4, there is a progressive and substantial increase in risk for future episodes of MD as a function of average daily cigarette consumption, ranging from 6.4% in nonsmokers to 20.7% in those smoking more than 20 cigarettes per day. Controlling for age and education, this relationship is highly significant ($\chi^2=31.65, df=1, P=\ldots$), resulting from both higher rates of MD in ever-smokers vs never-smokers ($\chi^2=21.96, df=1, P=\ldots$) and, among ever-smokers, a positive association between 1-year prevalence of MD and average number of cigarettes smoked ($\chi^2=8.83, df=1, P=\ldots$).
Fig 3.—A bivariate twin model for the liability to average lifetime smoking and a lifetime history of major depression. In the full model (top), the correlation between smoking and major depression is decomposed into three parts: (1) a correlation ($r_e$) in the additive genetic factors that influence the liability to smoking and major depression, (2) a correlation ($r_a$) in the common or familial environmental influences that affect smoking and major depression, and (3) a correlation ($r_c$) in the individual-specific environmental experiences that influence the liability to smoking and major depression. The additive genetic, common environmental, and individual-specific environmental factors influencing the liability to smoking are symbolized by, respectively, $A_e$, $C_e$, and $E_e$. The path or standardized partial regression coefficients between these factors and smoking are, respectively, $a_e$, $c_e$, and $e_e$. The additive genetic, common environmental, and individual-specific environmental factors influencing the liability to depression are symbolized by, respectively, $A_d$, $C_d$, and $E_d$. The path or standardized partial regression coefficients between these factors and depression are, respectively, $a_d$, $c_d$, and $e_d$. The other model shown (bottom) presents the parameter estimates for the best-fitting bivariate model for the relationship between average lifetime smoking and the lifetime history of major depression. The variables presented are path coefficients and one correlation coefficient ($r_s$). As a path coefficient is a standardized partial regression coefficient, the proportion of variance in the dependent variable accounted for by the independent variable is determined by squaring the path coefficient.

Fig 4.—The relationship between lifetime prevalence of major depression (±SE), defined by DSM-III-R, and average daily cigarette consumption.

Fig 5.—The relationship between prospectively assessed 1-year prevalence of major depression (±SE), defined by DSM-III-R, and average daily cigarette consumption.

Cotwin Control Analyses

Does MD Cause Smoking?—Our sample contained 116 MZ and 115 DZ twin pairs discordant for a lifetime history of MD. In discordant DZ twin pairs, ever smoking was more common in the twin with a lifetime history of MD (60/115 [52.2%]) than in the twin without a lifetime history of MD (51/115 [44.3%]). Controlling for age and education, the RR and 95% CIs for ever smoking given MD in discordant DZ twin pairs was 1.18 (0.88 to 1.47). In discordant MZ twins, the rate of ever smoking was essentially the same in the members without (53/116 [45.7%]) and with (52/116 [44.8%]) a lifetime history of MD, producing an RR for ever smoking given MD of 1.08 (95% CI, 0.71 to 1.62). The RR for ever smoking given a lifetime history of MD in the entire sample and in DZ and MZ twin pairs discordant for a history of MD are compared in Fig 2, bottom left.

The causal model (MD causing smoking) fitted the data poorly ($\chi^2=11.61$, df=2, $P<.005$, AIC=7.61), the noncausal family environment model fitted the results well ($\chi^2=1.43$, df=2, $P$ not significant, AIC=−2.57), and the noncausal genetic model fitted the data very well ($\chi^2=0.34$, df=2, $P$ not significant, AIC=−3.66). By AIC, the noncausal genetic model provided the best explanation for the results.

Does Smoking Cause MD?—Seventy-four MZ and 96 DZ twin pairs in our sample were discordant for ever smoking. Among DZ twin pairs discordant for ever smoking, the lifetime prevalence of MD was modestly higher in the ever-smoking (40/96 [41.7%]) than in the never-smoking (31/96 [32.3%]) member, producing an RR of MD given ever smoking of 1.20 (95% CI, 0.87 to 1.67). In DZ twin pairs discordant for ever smoking, the lifetime prevalence for MD was essentially the same in the never-smoking (27/74 [36.5%]) and the ever-smoking (26/74 [35.1%]) members, result-
The Correlations of Liability Between a Lifetime History of Smoking and Major Depression (MD) in Members of Monozygotic and Dizygotic Twin Pairs*

<table>
<thead>
<tr>
<th>Twin 1</th>
<th>Twin 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>MD</td>
</tr>
<tr>
<td>Twin 1</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>.24†</td>
</tr>
<tr>
<td>MD</td>
<td>.11</td>
</tr>
<tr>
<td>Twin 2</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>.54†</td>
</tr>
<tr>
<td>MD</td>
<td>.28†</td>
</tr>
</tbody>
</table>

*Values are positive correlations. Correlations in monozygotic twins are above the diagonal; those for dizygotic twins are below the diagonal.

+P<.0001.

ing in an RR for MD given ever smoking of 0.96 (95% CI, 0.59 to 1.42). Figure 1, bottom right, shows the RR for a lifetime history of MD given a history of ever smoking in the entire sample and in DZ and MZ twin pairs discordant for ever smoking.

The causal model fitted the data poorly (x^2=6.49, df=2, P<0.05, AIC=2.49). While the noncausal family environment model explained the results relatively well (x^2=1.81, df=2, P not significant, AIC=2.19), the noncausal genetic model fitted the data almost perfectly (x^2=0.03, df=2, P not significant, AIC=3.97). The AIC indicated that the noncausal genetic model best explained the results.

The Risk Factor Family History

Does MD Cause Smoking?—Applying the risk factor family history method, the probability of ever smoking increased as a function of the family history for MD in individuals with and without a personal history of MD (Fig 2, bottom left). Controlling for age, education, and a twin’s personal history of MD, the twin’s probability of ever smoking was significantly predicted by their family history of MD (x^2=8.24, df=1, P=0.004).

Does Smoking Cause MD?—In both never-smokers and ever-smokers, the lifetime prevalence of MD increased as a function of the number of relatives who were ever-smokers (Fig 2, bottom right). Controlling for the twin’s age, education, and personal level of smoking, risk for lifetime MD was additionally predicted by her family history of smoking (x^2=11.85, df=1, P=0.0006).

A Bivariate Twin Analysis of Smoking and MD

With use of our three-level categorization of smoking (never-smoker, chpper, and smoker), the multiple threshold model fit in both MZ and DZ twins (x^2=6.94 and 6.84, respectively, df=3, P not significant). Controlling for zygosity and the mean level of average lifetime smoking in the twins, twin similarity for lifetime average smoking was not significantly predicted by the similarity of childhood environment (x^2=2.06, df=1, P=0.15) or by frequency of contact as adults (x^2=2.96, df=1, P=0.09).

The correlation matrices for lifetime histories of smoking and MD in MZ and DZ twin pairs are shown in the Table. The correlations in liability in MZ twin pairs for both MD (r=.49) and smoking (r=.81) are substantially higher than those observed in DZ twin pairs (r=.23 and .54, respectively), suggesting that genetic factors play a causative role in both smoking and MD. The within-twin correlations between smoking and MD are similar in MZ twin pairs (mean, r=.27) and DZ twin pairs (mean, r=.28). The cross-twin cross-trait correlations (ie, smoking in twin 1 correlated with MD in twin 2) was substantially higher in MZ twin pairs (mean, r=.27) than in DZ twin pairs (mean, r=.19), suggesting that genetic factors play a significant role in the observed association between smoking and MD. Finally, the cross-twin cross-trait correlations between smoking and MD in MZ twin pairs (mean, r=.27) are indistinguishable from the within-individual correlations between smoking and MD (mean, r=.27). That is, in a pair of MZ twins, if you wish to predict the chances of twin 2 ever smoking, you can equally look at the history of MD in twin 1 or twin 2.

Detailed results of formal model fitting to these correlation matrices are available on request. Briefly, starting with the full model (Fig 3, top), it was possible, in turn, to set Co, a0, and r0 to zero with an improvement in the AIC. By contrast, r0 could not be set to zero or to unity without a substantial deterioration in fit. None of the other paths (a0, a1, c0, c1, or e0) could be set to zero without large deteriorations in the fit of the model. The best-fitting model, therefore, pictured in Fig 3, bottom, contained a0, a1, c0, c1, and e0. This model estimated the heritability of liability to smoking and MD to be 55% and 48%, respectively. Common environment accounts for 22% of the variance in liability to smoking but none for MD. The association between smoking and MD in the model is entirely the result of correlated genetic factors with the correlation estimated at r=.56.

COMMENT

We sought in this article to quantify the association between average lifetime smoking and MD in women and to gain insight into its etiology. Our major results are reviewed below.

Sample

In a population-based sample of female Virginia twins, although younger than most previous population cohorts studied for smoking, the rates of smoking were very similar to that reported in adult females in the southern United States by the National Health Survey. Our lifetime and 1-year prevalence rates for MD, diagnosed according to DSM-III-R criteria, of 9.8% and 31.5%, respectively, is somewhat higher than that found in most, but not all, previous epidemiologic surveys in women.

The Association Between Smoking and MD

Average levels of cigarette consumption were, in our data, strongly associated with the lifetime prevalence rate for MD. The relationship with MD was found across the entire spectrum of smoking behavior. That is, ever-smokers had substantially higher rates of MD than did never-smokers, and heavy ever-smokers had higher rates of MD than light ever-smokers. Our results are qualitatively similar to those of the two previous epidemiologic surveys that assessed lifetime prevalence of MD by personal structured psychiatric interviews. In particular, our results are consistent with those of Breslau et al, who found that the RR for MD increased with increasing levels of nicotine dependence. Our study is the first published report, to our knowledge, to document a strong association between smoking and future episodes of MD.

We also examined the extent to which the relationship between smoking and MD might be mediated by other psychiatric disorders. Similar to the results of Glassman et al and Breslau et al, we found that controlling for a lifetime history of either alcohol dependence or anxiety disorders only modestly reduced the observed association between smoking and MD.

The Causal Relationship Between Smoking and Depression

We sought to evaluate three hypotheses regarding the causal relationship between ever smoking and lifetime prevalence of MD: MD causes smoking, smoking causes MD, and both are caused by a third factor. Results of the cotwin control design suggested that smoking did not cause MD and that MD did not cause smoking. Our results
in discordant MZ twin pairs was striking: in twins discordant for a history of MD, there was no observed association between MD and ever smoking. In MZ twin pairs discordant for ever smoking, there was no association between ever smoking and MD. Because of the limited sample size of discordant twin pairs, the results of the cotwin control method were statistically consistent with either the noncausal family environment or the noncausal genetic model, although the fit of the latter model was clearly superior.

The risk factor family history method also indicated that the relationship between ever smoking and lifetime MD could not result entirely from a direct causal relationship between MD and ever smoking or vice-versa. Taking account of the personal history of smoking or MD, a family history of MD predicted the probability of smoking and a family history of smoking predicted the prevalence rate for MD.

Twin model fitting on the entire sample provided the most powerful method to determine the source of the association between ever smoking and lifetime MD. The best-fitting bivariate model indicated that this association could be entirely explained by a correlation between the genetic liability to ever smoking and the genetic liability to MD. Although individual specific experiences appear to play a major role in the etiology of MD and a more modest role in the etiology of smoking, the two sets of environmental risk factors appear to have little in common.

These results confirm findings from the cotwin control and family history analyses in suggesting that the relationship between ever smoking and MD is not a causal one and is, instead, mediated largely or entirely through genetic factors that influence the liability to both ever smoking and MD.

In accord with previous twin and family studies (A.C.H., R. Cates, N. G. Martin, J. Meyer, J. K. Hewitt, M.C.N., and L.J.E., unpublished data), we also found that the liability to ever smoking was powerfully influenced by genetic factors. Common environmental factors, which may have been extramendal (eg, social class or adolescent peer group) or familial (eg, parental attitudes toward smoking, transmitted culturally to their offspring), were also important for ever smoking. The results of our twin analysis of smoking and MD were unlikely biased by violations of the equal environment assumption, as we found no relationship between the similarity of childhood or adult environment and the twin similarity for smoking or MD.

Implications

Our findings suggest a genetically influenced common physiologic substrate for the predisposition to MD and to ever smoking. Although much uncertainty remains about the biologic processes involved in smoking and MD, nicotine is known to have strong effects on both central acetylcholine and catecholamine systems, which may play a role in the etiology of MD. Furthermore, smoking affects brain regions that influence mood and well-being. Genetic variation in certain brain neurotransmitter systems may influence both the probability of smoking, by affecting the self-reinforcing properties of nicotine, and the probability of MD. Alternatively, genetic factors might influence personality traits that in turn alter the risk both for smoking and MD.

Limitations

These results should be interpreted in the context of four potential limitations. First, these results apply only to women who, compared with men, have lower rates of smoking and higher rates of MD. Gender differences may exist in the causal relationship between smoking and MD.

Second, our assessment of smoking behavior was by self-report. When validated against reports by other relatives, or against serum or saliva cotinine values, self-report measures have been found to be relatively reliable.

Third, our analyses focused on a single relatively crude measure of smoking behavior: average lifetime cigarette consumption. Smoking behavior is a complex phenomenon, and our results might have differed had we separately examined patterns of smoking initiation, smoking cessation, or nicotine dependence. Our inability to examine the relationship between smoking cessation and MD means that smoking cessation could have precipitated MD in a modest subgroup of smokers, and this pattern remained undetected in our data.

Fourth, the test of our two causal hypotheses with use of the cotwin control method (MD causes smoking or smoking causes MD) were not independent but relied on an overlapping set of twins discordant for both traits.

This work was supported by grants MH-40828, AA-07728, and DA-05588 from the US Alcohol, Drug Abuse, and Mental Health Administration. The Virginia Twin Registry, established and maintained by W. Nance, MD, PhD, and L. Corey, PhD, is supported by National Institutes of Health grants HD-26746 and NS-25630.

J. Myers, MS, assisted in the data analysis.

References


Arch Gen Psychiatry—Vol 50, January 1993

Smoking and Major Depression—Kendler et al
35. Neale MC. Statistical Modeling: With Mr. Richmond, Va: Department of Human Genetics, Medical College of Virginia, Virginia Commonwealth University; 1991.