Research Article

DEPRESSION AND SMOKING: A 5-YEAR PROSPECTIVE STUDY OF PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Background: *Major depressive disorder (MDD) and smoking are major public health problems and epidemiologically strongly associated. However, the relationship between smoking and depression and whether this is influenced by common confounding factors remain unclear, in part due to limited longitudinal data on covariation.* **Methods:** *In the Vantaa Depression Study, psychiatric out- and inpatients with DSM-IV MDD and aged 20–59 years at were followed from baseline to 6 months, 18 months, and 5 years. We investigated course of depression, smoking, and comorbid alcohol-use disorders among the 214 patients (79.6% of 269) participating at least three time points; differences between smoking versus nonsmoking patients, and covariation of MDD, smoking, and alcohol-use disorders.* **Results:** *Overall, 31.3% of the patients smoked regularly, 41.1% intermittently, and 27.6% never. Smokers were younger, had more alcohol-use disorders and Cluster B and C personality disorder symptoms, a higher frequency of lifetime suicide attempts, higher neuroticism, smaller social networks, and lower perceived social support than never smokers. Smoking and depression had limited longitudinal covariation. Depression, smoking, and alcohol-use disorders all exhibited strong autoregressive tendencies.* **Conclusions:** *Among adult psychiatric MDD patients, smoking is strongly associated with substance-use and personality disorders, which may confound research on the impact of smoking. Rather than depression or smoking covarying or predicting each other, depression, smoking, and alcohol-use disorders each have strong autoregressive tendencies. These findings are more consistent with common factors causing their association than either of the conditions strongly predisposing to the other. Depression and Anxiety 30:580–588, 2013.*

Key words: *major depressive disorder; tobacco smoking; personality disorders; alcoholism*

INTRODUCTION

Major depressive disorder (MDD) and smoking are epidemiologically comorbid, and both are often long-standing disorders with recurrences and relapses. Tobacco smoking is a risk factor for more than 50 diseases,

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20 of which are fatal.[1] Numerous cross-sectional and some longitudinal studies have reported an association between smoking and major depression.[2–11] Smoking has also been associated with recurrence and even suicidal behavior in depressive subjects.[12–15]

However, the relationship between smoking and depression is complex, and contradictory hypotheses and evidence for causality exist. Smoking appears to increase the risk of depression approximately twofold[16,17] However, a self-medication hypothesis of depression causing smoking is supported by studies showing that smoking cessation results in depression,[18–20] and depressive mood is usually part of the nicotine withdrawal syndrome.[21,22] Smokers with a history of major depression who attempt to quit smoking are at a higher risk of failure than nondepressed smokers.[3,23] The risk remains high for at least 6 months. [23] According to more recent studies, long-term successful cessation of smoking might protect from depression.[10,24–26] A systematic review of longitudinal studies in younger nonclinical cohorts found a bidirectional association between nicotine dependence and depression, and recommended for future research (a) shorter intervals between surveys with longer follow-ups, (b) more accurate measurement of depression, and (c) adequate control of confounding factors.[27]

However, there is also a possibility of common third factors influencing the association between smoking and depression. These consist of genetic factors[4,5] or other confounding factors associated with both MDD and smoking, such as alcohol-use disorders,[6,28] other comorbid factors, or personality traits, including neuroticism or extraversion, hostility, alienation, aggression, novelty seeking, or lower agreeableness, conscientiousness, self-discipline, and constraint.[29,30] Cigarette smoking and weekly alcohol abuse seem to be risk factors for major depressive episode (MDE) in the general population.[31] The prevalence of smoking among alcohol-dependent people has been found to be three- to fourfold that of the general population, with about 80–95% reporting smoking.[32] Furthermore, a dose–response relationship between number of cigarettes smoked and amount of alcohol consumed has been reported.[6] In the NESARC study, over one-fifth of patients with current nicotine dependence had concurrent alcohol-use disorder, mood disorder, and anxiety disorder, and nearly one third had any current personality disorder.[33] In a Finnish study, the overall prevalence of smoking was 22.2% in the general population, but 47.5% among patients with current alcohol dependence.[34]

There is a lack of prospective, longitudinal studies with repeated measurements investigating the temporal relationship of smoking, depression, and confounding factors in patients with MDD, carefully diagnosed by semistructured interviews. In this prospective long-term study, our aim was to compare the characteristics of smoking and nonsmoking psychiatric MDD patients and to investigate the covariation of MDD, smoking, and comorbid alcohol-use disorders, the latter a likely confounding factor. We hypothesized that smoking would be associated with comorbid alcohol-use disorder, and as a consequence of this, also with personality disorders, suicidal behavior, temperamental factors (high neuroticism), and poor social support.

METHOD

The Vantaa Depression Study (VDS) is a collaborative depression research project between the Mood, Depression, and Suicidal Behavior Unit of the National Institute for Health and Welfare, Helsinki, Finland, and the Department of Psychiatry of Helsinki University Central Hospital (HUCH) at Peijas Hospital, which provides secondary care psychiatric services to all residents of Vantaa (169,000 inhabitants in 1997). The Ethics Committee of Helsinki University Central Hospital (HUCH) approved the study protocol. The background and methodology of VDS have been reported in detail elsewhere.[35–37]

SCREENING AND BASELINE EVALUATION

In the *first phase* of the study, 806 psychiatric subjects aged 20–59 years were screened for the presence of depressive symptoms during an 18-month period starting from February 1, 1997. Of the 703 eligible subjects, 542 (77%) agreed to participate and gave their written informed consent after the procedure had been fully explained.[35] In the *second phase*, a researcher using the WHO SCAN 2.0[38] interviewed these consenting patients, 269 of whom were subsequently diagnosed as having DSM-IV MDD and included in the study. All baseline interviewers received relevant training by a WHO-certified training center; this was supervised by the last author (ETI). Diagnostic reliability was investigated using 20 videotaped diagnostic interviews; the κ coefficient for MDD was 0.86 (0.58–1.0), with a 95% agreement rate. The Structured Clinical Interview for DSM-III-R personality disorders (SCID-II) was used to assess diagnoses on axis II.[39] The baseline measurements included the 17-item Hamilton Depression Rating Scale (HAM-D),[40] 21-item Beck Depression Inventory (BDI),[41] Beck Anxiety Inventory (BAI),[42] Beck Hopelessness Scale,[43] Scale for Suicidal Ideation,[44] Social and Occupational Functioning Assessment Scale (SOFAS) of DSM-IV,[45] Social Adjustment Scale Self-Report,[46] Interview for Recent Life Events,[47] Interview Measure of Social Relationships,[48]Perceived Social Support Scale-Revised,[49] and Eysenck Personality Inventory.[50] In addition, the number of chronic medical disorders (axis III) was investigated with a checklist. Only current comorbidities within a time frame of 1 month were recorded. At baseline, the majority of patients were female (73%) and outpatients (83%), half (50%) were married or cohabiting, and 60% were currently employed with a mean age of 39.6 years. Most (79%) of the patients had at least one comorbid disorder, and the majority (54%) two or more. Over half (57%) had an anxiety disorder, one-quarter (25%) alcohol abuse or dependence, and nearly one-half (44%) at least one personality disorder diagnosis.[35]

FOLLOW-UP

After baseline, subjects were investigated at 6 months, 18 months, and 5 years. Of the 269 subjects with current MDD initially included in the study, 229 participated in the 6-month follow-up, 207 in the 18-month follow-up, and 182 in the 5-year follow-up. Patients' consent was obtained. All available medical and psychiatric records were used to complement the interview data. The average duration of follow-up interviews was 2–3 hr, and they were conducted in psychiatric outpatient units. After baseline assessments, the subjects were prospectively followed up with a life-chart, and BDI was rated monthly until 6 months; the outcome of MDD and comorbid disorders was then investigated at 6 and 18 months by repeated SCAN 2.0 and SCID-II

interviews. In the 5-year follow-up interviews, we used SCID-I (for DSM-IV-TR)[51] instead of SCAN 2.0. All observer and self-report scales were included at follow-up assessments. The diagnoses and timing of depressive episodes were based on these structured interviews and patient records—a graphic life-chart was created after reviewing with the subject all information from the follow-up period. The life-chart was based on DSM-IV criteria and definitions; time after the first baseline interview was divided into periods of full remission, partial remission, and MDE.[36]

The information on smoking behavior was based on self-reported information at the follow-up interviews, using a scale with the following response items: the patient (1) has never smoked, (2) has quit smoking, (3) has smoked occasionally, or (4) has smoked regularly. The number of cigarettes per day was recorded. We required that information of smoking status from at least three follow-up interviews would be available. Thus, information on 214/269 patients (79.6%) was included in the analyses of smoking behavior and depression. Those dropping out from the analyses were subjects who did not participate in any follow-up ($n = 20$) or with information on smoking from only one or two time points. Over the 5-year follow-up, 29 subjects were diagnosed with bipolar disorder, one with schizophrenia, and two with schizoaffective disorder; they remained in the cohort until censored at change of diagnosis.

STATISTICAL ANALYSIS

Subjects who smoked regularly or intermittently during follow-up were first compared with nonsmoking subjects. Chi-square tests with Yates' continuity correction or Fisher's exact test were used as appropriate. Normally distributed continuous variables were analyzed by the two-sample *t*-test or by ANOVA test, and nonnormally distributed using the Mann–Whitney and Kruskal–Wallis tests. After univariate analyses, we omitted the statistically nonsignificant variables ($P > .05$) from the analyses, and chose variables to our models from different domains of risk factors, for example, sociodemographic features, out- or inpatient status, clinical features of MDD, symptom and functional ability scales, axes I and II comorbid disorders, number of axis III disorders, MDD subtype features, and various psychosocial and personality factors. The analyses were adjusted for age and gender. Multivariate methods were used to control for possible confounding factors, and these analyses constitute our main findings. The Predictive Analytics Software PASW statistics 18.0 (SPSS Inc., Chicago, IL) was used.

In discriminant analyses, we looked for a linear combination of predictor variables that would maximally separate two groups of interest (never smoked, has smoked) from one another. These linear combinations are called discriminant functions. In many ways, this method is "a mirror image" of a logistic regression analysis. The linear combination is created, by the discriminant analysis algorithm, such that it distinguishes smokers from nonsmokers in a maximally efficient manner. The variables for the discriminant analysis were selected using a stepwise method; by adding one by one variables that have discriminatory power.[52]

The relationships between smoking, alcohol-use disorders, and depression were estimated in both directions in a *multivariate autoregressive path model*. The goal was to examine the correlational structure of these variables over time. The analysis (1) took into account the autoregressive patterns in all three variables, and (2) also examined the cross-variable associations at all four time points. Alcohol-use disorders were operationalized as a categorical variable. Two alternative operationalizations were used for depression: (1) HAM-D and (2) a three-category ordinal variable (full remission, partial remission, and MDE from the life-chart). Smoking was also operationalized in two alternative manners: categorical (not smoking, smokes occasionally, and smokes regularly) and ordinal (number of cigarettes per day) at each time point. Whenever the predicted variable in a regression equation was categorical, the relationship between the predictor and the predicted variable was interpreted as a logistic regression. For instance, the path from alcohol-use disorders (baseline) to alcohol-use disorders (6 months) was a logistic regression. Whenever the predicted variable in a regression equation was ordinal, the relationship between the predictor and the predicted variable was interpreted as an ordinal (or cumulative logistic) regression. For instance, the path from alcohol-use disorders (6 months) to depression (6 months) was an ordinal regression when the three-category ordinal depression variable was used. When the HAM-D measure for depression was used, this path was interpreted as a classical regression path. Age and sex were controlled from all variables in the model, but they were omitted from the graphical depiction of the path model for clarity of presentation. Robust maximum likelihood (MLR) estimation was used for all models. This estimator is robust to non-normality of observed variables and produces unbiased confidence intervals and overall fit statistics. Because there are categorical (ordinal) dependent variables in the models, model estimation required the use of numerical Monte Carlo integration. Mplus 5.21 was used to estimate the models.[53]

RESULTS

Information on 214 (79.6%) of the 269 patients was included in the analyses. Over the 5-year follow-up, 31.3% (67/214) of the patients smoked regularly, 41.1% (88/214) had intermittent smoking behavior, and 27.6% (59/214) had never smoked. Of patients not smoking at baseline (50.9%, 109/214), 10 (9.2%, 10/109) began to smoke, and of patients initially smoking regularly (39.7%, 85/214), 10 (11.8%, 10/85) quit smoking during the follow-up.

SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Compared with nonsmoking patients, patients smoking regularly had a lower age at onset, and more often comorbid alcohol-use disorders, Cluster B and C personality disorder symptoms, higher HAM-D score, higher SOFAS score, smaller social network, lower perceived social support, higher neuroticism, and had more often attempted suicide prior to baseline. In addition, there was a nonsignificant tendency of younger age (Table 1).

DISCRIMINANT ANALYSES

In discriminant analyses, we compared the characteristics of patients who had never smoked with those who had smoked at some point (regular or intermittent smokers). According to these analyses, smoking patients were younger, more likely to suffer from an alcohol disorder at baseline, exhibited a greater number of Cluster B and C symptoms, had a higher frequency of lifetime suicide attempts, higher neuroticism, smaller networks, and lower perceived social support than nonsmokers (Table 2). All of these variables had at least a moderate correlation in the discriminant function, but alcohol disorder at baseline and Cluster B and C personality disorders had the highest correlations (Table 3). Predicting group membership based on the discriminant function correctly classified 66.5% of the cases.

TABLE 1. Baseline patient characteristics and smoking status during a 5-year follow-up in the Vantaa Depression Study ($n = 214$)

Smoking status	Never smoker	Intermittent smoker	Regular smoker	
	n (%)	*n* (%)	*n* (%)	
Characteristic	59 (27.6)	88 (41.1)	67 (31.3)	*P*-value
Sociodemographic factors				
Female	46 (78.0)	62 (70.5)	50 (74.6)	.588
Married or cohabiting	31 (52.5)	49 (55.7)	36 (53.7)	.928
Employed	32 (56.1)	61 (70.1)	39 (60.9)	.207
Professional education	23 (39.0)	36 (40.9)	25 (37.3)	.901
Low income	27 (51.9)	48 (59.3)	32 (52.5)	.622
Outpatient	49 (83.1)	79 (89.8)	51 (76.1)	.074
MDD subtype				
Melancholic	20 (33.9)	32 (36.4)	27 (40.3)	.751
Atypical	5 (8.5)	11 (12.5)	4 (6.0)	.370
Psychotic	4 (6.8)	6 (6.8)	4 (6.0)	.974
Axis I comorbidity				
Dysthymia	6 (10.2)	7 (8.0)	9 (13.4)	.538
Any anxiety disorder	35 (59.3)	51 (58.0)	33 (49.3)	.444
Phobic anxiety disorder	24 (40.7)	38 (43.2)	25 (37.3)	.762
Panic disorder with/without agoraphobia	3 (5.1)	6 (6.8)	5 (7.5)	.857
	6 (10.2)	8 (9.1)	5 (7.5)	.864
Agoraphobia	10 (16.9)	9 (10.2)	4 (6.0)	.136
Social phobia	11 (18.6)	16 (18.2)	11 (16.4)	.939
Specific phobia	14 (23.7)	26 (29.5)	17 (25.4)	.708
OCD	2 (3.4)	7 (8.0)	3 (4.5)	.444
GAD	10 (16.9)	8 (9.1)	10 (14.9)	.331
Alcohol-use disorder	5 (8.5)	19 (21.6)	24 (35.8)	.001
Abuse	3 (5.1)	11 (12.5)	7 (10.4)	.326
Dependence	2 (3.4)	8 (9.1)	17 (25.4)	<.001
Axis II comorbidity				
Any personality disorder	19 (32.2)	43 (48.9)	31 (46.3)	.116
Cluster A	8 (13.6)	20 (22.7)	12 (17.9)	.369
Cluster B	3 (5.1)	14 (15.9)	13 (19.4)	.056
Cluster C	12 (20.3)	35 (39.8)	21 (31.3)	.046
Clinical factors				
Suicide attempt prior to baseline	13 (22.0)	26 (29.5)	40 (52.2)	.001
Suicide attempt during follow-up	8 (13.6)	10 (11.4)	12 (17.9)	.505
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	*P*-value
Sociodemographic factors				
Age	43.7 (11.4)	39.3 (11.5)	40.2 (9.6)	.052
Clinical factors				
Age at onset	36.6 (13.5)	30.9 (12.4)	30.4 (11.8)	.006
No. of episodes prior to baseline	1.9 (3.4)	1.6 (2.4)	1.8 (2.9)	.838
HAM-D	18.7 (6.4)	18.4 (6.0)	20.9 (5.6)	.027
BDI	25.5 (8.8)	27.6 (7.7)	28.8 (8.3)	.083
BAI	20.2 (10.3)	22.7 (10.1)	22.3 (11.5)	.360
Hopelessness	9.1 (4.4)	10.6 (4.7)	10.2 (4.5)	.147
Suicide ideation	5.3 (7.8)	6.3 (7.5)	6.5 (8.3)	.639
SOFAS	52.1 (10.9)	54.2 (10.3)	49.7 (10.5)	.032
No. of recurrences	1.6 (1.5)	1.8 (1.8)	1.9 (1.8)	.665
Time spent in MDEs	9.4 (11.9)	12.0 (15.2)	9.7 (11.3)	.443
Comorbidity				
No. of axis I disorders	1.0 (0.9)	0.8 (0.9)	1.0 (1.0)	.416
Cluster A symptoms	1.9 (2.3)	2.5 (2.9)	2.8 (2.5)	.195
Cluster B symptoms	2.3 (2.6)	3.4 (3.3)	4.6 (4.1)	.001
Cluster C symptoms	4.6 (3.5)	6.7 (5.0)	6.4 (4.2)	.016
No. of psychiatric disorders	2.6 (1.6)	3.2 (1.8)	3.2 (1.9)	.122
No. of somatic disorders	0.9 (1.5)	0.6 (1.1)	0.3 (0.5)	.014
No. of psychiatric and somatic disorders	3.5 (2.2)	3.7 (2.2)	3.5 (2.1)	.669

TABLE 1. Continued

	Mean (SD)	*Mean (SD)*	*Mean (SD)*	*P*-value
Psychosocial and personality factors				
Perceived social support	42.9 (11.3)	37.5 (13.1)	38.9 (13.0)	.040
Size of social network	8.7 (3.7)	8.0 (3.6)	6.2 (3.0)	<.001
Neuroticism[a]	12.2 (4.9)	15.0 (5.4)	13.0 (5.7)	.010
Extraversion[a]	10.9 (4.2)	11.3 (5.7)	11.9 (4.3)	.412
Adverse life events[b]	7.7 (4.6)	8.1 (4.7)	9.2 (4.5)	.163

Statistical methods:
Categorical variables: Chi-square test with Yates' continuity correction, or Fisher's exact test when the expected cell count was less than 5.
For continuous variables: ANOVA for normal distribution, and Mann–Whitney and Kruskal–Wallis tests for nonnormal distribution.
[a]Eysenck Personality Inventory: for dimensions of neuroticism and extraversion (at lowest HAM-D).
[b]Interview for Recent Life Events: objective measure of negative impact of adverse life events.
MDE, major depressive episode; HAM-D, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; SOFAS, Social and Occupational Functioning Assessment Scale.

COVARIATION OF LEVEL OF DEPRESSION AND SMOKING

Smoking and depression had only limited covariation (Fig. 1). According to autoregressive models, level of depression, smoking, and also alcohol-use disorders all exhibit a strong autoregressive component; depressive symptoms, alcohol-use disorders, and smoking at $t + 1$ were each best predicted by the respective variable at t, for example, they predicted significantly themselves at the subsequent follow-up stage. We modeled smoking as the (self-reported) number of cigarettes smoked per day. This was measured at each time point. Alcohol-use disorder predicted the level of depression at all follow-up stages. The path from smoking to depression was significant at baseline, and at 5 years. A packet of cigarettes per day and alcohol abuse reflected in the relative sizes the same effects of topical depression symptoms: 2 points and 3 points in HAM-D. Error term arrows were added to those endogenous variables, which had one (depression and smoking). The equations, where alcohol-use disorder was the dependent variable, were logistic regressions, which did not have an error term. Although depression and smoking had limited covariation, that of smoking and alcohol-use

TABLE 2. Univariate mean comparison of smokers and nonsmokers during the 5-year follow-up ($n = 214$)

	Smoking					
	No			Yes		
		95% CI			95% CI	
	Mean	Lower	Upper	Mean	Lower	Upper
Age	**43.69**	**40.74**	**46.65**	**39.70**	**37.98**	**41.42**
Female	0.78	0.67	0.89	0.72	0.65	0.79
Duration of illness	6.76	4.23	9.29	9.03	7.39	10.68
HAM-D	18.66	17.01	20.32	19.52	18.56	20.48
Anxiety disorder	0.59	0.46	0.72	0.54	0.46	0.62
Alcohol-use disorder	**0.08**	**0.01**	**0.16**	**0.28**	**0.21**	**0.35**
No. of Cluster A personality disorder symptoms	1.97	1.37	2.56	2.65	2.21	3.09
No. of Cluster B personality disorder symptoms	**2.34**	**1.66**	**3.01**	**3.91**	**3.31**	**4.51**
No. of Cluster C personality disorder symptoms	**4.63**	**3.71**	**5.55**	**6.56**	**5.81**	**7.32**
Melancholic depression	0.34	0.21	0.46	0.38	0.30	0.46
Lifetime suicide attempt	**0.29**	**0.17**	**0.41**	**0.46**	**0.38**	**0.54**
Lifetime single/recurrent MDEs	1.83	1.73	1.93	1.76	1.69	1.83
Lifetime number of MDE's	3.88	3.00	4.76	3.65	3.17	4.12
Proportion of time depressed during follow-up	0.18	0.12	0.24	0.26	0.22	0.30
Married or cohabiting	0.53	0.39	0.66	0.55	0.47	0.63
Employed/unemployed	0.56	0.43	0.69	0.66	0.59	0.74
Neuroticism (at lowest HAM-D)	12.76	11.37	14.15	14.08	13.24	14.92
Professional education	0.39	0.26	0.52	0.39	0.31	0.47
Size of social network	**8.71**	**7.74**	**9.68**	**7.28**	**6.72**	**7.84**
Extraversion (at lowest HAM-D)	10.83	9.71	11.95	11.30	10.59	12.00
Perceived social support	**42.90**	**39.95**	**45.84**	**38.14**	**36.04**	**40.23**

Boldface font indicates a statistically significant difference between groups.

TABLE 3. Multivariate discriminate analysis of smoking status during the 5-year follow-up ($n = 214$)

Variable	Coefficient[a]	Correlation[b]
Age	– .406	–432
Alcohol-use disorder	.400	.544
No. of Cluster B personality disorder symptoms	.188	.534
No. of Cluster C personality disorder symptoms	.168	.508
Lifetime suicide attempt	.289	.422
Neuroticism (at lowest HAM-D)	.196	.301
Size of social network	– .234	– .473
Perceived social support	– .309	– .422

[a]Standardized canonical discriminant function coefficients.
[b]Overall correlations with the discriminant function in descending order.

disorders needed to be elaborated. At baseline, nearly 70% (35/54) of patients with alcohol-use disorder were regular smokers, compared with 33% (59/177) of patients without an alcohol problem. The contemporaneous correlations of alcohol-use disorders and smoking at baseline are significant, but just moderately (0.25). From the point of view of estimating model parameters, this correlation (not the percentages) is more relevant. This is true not just for the baseline, but for the other time points as well. Thus, the contemporaneous correlation between smoking and alcohol-use disorders did not create any notable problems in the analyses.

DISCUSSION

The aim of this study was to examine the long-term associations between smoking behavior and depression among psychiatric MDD patients and to investigate the covariation of tobacco smoking and MDD with comorbid alcohol-use disorder as a potential confounding factor. Smoking in our cohort of MDD patients was very prevalent; only one-fourth of subjects had never smoked. Smoking patients differed from nonsmoking patients with regard to age, alcohol-use disorders, personality disorders, lifetime suicide attempts, personality factors, and social support. The level of depression and smoking did not covary during the follow-up, they both had an independent course.

Our study has several strengths. To our knowledge, no previous long-term clinical study has investigated variations in the prevalence of smoking behavior in MDD patients or the covariation of tobacco smoking and MDD. We examined the aforementioned, also accounting for covariation with comorbid alcohol-use disorder, a major confounding factor. There are few long-term (up to 5 years) prospective studies of cohorts of patients with MDD and even fewer representative cohorts of outpatients (83% in our study). Two thirds of all depressed subjects in the city of Vantaa were treated (within the facilities investigated) at the time of the study.[54] For all patients, information on smoking was available from three or four phases of the longitudinal follow-up. The level of depression and the presence of comorbid disorders were investigated with semistructured interviews at each follow-up. The level of attrition was fairly low, as 79.6% (214/269) of the initial cohort contributed to this prospective study. Our evaluation methods included a wide range of predictors; we investigated associations of smoking with factors from different domains, including sociodemographic, clinical, comorbidity axes I–III, and temperamental/personality factors, and we also had information on the duration and outcome of depression.

Nonetheless, our study also had some limitations. The cohort consisted of depressive psychiatric patients, mostly outpatients, all suffering from MDD at baseline, which influences the generalizability of our findings. Despite a low level of attrition, we had prospective information from varying lengths of patients' follow-up. Two

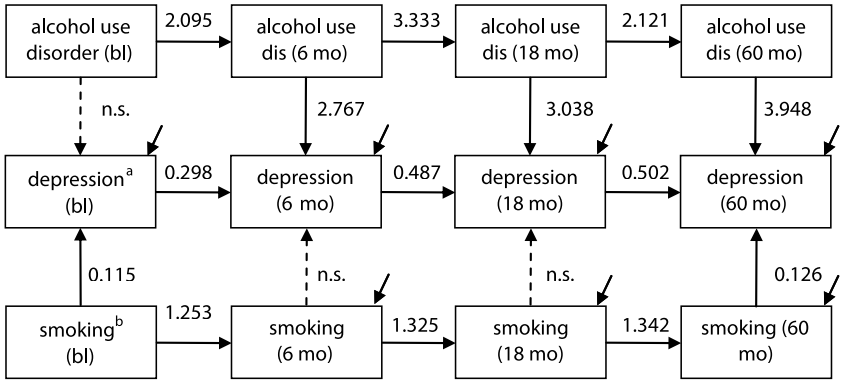

Figure 1. Autoregressive path model of depression, smoking, and alcohol abuse.
Note: **Unstandardized coefficients are shown (standardized coefficients are not available because there are categorical endogenous variables).**
[a]Hamilton Depression Rating Scale score.
[b]Number of cigarettes per day (zero or a positive integer, modeled in the Mplus analysis as a continuous variable censored from below).

thirds of the patients participated in the 5-year interview. Smoking behavior being ascertained by means of self-reported information is also a limitation. We did not use Fagerström's questionnaire[55] on nicotine dependence, nor did we have information on plasma cotinine concentrations. However, we did collect information of smoking behavior, including number of cigarettes smoked, at three to four time points during the follow-up. Furthermore, our investigation of covariation and autoregression was limited to three factors, and covariation with other possible confounding factors was not investigated. Finally, we studied an adult psychiatric cohort; as people usually start smoking before adult age, this sets limits to the generalizability of our findings.

Smoking in our cohort of MDD patients was prevalent, as nearly one third of patients smoked regularly during follow-up, two-fifths smoked intermittently, and only about one-fourth had never smoked. In another major cross-sectional MDD outpatient study, nicotine dependence was the most frequent lifetime individual disorder (38.2%) and the second most frequent current disorder (27.3%).[56] The prevalence of smoking among depressed patients was also markedly higher than in the Finnish general population, in which the prevalence was 22.2% in the Health 2000 Study.[34] In our study, smoking and nonsmoking MDD patients differed markedly in some of their characteristics. Compared with nonsmokers, regularly smoking patients had over four times more often alcohol-use disorders at baseline, nearly two times more Cluster B personality disorder symptoms, 1.5 times more Cluster C symptoms, and had attempted suicide 1.3 times more often. In addition, they were on average 3 years younger, had higher neuroticism, smaller social networks, and lower perceived social support than nonsmokers. Of these factors, alcohol-use disorder at baseline and Cluster B and C personality disorders had the highest correlations with smoking. These findings were, to the extent that they have been studied, in line with previous research. The association between alcohol-use disorders and smoking, found in numerous studies of MDD patients and the general population, is likely due at least in part to common genetic mechanisms.[57] In our earlier medium-term study, MDD patients with comorbid alcoholism or personality disorders also perceived less social support.[58] Previous studies have investigated mainly the association of personality traits, but less often comorbid personality disorders, with smoking. Current smokers have generally had higher levels of negative emotionality and less behavioral consistency than former smokers and those who have never smoked.[59] Previous reports have also demonstrated a connection between smoking and higher neuroticism, lower extraversion, aggression, and lower sociability and constraint.[30,60,61] However, in the general population, the prevalence of personality disorders among smoking individuals has also been observed to be high.[33] We found a similar strong association between smoking and personality traits or disorders among patients with depression. Of these, Cluster C personality disorders have been associated with a more chronic outcome of MDD [37] and Cluster B personality disorders also with alcohol-use disorders. According to our analyses, smoking patients also had a higher frequency of lifetime suicide attempts. Previous studies have reported a positive association between suicide and smoking status.[12–15] However, the nature of this association remains unclear. It is likely that it is partly or completely explained by confounding factors such as substance-use or Cluster B personality disorders. In our earlier study investigating risk factors for suicidal behavior, we found no independent association with smoking.[62] As smoking in MDD patients is strongly associated with several clinically significant characteristics, which themselves are predictors of adverse outcome, there is considerable risk of such confounding affecting the findings and leading to false attributions to impact of smoking per se.

To our knowledge, no previous clinical study has investigated covariation of depression and smoking in long term. Among patients who are initially depressed, smoking itself does not seem to increase their probability of remaining depressive in the future. Thus, the idea of smoking itself being depressogenic is not supported by our results, at least not in subjects who, for whatever reason, are already depressed. The proportion of smoking patients did not increase during follow-up, as less than 10% of patients began smoking after baseline, and a similar proportion quit. Smoking and depression had only limited covariation: the level of depression and smoking did not go hand in hand during follow-up. Thus, our findings do not support the self-medication hypothesis, which we tested in terms of association between smoking and clinical depression; this does not necessarily pertain to all possible aspects of emotional self-regulation. According to autoregressive models, level of depression, smoking, and also alcohol-use disorders exhibited strong autoregressive tendencies, each having an independent course over time. Overall, our findings provide support for neither smoking causing depression nor depression causing smoking, but are consistent with other factors causing their co-occurrence.

In conclusion, among adult psychiatric MDD patients, smoking is associated with several important clinical characteristics (particularly substance-use disorders) and personality factors (personality disorders and neuroticism), which may markedly confound research on the impact of smoking. Rather than depression or smoking covarying or predicting each other, depression, smoking, and alcohol-use disorders each have strong autoregressive tendencies. These findings are more consistent with common factors causing their association than depression resulting in increased smoking or smoking inducing depression.

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