Smoking and the course of anxiety and depression

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CHAPTER 3

Association of Smoking and Nicotine Dependence with Severity and Course of Symptoms in Patients with Depressive or Anxiety Disorder

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Abstract

Background. *Previous research has indicated a strong association of smoking with depression and anxiety disorders, but the direction of the relationship is uncertain. Most research has been done in general population samples. We investigated the effect of smoking and nicotine dependence on the severity and course of depressive and anxiety symptoms in psychiatric patients.*

Methods. *Data came from the Netherlands Study of Depression and Anxiety (NESDA) including participants with a current diagnosis of depression and/or an anxiety disorder (N=1,725). The course of smoking status and symptoms of depression, general anxiety, social anxiety, and agoraphobia were measured at baseline and after one and two years. Age, gender, education, alcohol use, physical activity, and negative life events were treated as covariates.*

Results. *At baseline, the symptoms of depression, general anxiety, and agoraphobia were more severe in nicotine-dependent smokers than in never-smokers, former smokers, and non-dependent smokers. These differences remained after adjusting for covariates. Smaller differences were observed for severity of social anxiety which were no longer significant after controlling for covariates. Over a two-year follow-up, the improvement of depressive and anxiety symptoms was slower in nicotine-dependent smokers than in the other groups even after controlling for covariates. There were no differences between the groups in the course of symptoms of social anxiety and agoraphobia over time.*

Conclusions. *In psychiatric patients, smoking is associated with higher severity of depressive and anxiety symptoms, and with slower recovery, but only when smokers are nicotine-dependent.*

Introduction

The relationship of smoking and nicotine dependence with depression[1-5] and anxiety disorders[6-10] has been well-established in epidemiological research. Cross-sectional studies have indicated an elevated level of depressive and anxiety symptoms in smokers than in never- and former smokers[3, 4, 8, 10-17]. Furthermore, successful quitters have fewer depressive symptoms and lifetime depression and anxiety diagnoses than unsuccessful quitters and current smokers[18]. However, smokers meeting criteria for major depression have a harder time quitting and are more likely to be heavy smokers[19]. The severity of symptoms is related to the number of cigarettes smoked per day or heavy smoking[13, 20, 21] and number of days smoked[12]. Further, nicotine-dependent smokers have more severe depressive and anxiety symptoms than non-dependent smokers[1, 4, 22]. Recurring depression is associated with worst smoking-related behaviours than a single episode or a history of depression. For example, smokers with recurrent episodes of major depression smoked more cigarettes, were nicotine-dependent more often and reported fewer quit attempts than never-depressed smokers. Those with a single episode were indistinguishable from the never-depressed smokers on most parameters, including lifetime cessation attempts[23]. A meta-analysis revealed that *a history* of major depression does not seem to predict the success or failure of a smoking cessation attempt[24].

Cross-sectional studies have also indicated a high prevalence of current smoking in individuals with lifetime depression, anxiety, or comorbid depression and anxiety[7, 25-30] than in the general population. Smoking prevalence is higher among severely depressed than among mildly and moderately depressed patients[31]. These associations of smoking with depressive/anxiety disorders remain even after controlling for potential confounders such as socio-demographic variables, substance use/dependence, increased work hours, social isolation, neuroticism, novelty seeking, childhood conduct problems and childhood abuse, adverse life events, parental smoking history, deviant peers, family instability and anxiety disorders[12, 15, 16, 20, 32-34].

The direction of causality of smoking-psychopathology association has not yet been fully understood[35]. Longitudinal studies have attempted to explain the mechanisms of the association by charting the timeline of smoking behaviour and depression/anxiety disorders. Several studies have demonstrated that depressive and anxiety disorders[33, 36, 37] and symptoms[38-41], and social fears and social phobia[9] increase the likelihood of starting smoking and progression to nicotine dependence[33]. These results lead to the assumption that smoking may serve as self-medication to ameliorate negative symptoms[42]. Other studies have found that smoking is a vulnerability factor in the development of depression / anxiety disorders[5, 32, 43-47]. Furthermore, nicotine-dependent smokers have more severe depressive and anxiety symptoms than non-dependent smokers in a 13-year longitudinal study[48]. Thus, these data lead to the assumption that smoking has a predictive role in the onset or increasing severity of these disorders[5]. Several longitudinal studies have found evidence for a bidirectional smoking-depression/anxiety relationship[2, 6, 48-58] in which the two conditions mutually influence each other. Finally, these co-occurring conditions may also be explained partly by common environmental[59, 60] and genetic factors[61-64]. [For further details, interested readers may refer to reviews on smoking and co-occurring depressive / anxiety disorders[65, 66].

In summary, the associations of smoking with depression and anxiety are well-established. Longitudinal studies suggest that this association is bidirectional. Moreover, the rates of depression and anxiety disorders are higher in current smokers, particularly in heavy, nicotine-dependent smokers and, comparatively lower symptoms have been observed in former smokers. Most of the studies in this area are conducted in non-clinical samples drawn from the general population or schools, and mainly focus on smoking behavior. The effect of nicotine dependence has been given relatively little research attention. Further, the majority of these studies look at sub-threshold symptoms, and not at diagnoses, of depression and anxiety disorders.

In the present study, we will examine the severity and course of depressive and anxiety symptoms over two years in smokers (non-dependent,

nicotine-dependent) and non-smokers (never-smokers, former smokers) with a current diagnosis of depressive and/or an anxiety disorder. We hypothesize that: (i) the symptoms of depression and anxiety would be more severe in nicotine-dependent smokers than in non-dependent smokers, who would have more severe symptoms than former smokers and never-smokers, and (ii) the rate of improvement of anxiety and depressive symptoms would be slower in current smokers, particularly in nicotine-dependent smokers than in never-smokers and former smokers.

Methods

Participants and Data

The data came from an on-going naturalistic cohort study, the Netherlands Study of Depression and Anxiety (NESDA), started in September 2004, and investigates the long-term course and consequences of depression and anxiety disorders. The baseline NESDA sample includes 2,981 participants (age range: 18-65 years; 66.4 % females), consisting of persons with a current depression and / or anxiety disorders (57 %), persons with a remitted history of the disorders (21 %) and healthy controls (22 %). Exclusion criteria were (i) a primary diagnosis of a psychotic disorder, addiction disorder, obsessive-compulsive disorder, or bipolar disorder, and (ii) non-fluency in Dutch. Participants were recruited from the community, general practice settings and mental health care organizations. The baseline data were collected using self-report questionnaires, interviews, a medical examination, a cognitive computer task, and collection of blood and saliva samples. Data were obtained on the presence, severity, and chronicity of anxiety and depression, as well as the demographic characteristics, psychosocial, psychological, physiological determinants, life events, health behaviors including alcohol intake, smoking, drugs, physical activity and genetic measures of the participants. Ethical approval for NESDA was obtained from the ethical review boards of participating centers, and all participants signed informed consent [for full details about NESDA design and sample, see Penninx et al.[67].

Depressive and anxiety symptoms were assessed again after one year (response rate = 82 %) and then after two years (response rate = 87.1 %). In the present study, only the participants currently diagnosed (past 6 months) with depression and / or anxiety disorders at the baseline assessment were selected (N = 1,725); healthy controls (N = 661) and remitted depressed participants (N = 595) were excluded. We used baseline, 1-year and 2-year data of all the variables included in the analyses: smoking status, confounding variables, and severity of symptoms of depressive and anxiety disorders.

Those dropped out from the current analyses (16.4 %) were significantly younger, had experienced more negative life events (*ps* < 0.05; Cohen's d*s* ≤ 0.2), and had higher symptoms of depression, anxiety (*ps* < 0.001; Cohen's d = 0.3) and agoraphobia (*p* < 0.01; Cohen's d = 0.2) than those in the study. However, no differences were found in alcohol consumption and symptoms of social anxiety (*ps* > 0.05). Similarly, the drop-outs were not different in gender distribution (*p* > 0.05) from those in the study. However, they had significantly low education and low physical activity (*p*s > 0.05) than those included in the study.

Measures

Smoking behavior

Participants were classified into current smokers (nicotine-dependent and non-dependent), former smokers, and never-smokers. Former smokers were those who had stopped smoking definitively, and never-smokers were those who never smoked during their lifetime. The Fagerstrom test for nicotine dependence (FTND) was used to assess nicotine dependence[68] in current smokers only. The reliability and internal consistency of FTND have been found to be adequate in previous research[69]. The FTND assesses daily smoking rate, interval between waking up and the first cigarette, frequency of smoking after waking up, difficulty refraining from smoking in places where it is forbidden, and despite medical illness, and also difficulty giving up the first cigarette in the morning. The sum score of FTND can range from 0 to 10. Current smokers with a score of 4 or higher on the FTND in the present study were defined as nicotine-dependent smokers[48, 70, 71]. Nicotine-dependent smokers were daily smokers who smoked on daily, regular basis. Of the non-dependent smokers, 87 % were daily smokers, smoking between 1 and 30 cigarettes per day, and the remaining 13 % smoked less than 7 cigarettes per week. Smoking status of the participants was relatively stable from baseline to wave 3. Never- and former smokers at baseline did not change their smoking status at wave 3. Of the total study sample, 3.2 % non-dependent smokers (N = 55) and 1.3 % dependent smokers (N = 22) quit smoking at wave 3. This data is included in longitudinal analysis.

Psychopathology

The lifetime diagnoses and age at onset of depression and anxiety disorders were ascertained using the Composite International Diagnostic Interview (CIDI v2.1). The CIDI is a structured interview designed to assess diagnoses of psychiatric disorders according to DSM-IV criteria. The CIDI has high inter-rater reliability, high test-retest reliability and high validity for depressive and anxiety disorders[72].

Depressive symptoms were assessed by the 30-item self-report Inventory of Depressive Symptomatology (IDS; score range: 0-84) which has shown high correlations with observer rated scales[73]. The 21-item Beck Anxiety Inventory (BAI; score range: 0-62), was used to assess anxiety symptoms[74] whereas the symptoms of fear were measured with the 15-item Fear Questionnaire[75]. In our analyses, we used two subscales of Fear Questionnaire[75]; (i) FQ items for social anxiety symptoms, and (ii) FQ items for agoraphobia symptoms. Both subscales have sufficient internal consistency[76], and the total score of each subscale ranges from 0 to 40.

Potential confounding variables

The Alcohol Use Disorder Identification Test (AUDIT; range: 0-40) was used to assess alcohol intake[77]. The International Physical Activity Questionnaire (IPAQ) was used to assess self-reported physical activity. IPAQ estimates weekly energy expenditure based on daily physical activities[78]. Negative life events in the past year were assessed with the Brugha questionnaire[79]. Other covariates under study were age, gender and education.

Statistical Analyses

Data were screened for accuracy, outlying scores, and the assumptions of univariate and multivariate analysis. First, we evaluated baseline differences among nicotine-dependent and non-dependent smokers, former smokers, and never-smokers on the socio-demographic variables and health behaviors using

one-way analyses of variance (ANOVA) with post hoc tests and chi-square tests for independence. Eta squared and Cramer's V were used as measures of effect size for ANOVA and chi-square, respectively. Then, the cross-sectional associations of smoking with depressive and anxiety symptoms were examined using a one-way multivariate ANOVA. Four dependent variables were the severity of symptoms of depression, anxiety, social anxiety and agoraphobia. The independent variable was smoking status. Multivariate ANOVA was followed by one-way ANOVAs with post hoc comparisons. Next, we performed four hierarchical multiple linear regressions to assess the association between smoking status and severity of the disorders while controlling for confounding variables. In each of the regression analyses, we fitted four models. In the first model, we entered age, gender, and education; the second model added negative life events and alcohol use to the previous model; similarly, in the third and fourth models, we added physical activity and smoking status, respectively, to the previous models. Thus the estimates provided from the final model include all variables.

Finally, to evaluate the change in the severity of the disorders in the four groups over time linear mixed models (LMMs) were built. The outcome variables were the severity of the symptoms of depression, anxiety, social anxiety, and agoraphobia. Smoking status was modeled both as a fixed factor and a random factor. The fixed effect of smoking status is the average effect in the entire study population, expressed by the regression coefficient. The random effect is specified to investigate group differences on severity of symptoms as it is assumed that the effect varies randomly within the participants. The covariates gender, education, and negative life events were modeled as fixed factors, while age, alcohol use and physical activity as random factors. In NESDA, the data on smoking status are available at baseline and at follow-up; however, the FTND data are available only at baseline. So while constructing the data file for LMM, we considered the participants as nicotine-dependent at follow-up if they were dependent at baseline. However, if they quit between baseline and follow-up period, they were grouped into former smokers. The parameters were estimated with maximum likelihood (ML) technique. We specified the *unstructured* repeated and random-effects covariance type because it imposes the fewest

assumptions and comparatively, a better fit of the model. Linear mixed model approach was preferred over repeated measures ANOVAs to analyze longitudinal data because (i) unlike repeated measures ANOVA, LMMs can fully accommodate unbalanced data sets resulting from missing data, common with longitudinal studies; (ii) repeated measures ANOVA requires all participants to be assessed at the same time point, and to have exactly the same number of observations, which is hardly possible in case of longitudinal study. LMMs can analyze such unbalanced data sets easily[80]. Analyses were run in PASW (V. 17.0) for windows.

Results

Sample Characteristics

Table 1 presents the socio-demographic and health behavior characteristics of the participants at baseline. The groups differed significantly in age ($F_{(3,1721)} = 37.9$; $p < 0.001$) and alcohol use ($F_{(3,1695)} = 39.4$; $p < 0.001$) with medium effect size ($\eta^2 = 0.06$). The groups also differed statistically in past year negative life events ($F_{(3,1721)} = 5.1$; $p < 0.01$) with small effect size ($\eta^2 = 0.01$). Post hoc comparisons using the Tukey HSD indicated that former smokers were significantly older than nicotine-dependent smokers and both were older than never-smokers and non-dependent smokers (Table 1). Former smokers consumed significantly more alcohol than never-smokers, however, when compared with current smokers they used significantly less alcohol (ps < 0.001). Both current smoking groups were not significantly different from each other in alcohol use ($p > 0.05$). Similarly, former smokers reported fewer negative life events than current smokers (both groups) ($p < 0.05$) and never-smokers were not different than any of the groups in life events ($p > 0.05$). A chi-square test indicated that at baseline, the groups differed significantly in gender ($\chi2$ (3) = 7.9; $p < 0.05$), education ($\chi2$ (6) = 63.0; $p < 0.001$), and physical activity ($\chi2$ (6) = 30.7; $p < 0.001$) with small to medium effect sizes (Table 1). The groups also differed significantly in the prevalence of current diagnoses of depression ($\chi2$ (3)=14.6; $p < 0.01$), generalized anxiety disorder ($\chi2$ (3)=29.9; $p < 0.001$), and panic with agoraphobia ($\chi2$ (3)=25.2; $p < 0.001$). However, no significant group differences were found (ps > 0.05) in the current diagnoses of anxiety, social anxiety, agoraphobia, and panic without agoraphobia (Table 1).[1]

Table 1. Baseline demographic and health behavior characteristics of the participants

Sociodemographic variables and health behaviors	Never-smokers	Former smokers	Current smokers		Effect size[a]
			Non-dependent	Nicotine-dependent	
	N= 438	N= 527	N= 411	N= 349	
Age (Mean, SD)	38.4 (13.0)	45.6 (11.9)	38.5 (11.9)	41.6 (11.0)	0.06***
Gender, F (%)	70.1	66.2	69.1	61.3	0.07*
Education (%)					0.14***
- basic	6.6	6.5	5.4	16.3	
- intermediate	61.0	57.9	67.4	65.6	
- high	32.4	35.7	28.2	18.1	
Alcohol intake(Mean, SD)	2.9 (3.5)	4.6 (4.6)	6.3 (5.5)	6.2 (6.7)	0.06***
Physical activity (%)					0.09***
- low	16.9	16.9	18.7	29.0	
- moderate	43.2	35.9	37.7	31.6	
- high	40.0	47.1	43.6	39.4	
Stressful events (Mean, SD)	0.7 (1.0)	0.6 (0.9)	0.8 (1.2)	0.8 (1.1)	0.01**
Current diagnoses (%)					
Anxiety	73.5	73.8	76.6	79.9	ns
- Generalized anxiety	30.4	18.6	28.0	33.8	0.13***
- Social anxiety	36.3	38.1	36.7	44.1	ns
- Panic					
-- without agoraphobia	15.5	12.1	16.5	13.5	ns
-- with agoraphobia	18.0	22.0	28.5	31.8	0.12***
- Agoraphobia	9.8	13.9	8.8	10.0	ns
Depression	71.9	63.2	66.7	73.9	0.10***

***$p < 0.001$; **$p < 0.01$; *$p < 0.05$

[a] Effect size of only significant results reported

Symptom Severity at Baseline

A multivariate ANOVA indicated a significant difference among groups on a linear combination of the dependent variables ($F_{(12,5076)} = 7.45$; $p < 0.001$; Pillai's Trace = 0.05; partial $\eta^2 = 0.02$). All four dependent variables

reached statistical significance: severity of depression ($F_{(3,1693)} = 18.4$; $p < 0.001$; partial $\eta^2 = 0.03$); anxiety ($F_{(3,1693)} = 20.9$; $p < 0.001$; partial $\eta^2 = 0.04$); social anxiety ($F_{(3,1693)} = 4.2$; $p < 0.01$; partial $\eta^2 = 0.01$); agoraphobia ($F_{(3,1693)} = 13.2$; $p < 0.001$; partial $\eta^2 = 0.02$). Tukey HSD revealed that on three of the dependent variables (severity of depression, anxiety and agoraphobia) nicotine-dependent smokers had higher scores than non-dependent smokers, former smokers and never-smokers (ps < 0.001). The latter three groups were not different from each other on these variables (ps > 0.05). For the severity of social anxiety, results were slightly different. Nicotine-dependent smokers were more socially anxious than former smokers ($p < 0.05$) and non-dependent smokers, but they were not different from never-smokers ($p > 0.05$). The mean scores are presented in table 2. We also repeated similar analyses by combining the two groups of current smokers and found that current smokers had significantly more severe depressive and anxiety symptoms than former and never-smokers ($p < 0.001$), except for social anxiety symptoms.[1]

[1] The demographic characteristics and severity of symptoms of the total sample of this study, and that of the combined current smoking groups can be viewed as supplementary material by accessing the online version of this paper. Please see Appendix A

Table 2. Mean (SD) severity of the symptoms in participants stratified by smoking status at baseline

Severity of symptoms	Never-smokers	Former smokers	Current smokers		η^2
			Non-dependent	Nicotine-dependent	
Depressive symptoms	29.1 (12.5)	27.2 (11.8)	28.0 (12.4)	33.3 (12.6)	0.03***
Anxiety symptoms	16.1 (10.6)	15.3 (9.6)	16.8 (11.0)	20.9 (11.5)	0.04***
Symptoms of social anxiety	15.1 (8.8)	14.4 (8.8)	14.3 (8.6)	16.4 (9.7)	0.01**
Symptoms of agoraphobia	8.8 (9.0)	8.7 (8.8)	9.3 (9.4)	12.6 (10.9)	0.02***

***$p < 0.001$; **$p < 0.01$

Finally, four regression analyses were run. In the regression analysis with symptoms of depression as the dependent variable, the overall variance explained was 8.4 % ($p < 0.001$). The regression analysis with symptoms of anxiety as the dependent variable explained 8 % of the significant overall variance ($p < 0.001$). Similarly, for the symptoms of social anxiety and agoraphobia, the overall variance explained was 2.3 % ($p < 0.05$) and 7.4 % ($p < 0.001$), respectively. For individual contribution of each variable in predicting symptom severity, see table 3.[2]

[2] The regression analyses with continuous baseline FTND score for all four dependent variables can be viewed as supplementary material by accessing the online version of this paper.

Table 3. Regression of smoking status on the severity of the disorders				
	B	**SE**	**β**	***p***
	Severity of depression			
Age	0.06	0.03	0.06	*
Gender	0.04	0.64	0.002	ns
Education	-0.61	0.09	-0.16	***
Stressful life events	0.87	0.28	0.07	**
Alcohol intake	-0.05	0.06	-0.02	ns
Low vs. moderate physical activity	-2.22	0.82	-0.09	**
Low vs. high physical activity	-3.80	0.80	-0.15	***
Never-smokers vs. current smokers (nD) †	-1.15	0.86	-0.04	ns
Never-smokers vs. current smokers (D) †	2.81	0.91	0.09	**
Never-smokers vs. former smokers	-2.06	0.81	-0.08	*
	Severity of anxiety			
Age	0.02	0.02	0.03	ns
Gender	0.98	0.56	0.04	ns
Education	-0.59	0.08	-0.18	***
Stressful life events	0.57	0.24	0.06	*
Alcohol intake	-0.02	0.05	-0.01	ns
Low vs. moderate physical activity	-1.31	0.71	-0.06	ns
Low vs. high physical activity	-1.80	0.69	-0.08	**
Never-smokers vs. current smokers (nD) †	0.64	0.74	0.03	ns
Never-smokers vs. current smokers (D) †	3.80	0.79	0.14	***
Never-smokers vs. former smokers	-0.71	0.70	-0.03	ns
	Severity of social anxiety			
Age	-0.01	0.02	-0.01	ns
Gender	1.35	0.48	0.07	**
Education	-0.25	0.07	-0.09	***
Stressful life events	-0.02	0.21	-0.002	ns
Alcohol intake	0.07	0.05	0.04	ns
Low vs. moderate physical activity	-0.33	0.61	-0.02	ns
Low vs. high physical activity	-1.21	0.59	-0.07	*
Never-smokers vs. current smokers (nD) †	-0.97	0.64	-0.05	ns
Never-smokers vs. current smokers (D) †	0.83	0.68	0.04	ns
Never-smokers vs. former smokers	-0.64	0.60	-0.03	ns
	Severity of agoraphobia			
Age	0.02	0.02	0.03	ns
Gender	2.04	0.49	0.10	***
Education	-0.51	0.07	-0.17	***
Stressful life events	-0.09	0.22	-0.01	ns
Alcohol intake	-0.08	0.05	-0.05	ns
Low vs. moderate physical activity	-0.91	0.63	-0.05	ns
Low vs. high physical activity	-1.32	0.61	-0.07	*
Never-smokers vs. current smokers (nD) †	0.67	0.66	0.03	ns
Never-smokers vs. current smokers (D) †	3.32	0.70	0.14	***
Never-smokers vs. former smokers	0.28	0.62	0.01	ns

***$p < 0.001$; **$p < 0.01$; *$p < 0.05$; ns=non-significant
† nD = non-dependent; D = nicotine-dependent

We carried out similar regression analyses by including baseline FTND score as continuous covariate. A significant positive linear relationship between FTND and severity of symptoms on all four measures were found, thus confirming our initially reported analyses (Table 3S).[2]

Smoking Status and the Course of Depression and Anxiety

The severity of depressive and anxiety symptoms in the participants over time was evaluated with linear mixed models. The intercept and linear slope parameters were statistically significant (*ps* $\leq$ 0.001), indicating a significant between-participants variation in the initial status of the dependent variable and linear growth rate (Table 4). The symptoms of depression, anxiety, social anxiety, and agoraphobia decreased over time in all four groups. However, we found statistically significant interaction of time with the symptoms of depression and anxiety only for nicotine-dependent smokers (*p*s < 0.05) suggesting that depressive and anxiety symptoms of dependent smokers improved more slowly as compared with the other three groups (Table 4). Social anxiety and agoraphobia symptoms decreased over time, but none of the smoking groups improved faster or slower than any of the other groups (*p*s > 0.05).

Table 4. Parameter estimates of mixed-effects models examining the relationship between symptom severity of the disorders over time[a]

	Symptoms of depression		Symptoms of anxiety		Symptoms of social anxiety		Symptoms of agoraphobia	
	β	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Intercept	38.4	24.3 , 52.4***	23.0	11.6, 34.5***	18.0	5.4, 30.5*	16.5	6.2, 26.8**
Time	-3.9	-4.6 , -3.1***	-1.9	-2.5, -1.3***	-1.3	-3.0, 0.4	-0.9	-1.5, -0.4**
Never-smokers	0		0		0		0	
Former smokers	-2.8	-16.0, 10.4	-1.3	-12.4, 9.8	-2.4	-11.9, 7.1	0.8	-8.3, 9.9
Current smokers (nD) †	-3.2	-15.8, 9.5	-1.8	-12.2, 8.5	-3.0	-12.7, 6.7	-0.7	-9.9, 8.5
Current smokers (D) †	1.4	-12.0, 14.7	1.4	-9.3, 12.1	-0.7	-10.5, 9.0	3.4	-6.6, 13.4
Interaction with time								
Never-smokers	0		0		0		0	
Former smokers	0.2	-0.6, 1.1	0.05	-0.7, 0.8	0.07	-1.4, 1.5	-0.3	-0.9, 0.3
Current smokers (nD) †	0.7	-0.3, 1.8	-0.2	-1.1, 0.6	-0.06	-1.2, 1.1	-0.2	-0.9, 0.6
Current smokers (D) †	-1.3	-2.4, -0.2*	-1.0	-1.8, -0.02*	-0.1	-1.9, 1.7	-0.7	-1.3, 0.3

***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.
† nD = non-dependent; D = nicotine-dependent
[a] Models adjusted for covariates

Discussion

We examined the severity and course of depressive and anxiety symptoms by smoking and nicotine dependence status in patients with current diagnosis of depression/anxiety disorders. Our results confirmed that the symptoms of depression, anxiety, and agoraphobia were more severe in nicotine-dependent smokers than in the other three groups. This pattern remained after controlling for the effects of covariates. The differences between the groups in the symptoms of social anxiety, however, were much smaller and were no longer significant after controlling for covariates. We also found that nicotine-dependent smokers had slower recovery of depressive and anxiety symptoms than never-smokers, former smokers, and non-dependent smokers. However, no differences were observed between the groups for the improvement of the symptoms of social anxiety and agoraphobia.

These results are in line with previous literature on the rates and severity of depression and anxiety disorders in nicotine-dependent smokers. After controlling for other substance disorders, nicotine-dependent smokers (unlike non-dependent smokers) had higher odds of major depression and anxiety disorders[22]. Similarly, heavy smoking[81] and nicotine dependence[48] were associated with elevated rates of depression and anxiety disorders and higher severity of depressive symptoms.

Inconsistent with our hypothesis and with previous findings, we found that never-smokers, non-dependent current smokers, and former smokers did not differ significantly from each other on baseline symptom severity of depression and anxiety. However, when we combined the current smoking groups, our results were not different from previous studies that observed less severe symptoms of depression and anxiety in former smokers than in current smokers[3, 11].

The previous studies did not distinguish between dependent and non-dependent smokers. Thus it seems that the association between smoking and severity of symptoms is mainly carried by nicotine-dependent smokers.

Our findings should be interpreted by taking into consideration the following limitations. Firstly, despite the longitudinal design and the large sample size, the follow-up period is relatively short. Secondly, the age-group of the participants is heterogeneous. Thirdly, a number of participants had dropped out during the follow-up period which might have biased our results because the drop-outs were significantly different from those in the study in a number of parameters including severity of symptoms. Fourthly, nicotine dependence was assessed only at baseline, and was not assessed in former smokers. Fifthly, though our findings are suggestive of an association of slower symptom recovery with nicotine dependence, these cannot be taken as inferring causality due to the naturalistic nature of the study. Sixthly, NESDA may not be representative of other ethnic groups. Finally, depression and anxiety disorders are highly comorbid with other mental health problems, so the exclusion criteria of NESDA may limit the generalizability of our findings[82]. However, as compared to NESDA, another large study of early-onset depression, *GENRED*, adopted a more stringent exclusion criteria[83]. Despite these limitations, our study focuses on psychiatric patients whereas most previous longitudinal studies used population samples. The NESDA's assessment of depression and anxiety disorders is based on DSM-IV criteria unlike most previous studies that assessed symptoms, not diagnoses, and relied mostly on self-report measures of depressive and anxiety symptoms. Moreover, anxiety disorders and nicotine dependence have received relatively little research attention; most studies have investigated the smoking status-depression association. Thus our findings of low improvement rate in anxiety and depressive symptoms in nicotine-dependent smokers are of particular importance

because nicotine-dependent smokers seem to have reduced mental health than non-dependent smokers.

The mechanisms underlying the association of smoking or nicotine dependence with depression and anxiety disorders are unclear. Our findings suggest that quitting smoking may not always be associated with reductions of depressive and anxiety symptoms, because the former smokers in our study were not significantly different from non-dependent current smokers. However, there is no assessment of how severe the symptoms of former smokers were prior to quitting smoking. Further, there is no information on how dependent the former smokers were when they quit. It may be that it is dependent smoking that exacerbates symptoms among this population, but that if these smokers quit they would notice symptom improvement. Thus, the findings are inconsistent with the assumption that quitting smoking is linked with aggravation in depressive or anxious symptoms[84, 85]. Quitting might be related with high symptoms in smokers with lower quitting self-efficacy[17] or with failed quit attempts[86], but not in those who remain abstinent for long period[87]. This cannot be implied, though, from our findings as there are no data on quitting self-efficacy or failed quit attempts in NESDA. The former smokers in our study remained abstinent at an average of approximately twelve years (data not shown) which might be the reason that their symptoms were comparable with never-smokers. However, it is still interesting that non-dependent smokers are not significantly different in their symptoms from the non-smoking groups. Thus our findings suggest that smoking might be associated with the onset or the increasing severity of anxiety disorders only when smokers are nicotine-dependent.

The worse outcome observed in nicotine-dependent smokers might be due to the fact that chronic nicotine use might have an adverse effect on the brain and the neurotransmission systems. For example, nicotine use and anxiety or depression have both been linked to elevated dopamine[88, 89], low brain-derived neurotrophic factor (BDNF)

levels[90, 91], and low Monoamine Oxidase (MAO) activity[92, 93]. Future investigations are needed on the impact of smoking or nicotine dependence on the dopamine, BDNF levels and MAO activity in relation to anxiety or aversive mood states in order to elucidate the mechanisms, and to help better our understanding of the complex association.

Regarding the notion of self-medication as motivator for smoking, our findings suggest that chronic and heavy nicotine use does not help to alleviate negative affect and may be even counterproductive. This may be used in educational programs for smokers who think that smoking helps them to control their mood states. Our findings also point to the importance of considering nicotine dependence symptoms in psychiatric patients in health prevention and intervention programs; thus more effective methods for managing depression and anxiety disorders should be developed. In psychiatric patients who smoke, a screening for nicotine dependence symptoms in medical settings would be useful to be implemented, and nicotine-dependent patients may be prioritized for smoking cessation programs.

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