Smoking is associated with first-ever incidence of mental disorders: a prospective population-based study

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ABSTRACT

Aims It is well established that tobacco use is associated with mental disorders. However, the association between tobacco use and mental disorders has not yet been examined sufficiently in prospective, population-based studies. The current study is aimed at examining whether smoking is associated with first-ever incidence of mental disorders. **Design, setting and participants** We conducted a prospective, population-based epidemiological study (the Netherlands Mental Health Survey and Incidence Study: NEMESIS) in which a representative sample of adults aged 18–64 years ($n = 7076$) were interviewed to establish the presence of a broad range of mental disorders. We re-interviewed them at 1 year ($n = 5618$; response 79.4%) and 3 years ($n = 4796$; 67.8%) after baseline. **Measurements** The presence of mental disorders was assessed according to DSM-III-R criteria with the Composite International Diagnostic Interview (CIDI), which was administered by trained lay interviewers. Tobacco use was assessed by asking respondents whether they had smoked in the past year, and how many cigarettes they smoked. **Findings** Subjects who smoked but never had a mental disorder in their life, had an increased risk of developing a mental disorder ($P < 0.01$), and this remained significant after correcting for major risk indicators of mental disorders. **Conclusions** Smoking is associated not only with the prevalence, but also with first-ever incidence of mental disorders. More research is needed to study the causal pathways.

Keywords Depression, depressive disorder, incidence, major depression, prospective, smoking, tobacco.

INTRODUCTION

It is well established that tobacco use is elevated in subjects with mental disorders [1], including schizophrenia [2], bipolar disorder [3], panic disorder [4], major depression [5–7] and alcohol-related disorders [8,9]. The exact causal pathways are not clear. It has been assumed that tobacco is used by people with mental disorders as self-medication [10–12]; in other words, that tobacco use is 'caused' by the mental disorder, and not the other way around. Several recent studies, however, suggest that smoking may be associated with an increased risk of triggering the onset of mental disorders, including panic [4], depression [6,7] and schizophrenia [13]. It is also entirely possible that both smoking and mental disorders are caused by a third, unrelated, factor [14,15]. The few prospective studies in this research area have examined the

association between smoking and depression. Some of these studies have found that smoking at baseline predicts the onset of depression [7,16], while others did not confirm this finding [17,18].

Epidemiological research in this area suffers from major limitations [1]. Many of the studies focus on only one mental disorder; do not use diagnostic interviews to assess the presence of mental disorders, but use self-rating questionnaires instead; are conducted in clinical and other non-representative samples; and are cross-sectional instead of prospective.

However, representative, prospective population-based studies examining a broad range of mental disorders and using rigorous diagnostic criteria can help in answering several important questions on the relationship between smoking and mental disorders. One important question is whether there is a temporal association

between smoking and first-ever incidence of mental disorders. Another question is whether there is a dose–response relationship between the number of cigarettes smoked and the onset of first-ever incidence of mental disorders. A dose–response relationship can be seen as an indication for a causal relationship between a risk indicator and an outcome [19]. A third important question is whether the presence of mental disorders is associated with the (re)starting of smoking. In this study, these questions were examined.

METHOD

Subjects and procedure

The Netherlands Mental Health Survey and Incidence Study (NEMESIS) was based on a multi-stage, stratified, random sampling procedure [20,21]. In brief, a sample of 90 municipalities was drawn, using urbanization as stratification criterion; the sample resulted in an adequate distribution of the respondents over the 12 Dutch provinces. A sample of private households was then drawn from the postal registers. The selected households were first sent a letter of introduction, followed by a telephone contact. In each household, the member with the most recent birthday was selected, on condition that (s)he was between 18 and 64 years and sufficiently fluent in Dutch to be interviewed. To establish contact, the interviewers made a minimum of 10 phone calls or visits to a given address at different times of the day and week.

In the initial data collection phase, 7076 respondents were interviewed (year of interview: 1996; response rate 69.7%). All participants in the first interview (t_0) were approached for the follow-up waves at 1 year (t_1) and 3 years (t_2) after t_0. Of the 7076 people who had taken part at t_0, 5618 could be re-interviewed at t_1 (response: 79.4%) and 4796 at t_2 (response of t_0 subjects: 67.8%). After adjustment for demographic variables, a 12-month disorder at t_0 only slightly increased the probability of loss to follow-up between t_0 and t_1 as well as between t_0 and t_2 (OR = 1.20, CI = 1.04–1.38; OR = 1.29, CI = 1.15–1.46) [22,23]. Smoking also somewhat increased the probability of loss to follow-up between t_1 and t_2 (OR = 1.24, CI = 1.06–1.45).

To correct for the combined effect of initial non-response and dropout, post-stratification weights were calculated.

Measures

Mental disorders

Mental disorders were assessed according to DSM-III-R criteria. The instrument used was the Composite International Diagnostic Interview (CIDI, version 1.1) [24], Dutch version [25]. The CIDI can be used by trained lay interviewers. It is known to have a high inter-rater and test–retest reliability [26]. In the current study, we use the diagnoses of the most common mood disorders, anxiety disorders and substance-use disorders. The specific disorders are described in Table 1. Schizophrenia and eating disorders were not included in this study because the numbers of subjects were very small ($n < 6$ for both disorders). The CIDI was administered to all respondents at all three measurements.

Tobacco use

Tobacco use was assessed at t_1 and at t_2 by asking respondents whether they had smoked in the past year at t_1 and past 2 years at t_2 (yes/no). We also asked how many cigarettes they smoked. For further analyses, we made four categories of the number of cigarettes smoked per day (zero; one to nine; 10–19; > 20). We did not assess other types of tobacco use (such as cigars, pipe or chewing tobacco), as these are hardly used in the Netherlands.

Risk indicators of mental disorders

In the prospective part of our study we controlled for other risk indicators of mental disorders, apart from smoking. We selected a number of risk indicators that were found to be predictive of mood and anxiety disorders in several other studies [27], including studies on the NEMESIS data [28,29]:

- Childhood trauma, i.e. emotional neglect, psychological abuse, physical abuse and sexual abuse before the age of 16. During the interviews, the abuse types were explained to the respondents and illustrated with examples. In our analyses, we used dichotomous variables which indicated the presence or absence of these four types of trauma at t_0.
- Parental history of psychopathology concerned depressive problems, anxiety or phobic problems and problem drinking in one or both biological parents, assessed at t_0. The presence or absence of parental history was assessed by single questions [30].
- Somatic illnesses: the presence of somatic disorders (migraine, lower back pain, complaints pointing towards cardiovascular, respiratory and non-specific abdominal problems) in the 12 months preceding t_1. We used one variable indicating the presence or absence of any somatic disorder in the past 12 months.
- Locus of control was measured with the Mastery Scale [31]. We defined low mastery, indicating an external locus of control (= 1, else =0) as a score below the mean of the sample at t_1 (M = 19.3; Cronbach's $\alpha = 0.81$).
- Neuroticism was assessed with the Groningse Neuroticism Questionnaire [32]. We used a cut-off at the mean to obtain an indicator for above-average levels of neuroticism (M = 38.5; $\alpha = 0.80$).

Table 1 Smoking in the past 12 months among subjects with mental disorders in the past 12 months and life-time.

	12 months					Life-time				
	Prevalence	% smoking	RR	95% CI	P	Prevalence	% smoking	RR	95% CI	P
Any anxiety disorder	7.1	50.9	1.33	1.18–1.50	***	21.5	48.9	1.26	1.15–1.37	***
GAD[a]	0.5	52.8	1.46	0.99–2.15	NS	2.5	53.0	1.33	1.11–1.59	**
Panic disorder[b]	1.3	58.5	1.49	1.19–1.87	**	4.7	51.1	1.26	1.08–1.47	**
Agoraphobia	1.1	65.0	1.68	1.39–2.03	***	4.0	54.2	1.43	1.25–1.64	***
Social phobia	2.2	56.0	1.44	1.20–1.73	***	8.2	51.2	1.31	1.17–1.47	***
Simple phobia	4.3	48.3	1.21	1.03–1.42	*	12.3	49.1	1.19	1.07–1.33	**
OCD[c]	0.4	45.2	1.00	0.53–1.87	NS	0.5	43.7	1.12	0.82–1.53	NS
Any mood disorder	5.8	53.1	1.39	1.22–1.57	***	21.1	51.2	1.44	1.33–1.56	***
Major depression	4.6	52.5	1.35	1.17–1.56	***	8.8	51.0	1.40	1.28–1.52	***
Dysthymia	1.1	61.8	1.73	1.37–2.19	***	7.2	50.4	1.38	1.23–1.54	**
Bipolar disorder	0.9	60.0	1.62	1.26–2.09	***	2.3	60.0	1.49	1.26–1.77	***
Any substance use disorder	6.0	62.4	1.43	1.18–1.74	***	20.9	58.7	1.49	1.36–1.64	***
Alcohol abuse	5.5	56.5	1.30	0.98–1.72	NS	14.7	55.8	1.34	1.19–1.49	***
Alcohol dependence	1.5	74.2	1.62	1.32–1.98	***	5.9	68.9	1.57	1.39–1.77	***
Drug abuse/	0.5	80.6	1.71	1.38–2.10	***	2.0	72.4	1.50	1.23–1.83	***
Drug dependence	0.6	78.5	1.59	1.22–2.07	**	2.2	71.9	1.65	1.42–1.91	***
Any diagnosis	15.8	53.2	1.36	1.22–1.51	***	45.1	49.9	1.41	1.31–1.53	***
0 diagnosis	84.2	37.3	1.00	Ref.	d	55.1	31.5	1.00	Ref.	d
1 diagnosis	11.4	48.9	1.21	1.06–1.38	**	24.4	44.5	1.26	1.13–1.39	***
2 diagnoses	2.7	62.8	1.55	1.34–1.80	***	10.6	54.3	1.56	1.40–1.75	***
≥ 3 diagnoses	1.7	67.4	1.76	1.50–2.06	***	9.9	59.2	1.69	1.52–1.87	***

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. [a]Generalized anxiety disorder; [b]with or without agoraphobia; [c]obsessive-compulsive disorder; [d]P for linear trend among number of diagnoses: < 0.001. NS: not significant.

Demographic variables

Demographic variables included: gender, age, education (lower versus higher), and having a paid job or not.

Analyses

Because smoking was assessed at t_1 and t_2, we used the data of these two waves in the current study.

At t_1, we examined whether there was a cross-sectional association between smoking and mental disorders. We conducted a series of Poisson regression analyses with smoking in the past year as the dependent variable (yes/no), and each of the mental disorders as a predictor, while adjusting for demographics. We conducted separate analyses for the 12-month and the life-time prevalences of mental disorders. In these cross-sectional analyses, Poisson regression models produce relative risks (RR), indicating whether having a mental disorder is associated with a higher probability of smoking than when there is no disorder.

We then examined longitudinally whether subjects who smoked at t_1 had an increased risk of developing a mental disorder for the first time in their lives at t_2. We selected the subjects who had never had any mental disorder in their life. In a new series of Poisson regression

analyses, we used each of the variables indicating first-ever incidence of a mental disorder as the dependent variable. Smoking in the year before t_1 (yes/no) was used as a predictor. In the first series of Poisson regression analyses, we adjusted the outcomes for demographics. In the second series, we adjusted for demographics and for all risk indicators as described in the 'Measures' section. In the context of longitudinal data analysis, the Poisson model produces incidence rate ratios (IRRs). These are the ratios of the incidence rate in the exposed group over the incidence rate in the unexposed group.

We next examined whether there is a dose–response relationship between the number of cigarettes smoked and the degree to which the risk of developing a first-ever mental disorder is elevated. In this series of Poisson regression analyses, we used first-ever incidence of mental disorders at t_2 as the dependent variable and the number of cigarettes smoked at t_1 as predictor, while adjusting for demographics. We conducted the same analyses again, with four categories of smoking (zero; one to nine; 10–19; ≥ 20 cigarettes).

To examine whether subjects with a mental disorder have an increased risk of (re)starting to smoke, we used another series of Poisson regression analyses. We selected subjects who had not smoked in the year prior to t_1, and

Table 2 Smoking as a risk indicator of first-ever incidence of mental disorders: incidence rate ratios (IRR).

	%[a]	Adjusted for demographics			Adjusted for demographics and other risk indicators		
		IRR	95% CI	P	IRR	95% CI	P
Any anxiety disorder	2.67	1.88	1.15–3.06	*	1.77	1.10–2.86	*
GAD[b]	0.64	4.57	1.53–13.67	**	3.80	1.09–13.21	*
Panic disorder[c]	0.39	1.15	0.31–4.17		0.94	0.28–3.24	
Agoraphobia	0.45	3.52	0.91–13.65	†	4.07	0.88–18.85	†
Social phobia	0.27	1.37	0.34–5.53		1.26	0.31–5.21	
Simple phobia	1.51	1.59	0.84–3.02		1.50	0.82–2.73	
Any mood disorder	2.76	1.53	0.93–2.51	†	1.41	0.84–2.39	
Major depression	2.35	1.28	0.76–2.16		1.17	0.68–2.01	
Dysthymia	0.53	6.61	1.77–24.62	**	7.54	1.64–34.56	**
Bipolar disorder	0.32	6.45	0.55–75.65		8.97	0.47–171.79	
Any substance use disorder	2.63	2.39	1.20–4.74	*	2.42	1.22–4.79	*
Alcohol abuse	2.29	2.32	1.09–4.98	*	2.32	1.09–4.96	*
Alcohol dependence	0.21	1.21	0.17–8.53		1.41	0.17–11.41	
Any diagnosis	6.80	1.62	1.15–2.30	**	1.56	1.10–2.22	*

†$P < 0.1$; *$P < 0.05$; **$P < 0.01$. [a]This indicates the percentage of the population at risk ($n = 2.726$) who developed the mental disorder; [b]generalized anxiety disorder; [c]with or without agoraphobia.

made a dummy variable indicating whether they had started to smoke at t_2 (yes/no). This variable was used as the dependent variable, while each of the mental disorders (separate analyses for 12-month prevalence and life-time prevalence) at t_1 were used as predictors, while adjusting for demographic variables.

In order to report correct 95% confidence intervals of the key statistics and P-values under weighting, so-called 'robust' variance-related estimates were obtained in all analyses, using the first-order Taylor series linearization method, as implemented in STATA. All analyses were conducted with STATA/SE for Windows, version 8.2 [33].

RESULTS

Cross-sectional association between prevalence of smoking and mental disorder

In the past year, 39.8% of the population had smoked and 15.8% had had a mental disorder. The prevalence of smoking was significantly higher among subjects with a mental disorder (53.2%) than among subjects without a mental disorder (37.3%; RR = 1.36; $P < 0.001$; Table 1). The prevalence of smoking in the past year was increased significantly in most mental disorders, except for generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD) and alcohol abuse. The prevalence of smoking increased with the number of comorbid mental disorders (P for linear trend < 0.001). Smoking in the past year was also related significantly to life-time mental disorders except for OCD, and again, more diagnoses were

associated with higher rates of tobacco use (P for linear trend < 0.001).

Do subjects who smoke have an increased risk of developing a mental disorder for the first time in their lives?

Among the subjects who had never had a mental disorder in their life at t_1 ($n = 2726$), 6.8% had developed a mental disorder for the first time in their life at t_2 ($n = 167$). Among the subjects who had never had a mental disorder, 27.6% smoked (9.5% smoked one to nine cigarettes per day, 10.5% 10–19 cigarettes and 7.5% more than 20 cigarettes; mean number of cigarettes smoked per day: 10.95; 95% CI: 11.63–1.24).

The risk of developing a mental disorder was significantly higher in subjects who smoked at t_1 than in subjects who did not smoke at t_1 (IRR = 1.62; $P < 0.01$; Table 2), and this remained significant after controlling for other risk indicators (IRR = 1.56; $P < 0.05$).

We also found that smoking was associated with developing an anxiety disorder (IRR = 1.77) and a substance-related disorder (IRR = 2.42), and both remained significant after controlling for other risk indicators. Specific disorders the incidence of which was related to smoking were GAD (IRR = 3.80), dysthymia (RR = 7.54) and alcohol abuse (RR = 2.32). Three subjects were first-ever incident cases of a drug-related disorder (abuse or dependence); all three of them had smoked at t_1 and two subjects were first-ever incident cases of obsessive-compulsive disorders; both had smoked

at t_1. Because of the small number of subjects, we did not conduct specific analyses for these disorders.

None of the analyses indicated any relationship between the number of cigarettes smoked and the risk of developing a mental disorder. This was true when the number of cigarettes was used as a continuous variable, and when we used four categories of number of cigarettes (zero; one to nine; 10–19; ≥ 20).

Do subjects with a mental disorder have an increased risk of starting to smoke?

Among the subjects who did not smoke at t_1, 4.9% ($n = 144$) started smoking at t_2. We examined whether the subjects who did not smoke at t_1 but did have a mental disorder had a higher probability of starting to smoke at t_2, compared with those who did not have that specific mental disorder. We found that generalized anxiety disorder was associated with an increased risk of starting to smoke, both 12-month (IRR = 4.46; $P < 0.05$) and life-time (IRR = 4.46; $P < 0.05$). The same was true for drug abuse (12-month: IRR = 5.88; $P < 0.001$; life-time: IRR = 4.97; $P < 0.01$).

DISCUSSION

The most important finding of this study is that there is a significant relationship between smoking and the development of first-ever incident mental disorder at follow-up. It has been well established in earlier studies that smoking is elevated in subjects with mental disorders, and some studies have found indications that smoking is associated with an increased incidence of major depression [7,16]. We have now provided evidence that smoking is associated with an increased risk of the first incidence of several mental disorders.

We found that smoking is associated with an increased risk for developing anxiety disorders and substance-related disorders, and more specifically generalized anxiety disorder, dysthymia and alcohol abuse. Some recent studies have found that smoking at baseline is associated with the onset of depression [7,16], while other studies did not find such an association [17,18]. In our study, we found no indication that smoking is associated with the incidence of major depression. Because all studies in this area suffer from serious methodological shortcomings, more research is needed to clarify this issue.

Our finding that smoking is associated with the incidence of alcohol abuse but not with the prevalence of alcohol abuse, is remarkable and difficult to interpret. It is, however, important to remember that these are two different groups, and that those who develop alcohol abuse during the follow-up period never met criteria for alcohol abuse before in their lives.

Our results suggest that smoking may be a causal factor in the aetiology of mental disorders. Such an aetiological claim can be made—within reasonable bounds—when the following criteria are met [19,34]: (1) there is a probabilistic association between the assumed 'cause' (smoking) and the 'effect' (a mental disorder); (2) the cause precedes the effect in time; and (3) the influence of a confounder that causes both smoking and the mental disorder can be ruled out. An aetiological claim can be strengthened further when a dose–response relationship can be found [19,34]. In our study, we found clear evidence for the first two criteria, and we were able to control for a considerable number of possible confounders. It is, however, never completely possible to rule out that a confounder which we did not examine has caused both the smoking and the mental disorder. For example, it is well established that physical activity levels are associated with both smoking [35] and mental disorders [36,37], and this could account for the associations observed in this study. We have to conclude, therefore, that the third criterion remains uncertain. Furthermore, we did not find a dose–response relationship between smoking and the risk for developing a mental disorder. We also found evidence that subjects with a mental disorder have an increased risk of starting to smoke, at least for generalized anxiety disorder and drug abuse. This may also point more towards a common cause for smoking and mental disorders than to a causal relation between smoking and the incidence of mental disorders.

Furthermore, it is remarkable that two of the mental disorders we found to be associated with new mental disorders are those that require the presence of symptoms over a long period of time (generalized anxiety disorder and dysthymia; 6 months in GAD and 2 years in dysthymia). Therefore, it is possible that symptoms of these disorders may have been present at baseline, but that the time criteria for the disorder were not yet present. In that scenario, subjects would have been already in the prodromal phase of the disorder during baseline, thus allowing some room for the alternative hypothesis of reversed causality (i.e. first the disorder, then smoking).

The results of this study should be considered in the light of its strengths and weaknesses. Its strengths include the representativeness and the size of the sample, the use of standardized diagnostic interviews in the full sample and its prospective character. There are also limitations, however. First, smoking was not assessed at the first measurement, but only in the second and third measurements. Because there was some dropout between the first and the second measurements and between the second and third measurements, and because there was a small but significant association between dropout and both mental disorders and smoking, the results may have been somewhat distorted. Secondly, we measured

smoking only in the past year, and not life-time. This limited further analyses on the relationship between life-time smoking and mental disorders, which is particularly important because most people start smoking in adolescence and our sample is older (18–65 years). Thirdly, smoking status was not validated by biological measures and so may be under-ascertained. Under-ascertainment could reduce the strength of the association found. Fourthly, the data are almost 10 years old and since then the prevalence of smoking in the Netherlands has decreased by about 6.3% (from 35.8% in 1997 to 29.5% in 2005; Statistics Netherlands). Fifthly, because we included only subjects who could speak Dutch, ethnic minority groups were under-represented in our sample, which may have influenced the results. Finally, although the original sample was large, only a small number of people developed a first-ever mental disorder during follow-up.

Another limitation is the loss to follow-up. Possibly this loss to follow-up is responsible for the association we found between smoking and the development of mental disorders. This seems unlikely, however. If there was truly no association between smoking and mental disorders, then among those lost to follow-up there would have to be a strong association in the opposite direction to that observed in those followed. Given that most people were followed (85.4%), the reverse association would have to be stronger than the one observed.

Despite these limitations, this study is the first to report evidence that smoking is associated with an increased risk of developing a mental disorder for the first time. This is an important finding, once again suggestive of the detrimental health effects of smoking.

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