Smoking and the course of anxiety and depression

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CHAPTER 2

Age at Smoking-Onset and the Onset of Depression and Anxiety Disorders

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Abstract

Background. *Smoking is a known risk indicator for depression and some of the anxiety disorders. No data are available on the role of age at smoking onset in the development of depression and anxiety disorders. We examined the association of smoking onset age on the onset age of depression and anxiety disorders.*

Methods. *Participants of the Netherlands Study of Depression and Anxiety Disorders (NESDA) who developed psychopathology after starting smoking were selected (N = 1,055). The dependent variable was the time to onset of psychopathology after starting smoking and the independent variable was age at smoking onset.*

Results. *The time period between smoking onset and the onset of depression and/or anxiety disorders was five years shorter for early-onset smokers than for late-onset smokers. Moreover, a greater percentage of early-onset smokers than late-onset smokers had the first onset of psychopathology within the first five years after starting smoking. Age at smoking onset predicted age at psychopathology onset after controlling for the effects of gender, education and childhood trauma. When separate analyses were done for depression and anxiety disorders, this pattern of results was found only for anxiety disorders.*

Conclusions. *A young age at smoking onset is associated with a shorter time to first onset of an anxiety disorder. This study with psychiatric patients extends previous findings in general population samples that smoking and depression and anxiety disorders are associated.*

Introduction

Smoking-related physical health problems are well-documented and well-known. It is not generally known, however, that smoking is also associated with an increased risk of mental health problems, particularly anxiety disorders and depression. Cross-sectional studies have shown that smokers as compared to non-smokers are more likely to report anxiety and depressive symptoms[1-19], a lifetime prevalence of major depression[15-17] and comorbid anxiety and depression[11, 16]. These associations with psychiatric symptoms are evident in smokers even after statistically controlling for common confounding factors such as age, gender, race, parental education, marijuana use, alcohol use, cocaine dependence, parental smoking, increased work hours, unemployment, and social isolation[1, 3, 5, 7, 9].

Similarly, individuals with high depression and anxiety are significantly more likely to smoke[1, 20-26] even after controlling for potential confounders such as gender, race, socioeconomic disadvantage, neuroticism, novelty seeking, childhood conduct problems, parental attachment, alcohol use, adverse life events, anxiety disorders, deviant peer affiliations, family instability, child abuse, and parental smoking[20, 21]. Smoking also appears to influence the severity of some anxiety disorders. Regular smokers with panic disorder report more severe and intense symptoms than non-smoking patients[27].

Thus, the association of smoking with depression and anxiety disorders is well established in cross-sectional studies. However, uncertainty remains about the causal mechanisms of this association[20, 24].Different hypotheses have been put forward to explain the high comorbidity between smoking and depression / anxiety disorders, each of which is supported by empirical evidence from longitudinal studies. The first hypothesis is that depression and anxiety disorders increase the likeliness of smoking initiation, or maintain smoking behavior. This hypothesis has gained support from a number of studies[28-34]. Some of these studies suggested that smoking may be used as self-medication[29, 32, 34] whereas others attributed the relation to peer influence[28, 30, 31, 33]. Secondly,

a temporal association exists between smoking and depression/ anxiety disorders in the direction from smoking initiation to the development of the disorder. Several longitudinal and retrospective cohort studies in adolescents and adults have demonstrated a strong association of starting smoking with an increased risk of developing depression[35-53] and anxiety disorders, specifically panic attacks and disorder[37, 49, 51, 52], agoraphobia[37, 52] and generalized anxiety disorder[39, 52]. These studies support the hypothesis that smoking increases the risk of depression and anxiety. Some longitudinal studies, however, found a two-way temporal relation[39, 54-58], suggesting that both conditions mutually influence each other. Thirdly, the comorbidity between smoking and depression and/or anxiety disorders may also be due to shared genetic or environmental factors[54, 59-62].

Research on smoking age onset indicates that starting smoking at an earlier age is associated with health-related and behavioral problems later in life. For example, early-onset smoking as opposed to late-onset smoking is a stronger predictor associated with adverse physical health outcomes such as the development of peripheral artery disease[63] and the risk of lung cancer[64] later in life. Early-age smoking is also associated with deviant or atypical smoking patterns. The earlier the age of onset of smoking, the higher the risk of regular smoking[65-67], smoking more cigarettes per day[66-69], decreased likelihood to quit[68, 70-73], and nicotine dependence[74]. Some studies have reported that early-onset smoking is associated with more health-risk behaviors. A study examining the relationship between early age of onset of cigarette, alcohol, marijuana, and cocaine and engagement in health-risk behaviors among middle school students, found a significant association between these variables, with the onset of cigarette use at 11 years or younger had the strongest association. However, this study is limited by its cross-sectional nature, so a causal relationship cannot be implied[75]. A five-year longitudinal study that investigated students from grade 7 found that by grade 12, early smokers were more likely to have academic problems, and to be engaged in substance use and delinquent behavior than non-smokers[76]. There is also evidence that early-onset/ adolescence smoking is associated with later substance use[77] and the development of substance use disorders[78], alcohol and illicit drug use, early pregnancy[79], psychological and

physical health problems[80], and problem behaviors such as delinquency and antisocial behavior[81]. These studies[75-78], however, lack a comparison group of late-onset smokers. This makes it difficult to say whether the problems were associated exclusively with early-onset smoking and not with late-onset smoking. Smoking in, both, adolescence and in adulthood is associated with depression and dysthymia, but only early-onset smoking is associated with bipolar disorders[82]. Early-onset smokers also have an increased prevalence of drug dependence[83], alcohol abuse and dependence[67, 83] than late-onset smokers. Research on animals has shown that early-age nicotine exposure induces more anxiety-like[84] and depression-like[85] states in adulthood than late-age nicotine exposure. It is not known, however, whether early-onset smoking as opposed to late-onset smoking is further associated with an increased risk of anxiety or depression in humans.

In summary, the association of smoking with depression and some of the anxiety disorders is well-established. From longitudinal studies, it is evident that smoking has a temporal association with these disorders. In this article, we will focus on smokers who were non-depressed or -anxious when they started smoking. The main goal of the present study is to investigate whether a young age at smoking onset is associated with an early onset of anxiety and depression as compared to late-onset smoking. To our knowledge no studies in humans have been conducted that show the importance of early-age nicotine-exposure (as compared to late-age nicotine-exposure) in the development of depression and anxiety disorders. The primary hypothesis of this study is that the time to first onset of psychopathology (depression and/or anxiety disorder) and depression or anxiety disorders after starting smoking is shorter for early-onset smokers than for late-onset smokers.

Methods

Participants and Data

Participants in the present study were drawn from an ongoing 8-year longitudinal naturalistic cohort study, the Netherlands Study of Depression and Anxiety (NESDA) which has started in September 2004 and investigates the long-term course and consequences of depression and anxiety disorders. NESDA includes 2,981 participants (66.4 % female) with the age range from 18 to 65 years (Mean Age = 41.9 years; SD = 13.0).

In order to represent various health care settings and developmental stages of psychopathology, NESDA recruited 19 % of the participants through the community settings, 54 % through primary care settings and 27 % through mental health care organizations. The community-based sample was based on two already-available cohorts, NEMESIS[86] and ARIADNE[87], from previous studies. The primary care participants were recruited from 65 general practitioners in three research sites, Amsterdam, Groningen, and Leiden, through a 3-stage screening procedure consisting of the Kessler-10 questionnaire (K-10)[88] and a telephone interview involving the short form of the Composite International Diagnostic Interview assessing major depressive disorder, dysthymia, generalized anxiety disorder, social phobia, agoraphobia, and panic. The participants from the mental health care were recruited from out-patient clinics around the three research sites, and they consisted of newly enrolled patients at these clinics. The diagnoses of depression and anxiety disorders were ascertained through a structured psychiatric interview (e.g., Mini International Neuropsychiatric Interview (MINI), and Structured Clinical Interview for DSM-IV (SCID)).

Of the 2,981 participants at baseline, 78 % had a lifetime depression and / or an anxiety disorder that included current diagnoses as well as diagnoses earlier in life, of which 57 % were diagnosed with current (six-month prevalence) anxiety or depressive disorder, 21 % with a remitted (lifetime but not current) anxiety or depressive disorder, and 22 % had no depression and/or

anxiety disorder. The general inclusion criterion was an age of 18 through 65 years. Exclusion criteria were (i) a primary diagnosis of a psychotic disorder, bipolar disorder, obsessive-compulsive disorder, or addiction disorder and (ii) non fluency in Dutch language.

The 4-hour baseline data were collected using self-report questionnaires, interviews, and a medical examination, a cognitive computer task, and collection of blood and saliva samples. The data was obtained on the presence, severity, and chronicity of anxiety and depressive disorders, as well as the demographic characteristics, psychosocial, psychological, physiological determinants, major life events, health behaviors including alcohol intake, smoking, drugs, physical activity and genetic measures of the participants. Further details about the NESDA design and sample can be found in Penninx et al.[89]. Ethical approval for the NESDA study protocol was obtained centrally from the Ethical Review Committee of the VU University Medical Center and locally from the review boards of each participating center. All participants signed informed consent.

In the present study, only the participants (N= 1,055) who developed psychopathology, that is, anxiety disorders and / or depression, after starting smoking, were selected.

Measures

Smoking

Smoking behavior was measured by a self-constructed questionnaire including past and current smoking questions. Age at smoking-onset was defined as the age at which the respondents started smoking regularly. Two types of variables were created for age at smoking onset: a continuous variable (age in years) and a categorical variable that had two levels, early-onset smokers (10 - 15 years) and late-onset smokers (> 15 years). This represented a median split of age at onset of smoking.

Psychopathology

The lifetime diagnoses and age at onset of depression and anxiety disorders (GAD, social phobia, agoraphobia, and panic) were ascertained using the lifetime version of the Composite International Diagnostic Interview (CIDI version 2.1)[90]. The CIDI is a structured interview designed to produce diagnoses of psychiatric disorders according to both the DSM-IV and the ICD-10 definitions and criteria. The CIDI has high inter-rater reliability, high test-retest reliability and high validity for depressive and anxiety disorders[90, 91]. Throughout this paper, the term psychopathology refers to depression and/or anxiety disorders.

Other Covariates

Other covariates under study were gender, education, and childhood trauma. We included childhood trauma in the analysis because it was found to have an association with anxiety and depression[92]. Childhood trauma was assessed with the semi-structured Childhood Trauma Interview[93]. The participants were asked if they had any type of traumatic experience including emotional and/or psychological neglect, and physical and/or sexual abuse before age 16. These four kinds of childhood trauma were assessed by questions such as whether the participants had encountered any such experience caused by their natural or step parents, siblings, relatives, or somebody else before age 16. Participants answered "yes" or "no" to each category of childhood trauma; they also recorded the frequency of these trauma on a five-point scale: (1: once, 2: sometimes, 3: regular, 4: often, 5: very often). A cumulative index, childhood trauma index, was calculated consisting of sum scores of frequency ranging from 0-5. A higher score indicated higher frequency and more types of trauma.

Statistical Analyses

Preliminary analyses were conducted to ensure no violation of the assumptions of multivariate analysis. Multicollinearity, heterogeneity of

variance, normality of distributions, outlying scores, and coding errors were checked.

First, the differences between early- and late-onset smokers on age, gender, education, and childhood trauma and lifetime diagnoses of depression and anxiety disorders were compared using independent-samples t-test and chi-square test for independence. Cohen's d and Phi coefficient were used to measure effect sizes for t-tests and chi-squares, respectively. Cohen's d was defined as the difference between two means divided by the pooled standard deviation[94].

Next, to see if there is a difference between the two groups in the time period between smoking onset and the onset of psychopathology, a t-test was carried out. Furthermore, two t-tests were run separately for (i) time period between smoking-onset to depression-onset, and (ii) time period between smoking-onset to anxiety-onset. Cases that developed depression after the onset of anxiety disorder were not included in the time-to-depression-onset analysis. Similarly, cases that developed an anxiety disorder after the onset of depression were not included in the time-to-anxiety-onset analysis. Furthermore, we conducted two-way between-groups ANOVAs to examine gender differences on the time to the first onset of depression, and anxiety disorders in early- and late-onset smokers. The significance level was set to .01 because the variance of the dependent variable across the groups was not equal.

Finally, a hierarchical multiple linear regression analysis was conducted with the time between smoking onset and psychopathology onset as the outcome variable. The main predictor was the age at the onset of smoking. The model was adjusted for gender, education, and childhood trauma. Additionally, two similar regression analyses were conducted separately for depression and anxiety disorders. All analyses were conducted using PASW (V. 17.0) for Windows.

Results

Of the 1,055 smokers (current and former smokers) who developed depression and / or anxiety disorders after starting smoking, 51.7 % were early-onset smokers who started smoking before or at the age of 15 years. Table 1 presents the demographic and clinical characteristics of the participants. The differences between early- and late-onset smokers on the clinical characteristics were statistically non-significant.

Table 1. Participants characteristics stratified by age at the onset of smoking

Demographic and clinical characteristics	Early-onset smokers		Late-onset smokers		Effect size[a]
	N = 545		N = 510		
Age at baseline (Mean, SD)	42.0	12.3	47.1	11.1	-0.4***
Gender, F (%)	67.3		61.2		-
Education (%)					-
- basic	11.4		6.5		
- intermediate	62.6		61.8		
- high	26.1		31.8		
Childhood trauma (Mean, SD)	1.99	2.21	1.49	2.02	-0.12*
Lifetime diagnosis (%)					
Anxiety	70.5		66.9		-
- GAD	33.0		26.5		-
- Social phobia	29.2		20.4		-
- Panic					
-- without agoraphobia	12.8		17.3		-
-- with agoraphobia	23.1		19.6		-
- Agoraphobia	13.4		10.2		-
Depression	84.4		81.8		-

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

[a.] Only significant results reported.

The groups differed significantly on age at baseline interview ($p < 0.001$) and childhood trauma ($p < 0.05$) with small effect size (Cohen's d < 0.5).

In early-onset smokers, the first diagnosis was made after a smaller number of years after starting smoking than in late-onset smokers (Table 2). Early-onset smokers developed their first disorder almost five years sooner than late-onset smokers ($t_{(1015.2)} = -8.02$; $p < 0.001$; Cohen's d = -0.5). Table 2 shows that 23.2 % of the early-onset smokers and 12.8 % of the late-onset smokers were diagnosed with a disorder within the first five years after starting smoking, and this difference was statistically significant ($p < 0.05$). Further, we conducted separate t-tests for depression and anxiety disorders (Table 2). Early-onset smokers developed an anxiety disorder approximately 4.5 year earlier than late-onset smokers ($t_{(597)} = -5.72$; $p < 0.001$; Cohen's d = -0.5). However, depression was diagnosed only approximately 1.5 years earlier in early-onset smokers, and this difference was non-significant ($t_{(640)} = -1.89$; $p = 0.6$).

Three analyses of variance were run to see whether males and females differ in the number of years between the onset of the disorder and smoking. In the first ANOVA, the dependent variable was years to the onset of psychopathology (depression and/or anxiety). A significant main effect of gender ($F_{(1, 1051)} = 10.1$; $p = 0.002$; partial $\eta^2 = 0.01$) and smoking age onset ($F_{(1, 1051)} = 58.5$; $p < 0.001$; partial $\eta^2 = 0.053$) and a non-significant interaction effect of gender and smoking age onset ($F_{(1, 1051)} = 0.17$; $p > 0.05$) was found. Estimated marginal means show that early-onset smokers developed psychopathology earlier (Mean = 9.9 years) than late-onset smokers (Mean = 14.8 years). Similarly, females smokers (Mean = 11.4 years) were diagnosed with an earlier onset of psychopathology than male smokers (Mean = 13.4 years).

Table 2. Mean (SD) of years to the onset of psychopathology after smoking initiation in early- vs. late-onset smokers

	Early-onset smokers		Late-onset smokers		Effect size[c]
Years to the onset of psychopathology	9.7	9.3	14.6	10.5	-0.5**
Years to the onset of depression[a]	14.1	10.9	15.7	10.4	-
Years to the onset of anxiety disorders[b]	8.9	8.3	13.3	10.3	-0.5**
Psychopathology diagnosis within 5 years after starting smoking (% of the sample)	23.2%		12.8%		*

$^{**}p < 0.001$; $^{*}p < 0.05$

[a.] Cases who developed only depression after starting smoking, or who developed both depression and anxiety disorders but depression preceded anxiety disorders.

[b.] Cases who developed only anxiety disorders after starting smoking, or who developed both anxiety disorders and depression but anxiety disorders preceded depression.

[c.] Only significant results reported.

A similar ANOVA with years to the onset of depression as the dependent variable revealed a significant main effect of gender ($F_{(1, 638)} = 23.9$; $p < 0.001$; partial $\eta^2 = 0.04$) and a non-significant main effect of smoking age onset ($F_{(1, 638)} = 1.38$; $p > 0.05$). The interaction effect of gender and smoking age onset was also non-significant ($F_{(1, 638)} = 3.33$; $p > 0.05$). Female smokers had their depression diagnosis earlier (Mean = 13.4 years) than male smokers (Mean = 17.6 years). Finally, an ANOVA with years to the onset of anxiety disorder was run. The main effect of smoking age onset was significant ($F_{(1, 595)} = 26.0$; $p < 0.001$; partial $\eta^2 = 0.04$). Early-onset smokers had an earlier onset of anxiety (Mean = 9.2 years) than late-onset smokers (Mean = 13.4 years). The main effect of gender and the interaction effect of gender and smoking age-onset did not reach significance (ps > 0.05).

Last, a hierarchical multiple linear regression analysis was run. The outcome variable was the time to first onset of psychopathology after starting smoking. The predictor was age at the onset of smoking. Two models were fitted. The first model, including gender, education and childhood trauma, accounted for 2 % of the significant variance in the outcome variable (Table 3). The second model with gender, education, childhood trauma, and age at the onset of smoking explained 4 % of the total variance with 2 % additional variance being explained by age at the onset of smoking. Gender and age at the onset of smoking recorded significant beta values ($p < 0.001$); however, the highest beta value was obtained for age at the onset of smoking (*beta* = .14; $p < 0.001$) (See table 3).

Two additional regression analyses were run for depression and anxiety disorders separately. In the first regression analyses, participants who developed depression after they started smoking were selected; those participants who developed anxiety disorders before depression were excluded from the analysis. Two models were fitted. The outcome variable was time to the first onset of depression after starting smoking. The first model, adjusted for gender, education, and childhood trauma, explained 6 % of the variance in the outcome variable. The second model with smoking age onset as the predictor accounted for negligible amount of variance. Significant beta values were obtained for gender, education, and childhood trauma (Table 3).

Table 3. Regression of age at smoking onset on the time between smoking onset and the onset of psychopathology

		B	SE	β	*p*
	Years to the onset of psychopathology				
Model 1	Gender	2.4	0.6	.11	***
	Education	-0.1	0.1	-.03	0.3
	Childhood trauma	-0.3	0.1	-.05	0.1
Model 2	Gender	2.3	0.7	.11	***
	Education	-0.2	0.1	-.05	0.1
	Childhood trauma	-0.2	0.1	-.04	0.2
	Age at smoking onset	0.4	0.1	.14	***
	Years to the onset of depression				
Model 1	Gender	4.2	0.9	.2	***
	Education	-0.3	0.1	-.1	*
	Childhood trauma	-0.5	0.2	-.1	**
Model 2	Gender	4.2	0.9	.2	***
	Education	-0.3	0.1	-.1	*
	Childhood trauma	-0.5	0.2	-.1	**
	Age at smoking onset	-0.1	0.1	-.02	0.6
	Years to the onset of anxiety				
Model 1	Gender	1.9	0.8	.09	*
	Education	-0.1	0.1	-.04	0.4
	Childhood trauma	-0.2	0.2	-.04	0.3
Model 2	Gender	1.7	0.8	.08	*
	Education	-0.1	0.1	-.05	0.2
	Childhood trauma	-0.1	0.2	-.02	0.6
	Age at smoking onset	0.4	0.1	.13	**

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

In the second regression analyses, the participants who developed anxiety disorders after they started smoking were selected and those participants who developed depression before anxiety disorders were excluded from the analysis. Two models were fitted. The outcome variable was time to the first onset of anxiety disorders after starting smoking. The first model, adjusted for gender, education, and childhood trauma explained 1 % non-significant variance in the outcome variable. The second model with smoking age onset as the

predictor accounted for 3 % of the total variance with 2 % additional significant ($p = 0.001$) variance being explained by age at the onset of smoking. Gender ($\beta = 0.08$; $p < 0.05$) and age at smoking onset ($\beta = 0.13$; $p < 0.01$) recorded significant beta values (see Table 3).

Discussion

In this study, we investigated the relationship between age at smoking onset with the age at the onset of psychopathology in a large sample of smokers recruited from different settings. Although the study was cross-sectional and retrospective, we used a quasi-prospective design by selecting only the participants who started smoking before they were diagnosed with anxiety and/or depression.

We found that in early-onset smokers the first diagnosis of depression and/or anxiety disorders was made significantly earlier than in late-onset smokers. When we run separate statistical tests for depression and anxiety disorder, we observed this pattern of results for anxiety disorder only. After starting smoking, anxiety disorder was diagnosed significantly earlier in smokers who started smoking early in their life. Both of these results were observed with moderate effect sizes. However, we found a non-significant relation of age at the onset of smoking and time to the onset of depression.

We also found that female smokers developed depression and/or anxiety disorder, and depression alone, earlier than male smokers, though the strength of the association was not big. With respect to the diagnosis of anxiety disorders, there were no gender differences.

Finally, regression analyses indicated that young age at smoking onset was the most powerful predictor of years to the onset of psychopathology. However, when separate regression analyses were conducted for depression and anxiety disorders, age at the onset of smoking significantly predicted only anxiety disorders.

Our findings are consistent with the literature on the health effects of age at onset of smoking. For example, as opposed to late-onset smoking, starting smoking at an earlier age is associated with unfavorable physical health consequences[63, 64]. Early-onset smoking has also been reported to be associated

with later drinking problems. Grant[67] found that early-onset smoking predicted lifetime drinking and the subsequent development of alcohol abuse and dependence. Further, early-onset smoking was associated with excessive alcohol consumption, alcohol disorders, and heavy and longer smoking as compared to late-onset smoking. Another study comparing the outcomes of smoking in adolescence versus in adulthood, found that both smoking groups showed a significant association with depression and dysthymia; however, only early-onset smoking was associated with behavioral problems[82]. Similarly, early-onset smokers are more likely to be drug-dependent than late-onset smokers[83]. Given that smoking is often initiated in adolescence, it is surprising that despite the diverse empirical evidence of smoking-depression/anxiety link, the relation between early-onset smoking and depression/ anxiety disorders has not been addressed before in human studies. There are, however, some animal studies that have demonstrated that early-age nicotine exposure leads to behaviors that can be characterized as features of depression or anxiety disorders. For example, Iniguez et al.[85] showed that nicotine exposure in rats led to increased sensitivity to aversive or anxiogenic stimuli and decreased sensitivity to rewarding stimuli. However, this state was observed only in rats that were exposed to nicotine during adolescence, and not in those exposed during adulthood. Similarly, rats that were exposed to nicotine as adolescents showed increased anxiety-like behaviors, for example, low motor activity and decreased interest in food[84].

With small effect size, our finding that female smokers develop depression and anxiety disorder earlier than male smokers, is in agreement with research on gender differences in anxiety and depression[95].

In general, our findings extend previous research showing an association between smoking and a diagnosis of depression and/or anxiety disorders. In this association, age at smoking onset might be a crucial factor which has been overlooked in the research on smoking and depression or anxiety disorders.

The mechanisms underlying the relation between early-onset smoking and psychopathology are unclear; however, a young and developing brain is

probably more sensitive to the detrimental effects of nicotine which manifests in adverse health outcomes later in life. This view is consistent with animal models showing that nicotine exposure in critical and early periods of brain development produces profound and long-term changes in brain and behavior[96] and catecholamine systems[97] which may play a role in depression and anxiety disorders.

There are several methodological limitations inherent to the study design that warrant consideration. The first and most important limitation is the cross-sectional nature of the study which makes it more difficult to investigate the temporal sequencing of smoking and depression/ anxiety disorders. Second, the data on age of onset of smoking, depression and anxiety disorders are based on retrospective reports of the participants and may be subject to recall bias. Thus it is difficult to determine precisely the onset-time of depression and anxiety disorders; however, we found a five year difference between early- and late-onset smokers which is unlikely to be due to recall bias. Third, the effect of pre-existing drug and alcohol use and other confounding factors, such as, nicotine dependence, was not controlled because data on age-onset of these variables were not available. Fourth, because the sample is pre-dominantly Dutch, therefore other ethnic groups were under-represented in our study.

The current study, as an initial investigation of this association, provides an opportunity to stimulate longitudinal and prospective research on the relationship of early-onset smoking with depression and anxiety disorder. This study provides one more reason why smoking prevention and cessation programs should focus on children and adolescents. An important issue that may help improving these programs would be to elucidate the underlying mechanisms that link early-onset smoking and psychopathology.

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