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## Smoking and the course of anxiety and depression

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# CHAPTER 1

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## General Introduction

## **Background**

Despite effective campaigns to reduce cigarette smoking, smoking remains a significant public health burden and one of the largest causes of death worldwide. It is estimated that in Europe and the Central Asia region, 122 million people smoke, with a higher prevalence in males (56 %) than in females (17 %)<sup>1</sup>. In the United States, 40 % of 45 million smokers attempt to quit each year; however, only 3 % are successful<sup>2</sup>. The detrimental effects of smoking on physical health are widely publicized and well-understood. Recently, there is growing interest to investigate its effects on mental health. This interest is instigated by the strong empirical association of smoking with psychiatric disorders. The prevalence of smoking is higher among psychiatric patients than in the general population<sup>3,4</sup>. In a study assessing rates of smoking and smoking cessation in adults, it was found that respondents with a current mental illness had the highest current and lifetime smoking rates and lowest quitting rates compared to those with remitted mental illness and those with no history of mental illness<sup>4</sup>.

### **Smoking-Psychopathology Association Studies**

Cross-sectional studies have indicated that smokers experience certain signs of depression such as sadness, hopelessness, or trouble sleeping more often than non-smokers<sup>5,6</sup>. Similarly, smokers are more likely to have higher rates of depressive symptoms than non-smokers<sup>7,8</sup>. Other studies have distinguished between current smokers, former smokers and never-smokers. In a report from the National Household Survey on Drug Abuse (NHSDA), current adolescent smokers had the highest odds of depressive symptoms, followed by former smokers, and then never-smokers<sup>9</sup>. Consistent with these findings in adolescents, studies in adults<sup>10-14</sup> and elderly<sup>15</sup> have also found significant differences among current smokers, former smokers and never-smokers in their symptoms of depression.

There seems to be a dose-response relationship between smoking and depression. Heavy smoking, as opposed to light smoking, is related to increased

severity of depressive symptoms<sup>7, 10, 16, 17</sup>. Similarly, the number of days smoked predicts depressive symptoms<sup>8</sup>. Many heavy smokers fulfill criteria for nicotine dependence. It is, therefore, not surprising that high levels of depressive symptoms are associated with nicotine dependence. In one study, it was found that as compared to non-dependent-, former, and never-smokers nicotine-dependent current smokers had higher scores on CES-D<sup>18</sup>.

The smoking-anxiety association has received relatively little research attention. Regular smokers diagnosed with panic disorder have greater severity and intensity of anxiety symptoms than patients who do not smoke<sup>19</sup>. Similarly, heavy smokers have more severe anxiety symptoms than light smokers<sup>20</sup>.

Depression and anxiety disorders often co-occur. In a large population-based survey of adults, depression was only marginally associated with smoking except in the presence of comorbid anxiety. Comorbid disorders had the strongest association with smoking, followed by anxiety, and then depression<sup>21</sup>.

Cross-sectional studies have also shown that the prevalence of smoking in depressed individuals is higher than in the general population. Depressed individuals are more likely to have ever smoked, and they are less successful in their attempts to quit smoking than those with no history of major depression<sup>22</sup>. Individuals with depressed mood, a history of major depression, or both conditions have greater likelihood of ever smoking and smoking initiation than never-depressed<sup>23</sup> across all developmental stages. The prevalence of smoking seems to be related to the severity of depression<sup>24, 25</sup>.

Studies that examine smoking prevalence in individuals with anxiety disorders usually focus on patients with panic disorder. Zvolensky et al.<sup>26</sup> put forward a theory suggesting that the association of smoking with anxiety disorders is specific to panic disorder and not generally to other anxiety disorders. To test this theory McCabe et al.<sup>27</sup> examined smoking behaviors across three anxiety disorders and found that smoking prevalence was higher in patients with panic disorder than in patients with social phobia or obsessive-

compulsive disorders. Moreover, patients with panic disorder were more likely to be heavy smokers.

## **Developmental Pathways to the Co-occurrence of Smoking and Psychopathology**

### ***Depression and Anxiety Preceding Smoking***

The self-medication hypothesis posits that the motivation to continue to smoke is to alleviate depressive symptoms and so, depression is a predisposing factor in smoking initiation. This has been investigated in a number of longitudinal studies. For example, two six-wave longitudinal school-based studies found that depressive symptoms predicted later cigarette use<sup>28, 29</sup>. Another study found that adolescents with depressive symptoms were more likely to start smoking than those with no depressive symptoms<sup>30</sup>. These studies investigated the relation of smoking with depressive symptoms and not with a clinical diagnosis of depression, which also seems to be associated with smoking. For example, young people who met DSM-IV criteria for major depression were interviewed at 16, 18, and 21 years of age and were found to have elevated daily smoking rates and nicotine dependence<sup>31</sup>.

Anxiety disorder as a predisposing factor in the onset of smoking has not been studied extensively. One population-based study found that non-smokers and non-dependent smokers with social fears had increased odds of subsequent nicotine dependence during a 4-year follow-up<sup>32</sup>.

Few studies have assessed the role of both depressive and anxiety symptoms in smoking initiation. In a recent 10-year longitudinal school-based study, increasing severity of the symptoms of depression and anxiety in teenage was associated with an increased risk of nicotine dependence in young adulthood<sup>33</sup>. In a population-based study, it was found that pre-existing, currently active psychiatric disorders (unlike remitted disorders) including major depression and anxiety predicted subsequent onset of daily smoking and progression to nicotine dependence. Individuals with more than one pre-existing

disorder were at higher risk to starting smoking and progressing to nicotine dependence than individuals with one currently active psychiatric disorder<sup>34</sup>.

### ***Smoking Preceding Depression and Anxiety***

The role of smoking as a vulnerability factor in the development of depression has been examined in significant epidemiological investigations and population-based surveys using longitudinal design. The question of whether adolescent cigarette smoking predicts the development of depressive symptoms was addressed in a longitudinal follow-up survey of adolescents who were not depressed at baseline. Cigarette smoking was found to be the stronger determinant of developing depressive symptoms. Moreover, a dose-response relationship was observed between smoking level and depressive symptoms<sup>35</sup>. In two large population-based studies on adolescents, smokers exhibited high depressive symptoms at follow-up than non-smokers<sup>36, 37</sup>.

Smoking is associated not only with elevated depressive symptoms but also with an increased risk of clinical depression as assessed according to DSM criteria. In population-based, longitudinal studies on adults, a strong association was found between smoking and subsequent depression<sup>38, 39</sup>. Furthermore, total smoking years and number of cigarettes smoked per day were associated with increasing risk of major depression<sup>38</sup>. Another population-based prospective investigation revealed that pre-existing daily smoking predicted the onset of major depression, dysthymia, panic disorder, agoraphobia, alcohol- and drug-use disorders. Furthermore, independent of nicotine dependence, current smokers were more likely than former smokers to have subsequent onset of panic disorder, agoraphobia and substance use disorders<sup>40</sup>.

### ***Investigating the Bi-directionality of Smoking-Depression / Anxiety Association***

Smoking and depression may mutually influence each other. A number of longitudinal studies have found a two-way temporal relation. For example, in adolescents, heavy and persistent smoking predicted increase in depressive

symptoms in a 1.5 year period after controlling for baseline depressive symptoms and other potential confounders; conversely, severe and persistent depressive symptoms predicted increases in smoking rates across the same time period after controlling for baseline smoking and other confounding variables<sup>41</sup>. In another longitudinal study it was found that never-smokers at follow-up (1 year later) had lower depressive symptoms at baseline than those who were current or former smokers at follow-up. Baseline never-smokers with high depressive symptoms had a higher likelihood of being a smoker one year later. The study also found that current smokers and former smokers developed high depressive symptoms over time than never-smokers. Moreover, baseline never-smokers who started smoking at follow-up had high depressive symptoms at both waves than baseline never-smokers and former smokers whose smoking status did not change at follow-up<sup>42</sup>. Consistently, history of major depression at baseline has increased the risk for progression to daily smoking and vice versa in a population-based study of young adults<sup>43</sup>. A history of major depression has increased the risk for progression to nicotine dependence. Similarly, a history of nicotine dependence was associated with first-incident of major depression than no history of nicotine dependence in a prospective population-based study of young adults<sup>44</sup>.

Several longitudinal studies that examined two-way smoking-depression temporal association found evidence for a uni-directional relation from smoking initiation to the development of depressive symptoms. For example, in one study, a one-way temporal relation was found; prior smoking was associated with a modest increased risk of subsequent depressed mood; however, prior depressed mood was not associated with a risk to starting smoking<sup>45</sup>. Similarly, in a large population-based study, it was found that at 1-year follow-up, current smoking was the strongest predictor of developing high levels of depressive symptoms; however, baseline high rates of depressive symptoms were not predictive of heavy smoking<sup>46</sup>. Similar uni-directional temporal relation from starting smoking to developing depressive symptoms<sup>47, 48</sup> or major depression<sup>49</sup> was observed in other studies.

Studies that investigated the directionality of smoking-anxiety association found a one-way temporal association from starting smoking to the onset or increasing risk of an anxiety disorder. No evidence for the reverse association, in which anxiety was a predisposing factor to start smoking, was found. Breslau and Klein<sup>50</sup> found that daily smoking was associated with an increased risk of the first onset of panic attack, and the risk was higher in current than in former smokers. However, prior panic attacks did not predict the onset of daily smoking<sup>50</sup>. A similar pattern of uni-directional association between smoking and panic disorders was reported in a school-based study<sup>51</sup>. Cigarette smoking may also be associated with an increased risk of other anxiety disorders. In a 3-wave community-based prospective investigation of adolescents, it was found that heavy smoking during adolescence was associated with an increased risk of generalized anxiety disorder, agoraphobia and panic disorder during early adulthood after controlling for demographics, anxiety and depression during adolescence, alcohol and drug use, and parental smoking. No association of smoking with obsessive-compulsive disorder or social anxiety was found. Anxiety disorders during adolescence were not associated with starting smoking in young adulthood<sup>52</sup>. Another study found that regular smokers and nicotine-dependent smokers at baseline had an increased risk for new onset of panic attacks and disorder and other anxiety disorders except for generalized anxiety disorder and obsessive-compulsive disorder at a 4-year follow-up period; however, after controlling for comorbid disorders including depression, anxiety and substance-use disorders, smoking or nicotine dependence increases the risk of only panic attacks and disorders. Pre-existing panic attacks or disorder was not associated with subsequent smoking initiation or the development of nicotine dependence<sup>53</sup>.

Some studies investigated the temporal association of smoking with comorbid anxiety and depressive disorders. In a prospective population-based study, a bidirectional association between a mental disorder and smoking was found; starting smoking was associated with the subsequent first-ever incidence of generalized anxiety disorder and dysthymia, whereas generalized anxiety disorder was associated with subsequent onset of smoking<sup>54</sup>. In a 13-year

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population-based study, nicotine-dependent young adults had elevated rates of anxiety and depression after controlling for history of mental health problems and other covariates. However, reduced mental health did not predict subsequent smoking initiation or the development of nicotine dependence<sup>55</sup>.

# Theories Explaining Smoking-Depression / Anxiety Association

## Causal Theories

Two different causal hypotheses have been put forward to explain these co-occurring conditions: (i) depression and anxiety disorders instigate smoking initiation, or maintain smoking behavior as a means of self-medicating negative affect<sup>17, 56, 57</sup> which might be the result of neuropharmacological actions of nicotine in the brain leading to pleasure stimulation and the reduction of anxiety and tension<sup>58</sup>. This hypothesis is consistent with a finding that the level of monoamine oxidase B (which is inhibited or lowered by anti-depressants) is lower in the brains of smokers than in former smokers or non-smokers<sup>59</sup>; (ii) smoking initiation is temporally associated with the development of depression and anxiety disorders<sup>60</sup> probably because of the effect of nicotine on the neurotransmission systems that are implicated in depression and anxiety disorders<sup>61</sup>. Studies that have found a dose-response relationship between smoking and the symptom severity of depression or anxiety disorders<sup>7, 8, 10, 16, 17, 20</sup>, relatively high rates and symptoms of depression and/ or anxiety in nicotine-dependent current smokers than non-dependent, former- or never-smokers<sup>18, 44, 55, 62-66</sup>, higher rate of cigarette use and low mental health<sup>67</sup>, or longitudinal uni-temporal association in either direction<sup>28-40, 46-50, 52, 53, 55, 68</sup> can further support these causal hypotheses.

## Non-Causal Theories

Non-causal theories have been suggested when a bidirectional association between smoking/ nicotine dependence and the affective disorders was found<sup>41, 44, 54, 69, 70</sup>. These theories have gained support from a number of twin studies that proposed that these co-occurring conditions can both be explained by shared genetic<sup>71-75</sup> and environmental factors<sup>71, 75-77</sup> that increase both smoking as well as depression risks, independent of each other.

## **Shared Vulnerability Factors Explaining Smoking-Depression / Anxiety Association**

As mentioned earlier, some longitudinal studies, that investigated the nature of the direction of smoking-psychopathology association, found a bi-directional temporal association in which smoking was associated with the onset of an affective disorder, and vice versa. These studies suggested the shared vulnerability hypothesis of smoking-psychopathology association, and conceptualized that common vulnerability factors might operate that reflect this association<sup>44, 69</sup>. This hypothesis has gained support from twin studies. In these studies evidence has been found for genetic and environmental factors accounting for the co-variation between depression and smoking. A prospective study on female twins tested both causal and non-causal models for evaluating smoking-major depression association. No direct causal relation in either direction was observed. However, controlling for the personal history of smoking and of major depression, a family history of major depression predicted smoking and a family history of smoking predicted major depression. Environmental factors also played some role which were mainly individual-specific and had little in common. Thus the study supported the non-causal model whereby the comorbidity was mainly due to genetic factors<sup>72</sup>. Another study examined the relationship between depression, smoking and nicotine dependence in male twins and explored genetic and environmental influences. Genetic factors predisposed to both depression and smoking and nicotine dependence. The odds of smoking in co-twins of depressed probands was greater than those in which neither of the twins had a lifetime history of depression. Moreover, the non-depressed co-twins of the depressed probands reported more withdrawal symptoms and depressed mood after quitting<sup>74</sup>. After controlling for familial factors, that is, by using discordant twin-pairs, smoking remained a gender-sensitive predictor of depressive symptoms, thus supporting the causal association. However, after controlling for genetic factors, that is, by using monozygotic and dizygotic twin-pairs, the persistent smokers and the quitters among the monozygotic twin-pairs were at higher risk for depression than among the dizygotic twin-pairs. The stronger association in men was modestly accounted for by underlying shared genes<sup>73</sup>. Similarly, the question of

whether major depression, smoking and nicotine dependence share a common genetic and /or environmental liability, and whether there is a difference between these different trajectories of smoking, was addressed in another study. A non-causal association was found, which, in males, was entirely accounted for by shared underlying genes, whereas in females, both genetic and environmental liabilities accounted for this comorbidity<sup>71</sup>. Inconsistent with these findings, McCaffery and colleagues found that the significant association of current and lifetime smoking with depressive symptoms in late-adult male twins<sup>76</sup> and adolescent male twins<sup>75</sup> was predominantly influenced by non-shared environmental factors while in adolescent female twins<sup>75</sup> both genetic and non-shared environmental factors accounted for the co-variation. A study investigating the genetic and environmental liability factors of smoking-panic association in female twin-pairs found that panic attacks and lifetime smoking had shared or familial environmental factors and no genetic liability factors in common<sup>77</sup>.

## **Other Risk Factors**

Other studies in general population and schools have found common risk factors that explain smoking-psychopathology association. For example, after controlling for the effects of demographic variables, comorbid depression, neuroticism, generalized anxiety disorder, and substance-use disorders, neuroticism was an independent predictor of the co-occurrence of smoking and panic attacks in adults<sup>78</sup>. A birth cohort was examined until the age of 16 years (N = 947), and it was found that significant associations between depressive symptoms and nicotine dependence were largely explained by common risk factors such as affiliation with deviant peers and lower self-esteem<sup>63</sup>. Another longitudinal investigation that followed students from teenage to young adulthood found that the association between smoking and panic attacks was no longer significant after adjusting for parental smoking and parental anxiety disorder<sup>51</sup>. Another risk factor explaining smoking-depression association was a history of conduct problems which was a predictor of both smoking and depression, and partially accounting for this association<sup>43</sup>.

To explain conflicting findings in the literature regarding smoking-depression association, Johnson et al.<sup>79</sup> in a population-based sample of young adults tested Neale and Kendler's<sup>80</sup> etiological models of comorbidity for lifetime major depression and different smoking levels. The correlated liability model explained the comorbidity of depression with daily smoking, heavy smoking and nicotine dependence where familial liability explained the substantial amount of variance shared between depression and these levels of smoking; and in case of ever-smoking, it was associated with depression only when the smokers exceeded a higher threshold on the liability of smoking. Thus, depression is associated with regular (heavy) smoking, and ever-smokers would have depression only in case of heavy smoking.

## Smoking-Depression / Anxiety Possible Linking Mechanisms

To date, the mechanisms underlying the association of smoking with depression and anxiety disorders have rarely been investigated.

### BDNF Val<sup>66</sup>Met Polymorphism

One possible mechanism linking smoking to an affective disorder may be BDNF Val<sup>66</sup>Met polymorphism. The *BDNF* gene which, in humans, is located on chromosome 11, encodes the BDNF protein<sup>81</sup>. The single nucleotide polymorphism (SNP) rs6265 in BDNF gene results in an amino acid Valine-to-Methionine substitution at codon 66 (Val<sup>66</sup>Met)<sup>82</sup>.

The Val<sup>66</sup>Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene may be a plausible candidate gene polymorphism underlying smoking-depression/ anxiety association. An association of this polymorphism has been found with affective disorders<sup>83-86</sup>, and to some extent, with smoking<sup>87, 88</sup> and other addictive behaviors<sup>89, 90</sup>.

Several studies have supported the association of BDNF Val<sup>66</sup>Met polymorphism with clinical major depression. For example, Met<sup>66</sup> carriers were more often diagnosed with major depression than Val<sup>66</sup>Val carriers<sup>85</sup>. Few studies that investigated the relationship of combination of gene markers including BDNF Val<sup>66</sup>Met polymorphism with depression, found that haplotype analysis of the combination of markers including BDNF rs6265 produced significant associations with major depression<sup>83, 84, 86</sup>. With the exception of one study in a community sample of children and adolescents<sup>91</sup>, no association of BDNF Val<sup>66</sup>Met polymorphism has been found with anxiety disorders including generalized anxiety disorder and panic disorder<sup>92-94</sup>.

Though not extensively, the polymorphism has also been investigated in relation to addictive behaviors. Heroin-dependent individuals were more often involved in drug-seeking behaviors and higher rates of cigarette use if they

carried the Met<sup>66</sup> allele of BDNF gene polymorphism as compared to those having Val<sup>66</sup>Val genotype<sup>90</sup>. Similarly, Met<sup>66</sup> carriers were more likely to be current and former smokers than never-smokers<sup>87</sup>; however, a following study failed to replicate these findings<sup>88</sup>. A recent study with healthy Chinese male participants reported that smokers with the Met<sup>66</sup> allele of the BDNF gene initiated smoking significantly earlier than the Val<sup>66</sup>Val carriers<sup>95</sup>.

These studies indicate that BDNF Val<sup>66</sup>Met polymorphism may be involved in psychopathology and in addictive behaviors, however, there are some inconsistencies in findings, and the number of studies and sample size are small. Moreover, there is no study that has investigated smoking-psychopathology association taking into account the role of this polymorphism. It has been suggested that gene-environment interaction studies may be more useful to elucidate the underlying molecular mechanisms that may explain the association between different phenotypes<sup>96</sup>. We investigate the smoking-psychopathology association and examine the role of BDNF Val<sup>66</sup>Met polymorphism in this association.

## **Serum Brain-Derived Neurotrophic Factor**

Another possible linking mechanism may be serum brain-derived neurotrophic factor (BDNF) which has been shown to be associated, both, with smoking and with depression and anxiety. BDNF is a small dimeric protein densely expressed in the central and the peripheral nervous system with high concentrations in the hippocampus and cerebral cortex<sup>97, 98</sup>. It is involved in the growth, development, survival, and function of neurons in the nervous system<sup>99</sup>. Animal studies have shown that stress decreases the expression of BDNF mRNA and protein in rat brain<sup>100, 101</sup>. Human postmortem studies have found reduced expression of BDNF mRNA and proteins in the brain of suicide victims diagnosed with different psychiatric disorders including depression, as compared to those with no psychiatric diagnosis<sup>102</sup>.

Clinical studies have consistently reported the down regulation of serum BDNF expression with regard to depression. Various studies have shown that

depressed patients are characterized by lower serum BDNF levels than normal healthy controls<sup>103-113</sup> and that, the severe the depressive symptoms, the lower the serum BDNF levels<sup>104, 109, 111, 114-118</sup>. Two recent meta-analyses have confirmed these findings<sup>119, 120</sup>.

Given that depression and anxiety disorders are highly comorbid, and may share similar pathophysiological factors<sup>121-124</sup>, few studies have also investigated serum BDNF levels in patients with anxiety disorders. One study found lower baseline serum BDNF in patients with panic disorder as compared to normal controls<sup>125</sup>. A recent study reported gender-specific association of serum BDNF with anxiety: female patients diagnosed with anxiety had lower serum BDNF than female healthy participants, while no differences were found in male participants<sup>126</sup>. However, one study did not find significant difference in serum BDNF between patients with panic disorder and healthy participants<sup>127</sup>. Taken together, these preclinical and clinical studies adequately support the role of BDNF in the pathophysiology of depression and anxiety disorders.

There is also an evidence of an association of serum BDNF with smoking/ nicotine exposure, however, research in this area is sparse. An animal study has found that the expression of BDNF mRNA and protein in the hippocampus of neonatal piglets is significantly increased following nicotine infusion<sup>128</sup>. Few studies in humans have also investigated an association of serum BDNF with smoking and nicotine dependence. With the exception of a small Japanese study (N = 29; 16 smokers)<sup>129</sup>, these studies have found that smoking was associated with increased serum BDNF levels<sup>130, 131</sup>.

Given that smoking and nicotine dependence are highly associated with depression and anxiety disorders, there is reason to examine serum BDNF levels in relation to smoking/ nicotine dependence and depression/ anxiety. This issue has not been addressed before.

## Attentional Control

Attentional bias in smokers to smoking-related cues has widely been documented, and it has been reported that smokers preferentially allocate their attention to such cues<sup>132-151</sup>. This attentional tendency has been thought to be important in maintaining drug-seeking behavior by enhancing the perception of drug-related cues in the environment, increasing drug-related cognitions for the cues and making it difficult to draw attention away from them; and because of the limited capacity of attention, the attentional resources left of competitive cues are depleted. The smoker may relapse to smoking after quitting because it is difficult for the addict to apply attentional resources to prevent relapse<sup>152</sup>.

The ability of an individual to use executive functioning to selectively keep focus on task-relevant stimuli and to inhibit interference from distracting stimuli has been termed as attentional control<sup>153</sup>. In high-anxious individuals, inhibiting processing of task-irrelevant threatening stimuli seems to be difficult as compared to low-anxious individuals<sup>154</sup>. Similarly, low attentional control is associated with distracting effect of task-irrelevant threat-related emotional cues<sup>155-157</sup>. These findings suggest that anxiety is associated with impaired inhibition, and that better attentional control might help reducing anxiety by disengaging a person's attention from threat.

Attentional control might be another possible mechanism linking smoking with negative mood. There is no study investigating the role of attentional control in smoking-psychopathology association. However, it can be speculated that smokers with better attentional control might be able to disengage their attention from smoking-related cues in the environment, and thus may be able to control their smoking urges which might help improve their mood states.

## Aims and Outlines of the Thesis

The main objective of this thesis is to enhance our understanding of the association of smoking with depression and anxiety disorders, and to find possible explanations of this association. We used data from Netherlands Study of Depression and Anxiety, or NESDA<sup>158</sup> to address our research questions regarding smoking-psychopathology association (chapter 2 to chapter 5). In chapter 6, we investigated the role of attentional control in attentional bias to smoking-related pictures. The data for this project were collected using the students of Leiden University.

1. Given that early-age nicotine exposure has adverse effects on brain and behavior (see for example, Slawecki et al.<sup>159</sup>, Iniguez et al.<sup>160</sup>, Thapar et al.<sup>161</sup>), chapter 2, retrospectively, examines the association of smoking age-onset with the onset of depression and/ or an anxiety disorder. The chapter is based on the data of those psychiatric patients who developed depression and / or an anxiety disorder after they started smoking.
2. In chapter 3, the severity and course of depressive and anxiety symptoms in never-smokers, former smokers, current smokers without nicotine dependence, and current smokers with nicotine dependence is investigated. The data of only those patients are used who had a current diagnosis (past 6 months) of an affective disorder. The chapter is based on baseline and 2-year follow-up NESDA data.
3. In chapter 4, the interaction between the BDNF gene Val<sup>66</sup>Met polymorphism and smoking status with symptom severity of depression and anxiety disorders is investigated. The data is based on the same NESDA sample that was used in chapter 3, that is, patients with a current diagnosis of an affective disorder. The sample is stratified into never-smokers, former smokers, and current smokers with and without nicotine

dependence. This chapter is based on the baseline NESDA data.

4. Chapter 5 focuses on the association of serum BDNF with smoking or nicotine dependence in participants stratified according to their smoking status. The interaction of the BDNF gene Val<sup>66</sup>Met polymorphism and smoking status with serum BDNF is also examined. The analyses were controlled for the diagnosis of an affective disorder, as well as other demographic and health variables.
5. In chapter 6, attentional bias across information processing phases, that is, the initial orienting and the maintenance phases of attention, and the role of attentional control in each of these phases is investigated using a dot-probe task with smoking-related and neutral pictures in smokers and non-smokers. Participants are students from Leiden university with age range from 18 to 35 years.
6. Finally, chapter 7 summarizes the main findings of the studies, discusses possible mechanisms, and provides clinical implications and future research directions.

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