

# Tobacco Smoking and Depression – Results from the WHO/ISBRA Study

G.A. Wiesbeck<sup>a</sup> H.-C. Kuhl<sup>a</sup> Ö. Yaldizli<sup>a</sup> F.M. Wurst<sup>b</sup> on behalf of the WHO/ISBRA Study on Biological State and Trait Markers of Alcohol Use and Dependence

<sup>a</sup>Psychiatric University Clinics, Basel, Switzerland; <sup>b</sup>Christian-Doppler-Clinic, Paracelsus Medical University, Salzburg, Austria

## Key Words

Tobacco smoking · Major depression · Alcohol dependence · Cocaine dependence

## Abstract

**Aims:** To elucidate the relationship between tobacco smoking and depression, and to estimate the impact of other substance dependencies. **Design:** Cross-sectional. **Participants:** A total of 1,849 men and women were interviewed face-to-face using a validated structured questionnaire. According to their tobacco smoking behavior, participants were grouped into never smokers, ex-smokers and current smokers. **Measurements:** Data were generated through the WHO/ISBRA study, an international multicenter study with a cross-sectional design. A standardized questionnaire was administered face-to-face by trained interviewers. Logistic regression analysis was used to predict depression. **Results:** There was a significant difference across the 3 smoking groups in the number of subjects who had major depression (DSM-IV) during their lifetime. The highest rate of depressives was found in current smokers (23.7%), the lowest rate in never smokers (6.2%), while the rate of those who had quit smoking (14.6%) was between both. In a logistic regression analysis, alcohol dependence (both current and during lifetime) as well as cocaine dependence were significant predic-

tors of depression. However, the association between smoking and depression still remained statistically significant. **Conclusions:** This study adds support to the evidence that smoking is linked to depression. It also elucidates the importance of taking into account alcohol and cocaine dependence since they have a significant impact on the relationship between smoking and depression.

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## Introduction

There is sound evidence of an association between smoking and depression, e.g. depressive symptoms during adolescence predict later smoking [1, 2], and major depression seems to be a risk factor for the progression from regular smoking to tobacco dependence [3]. Smokers revealed higher rates of depression than non-smokers [4–7]. Such an association has been reported across different age groups, such as adolescents [8], young and mid-

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dle-aged adults [9, 10], as well as people aged 60 or over [11]. However, smokers are not only at an elevated risk of depression, but also of suicidal behavior independent of prior depression [12]. Hemmingsson and Kriebel [13] even found a significant dose-response relationship between smoking and the risk of suicide, with heavy smokers (>20 cigarettes/day) having a more than 2-fold risk of committing suicide compared to non-smokers.

Some authors reported a gender-specific effect. For example, Wang et al. [14] found male smokers were 4 times more likely to be depressed than male non-smokers, while there was not such an elevated risk in female smokers. Steuber and Danner [15] reported that females, but not males, revealed increased rates of depression around the onset of smoking and decreased rates of depression around smoking cessation. Karam-Hage et al. [16] used an experimental design: they demonstrated that men rather than women and highly depressed smokers rather than mildly depressed ones experienced pleasurable effects in a smoke exposure test after several days of abstinence. So far, the relation between smoking and depression is not clear, but gender seems to be an important intervening variable.

In population-based samples, depressed smokers are less likely to stop smoking than non-depressed smokers [17], while in treatment samples, depression does not seem to be related to the outcome of the smoking cessation treatment [18, 19]. However, smokers with a history of depression who give up smoking are at an increased risk of developing a new depressive episode, even if such episodes have not occurred for many years [10].

Although the comorbidities between smoking and depression have been well documented, so far there has been no study investigating the impact of substance dependencies other than alcoholism on the relationship between smoking and depression. In the present study, we wanted to bridge that gap. Therefore, this study had 2 major objectives: (1) to investigate the reported association between smoking and depression; (2) if one is found, to quantify this risk and identify other variables – specifically substance dependencies – which contribute to it.

## Methods

### *Data Source*

The data reported here were generated through the WHO/ISBRA Study on State and Trait Markers for Alcohol Use and Dependence, a multinational investigation recruiting participants in Australia, Brazil, Canada, Finland, Japan, Sweden and the United States. The cross-sectional design of this study, the diagnostic in-

struments used, as well as the characteristics of its participants have been described in detail previously [20].

### *Participants*

Participants were recruited by all centers after written informed consent. A total of 1,863 men and women were included across all drinking levels ranging from non-drinkers to heavy drinkers as well as dependent drinkers in treatment. Except for alcohol-related problems, all individuals were in good mental and physical health, as verified by both interview and physical examination. Individuals suffering from a current major medical or psychiatric disorder were excluded. Detailed information on the participants as well as on their alcohol-related problems were published by Glanz et al. [20]. Due to missing data on smoking, 14 cases had to be excluded from the evaluation. Therefore, the present analysis refers to a total of 1,849 participants.

### *Instruments*

All participants were evaluated with the WHO/ISBRA Interview Schedule, a structured questionnaire, which was carried out face-to-face by trained interviewers. The information gathered through this instrument allowed the diagnoses of various psychiatric disorders according to DSM-IV criteria. Before being applied to this study, the interview had been tested and revised in order to optimize its reliability [20].

Overall, the WHO/ISBRA interview collected information on recruitment setting, background characteristics, alcohol and drug use, lifetime and past 30 days occurrence of medical conditions as well as on family history. The interview also covered a section on tobacco smoking which gathered detailed information on past and present smoking behavior. These data were the basis of the present analysis.

### *Statistical Analysis*

For statistical analysis, SPSS 13 (SPSS Inc., Chicago, Ill., USA) was used. In the first step, we analyzed the association of smoking status (never smoker, ex-smoker, current smoker) and lifetime occurrence of depression. Here, differences between groups were compared by using the  $\chi^2$  test for categorical data and ANOVA for continuous variables. In a second analysis, we searched for correlated factors that could potentially confound the association between smoking and depression. Finally, those factors were entered into a logistic regression analysis to calculate their relative impact on the occurrence of depression.

## Results

The present analysis refers to a total of 1,849 participants who were grouped according to their smoking status as never smokers, ex-smokers and current smokers. These 3 groups differed significantly on major demographic characteristics as well as on several variables characterizing alcohol and drug dependencies (tables 1 and 2).

There is a major difference across the 3 groups in the number of subjects who had experienced a depressive

**Table 1.** Demographic characteristics of 1,849 participants grouped according to smoking status

	Never smoked (n = 663, 35.9%)	Ex-smoker (n = 314, 17.0%)	Current smoker (n = 872, 47.2%)	F or $\chi^2$
Age, years	36.6 ± 12.71	41.0 ± 11.53	36.6 ± 11.30	18.12***
Categorical data, %				
Gender female	37.3	27.1	31.7	11.15**
Race (6 d.f.)				25.26***
White	71.5	80.5	77.2	
Black	6.8	1.6	5.9	
Asian	16.9	14.1	11.0	
Other	4.8	3.8	5.9	
Marital status (4 d.f.)				38.97***
Married or living together	42.8	52.6	35.8	
Separated, divorced, or widowed	13.8	16.0	21.9	
Never married	43.4	31.4	42.3	
Area living (4 d.f.)				14.92**
Inner city	44.5	39.2	50.3	
Suburban city	38.1	44.9	34.4	
Other	17.4	15.9	15.2	
Currently unemployed	33.2	32.2	41.4	12.60**

Differences between groups were compared by using the  $\chi^2$  test for categorical data and ANOVA for continuous variables. \*\* p < 0.01, \*\*\* p < 0.001.

**Table 2.** Alcohol and drug dependencies grouped according to smoking status in 1,849 participants

	Never smoked (n = 663, 35.9%)	Ex-smoker (n = 314, 17.0%)	Current smoker (n = 872, 47.2%)	F or $\chi^2$
Alcohol dependence (4 d.f.), %				393.46***
Never dependent	81.1	57.6	32.9	
Lifetime but not current	4.8	18.8	13.0	
Current	14.0	23.6	54.1	
Lifetime drug dependence, %				
Sedatives	0	0	0.7	6.74*
Tranquilizers	0	0.6	1.3	8.61*
Opiates	0.2	0	0.8	5.36
Stimulants	0	0	0.9	9.00*
Marijuana	0.5	4.1	4.8	24.86***
Cocaine	0.9	2.9	9.6	61.24**
Heroin	0	0.3	1.4	11.02**
Inhalants	0	0.3	0.2	1.79
Hallucinogens	0	1.0	2.2	15.39***

Differences between groups were compared by using the  $\chi^2$  test for categorical data and ANOVA for continuous variables. \* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001.

episode during their lifetime (table 3). Almost 1 out of 4 smokers stated having such an episode compared to only 1 out of 15 among never smokers. Interestingly, ex-smokers were placed between both. Fifty percent of depres-

sions occurred within the first 3 years after smoking cessation and 20% even occurred within the first 12 months. The 3 groups did not vary significantly in their frequency of depressive episodes nor in their age of depression

**Table 3.** Relationship between smoking status and major depression

	Never smoked (n = 663, 35.9%)	Ex-smoker (n = 314, 17.0%)	Current smoker (n = 872, 47.2%)	F or $\chi^2$
Lifetime diagnosis of major depression, %	6.2	14.6	23.7	87.24*
Number of depressive episodes in those with major depression	4.9 ± 12.61	3.2 ± 4.57	5.8 ± 14.68	0.93
Age at onset of depression in those with major depression, years	27.1 ± 12.03	30.3 ± 11.82	27.5 ± 10.43	1.78

Differences between groups were compared by using the  $\chi^2$  test for categorical data and ANOVA for continuous variables. \*  $p < 0.001$ .

**Table 4.** Logistic regression analysis of factors associated with lifetime diagnosis of major depression grouped according to DSM-IV

	Lifetime diagnosis of major depression (yes/no)		
	Odds ratio	95% CI	p
Gender, female	2.43	1.78–3.31	<0.001
Smoking status			
Never smoker	Referent category		
Ex-smoker	2.37	1.44–3.92	<0.001
Current smoker	2.62	1.73–3.96	<0.001
Alcohol dependence			
Never	Referent category		
Lifetime but not current	1.64	1.01–2.68	<0.05
Current	2.84	1.97–4.08	<0.001
Lifetime drug dependence			
Sedatives	0.44	0.03–6.10	n.s.
Tranquilizers	1.10	0.24–5.09	n.s.
Opiates	3.39	0.54–21.30	n.s.
Stimulants	3.04	0.53–17.43	n.s.
Marijuana	1.76	0.91–3.40	n.s.
Cocaine	2.02	1.21–3.37	<0.01
Heroin	0.33	0.06–1.76	n.s.
Inhalants/solvents	5.10	0.42–61.95	n.s.
Hallucinogens	1.81	0.62–5.32	n.s.
Race			
White	Referent category		
Black	1.39	0.77–2.48	n.s.
Asian	0.24	0.10–0.57	<0.01
Others	0.73	0.39–1.39	n.s.
Marital status			
Married, living together	Referent category		
Separated, divorced, widowed	1.39	0.92–2.08	n.s.
Never married	1.16	0.82–1.66	n.s.
Unemployed	1.24	0.92–1.69	n.s.
Area living in			
Inner city	Referent category		
Suburban city	0.85	0.61–1.18	n.s.
Other	0.82	0.52–1.29	n.s.
Nagelkerke's R-square	0.234		

onset (table 3). Never smokers, ex-smokers and current smokers differed significantly in most of the demographic characteristics as well as on those variables referring to drug and alcohol dependencies. To quantify the relative impact of these potential confounders together with smoking on the occurrence of depression, we performed a logistic regression analysis with DSM-IV lifetime depression (yes/no) being the dependent variable. Smoking status as well as the other characteristics described in tables 1 and 2 were entered simultaneously as predictor variables. This yielded a model that is described by table 4 and achieves a Nagelkerke's R-square value of 0.23. Importantly, the association between smoking and depression still remained statistically significant, despite taking into account those confounders. Both smokers and ex-smokers have a more than 2-fold risk of depression than never smokers (table 4). However, the model clearly demonstrates the significant effect of other predictor variables such as alcohol dependence (both current and lifetime) and cocaine dependence.

## Discussion

This analysis was based on data gathered through the WHO/ISBRA study, an international multicentre investigation which comprised both healthy and substance-dependent participants who had been profiled in detail by using face-to-face structured interviews.

The major findings are: (1) there is a significant difference across the 3 smoking groups in the number of subjects who had ever experienced major depression (DSM-IV) during their lifetime; (2) alcohol dependence (both current and during lifetime) as well as cocaine dependence were significant predictors of depression; (3) even after adjustment for substance dependency, the associa-

tion between smoking and depression still remained statistically significant.

This analysis is, to the best of our knowledge, the first one that takes into account the impact of other substance dependencies on the relationship of smoking and depression. In addition, it confirmed the findings of previous research (see 'Introduction') that reported an association between both disorders: we found an almost 4-fold higher rate of depressives among current smokers than among never smokers. So far, there is convincing evidence that major depression is comorbid with smoking [3–7, 9].

Interestingly, ex-smokers carried a risk of depression which was significantly lower than current smokers, but still higher than never smokers. This would be in accordance with the hypothesis that tobacco smoking facilitates the occurrence of depression or, in other words, that smoking cessation is an effective way to reduce an individual's risk of depression. If so, there should be a relation in ex-smokers between when the last period of smoking occurred and the frequency of depression: depression should be less frequent in ex-smokers who stopped smoking a long time ago compared to those who stopped recently. Indeed, 50% of depressions occurred within the first 3 years after smoking cessation and 20% even occurred within the first 12 months, which suggests a rebound phenomenon. However, this difference between distant and recent smoking cessation failed to reach statistical significance ( $p = 0.057$ ), so the present study cannot add support to the 'smoking facilitates depression hypothesis'.

Several authors pointed to the role of monoamine oxidases (MAO) as an important biological link between smoking and neurotransmitter processes in the brain [21–23]. Since tobacco smoking leads to potent inhibition of MAO [22], smoking cessation may also affect these pathways, increasing an individual's vulnerability to depression during the period of withdrawal and thereafter [24]. Smoking-induced MAO inhibition might be a kind of self-medication of pre-existing depressive symptoms, which in turn might increase the risk of depressive symptoms recurring after the cessation of smoking (and MAO inhibition).

As many other studies, this investigation cannot make firm conclusions regarding the direction of the relation between smoking and depression. However, our findings are in accordance with the results reported by Steuber and Danner [15], who also reported an increased risk of depression depending on whether somebody never started, quit or maintained smoking. While neither their results nor ours prove that smoking leads to depression, they would be in agreement with such a hypothesis.

In the second phase of the analysis, the comorbidity of smoking and depression was controlled for a wide range of confounding variables that included sociodemographic factors as well as alcohol and drug dependencies. In the logistic regression analysis, it turned out that the probability of developing a major depression was partly explained by certain demographic factors (marital status, race), but to a greater extent by current and former alcohol dependence. Given the high prevalence rate of alcoholism and its high comorbidity with depression, and given the fact that as many as 80% of people who are alcohol dependent are also smokers [25, 26], most former investigations – which disregarded the impact of alcoholism on the association between smoking and depression – failed to notice a most important confounding variable. In our study, current alcohol dependence contributed as much as current smoking to the risk of depression.

Cocaine dependence had an equally strong impact upon depression as alcohol dependence. Among the variety of drug dependencies that have been included into the logistic regression model, cocaine dependence was the only one that contributed significantly to the risk of depression. Therefore, in future studies on the relationship of smoking and depression, cocaine and alcohol dependence should be considered as possible confounders.

Among the limitations of this analysis are: (1) the cross-sectional design of the study did not permit conclusions about the causal relationship between smoking and depression; as there were no data on the onset of each disorder, the question which came first can not be answered; (2) factors which were not assessed, such as traumatic life events, may partly account for the reported association between smoking and depression; for this reason, an unknown bias may have been present; (3) the participants of this study were selected by specific criteria as described above, and did not reflect a community-representative sample; therefore, the findings reported here cannot be transferred unrestrictedly to the general population; (4) we could not control for differences in the prevalence of treatment and the use of mental health services between the 7 countries of this multinational investigation.

Despite these limitations the results reported here are in line with others. Klungøy et al. [27] reported a risk of depression which was 4 times higher for heavy smokers compared to never smokers, as well as a dose-response relation with an increasing hazard for past smokers. Both go well with our finding of a significant association between smoking and depression with current smoking being more associated than former smoking, and former smoking more than never smoking.

In conclusion, the results of this analysis point to an association between smoking and depression. Future investigations on this comorbidity should take into consideration alcohol and cocaine dependence as essential confounding variables. Prospective studies will be necessary to interpret the direction of the relationship between smoking and depression.

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