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Tobacco smoking as a risk factor for major depressive disorder: population-based study

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Background
Smoking is disproportionately prevalent among people with psychiatric illness.

Aims
To investigate smoking as a risk factor for major depressive disorder.

Method
A population-based sample of women was studied using case-control and retrospective cohort study designs. Exposure to smoking was self-reported, and major depressive disorder diagnosed using the Structured Clinical Interview for DSM-IV-TR (SCID-I/NP).

Results
Among 165 people with major depressive disorder and 806 controls, smoking was associated with increased odds for major depressive disorder (age-adjusted odds ratio (OR)=1.46, 95% CI 1.03–2.07). Compared with non-smokers, odds for major depressive disorder more than doubled for heavy smokers (>20 cigarettes/day). Among 671 women with no history of major depressive disorder at baseline, 13 of 87 smokers and 38 of 584 non-smokers developed de novo major depressive disorder during a decade of follow-up. Smoking increased major depressive disorder risk by 93% (hazard ratio (HR)=1.93, 95% CI 1.02–3.69); this was not explained by physical activity or alcohol consumption.

Conclusions
Evidence from cross-sectional and longitudinal data suggests that smoking increases the risk of major depressive disorder in women.

Declaration of interest
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Tobacco smoking is a major public health problem and several preventive public health strategies have been implemented. However, smoking remains disproportionately prevalent among people with psychiatric illness and is often considered within the mental health profession to be a secondary or deferrable treatment goal to the control of the psychiatric illness. It is becoming increasingly clear that smoking is not innocuous to mental health, and may in fact aggravate mental illness or contribute to its onset. On a neurobiological level, this may be related to the impact of nicotine on monoamine neurotransmitter regulation, including dopamine, via the diffuse cholinergic pathways. This may underlie the circadian dysrhythmicity and hedonic dysregulation in smokers, and may predispose to the development of mood disorders. Smoking also has other systemic and metabolic consequences that may likewise increase this vulnerability.

There is already evidence that smoking is a risk factor for depression. Association data from cross-sectional studies support evidence from prospective studies to suggest that smoking precedes the onset of depression. However, there is only limited longitudinal data in the existing literature, and most longitudinal studies have involved time frames under 2 years, which may not be adequate to demonstrate the insidious effects of nicotine dependence. In this epidemiological study, we investigated the status of tobacco smoking as a risk factor for major depression using not only cross-sectional data but also longitudinal data that extend over a period of 10 years.

Method
Participants
This study is nested within the Geelong Osteoporosis Study, a programme of research originally designed to investigate the epidemiology of osteoporosis in Australian women, but recently expanded to examine both psychiatric illness and non-psychiatric diseases. The criterion for inclusion into the Geelong Osteoporosis Study is women listed on the current Australian Commonwealth electoral roll for the region known as the Barwon Statistical Division and the criteria for exclusion are inability to provide informed consent, death, and not able to be contacted. Reasons for non-participation are described elsewhere. During the period 1994–1997, 1494 women recruited into the Geelong Osteoporosis Study have been prospectively followed for a decade. At the time of writing, a further 208 had been recruited during 2005–2007. A total of 1043 women (aged 20–93 years) participated in a psychiatric assessment during the period 2004–2007, thus fulfilling the inclusion criteria for this study. The Barwon Health Research and Ethics Advisory Committee approved the study, and all participants provided informed, written consent.

Data
Lifestyle practices including smoking, alcohol consumption, habitual physical activity levels and exposure to disease were self-reported. Smoking was recognised if individuals reported regularly smoking more than one or two cigarettes per day for at least 6 months, and recorded details of smoking included frequency and period of exposure. Alcohol intake was recognised if alcohol was consumed several times per week or every day. Habitual physical activity was classified as active if participants reported ‘moving, walking and working energetically and participating in vigorous exercise’, otherwise they were classified as sedentary. Cardiovascular disease included hypertension, angina and coronary artery disease; diabetes encompassed both types 1 and 2. Socio-economic status was ascertained using Socio-Economic Index for Areas index scores based on census data from the Australian Bureau of Statistics. These data were...
used to derive an Index of Economic Resources (IER), which was
categorised into five groups, according to quintiles of IER for the
study region.

The Structured Clinical Interview for DSM–IV–TR Research
Version, Non-patient Edition (SCID–I/NP)\(^4\) was used to identify
women with a lifetime history of major depressive disorder and to
determine age at onset. Psychiatric interviews were conducted by
trained personnel.

**Study designs**

**Case–control**

Among 1043 women who underwent psychiatric assessment, 237
were diagnosed with major depressive disorder and 806 had no
history of major depressive disorder. Exposure to smoking was
recognised if smoking was practised prior to the onset of major
depression. Sixty-eight individuals were excluded because their
age at major depressive disorder onset was less than 20 years
(the minimum age for controls) and four were excluded because
it was unclear whether smoking pre- or post-dated major
depressive disorder onset. Thus, 165 individuals with major
depressive disorder and 806 controls were eligible for analysis in
this case–control study.

**Retrospective cohort**

Among 1043 women who underwent psychiatric assessment, a
decade of longitudinal data was available for 835. Based on
retrospective data, 164 were excluded because they had experi-
enced a major depressive disorder episode prior to baseline.
Among the 671 women aged 20–84 years with no history of major
depressive disorder at baseline and who were thus eligible for
analysis in this retrospective cohort study, 51 developed de novo
major depressive disorder and 620 remained major depressive
disorder-free during follow-up. Participants were classified as
smokers if they were current smokers at baseline, otherwise they
were classified as non-smokers.

**Statistics**

Statistical analyses were performed using Stata (version 9.0) and
Minitab (version 13). Standard descriptive statistics were used to
characterise the participants in each study.

In the case–control study, participants were selected as cases
(people with major depressive disorder) or controls (people with
no major depressive disorder), and exposure to smoking was
documented for each group. Logistic regression modelling was
performed to determine the association between smoking and
major depressive disorder. Age was defined as the age at major
depressive disorder onset for cases and age at baseline for
controls, and was categorised into age groups for analysis.
Smoking was investigated as a binary variable and was also
categorised into groups according to the average number of
cigarettes smoked per day (0, \(\leq 10\), 11–20, >20 cigarettes/day).
Age, socio-economic status, physical illness, physical activity and
alcohol consumption were tested in the models as potential
confounders and effect modifiers.

In the cohort study, participants with no history of
major depressive disorder at baseline were selected, categorised
as current smokers or not, and followed until a first major
depressive disorder episode or until the end of the follow-up
period. The effect of smoking on development of de novo major
depressive disorder was examined using multivariate Cox
proportional hazards regression analysis, using age as the time
axis. The proportional hazards assumptions were checked using

**Schoenfeld residuals before and after adjusting for potential
confounding by socio-economic status, physical illness, physical
activity and alcohol consumption.**

**Results**

**Case–control study**

Characteristics of the participants involved in the case–control
analysis are shown in Table 1. Participants with major depressive
disorder were younger and were more often smokers. Exposure
to smoking was documented for 73 of the 165 people with major
depressive disorder and for 269 of 806 controls. Prevalence of
smoking was thus greater among women with major depressive
disorder (0.44 (95% CI 0.37–0.52) v. 0.33 (95% CI 0.30–0.37),
\(P=0.008\)). Exposure to smoking increased the odds for major
depressive disorder (odds ratio OR=1.58, 95% CI 1.13–2.23,
\(P=0.008\)) and this association persisted, albeit attenuated, after
adjusting for age (age-adjusted OR=1.46, 95% CI 1.03–2.07,
\(P=0.031\)). Socio-economic status did not confound the associa-
tion between smoking and major depressive disorder (age- and
socio-economic status-adjusted OR=1.49, 95% CI 1.05–2.11,
\(P=0.026\)). Similarly, the association was not explained by a history
of self-reported cardiovascular disease or diabetes (adjusted
OR=1.47, 95% CI 1.04–2.09, \(P=0.030\)). Among the 342 smokers,
participants with major depressive disorder smoked more heavily
than those in the control group (median (interquartile range), 15
(10–20) v. 10 (8–20) cigarettes per day, \(P=0.059\)). Compared with
non-smokers, the odds for major depressive disorder tended to
increase 1.47-fold for women who smoked 11–20 cigarettes per
day (\(P=0.094\)) and more than doubled for those who smoked
more than 20 cigarettes per day (\(P=0.003\)) (Table 2).

Being physically active was found to be protective against
major depressive disorder (age-adjusted OR=0.58, 95% CI 0.37–
0.91, \(P=0.017\)). None the less, the association between smoking
and major depressive disorder was not explained by differences
in physical activity. The independent relationships between
smoking and physical activity on the risk for major depressive
disorder are shown in Fig. 1. Alcohol consumption did not affect
this association.

**Retrospective cohort study**

Characteristics of women included in this analysis are shown in
Table 3. Among 87 women who were current smokers at baseline,
13 developed de novo major depressive disorder during 781
person-years of observation, whereas among 584 non-smokers,
38 developed major depressive disorder during 5384 person-years
of observation. Estimated rates of major depressive disorder were
16.6 (95% CI 9.7–28.7) per 1000 person-years for smokers and 7.1
(95% CI 5.1–9.7) per 1000 person-years for non-smokers.

Exposure to smoking was found to increase the risk for
developing a first episode of major depressive disorder by 93%,
hazard ratio (HR)=1.93 (95% CI 1.02–3.69, \(P=0.045\)). A Kaplan–Meier survival plot showing the probability of remaining
free of major depressive disorder over a 10-year period for women
exposed and unexposed to smoking at baseline is shown in Fig. 2.
Adjustment for socio-economic status enhanced the risk (adjusted
HR= 2.01, 95% CI 1.03–3.93, \(P=0.042\)). Further adjustment for
alcohol consumption, physical activity or physical illness did not
attenuate this association.

**Discussion**

This study provides both cross-sectional and longitudinal
evidence consistent with the hypothesis that tobacco smoking is
associated with major depression. Our cross-sectional data demonstrate that exposure to smoking is associated with a 1.46-fold increase in the odds for major depressive disorder. Furthermore, our findings are suggestive of a dose-dependent association, with more than a two-fold increase in the odds of major depressive disorder for heavy smokers compared with non-smokers.

With the advantage of temporal sequencing, our longitudinal data demonstrate that smoking is associated with a near doubling of risk for developing de novo major depressive disorder over a 10-year period. These effects were independent of age and physical activity, and not explained by alcohol consumption.

Other cross-sectional studies have reported increased odds of depression in smokers, with results retaining statistical significance after adjusting for other major risk factors. Prospective studies, although limited, have further strengthened the suspected role of smoking in depression. In an 11-year population-based longitudinal Norwegian study, the hazard ratio for a first depressive episode increased with smoking in a dose-dependent fashion, such that the heaviest smokers (exceeding 20 cigarettes per day) had over four times the risk of those who had never smoked.

Increased incidence of major depression in smokers has been reported in other shorter studies, including data from adolescents. Longitudinal studies have also shown a reverse relationship, in which the presence of depression increased the risk of smoking progression. Positive effects on psychomotor performance and enhanced craving, as demonstrated in a

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**Table 1** Participant characteristics in the case–control study

<table>
<thead>
<tr>
<th>Age, years: median (IQR)</th>
<th>Major depressive disorder (n=165)</th>
<th>No major depressive disorder (n=806)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers, n (%)</td>
<td>73 (44)</td>
<td>269 (33)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Socio-economic status, n (%)</td>
<td>0.857</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintile 1 (low)</td>
<td>23 (14)</td>
<td>125 (14)</td>
<td></td>
</tr>
<tr>
<td>Quintile 2</td>
<td>33 (20)</td>
<td>184 (23)</td>
<td></td>
</tr>
<tr>
<td>Quintile 3</td>
<td>41 (25)</td>
<td>183 (23)</td>
<td></td>
</tr>
<tr>
<td>Quintile 4</td>
<td>29 (18)</td>
<td>142 (18)</td>
<td></td>
</tr>
<tr>
<td>Quintile 5</td>
<td>39 (24)</td>
<td>172 (21)</td>
<td></td>
</tr>
<tr>
<td>Alcohol users, n (%)</td>
<td>28 (17)</td>
<td>144 (18)</td>
<td>0.784</td>
</tr>
<tr>
<td>Physically active, n (%)</td>
<td>31 (19)</td>
<td>168 (21)</td>
<td>0.551</td>
</tr>
<tr>
<td>Cardiovascular disease, n (%)</td>
<td>0.290</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>11 (7)</td>
<td>48 (6)</td>
<td>0.727</td>
</tr>
</tbody>
</table>

IQR, interquartile range.

**Table 2** Smoking frequency (number of cigarettes per day) and the risk for major depression

<table>
<thead>
<tr>
<th>Cigarettes per day</th>
<th>Unadjusted OR (95% CI)</th>
<th>Age-adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>1.02 (0.56–1.88)</td>
<td>0.88 (0.48–1.64)</td>
</tr>
<tr>
<td>11–20</td>
<td>1.62 (1.04–2.52)</td>
<td>1.47 (0.94–2.32)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>2.17 (1.31–3.58)</td>
<td>2.18 (1.31–3.65)</td>
</tr>
</tbody>
</table>

a. Non-smokers form the reference group.

---

**Fig. 1** Independent contributions of tobacco smoking and physical activity to the risk for major depression. Non-smokers who are physically active form the reference group.

**Fig. 2** Survival plot (Kaplan–Meier) showing the probability of remaining free of de novo major depressive disorder over a 10-year period for smokers and non-smokers at baseline.
physiological study,15 may be pertinent factors for this observation. Other studies have provided support for a third possibility, that depression and smoking coexist as epiphenomena of a common underlying cause, such as genetic factors.16,17 The efficacy of bupropion in the treatment of both depression and nicotine dependence18 may indicate some commonality between the two conditions on a neurochemical level. 

Dopamine is one such factor, which is believed to have a dual role in depression and in the mechanism of addiction. Neurochemical studies of depression, particularly with psychomotor retardation, reported an association with diminished dopamine metabolism, as evidenced by decreased levels of cerebrospinal fluid homovanillic acid.19,20 Reduced striatal dopamine function has also been shown in dopamine D2 receptor neuroimaging binding studies.21,22 Dopamine is regarded as the central neurotransmitter of reward, and as having a key role in the reinforcement of the pathways to addiction.23 Dysregulation of the dopaminergic system in addictive states is also a plausible mechanistic pathway to depressive vulnerability.24

Smoking-induced oxidative stress is another factor. Tobacco smoke generates free radicals, causing lipid peroxidation, oxidation of proteins and other tissue damage in smokers.25,26 Depression has been characterised by elevated markers of oxidative stress27–29 that demonstrates a positive correlation with depressive severity30 and a return to normal levels after treatment.31 It seems plausible that depression could be among the oxidative stress sequelae of smoking.

There are several strengths and potential weaknesses in our study. The length of the follow-up period is a key strength, especially when published longitudinal studies have rarely exceeded a few years at most. Given that smoking effects insidious biochemical changes that are naturally accommodated by the body’s homeostatic responses, long-term sequelae such as depression, cancers, cardiovascular and pulmonary diseases may only be reliably demonstrated over an extended time frame. Recall limitations may have affected our ability to accurately diagnose the time of onset of depressive episodes and, in the case–control analysis, the potential exists for differential recall bias of smoking practices. However, as this study was nested within a larger prospective study, the latter risk was minimised as exposure to smoking had been documented prior to psychiatric interview. Furthermore, documentation of exposure to smoking and assessment of outcome were performed by different study personnel. The duration of smoking prior to the onset of depression was unknown, precluding estimation of duration of exposure on depression. Inconsistencies in the number of cigarettes smoked per day may have resulted in misclassification of smoking frequency in the case–control analysis but the apparent dose–dependent association strengthens the notion that smoking is a risk factor for major depression. Small numbers limited a comparable investigation in the longitudinal analysis. Also in the longitudinal analysis, changes in exposure status during follow-up have not been identified. Finally, as in all observational studies, there may be unrecognised confounding.

We relied on self-reported history of cardiovascular disease and diabetes as indicators of physical illness that may be affected by smoking status. However, we cannot exclude possible confounding by unrecognised comorbidity as individuals were not clinically screened for all potential physical illnesses. Physical activity and alcohol consumption were explored as concomitant lifestyle factors with a potential for confounding because physical activity had been previously reported as protective against depression,35 whereas physical inactivity32–34 and alcohol misuse36 are regarded as risk factors. In this study, alcohol consumption did not appear to confound the association between smoking and depression; however, we acknowledge that our criteria for alcohol consumption may have been too broad to confidently exclude its contribution. Other factors predisposing to depression, such as personality traits, developmental and family history of depression, IQ or stress, were not considered as these data were not available.

Within these limitations, however, our data corroborate literature that reveals a malevolent role of smoking in depression and suggest that greater efforts are required in targeting smoking as a routine intervention.35 Depression’s status as a leading cause of global disease burden,36–37 one that is not anticipated to yield in the coming decades,36 can only underscore the potential impact of any effective preventive measures.

Table 3 Participant characteristics in the retrospective cohort study

<table>
<thead>
<tr>
<th></th>
<th>Smokers (n=67)</th>
<th>Non-smokers (n=584)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years: median (IQR)</td>
<td>39 (31–52)</td>
<td>50 (37–63)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Major depressive disorder, n (%)</td>
<td>13 (15)</td>
<td>38 (7)</td>
<td>0.006</td>
</tr>
<tr>
<td>Socio-economic status, n (%)</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Quintile 1 (low)</td>
<td>26 (30)</td>
<td>93 (16)</td>
<td></td>
</tr>
<tr>
<td>Quintile 2</td>
<td>19 (22)</td>
<td>137 (23)</td>
<td></td>
</tr>
<tr>
<td>Quintile 3</td>
<td>22 (25)</td>
<td>107 (18)</td>
<td></td>
</tr>
<tr>
<td>Quintile 4</td>
<td>6 (7)</td>
<td>114 (20)</td>
<td></td>
</tr>
<tr>
<td>Quintile 5</td>
<td>14 (16)</td>
<td>133 (23)</td>
<td></td>
</tr>
<tr>
<td>Alcohol users, n (%)</td>
<td>20 (23)</td>
<td>96 (16)</td>
<td>0.132</td>
</tr>
<tr>
<td>Physically active, n (%)</td>
<td>14 (16)</td>
<td>69 (12)</td>
<td>0.258</td>
</tr>
<tr>
<td>Cardiovascular disease, n (%)</td>
<td>20 (23)</td>
<td>220 (38)</td>
<td>0.006</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>3 (3)</td>
<td>44 (8)</td>
<td>0.129</td>
</tr>
</tbody>
</table>

IQR, interquartile range.

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