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Research paper

Smoking status as a predictor of antidepressant medication use

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ABSTRACT

Background: Cigarette smoking and depression are major public health concerns, but longitudinal research on the association between smoking and antidepressant use is scarce. The purpose of this study was to investigate, whether smoking predicts antidepressant medication during a 10-year follow-up.

Methods: A questionnaire was administered to Finnish adult twins in 1990. Antidepressant prescription data during 1995–2004 were obtained from the register of the Finnish Social Insurance Institution and linked to the survey data. Cox Proportional Hazard Models among 10,652 individuals (1075 cases, 9577 controls) assessed the risk for depression in the cohort, whereas within-pair comparisons of smoking twins with their non-smoking co-twins controlled for shared familial influences.

Results: Daily smokers had a significantly elevated likelihood for having antidepressant prescriptions in the follow-up. Based on the analysis among those without baseline depression, heavy daily smokers had a significantly elevated likelihood (HR 1.56, 95% CI 1.17–2.08) for antidepressant prescription when adjusted for all confounders. Similar analysis using pairs discordant for antidepressant medication confirmed that daily smoking twins had a higher likelihood for prescriptions (HR 1.98, 95% CI 1.11–3.54) compared with their non-smoking co-twins. The estimates were for MZ pairs (HR 1.78, 95% CI 0.48–6.55) and DZ pairs (HR 1.92, 95% CI 0.99–3.72), respectively.

Limitations: Changes in smoking status after baseline cannot be accounted for. Reversed association between depression and smoking cannot be ruled out.

Conclusion: Daily smoking predicts antidepressant medication, even when controlling for essential confounders and familial factors. This study highlights the need of systematically assessing depressive symptoms among smokers.

1. Introduction

Smoking and depression are major public health concerns (Royal College of Psychiatrists, 2013; World Health Organization, 2013). Depression is common and poses a substantial burden both societally, economically and individually (Kessler and Bromet, 2013; World Health Organization, 2012). Daily smoking is reported among 19% of men and 13% of women in Finland (Helldan et al., 2013) and the prevalence of nicotine dependence among Finnish ever smokers is very high (48–52%) (Broms et al., 2012).

The nature of this association between smoking behavior, nicotine dependence and depression can be discussed under various scenarios (Fluharty et al., 2016). First, the association may be causal between smoking and depression and that cigarette smoking behavior increases the risk of depressive symptoms (Goodman and Capitman, 2000; Korhonen et al., 2007, 2011) or, nicotine dependence does indeed increase the risk of depressive symptoms (Boden et al., 2010). Second, depression may increase the level of nicotine dependence and thus, urge for smoking through a self-medication mechanism (Balfour and Ridley, 2000; Royal College of Psychiatrists, 2013). A reciprocal relation between cigarette smoking and depression has also been reported (Breslau et al., 1998; John et al., 2004). Third, there may be underlying factors common to both that are responsible for the association between nicotine dependence and major depressive disorder. One such factor may be genetic, given that there is a genetic component shared by both conditions (Broms et al., 2012; Korhonen et al., 2014; Sullivan et al., 2000). It is still unclear whether smoking ameliorates the symptoms of depression or whether depression pro-

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motes nicotine addiction (Balfour and Ridley, 2000; Royal College of Psychiatrists, 2013). The longitudinal association between smoking and depression has been addressed in several studies (Boden et al., 2010; Breslau et al., 1998; John et al., 2004). However, hardly any longitudinal research has been conducted on the association between smoking behavior and future use of prescribed antidepressant medications.

Antidepressant prescription may be used as an indicator of depression in register based studies. Such an outcome measure is justified because it is independent of the study investigators and of the participation in follow-up assessments, therefore this methodological approach is robust. The aim of the present study was to investigate whether smoking predicts prescriptions of antidepressant medication during 10 years' follow-up in a large sample of twins who were analyzed as individuals and as pairs discordant for antidepressant medication.

2. Materials and methods

2.1. Sample

The Finnish Twin Cohort is a population based sample that is compiled from the Central Population registry comprising all same sex twin pairs born in Finland before 1958, who were alive in 1967. The first questionnaire survey of the twins was conducted in 1975 and the second in 1981. The present study is based upon the third survey conducted in 1990. A questionnaire was sent in 1990 to all twin pairs born in 1930–1957, who had replied to at least one of the previous surveys, and with both co-twins resident in Finland in 1987 (n=16,177). Among the 16,177 who had been sent the 1990 questionnaire, 12,502 responded (77.3% response rate).

The Finnish Twin Cohort was linked to the reimbursed prescriptions of anti-depressants purchased from community pharmacies, using the Prescription Register of the Finnish Social Insurance Institute (SII). The antidepressant prescriptions of these individuals were followed up for the 1995–2004 period (1995 was the first year when such data were available). Approval for the register linkages was obtained from the Ethics committee of the Department of Public Health, University of Helsinki and the appropriate authorities at SII. The zygosity of the twins, monozygotic (MZ) or dizygotic (DZ), had been determined by validated questionnaire in a previous study (Sarna et al., 1978).

2.2. Measures

2.2.1. Outcome

The outcome variable was having register-based antidepressant prescriptions (ATC code N06A) during years 1995–2004. The SII prescription register was set up in 1995, and our linkage was restricted to the end of 2004. The twins who had prescriptions were linked to the completed questionnaire via their personal national insurance number (assigned to each resident in Finland) as the identifier. Those who had at least four consecutive prescriptions within one year or four non-consecutive prescriptions during the 10 years of follow-up were considered as cases. Persons with 1–3 medication prescriptions were excluded from the analyses. Controls were those who had no antidepressant prescriptions; no missing data on antidepressant prescription existed.

The prescription register includes data on the diagnoses for which the fully reimbursed medicines had been received. We matched the individuals' antidepressant prescription data with those in the 1990 survey data and defined the case versus control status of the identified individuals. Data on depressive symptoms were available from 12,063 individuals, however, there was missing information on smoking status and/or on amount of smoking for 615 of them.

From the 12,502 persons available from the SII register, we excluded persons with psychotic disorders or mental retardation. Further, from the merged data set we removed individuals with other serious chronic mental illnesses and persons who were in disability pensions. A total of 1116 cases identified in the register data were successfully matched with the 1990 survey data, whereas the number of persons with no antidepressant prescription (controls) was 9968. Our sample was restricted to those who provided data for both depression and smoking in 1990, thus there were valid data available for the analysis from total of 10 768 persons (1075 cases, 9693 controls). Finally, the time-to-event analysis removed those persons who were lost to follow-up (death or emigration) between 1990 and1994, when the outcome events for survival analysis were started (n=116). Thus, our time-to-event analyses were restricted to 10,652 persons (1075 cases, 9577 controls).

2.2.2. Predictor

Participants were categorized according to their baseline smoking status as follows: 1) Never smokers (n=5174); 2) Non-daily smokers (n=373); 3) Former smokers (n=2479); 4) Light/moderate daily smokers, n=1785), and 5) Heavy daily smokers (n=957). The subjects were asked if they have ever smoked more than 5–10 packs of cigarettes (100 cigarettes) during their lifetime. Those responding negatively were categorized as "never smokers" and were considered as the reference group. Those responding positively were asked "Do you smoke or have you smoked cigarettes regularly, say daily, or almost daily during your lifetime? " Positive responders were further asked if they still smoked regularly. If so, they were classified as current daily smokers. Persons who had smoked more than 100 cigarettes but were not regular smokers were considered as non-daily smokers. Former smokers were those regular smokers who had responded that they no longer smoked at the time of the survey. In our data the self-reported length of smoking abstinence among former smokers ranged mainly between 1 and 39 years. However, there was a minor group of participants (5.53%) who had quit smoking less than 12 months ago.

Among current daily smokers the mean daily cigarette consumption was defined. The response categories to the question "How many cigarettes do you smoke daily on average? " were as follows: < 5, 5–9, 10–14, 15–19, 20–24, 25–39, and > 40. Light/moderate daily smokers included those smoking < 20 cigarettes/day (CPD) and heavy daily smokers included those smoking ≥20 CPD (i.e. a pack a day).

2.2.3. Confounders

Potential confounders at the baseline included socio-demographic background (age, gender, social class), other substance use than smoking (binge drinking), and health status (somatic health) and these were used to adjust the analyses. Individuals were divided into three groups by years of education and physical activity performed during work to determine the individual's broad socio-economic class (Appelberg et al., 1991). Those with a minimum of 12 years of education and sedentary work were considered "white collar"; those with fewer than 9 years of education and ambulatory work consisting of walking and lifting or hard physical work were "blue collar" and the remainder formed an intermediate group of individual (Romanov et al., 2003).

Binge drinking was defined as drinking more than five bottles of beer, or more than a bottle of wine, or more than half a bottle of spirits on the same occasion at least once a month; only a "yes" or "no" response was recorded (Kaprio et al., 1987).

In the 1990 questionnaire the subjects were asked if they had ever been told by their physician that they have or have had any somatic disease listed. The response to each item was scored 0 if 'No' and 1 if 'Yes'. A Somatic Disease Index (SDI) was formed in which the subject was considered to have 'any somatic disease' if in the 1990 questionnaire he/she had (i) any self-reported disease diagnosed by a physician, or (ii) a self-reported life event of serious injury/illness, or (iii) self-reported work disability. Other subjects were classified as

'healthy'. Examination of the validity of self-reported illness in a recent population study had confirmed that the agreement between questionnaire data and the individual's medical records was very good for well-known diseases with clear diagnostic criteria that are easily communicated to the patient (Romanov et al., 2003). Therefore, even after excluding persons with serious mental illnesses and disability pensions from the 1990 data set, our analyses still included individuals who have had any of the above mentioned somatic illnesses based on the SDI. Thus, because these people were not excluded from the analyses, these somatic conditions were adjusted for by using the SDI (yes/no) as a baseline confounder.

2.2.4. Other baseline variables

Severity of depressive symptoms at baseline was assessed by the Beck Depression Inventory (BDI) (Beck et al., 1961) in 1990. The BDI includes 21 items, in which each statement measures the degree of severity intensity from 0 to 3. The BDI demonstrates high internal consistency, with alpha coefficients of 0.86 and 0.81 for depressed and non-depressed populations respectively (Beck et al., 1988). We used the total BDI score 10 or more as a cut-off for 'depressed' according to BDI guideline, whereas those with BDI score 0–9 were categorized as "non-depressed" (Beck and Beamesderfer, 1974) to be able to stratify the participants into depressed and non- depressed groups. When adjusting for baseline depressiveness, we used the BDI sum score as a continuous variable.

2.3. Statistical analysis

The twins were considered as individuals in the primary analysis. Observations on twins within the twin pairs may be correlated. Thus, twinship was statistically accounted for by using robust estimators of variance and cluster option when estimating standard errors (Williams, 2000). Our study examined the associations between the smoking status categories defined above and having antidepressant prescriptions (defined above as no=0 or yes=1) during the 10-year follow-up period. We used Cox Proportional Hazard Model [Hazard Ratio (HR) and 95% Confidence Interval (CI)], in order to perform time to event analysis. P-values below 0.05 were considered to be statistically significant. We tested potential sex by smoking interactions on depression medications. Data for men and women were pooled together in the analyses because there were no significant interactions. Eventually, the survival analysis excluded all those persons who were lost (died or emigrated) during the follow up. Therefore, our time-to-event analysis was restricted to 10,652 persons (1075 cases, 9577 controls).

First, age and sex adjusted HR was calculated in order to estimate the strength of association between baseline smoking status and having antidepressant prescriptions in the follow-up. Next, the analysis was adjusted for potential confounders (baseline BDI, social class, binge drinking, somatic health). Furthermore, an incidence analysis was conducted excluding those with at least mild baseline depressive symptoms (BDI > 9) (n=1689) with adjustment for covariates. The HRs indicating the associations between smoking status and antidepressant prescription were computed.

Finally, in order to control for familial confounding, discordant twin pair analysis was conducted. For this, incidence analysis was conducted among 320 discordant twin pairs (depressed case versus non-depressed control at follow-up) where both co-twins were non-depressed (BDI < 10) at baseline. The analyses initially disregarded zygosity, but then those analyses were conducted separately for the MZ and DZ twin pairs who were discordant for depression medication (Korhonen et al., 2007) to control for genetic background. All these analyses were adjusted also for the above mentioned confounders. All analyses were conducted using the Stata statistical package (version 13).

Table 1
Demographic characteristics of the study sample at the baseline in relation to future case status.

Demographic Characteristic	Total (N=10,768)	Cases[a] (N=1075)		Controls[b] (N=9693)	
Age, years; M (SD)	43.7 (7.70)	43.6 (7.60)		43.7 (7.72)	
Gender		N	%	N	%
Male	4 994	351	32.6	4643	47.9
Female	5 774	724	67.4	5050	52.1
Smoking status					
Never smokers	5 174	496	46.1	4 678	48.3
Non-daily smokers	373	37	3.44	336	3.47
Former smokers	2 479	222	20.6	2 257	23.3
Light or moderate daily smokers	1 785	212	19.7	1 573	16.2
Heavy daily smokers	957	108	10.0	849	8.76

M=Mean.
SD=Standard Deviation
N=Total number
[a] Those who had at least four antidepressant prescriptions during one year or during the 10 years of follow up.
[b] Those who did not have any antidepressant prescriptions.

3. Results

3.1. Descriptive results

There were a total of 10,768 persons (53% females) linked with the SII registry and with valid data for these analyses. They comprised 1075 future cases and 9693 controls (i.e. no medication prescriptions). The mean age of the participants was 44 years in both cases and controls (Table 1). Proportion of females among the cases was 67% and 52% among the controls. Proportion of daily smokers was 30% among the cases and 25% among the controls.

3.2. Smoking status and use of antidepressants

The results of the first cox proportional hazard models are shown in Table 2. Smoking status and antidepressant medication prescriptions were significantly associated. Those who were light or moderate, or heavy daily smokers at the baseline had higher risk of antidepressant medication during the follow-up period when adjusted for age and sex compared to never smokers. When adjusted for age, sex, and baseline BDI, heavy daily smokers (HR 1.30, 95% CI 1.03–1.64) were more likely to have antidepressant prescriptions compared to never smokers. Further, when adjusted for age, sex, and social class, the use of antidepressants remained significant among light or moderate daily smokers (HR 1.29, 95% CI 1.09–1.53) and among heavy daily smokers (HR 1.63, 95% CI 1.30–2.04). There was slight decrease in risk estimates when adjusted for age, sex and binge drinking, but still light or moderate daily smokers (HR 1.23, 95% CI 1.03–1.47) and heavy daily smokers (HR 1.56, 95% CI 1.24–1.97), were more likely to receive antidepressants than never smokers. These associations remained significant also after adjusting for age, sex and somatic health. When adjusted for all the confounders simultaneously, the results no longer remained significant. As a post hoc test, we compared the risk estimates of heavy daily smoking men and women in terms of antidepressant medication but found no significant difference, which indicated that heavy daily smoking poses a similar risk on men and women in terms of depression treated by medication.

Further, we obtained results that were unaffected by baseline depressiveness by conducting incidence analysis on those individuals without baseline depression i.e. those who did not have depressive symptoms in the 1990 survey (BDI score < 10) (Table 3). When adjusted for age and sex, light or moderate daily smokers and heavy

Table 2
Hazard Ratios for having antidepressant medication prescriptions (1995–2004) by smoking status in 1990.

Smoking status	Model I[a]			Model II[b]			Model III[c]			Model IV[d]			Model V[e]			Model VI[f]		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Never smokers	1.00			1.00			1.00			1.00			1.00			1.00		
Non-daily smokers	1.14	0.80–1.61	0.463	1.15	0.81–1.62	0.442	1.13	0.80–1.60	0.475	1.13	0.80–1.60	0.483	1.17	0.82–1.65	0.383	1.17	0.83–1.66	0.369
Former smokers	1.06	0.90–1.25	0.467	1.03	0.87–1.22	0.728	1.06	0.90–1.25	0.492	1.02	0.86–1.21	0.798	1.04	0.88–1.22	0.679	0.98	0.83–1.16	0.846
Light or moderate daily smokers	1.28	1.08–1.52	0.004	1.15	0.97–1.36	0.113	1.29	1.09–1.53	0.003	1.23	1.03–1.47	0.021	1.25	1.06–1.48	0.010	1.11	0.93–1.33	0.240
Heavy daily smokers	1.62	1.29–2.02	2.7e−05	1.30	1.03–1.64	0.027	1.63	1.30–2.04	1.9e−05	1.56	1.24–1.97	2.0e−04	1.50	1.20–1.88	3.9e−04	1.24	0.97–1.59	0.079

HR=Hazard Ratio, CI=Confidence Interval, *P*=P-Value

[a] Adjusted for age and sex.

[b] Adjusted for age, sex and baseline depressiveness (BDI score).

[c] Adjusted for age, sex and social class.

[d] Adjusted for age, sex and binge drinking.

[e] Adjusted for age, sex and somatic health.

[f] Adjusted for age, sex, BDI score, social class, binge drinking and somatic health simultaneously.

daily smokers had increased risk for antidepressant medication (HR 1.29, 95% CI 1.05–1.59) and (HR 1.58, 95% CI 1.20–2.08), respectively. Similar results were obtained when the incidence analysis was adjusted for other potential confounders. We found that the risk estimates for smoking changed only marginally after adjustment of social class, binge drinking and somatic illness compared to age and sex adjusted results. Finally, when adjusted for all confounders simultaneously, the associations were robust, i.e. the estimates were for light or moderate daily smokers (HR 1.28, 95% CI 1.03–1.58) and heavy daily smokers (HR 1.56, 95% CI 1.17–2.08), respectively.

Within-pair analysis was conducted among twin pairs discordant for the case control status in order to control for familial confounding (Table 4). Survival analysis registered the actual time of the first antidepressant prescription among the cases. Therefore, this analysis initially included all the concordant and discordant pairs. However, the risk estimates were based on the informative discordant pairs only. There were total of 320 discordant twin pairs, in which one of the twins was a case and the other twin a control, while neither twin was depressed at the baseline period (incidence analysis). The proportion of pairs in which one twin was a daily smoker and had antidepressant prescriptions while the respective co-twin was a never smoker and had no antidepressant prescriptions was higher compared to proportion of twin pairs where the smoking versus antidepressant condition was reversed. The within-pair analysis revealed that current daily smoking remained a significant predictor (HR 1.86, 95% CI 1.09–3.18) of the outcome. Further, when adjusted for potential confounders, this association remained significant. Similarly, current daily smokers among MZ pairs (HR 1.39, 95% CI 0.43–4.48) and DZ pairs (HR 1.95, 95% CI 1.06–3.60), were at similarly elevated risk for antidepressants, yet the risk estimate was statistically significant for the DZ pairs only.

4. Discussion

Several studies relate cigarette smoking with the occurrence of depression (Elmasry et al., 2014; Goodman and Capitman, 2000; Korhonen et al., 2007, 2011). In this study, we aimed to investigate whether cigarette smoking was associated with antidepressant prescription over a 10 year follow-up period. We found that daily smokers in 1990 had higher likelihood for using prescribed antidepressant medication during the 1995–2004 period. Our findings are in line with the previously found association between smoking and self-reported depressive symptoms within the same twin cohort (Korhonen et al., 2007).

The mean age of the participants in this study was 44 years at the time when the smoking behavior was assessed. Thus, our sample represents adult twin population in Finland. A study conducted in the US among the teenagers who were not depressed during the baseline, found that cigarette smoking was the strongest predictor of developing depressive symptoms over a one year of follow-up (Goodman and Capitman, 2000). That suggests that smoking and depression can be associated – not only in adults - but already at an early age.

Depression is twice more common among women than in men (Kessler, 2003). This is also reflected in our study where twice as many cases among women compared to men were observed. The question is, whether the association between smoking and depression is different between men and women. Previous studies reported that women who smoked were at higher risk of depression than men, suggesting that smoking may pose higher risk for women (Husky et al., 2008; Royal College of Psychiatrists, 2013). However, in our sample, we did not see any significant sex by smoking –interaction. Thus, we did not analyze men and women separately. We also tested the difference in the risk estimates of heavy daily smoking men and women in terms of use of antidepressants. We did not find statistically significant difference, indicating that in our sample heavy smoking poses a similar risk among men and women in terms of depression treated by antidepressant

Table 3
Hazard Ratios for having antidepressant medication prescriptions by smoking status in 1990 among persons without baseline depression.

Smoking status	Model I[a]			Model II[b]			Model III[c]			Model IV[d]			Model V[e]		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Never smokers	1.00			1.00			1.00			1.00			1.00		
Non-daily smokers	1.01	0.66–1.55	0.958	1.01	0.66–1.54	0.971	1.03	0.67–1.58	0.889	1.02	0.67–1.57	0.913	1.04	0.68–1.60	0.847
Former smokers	1.16	0.95–1.40	0.137	1.15	0.95–1.40	0.143	1.14	0.94–1.40	0.190	1.13	0.93–1.37	0.203	1.11	0.91–1.36	0.295
Light or moderate daily smokers	1.29	1.05–1.59	0.014	1.31	1.07–1.61	0.010	1.29	1.04–1.60	0.019	1.27	1.03–1.56	0.024	1.28	1.03–1.58	0.025
Heavy daily smokers	1.58	1.20–2.08	0.001	1.60	1.21–2.11	0.001	1.61	1.21–2.15	0.001	1.50	1.14–1.98	0.004	1.56	1.17–2.08	0.003

HR=Hazard Ratio, CI=Confidence Interval, *P*=P-Value
[a] Adjusted for age and sex.
[b] Adjusted for age, sex and social class.
[c] Adjusted for age, sex and binge drinking.
[d] Adjusted for age, sex and somatic health.
[e] Adjusted for age, sex, social class, binge drinking and somatic health simultaneously.

Table 4
Discordant twin pair analyses for having antidepressant medication prescriptions by smoking status in 1990 among those without baseline depression.

Smoking status	Model I			Model II[b]			Model III[c]			Model IV[d]			Model V[e]		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
All (N=320 pairs)															
Never smokers	1.00			1.00			1.00			1.00			1.00		
Non-daily smokers	1.60	0.54–4.72	0.394	1.61	0.54–4.77	0.387	1.65	0.56–4.89	0.366	1.61	0.54–4.78	0.389	1.67	0.56–5.00	0.358
Former smokers	1.38	0.81–2.34	0.241	1.38	0.81–2.35	0.239	1.42	0.81–2.48	0.220	1.33	0.78–2.28	0.296	1.36	0.77–2.39	0.290
Daily smokers[a]	1.86	1.09–3.18	0.023	1.86	1.09–3.18	0.023	2.10	1.19–3.73	0.011	1.77	1.02–3.06	0.040	1.98	1.11–3.54	0.021
Monozygotic (N=87 pairs)															
Never smokers	1.00			1.00			1.00			1.00			1.00		
Non-daily smokers	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Former smokers	0.54	0.18–1.60	0.266	0.54	0.18–1.61	0.271	0.57	0.18–1.77	0.331	0.54	0.18–1.60	0.265	0.54	0.17–1.71	0.296
Daily smokers[a]	1.39	0.43–4.48	0.583	1.37	0.42–4.45	0.597	1.95	0.55–6.97	0.303	1.36	0.41–4.60	0.616	1.78	0.48–6.55	0.387
Dizygotic (N=230 pairs)															
Never smokers	1.00			1.00			1.00			1.00			1.00		
Non-daily smokers	1.32	0.41–4.25	0.643	1.33	0.41–4.29	0.634	1.34	0.41–4.34	0.627	1.35	0.42–4.40	0.614	1.38	0.42–4.54	0.593
Former smokers	1.94	1.02–3.68	0.042	1.94	1.02–3.68	0.042	2.01	1.02–3.97	0.043	1.88	0.98–3.57	0.055	1.93	0.97–3.84	0.060
Daily smokers[a]	1.95	1.06–3.60	0.032	1.95	1.06–3.60	0.032	2.02	1.06–3.88	0.034	1.86	1.00–3.46	0.051	1.92	0.99–3.72	0.052

NA=Not Accessible (very few observations) HR=Hazard Ratio, CI=Confidence Interval,
[a] Including light, moderate or heavy daily smokers.
[b] Adjusted for social class.
[c] Adjusted for binge drinking.
[d] Adjusted for somatic health.
[e] Adjusted for social class, binge drinking & somatic health simultaneously.

medication.

We found that light/moderate and heavy daily smokers had a higher likelihood for use of antidepressants in the follow-up compared to never smokers, when adjusted for age and sex. Heavy daily smokers had a two-fold risk for antidepressants over never smokers. However, non-daily and former smokers did not show any significant association for antidepressant medication use in the follow-up. This finding may reflect a dose-relationship between smoking and depression. A previous study based on earlier surveys in the same twin cohort, found that persistent smoking increased the risk for BDI-defined depression but former smoking did not significantly elevate the risk for later depression across depression dimensions (Korhonen et al., 2011) which is in line with our findings.

Our results are supported also by the findings from a cross sectional Finnish study, which showed that current smoking was significantly associated with antidepressant treatment among both men and women (Laukkala et al., 2001). In our study, former smokers did not show any significant association, however, in a meta-analysis, quitting smoking was associated with reduced depression and improved quality of life compared to continuing smoking (Taylor et al., 2014). However, another study showed no significant change in depression level between those who had quit and those who remained smokers (Kinnunen et al., 2006).

In our study, the incidence analysis among those who were not depressed at the baseline, the risk estimates for smoking changed only slightly after adjustment for socio-demographic confounders, somatic illnesses and binge drinking. Even when adjusted for all the confounders simultaneously, the results remained similar. Thus, the effect of smoking seems to be robust. Our previous study also showed similar results, specifically: persistent smoking was associated with higher risk of depression among men, even after adjustment of socio-demographic and other confounders (Korhonen et al., 2007). Such confounders should be considered because they might contribute to the associations between predictor and outcome variables. For example, excessive use of alcohol has been related with depressive symptoms (Davidson, 1995), and somatic illness can also increase vulnerability to depression (Romanov et al., 2003) while both are associated with smoking.

Our findings can be discussed according to different assumptions: First, nicotine addiction among current smokers might increase the probability of depressive states or depression medication use. The main body of our results supports this hypothesis. This “addiction hypothesis” is also in line with our finding about alcohol drinking because binge drinkers were more likely to use antidepressants than non-binge drinkers (data not shown). However, there may be alternative inter-

pretations. For example, living free of depression may have increased a smoker's self-efficacy to quit smoking, i.e. non-depressed subjects are more likely to quit smoking than depressed patients (Killen et al., 2003). Finally, living with depression can increase the risk of smoking through a self-medication mechanism (Balfour and Ridley, 2000; Royal College of Psychiatrists, 2013). Thus, this can further explain why depressed patients are more likely to use tobacco to obtain nicotine. However, ascertaining which of these alternative assumptions is correct or whether they both apply is beyond the scope of this study.

When we controlled for familial and genetic background using discordant twin pairs, smoking status remained a predictor of subsequent antidepressant use, although the association was not statistically significant for MZ pairs. Such analyses of MZ and DZ pairs suggest that having antidepressant prescriptions is essentially related to smoking and not to shared genetic background, but the analysis of MZ pairs may lack statistical power. This finding is also supported by our previous study finding where both MZ pairs and DZ pairs showed increased risk for self-reported depressive symptoms among persistent smokers and also among quitters (Korhonen et al., 2007).

Our findings demonstrate that daily smoking may be associated with future depression, which is reflected in the need for antidepressant treatment. This may be the case particularly when depression is severe or moderately severe, and antidepressant medication is required (National Collaborating Centre for Mental Health, 2010). Cigarette smoking leads often to nicotine dependence, and individuals with nicotine dependence have a higher likelihood for lifetime major depressive disorder, while certain neurochemical mechanisms are suggested to be responsible for this association (Balfour and Ridley, 2000).

4.1. Strengths and limitations

The main strength of the study is the use of register based data on antidepressant prescriptions, which excludes the confounding effects of recall bias and lack of participation in follow-up surveys. Using register data as a proxy indicator of depression may also be considered as a limitation, although purchasing antidepressant medication is objective evidence that was available for all participants in the 10 years follow-up survey. However, mild depression is not necessarily treated by prescribed medications, which implies that the register based outcome in our study may represent only the more severe depression cases. Second, this population-based cohort was followed-up and reported 15 years later and provides reliable data on long-term effects of smoking on the use of antidepressants. Third, the analyses were adjusted for several potential confounders. In addition, within-pair analysis in this genetically informative sample was applied to twin pairs discordant for the case-control status in order to control familial and genetic confounding.

We acknowledge the limitation that although antidepressants are mainly used for treating depression, they are also used in the treatment of other mental disorders (Sadock and Sadock, 2008), which may cause some clinical heterogeneity in our sample. However, when antidepressants are used, depression is most probably also present at least as a comorbid condition. Another limitation is that the register-based information of antidepressant prescriptions was used as the proxy of quantifying the numbers suffering from depression. Thus, among the controls, who did not have antidepressant prescriptions, there may have been individuals with depressive symptoms without seeking medical attention. However, this probable depression has supposedly been mild. A further limitation of this study is that we were not able to fully test the possibility of reciprocal relationships between smoking and antidepressant medication. Specifically, it may be argued that although smoking leads to increased likelihood of depression and consequently antidepressant medication, the use of medication may reduce both depression and smoking. Unfortunately, in this study we could not test the reverse causal association, i.e. whether depression predicts smoking. A further limitation is that we could only use the 1990 smoking status in this analysis and could not take into account changes in smoking status after the baseline assessment. However, because our data include middle age to older adults, the option of smoking initiation would not be issue of concern here. However, we acknowledge that smoking cessation after 1990 would be an issue of concern and thus, we consider this as a limitation.

We conclude that daily cigarette smoking predicts antidepressant medication, even when controlling for essential confounders and familial factors. This study highlights the need of carefully and systematically assessing smoking behavior among the patients suffering from or being at risk for developing depressive symptoms.

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References

Appelberg, K., Romanov, K., Honkasalo, M.L., Koskenvuo, M., 1991. Interpersonal conflicts at work and psychosocial characteristics of employees. Soc. Sci. Med. 32, 1051–1056.
Balfour, D.J.K., Ridley, D.L., 2000. The effects of nicotine on neural pathways implicated in depression: a factor in nicotine addiction? Pharmacol. Biochem. Behav. 66, 79–85.
Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Arch. Gen. Psychiatry 4, 561–571.
Beck, A.T., Beamesderfer, A., 1974. Assessment of depression: the depression inventory. Mod. Probl. Pharm. 7, 151–169.
Beck, A.T., Steer, R.A., Carbin, M.G., 1988. Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. Clin. Psychol. Rev. 8, 77–100.
Boden, J.M., Fergusson, D.M., Horwood, L.J., 2010. Cigarette smoking and depression: tests of causal linkages using a longitudinal birth cohort. Br. J. Psychiatry 196, 440–446.
Breslau, N., Peterson, E.L., Schultz, L.R., Chilcoat, H.D., Andreski, P., 1998. Major depression and stages of smoking. A longitudinal investigation. Arch. Gen. Psychiatry 55, 161–166.
Broms, U., Wedenoja, J., Largeau, M.R., Korhonen, T., Pitkaniemi, J., Keskitalo-Vuokko, K., Happola, A., Heikkila, K.H., Heikkila, K., Ripatti, S., Sarin, A.P., Salminen, O., Paunio, T., Pergadia, M.L., Madden, P.A., Kaprio, J., Loukola, A., 2012. Analysis of detailed phenotype profiles reveals CHRNA5-CHRNA3-CHRNB4 gene cluster association with several nicotine dependence traits. Nicotine Tob. Res. 14, 720–733.
Davidson, K.M., 1995. Diagnosis of depression in alcohol dependence: changes in prevalence with drinking status. Br. J. Psychiatry 166, 199–204.
Elmasry, H., Goodwin, R.D., Terry, M.B., Tehranifar, P., 2014. Early life exposure to cigarette smoke and depressive symptoms among women in midlife. Nicotine Tob. Res. 16, 1298–1306.
Fluharty, M., Taylor, A.E., Grabski, M., Munafo, M.R., 2016. The association of cigarette smoking with depression and anxiety: a systematic review. Nicotine Tob. Res.
Goodman, E., Capitman, J., 2000. Depressive symptoms and cigarette smoking among teens. Pediatrics 106, 748–755.
Helldan, A., Helakorpi, S., Virtanen, S., Uutela, A., 2013. Health Behaviour and Health among the Finnish Adult Population. Spring 2013. National Institute of Health and Welfare, Helsinki.
Husky, M.M., Mazure, C.M., Paliwal, P., McKee, S.A., 2008. Gender differences in the comorbidity of smoking behavior and major depression. Drug Alcohol Depend. 93, 176–179.
John, U., Meyer, C., Rumpf, H.J., Hapke, U., 2004. Smoking, nicotine dependence and psychiatric comorbidity–a population-based study including smoking cessation after three years. Drug Alcohol Depend. 76, 287–295.
Kaprio, J., Koskenvuo, M., Langinvainio, H., Romanov, K., Sarna, S., Rose, R.J., 1987. Genetic influences on use and abuse of alcohol: a study of 5638 adult Finnish twin brothers. Alcohol. Clin. Exp. Res. 11, 349–356.
Kessler, R.C., 2003. Epidemiology of women and depression. J. Affect. Disord. 74, 5–13.
Kessler, R.C., Bromet, E.J., 2013. The epidemiology of depression across cultures. Annu. Rev. Public Health 34, 119–138.
Killen, J.D., Fortmann, S.P., Schatzberg, A., Hayward, C., Varady, A., 2003. Onset of major depression during treatment for nicotine dependence. Addict. Behav. 28, 461–470.
Kinnunen, T., Haukkala, A., Korhonen, T., Quiles, Z.N., Spiro, A., Garvey, A.J., 2006. Depression and smoking across 25 years of the Normative Aging Study. Int. J. Psychiatry Med. 36, 413–426.

Korhonen, T., Broms, U., Varjonen, J., Romanov, K., Koskenvuo, M., Kinnunen, T., Kaprio, J., 2007. Smoking behaviour as a predictor of depression among Finnish men and women: a prospective cohort study of adult twins. Psychol. Med. 37, 705–715.

Korhonen, T., Koivumaa-Honkanen, H., Varjonen, J., Broms, U., Koskenvuo, M., Kaprio, J., 2011. Cigarette smoking and dimensions of depressive symptoms: longitudinal analysis among Finnish male and female twins. Nicotine Tob. Res. 13, 261–272.

Korhonen, T., Loukola, A., Wedenoja, J., Nyman, E., Latvala, A., Broms, U., Happola, A., Paunio, T., Schrage, A.J., Vink, J.M., Mbarek, H., Boomsma, D.I., Penninx, B.W., Pergadia, M.L., Madden, P.A., Kaprio, J., 2014. Role of nicotine dependence in the association between the dopamine receptor gene DRD3 and major depressive disorder. PLoS One 9, e98199.

Laukkala, T., Isometsa, E., Hamalainen, J., Heikkinen, M., Lindeman, S., Aro, H., 2001. Antidepressant treatment of depression in the Finnish general population. Am. J. Psychiatry 158, 2077–2079.

National Collaborating Centre for Mental Health, 2010. Depression: the Treatment and Management of Depression in Adults. The British Psychological Society & The Royal College of Psychiatrists, Leicester, (updated ed.).

Romanov, K., Varjonen, J., Kaprio, J., Koskenvuo, M., 2003. Life events and depressiveness - the effect of adjustment for psychosocial factors, somatic health and genetic liability. Acta Psychiatr. Scand. 107, 25–33.

Royal College of Psychiatrists, 2013. Smoking and Mental Health. Royal College of Physicians, London.

Sadock, B.J., Sadock, V.A., 2008. Kaplan & Sadock's Concise Textbook of Clinical Psychiatry third ed.. Lippincott Williams & Wilkins/Wolters Kluwer, Philadelphia, PA.

Sarna, S., Kaprio, J., Sistonen, P., Koskenvuo, M., 1978. Diagnosis of twin zygosity by mailed questionnaire. Hum. Hered. 28, 241–254.

Sullivan, P.F., Neale, M.C., Kendler, K.S., 2000. Genetic epidemiology of major depression: review and meta-analysis. Am. J. Psychiatry 157, 1552–1562.

Taylor, G., McNeill, A., Girling, A., Farley, A., Lindson-Hawley, N., Aveyard, P., 2014. Change in mental health after smoking cessation: systematic review and meta-analysis. Br. Med. J. 348, g1151.

Williams, R.L., 2000. A note on robust variance estimation for cluster-correlated data. Biometrics 56, 645–646.

World Health Organization, 2012. Depression: A Global Public Health Concern. WHO, Geneva.

World Health Organization, 2013. WHO Report on the Global Tobacco Epidemic. WHO, Geneva.