ORIGINAL ARTICLE
COPD

Depressive symptoms among patients with COPD according to smoking status: a Danish nationwide case–control study of 21 184 patients

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ABSTRACT

Introduction: Depressive symptoms appear more often among patients with COPD and are associated with reduced disease control and increased mortality. Both smoking and COPD increase the risk of depressive symptoms. Whether smoking cessation among COPD patients affects the occurrence of depressive symptoms is unknown. We hypothesised that smoking cessation in patients with COPD leads to reduced use of antidepressants and fewer admissions to psychiatric hospitals with depression, anxiety or bipolar disorder.

Methods: We conducted a nationwide retrospective case–control study, in patients from The Danish Register for COPD with spirometry-verified COPD, age ⩾40 years, a history of smoking and absence of cancer. Consistent smokers were matched 1:1 with ex-smokers using a propensity score model. Prescription fillings of antidepressants and risk of admissions to psychiatric hospitals with either depression, anxiety or bipolar disorder both descriptively was assessed by Cox proportional hazard models.

Results: We included 21 184 patients. A total of 2011 consistent smokers collected antidepressant prescriptions compared with 1821 ex-smokers. Consistent smoking was associated with increased risk of filling prescription on antidepressants (HR 1.4, 95% CI 1.3–1.5, p<0.0001) and with increased risk of psychiatric hospital admission with either depression, anxiety or bipolar disorder (HR 2.0, 95% CI 1.6–2.5). The associations persisted after adjustment for former use of antidepressants.

Conclusion: Consistent smoking among COPD patients was associated with increased use of antidepressants and admissions to psychiatric hospitals with either depression, anxiety or bipolar disorder, compared to smoking cessation.

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COPD patients who stop smoking have a lower risk of needing antidepressants and a lower risk of depression-related hospitalisations than their still-smoking peers https://bit.ly/2RKmy9v

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Introduction

COPD is responsible for an increasing number of deaths worldwide, and COPD is expected to be the third-largest cause of death in the world by 2030 [1]. Smoking is well established as the main risk factor for developing COPD [2].

Depressive symptoms are more frequent among patients with COPD [3]. Depressive patients with COPD have an increased frequency of exacerbations [4, 5], less effective pulmonary rehabilitation, impaired quality of life, aggravated dyspnoea [6] and increased mortality [7, 8]. Separately, both smoking and COPD are associated with increased risk of depressive symptoms [2, 9–11].

Several studies conducted in the general population have investigated the effect of smoking cessation on both development of depressive symptoms and the effect on existing depressive symptoms. In studies on a multinational cohort of smokers, who were randomly selected from the general population, smoking cessation tended to decrease the occurrence of depressive symptoms [12], and among those with no prior depressive symptoms smoking cessation did not increase risk of depressive symptoms [13]. Moreover, in large cross-sectional studies, ex-smokers were less likely to have depression [14] or comorbid depression/anxiety [15] than active smokers. Further, continued smoking may be associated with guilt and shame and thus, may lead to depression [16]

However, all the above-mentioned studies were performed in highly selected patients, and a possible history of COPD was not considered. Whether smoking cessation in COPD patients affects the occurrence of depressive symptoms is unknown and has to our knowledge not previously been described.

The hypothesis in the current study is that COPD patients who stop smoking have a reduced occurrence of depressive symptoms, both measured as use of antidepressant medication and as admissions to psychiatric hospitals with mental depression, bipolar disorder or anxiety.

Methods

We conducted a nationwide retrospective case–control study in outpatients with COPD. As a proxy for depressive symptoms, we examined rates of collection of prescription antidepressants and rates of hospitalisation due to either depression, anxiety or bipolar disorder.

Data

Data were obtained from the following Danish registers

1. The Danish Register for COPD (DrCOPD). A nationwide register including outpatients with COPD and inpatients admitted with acute exacerbation of COPD since January 1, 2010. The COPD diagnoses were specialist-verified and with spirometry with a Tiffeneau–Pinelli index <0.7 All Danish hospitals treating COPD report to DrCOPD, and data consistency and completeness is monitored annually [17, 18]. Main variables recorded are forced expiratory volume in 1 s (FEV_1), body mass index, Medical Research Council dyspnoea scale (MRC), smoking status, treatment with long-acting β-adrenoceptor agonists (LABAs) or long-acting muscarinic receptor antagonists (LAMAs) and treatment with inhaled corticosteroids. Information on survival is provided from the Danish Civil Registration System [18].
2. The Danish National Patient Registry (DNPR). A nationwide register containing information on all contacts with the public Danish Health Service, including hospital admissions and visits to outpatient clinics. Every contact contains a physician-coded primary diagnosis and one or more secondary diagnoses, all according to ICD (International Classification of Diseases), 10th revision (ICD-10) since 1994. DNPR receives information from both somatic and psychiatric sectors [19].
3. Danish National Health Service Prescription Database (DNHSPD). A nationwide register comprising information on all redeemed prescription medicine since 2004. Data from all Danish community pharmacies and hospital-based outpatient pharmacies are reported to DNHSPD. Every redeemed medication has information on strength, dose, Anatomical Therapeutic Chemical classification code and product name [20].

Study population

We identified COPD outpatients from DrCOPD, with a visit between January 1, 2010 and October 31, 2017. Inclusion criteria were age ⩾40 years and a history of smoking. We excluded patients diagnosed with cancer, apart from basal cell carcinoma of the skin, in DNPR within 10 years prior to study entry.

The observation period for each patient was defined as the time between the first outpatient visit with registered smoking status (inclusion date) and the registered end date of observation or the time of death. In case there was no registered end of observation, the end date was defined as October 31, 2017. In case of missing smoking status at any visit, the last observation was carried forward.

Based on data from the entire observation period, patients were divided into consistent smokers and ex-smokers. Ex-smokers were defined by consistent registration of smoking status as former smoker during the study period. Patients observed with an inconsistent smoking status were excluded. We defined inconsistent smoking as registration of smoking status as both active and former during the study period.

Propensity matching was performed using the Greedy matching algorithm [21] to match consistent smokers 1:1 with ex-smokers. We estimated a propensity score conditional on sex, age, body mass index, FEV_1, MRC and major comorbidities (cerebrovascular disease, heart failure, diabetes mellitus, chronic kidney failure, acute myocardial infarction, peripheral artery disease, atrial fibrillation and arterial hypertension) with smoking as the dependent variable. All further analyses were performed on the propensity-matched population.

Data from DNPR were used to characterise comorbidities and to estimate the number of exacerbations of COPD prior to inclusion and in the study period. Comorbidities included were cerebrovascular disease, heart failure, diabetes mellitus, chronic kidney failure, acute myocardial infarction, peripheral artery disease, atrial fibrillation and arterial hypertension.

The study was approved by the Danish Data Protection Agency (journal no.: VD-2018-264, I-Suite 6504). The study protocol was published online at www.coptrin.dk before statistical analyses were performed.

Outcomes

The primary outcome was collection of prescription antidepressants (Anatomical Therapeutic Chemical classification codes N06AA01-N06AX26 except N06AAX12). The primary end-point was investigated separately and combined with all-cause mortality treated as a competing risk. The secondary outcome was admission to a psychiatric hospital with either depression, anxiety or bipolar disorder (ICD-10 codes DF31-34 and DF40-41). Collection of prescription antidepressants was identified in DNHSPD and admissions with either depression, anxiety or bipolar disorder were identified in DNPR. The mortality date was drawn from DrCOPD.

Statistical analysis

All analyses were performed on a propensity-matched population of consistent smokers and ex-smokers.

For descriptive statistics we estimated median values and interquartile ranges for continuous variables and frequencies and proportions for categorical variables.

Use of prescription antidepressants was quantified by rates of World Health Organization Defined Daily Doses (WHO-DDD) per 1000 observation days. Rates of used WHO-DDD per 1000 were calculated for all antidepressants cumulated (table 1) and of major antidepressant drug groups (table 2).

Cox proportional hazard regressions were performed to estimate the risk of collection of prescription antidepressant or all-cause mortality. We performed competing risk analyses to further investigate all-cause mortality as a competing event to the collection of prescription antidepressant. The above-mentioned Cox model was fitted with both Fine–Gray analyses of subdistribution hazard and with

TABLE 1 Prescription antidepressants collected at any community or hospital-based outpatient pharmacy and admissions to a psychiatric hospital with either depression, anxiety or bipolar disorder during the study period

Smoking status	Consistent smokers	Ex-smokers
WHO-DDD of antidepressants collected per 1000 study days		
Any antidepressants	310.9	216.5
TCA	14.2	8.3
SSRI	186.7	137.4
NaSSA	49.1	38.5
SNRI	55.4	29.6
Others	3.1	1.6
Admissions to psychiatric hospital under the diagnosis of depression, anxiety or bipolar disorder per 100 000 study days	3.7	1.8

WHO-DDD: World Health Organization defined daily dose; TCA: tricyclic antidepressants; SSRI: selective serotonin reuptake inhibitor; NaSSa: noradrenergic and specific serotonergic antidepressants; SNRI: serotonin–norepinephrine.

TABLE 2 Association between ongoing smoking and use of antidepressants or all-cause mortality and between ongoing smoking and risk of psychiatric hospital admission with either depression, anxiety or bipolar disorder

	HR (95% CI)	p-value
Collection of any antidepressant or all-cause mortality[#]	1.6 (1.5–1.6)	<0.0001
Collection of any antidepressant	1.4 (1.3–1.5)	<0.0001
All-cause mortality	1.8 (1.7–1.9)	<0.0001
Admission with either depression, anxiety or bipolar disorder[¶]	2.0 (1.6–2.5)	<0.0001

[#]: HRs for collection of any prescription antidepressant or all-cause mortality and cause-specific HR for collection of any prescription antidepressant and all-cause mortality respectively; all-cause mortality was defined as death of any cause with no prior collection of any prescription antidepressant. [¶]: HRs for admission to a psychiatric hospital with either depression, anxiety or bipolar disorder.

TABLE 3 Baseline characteristics of propensity-matched COPD outpatients between 1 January 2010 and 31 October 2017

Smoking status	Smoker	Ex-smoker
Subjects n	10592	10592
Demographics		
Women	5363 (50.3)	5490 (50.6)
Age years	66.9 (59.9–74.3)	67.6 (60.2–74.7)
BMI kg·m^{-2}	24.0 (21–29)	24.7 (21.9–29.0)
<18.5	824 (7.8)	670 (6.3)
18.5–24.9	4613 (43.6)	4682 (44.2)
25–29.9	2841 (26.8)	3090 (29.2)
30–34.9	1463 (13.8)	1391 (13.1)
>35	851 (8.0)	759 (7.2)
MRC		
1	1199 (11.3)	1327 (12.5)
2	3274 (30.9)	3275 (30.9)
3	3206 (30.3)	3112 (29.4)
4	1877 (17.7)	1829 (17.3)
5	1036 (9.8)	1049 (9.9)
FEV_1 % predicted	50 (37–64)	51 (37–65)
>80	739 (7.0)	912 (8.6)
50–79	4765 (45.0)	4656 (44.0)
30–49	3779 (35.7)	3648 (34.4)
<30	1309 (12.4)	1376 (13.0)
Exacerbations in past year		
0	5517 (52.1)	5544 (52.3)
1	2447 (23.1)	2410 (22.8)
⩾2	2628 (24.8)	2638 (24.9)
Inhaled LABA or LAMA	8151 (80.4)	9096 (85.9)
Inhaled corticosteroids	6957 (65.7)	7867 (74.3)
Atrial fibrillation	1228 (11.6)	1174 (11.1)
Heart failure	1262 (11.9)	1204 (11.4)
Acute myocardial infarction	723 (6.8)	667 (6.3)
Hypertension	2875 (27.1)	2745 (25.9)
Diabetes mellitus	1141 (10.8)	1092 (10.3)
Cerebrovascular disease	963 (9.1)	888 (8.4)
Peripheral artery disease	1179 (11.1)	1195 (11.3)
Chronic renal failure	391 (3.7)	330 (3.1)

Data are presented as n (%), median (interquartile range), unless otherwise stated. BMI: body mass index; MRC: Medical Research Council dyspnoea scale; FEV_1: forced expiratory volume in 1 s; LABA: long-acting β-adrenoceptor agonist; LAMA: long-acting muscarinic receptor antagonist.

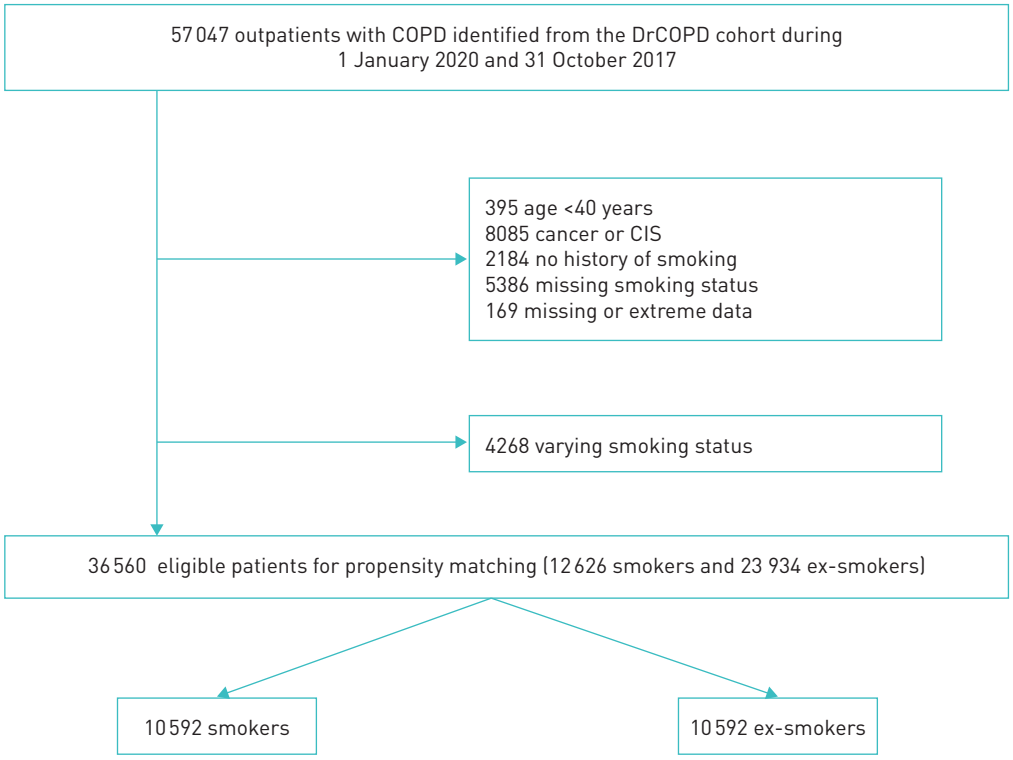

FIGURE 1 Study population included from the Danish Registry for Chronic Obstructive Pulmonary Disease (DrCOPD) between 1 January 2010 and 31 October 2017 with propensity matching of consistent smokers with ex-smokers. Cancer: patients with any cancer except basal cell carcinoma of the skin were excluded. Propensity matching: using Greedy matching consistent smokers were matched with ex-smokers by sex, age, body mass index, forced expiratory volume in 1 s, Medical Research Council dyspnoea scale, cerebrovascular disease, heart failure, diabetes mellitus, chronic kidney failure, acute myocardial infarction, peripheral artery disease, atrial fibrillation and hypertension. CIS: carcinoma *in situ*.

cause-specific analyses of the combined primary end-point by mutual censoring of end-point elements. Finally, a Cox analysis was made to estimate the risk of admission to a psychiatric hospital due to either depression, anxiety or bipolar disorder.

Sensitivity analyses were performed by repeating the above-mentioned Cox analyses extended with a stratification based on collection of either "no" or "any prescription" of antidepressants 5 years prior to study entry.

Results were presented as hazard ratios (HRs) with 95% confidence intervals and as subdistribution HRs (sHRs) with 95% confidence interval.

To predict the cumulated incidence functions the Fine–Gray model was fitted to evaluate the risk of collection of prescription antidepressant and the risk of psychiatric hospital admissions due to either depression, anxiety or bipolar disorder.

Statistical analyses were performed using SAS statistical software 9.4 (SAS Institute Inc., Cary, NC, USA)

Results

We identified 57 843 outpatients with COPD between January 1, 2010 and October 31, 2017 and among those we identified 36 560 eligible patients comprising of 12 626 (34.5%) consistent smokers and 23 934 (65.5%) ex-smokers. In total, 10 592 consistent smokers and 10 592 ex-smokers were matched by propensity score (figure 1). The c-statistics of the logistic regression model used for calculation of the propensity score was 0.69. Baseline characteristics of the propensity-matched population are presented in table 3. The two groups were overall similar, although there was a trend towards more ex-smokers than consistent smokers being treated with inhaled corticosteroids, LABAs or LAMAs.

Use of antidepressants and admissions to psychiatric hospitals

The use of prescription antidepressants and psychiatric hospital admissions among consistent smokers and ex-smokers is shown in table 1. Ex-smokers collected 30.4% fewer prescription antidepressants than

consistent smokers measured as WHO-DDD per 1000 study days. Additionally, ex-smokers collected fewer prescription antidepressants of any drug class. Further details are described in supplementary table 1.

The rates of psychiatric hospital admissions per 100 000 study days for ex-smokers and consistent smokers were 1.8 and 3.7 respectively. The main part of admissions in both groups were due to depression and more ex-smokers than consistent smokers were admitted with anxiety (supplementary table 2).

The rates of hospital-requiring acute COPD exacerbations per 1000 study days for ex-smokers and consistent smokers were 1.5 and 2.3 respectively. Patients who collected any amount of prescription antidepressants during the study period did not have a higher exacerbation frequency (supplementary table 3).

Outcome analyses

The risk of use of any prescription antidepressant and all-cause mortality and the risk of admission to a psychiatric hospital with either depression, anxiety or bipolar disorder is presented for consistent smokers *versus* ex-smokers in table 2. Smoking was associated with a significantly increased risk of collection of any prescription antidepressant or all-cause mortality (HR 1.6, 95% CI 1.5–1.6, p<0.0001) and in cause-specific analyses consistent smoking was also associated with an increased risk of use of prescription antidepressant alone (HR 1.4, 95% CI 1.3–1.5, p<0.0001), ex-smoking as reference

In competing event analysis using the Fine–Gray method, smoking was associated with significantly increased subdistribution hazard of collection of any antidepressant prescription (sHR 1.3, 95% CI 1.2–1.3, p<0,0001) with a cumulative incidence function showing a constantly increased risk of smoking over time (figure 2).

The risk of admission to a psychiatric hospital with either depression, anxiety or bipolar disorder was larger for consistent smokers *versus* ex-smokers (HR 2.0, CI 1.6–2.5, p<0,0001) as presented in table 2. This result was largely unchanged in the competing event analyses with all-cause mortality using the Fine–Gray Model (sHR 1.6, 95% CI 1.3–2.0, p=0.0002) with a cumulative incidence function showing a constantly increased risk of smoking over time (figure 3).

Sensitivity analyses

We performed stratification of the propensity-matched population based on either no use or any use of prescription antidepressants 5 years prior to baseline and subsequently repeated the main analyses with this stratification. Although weakened a little in strength, the signal was largely unchanged that consistent smoking was associated with an increased risk of both use of prescription antidepressants or all-cause mortality (HR 1.4, 95% CI 1.3–1.5, p<0,0001), use of prescription antidepressants alone (HR 1.1, 95% CI 1.01–1.14, p=0.03) and admission to a psychiatric hospital with either depression, anxiety or bipolar disorder (HR 1.6, 95% CI 1.57–1.73, p<0.0001).

Discussion

In this study, we found a strong and substantial association between consistent smoking among COPD patients and the use of antidepressants as well as admission to a psychiatric hospital with either depression, anxiety or a bipolar disorder. All analyses were made on a cancer-free, propensity-matched

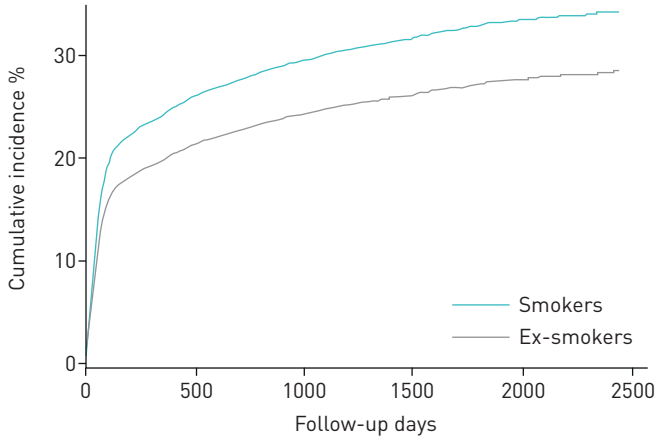

FIGURE 2 Cumulative incidence functions on the risk of collection of antidepressants or all-cause mortality among consistent smokers and ex-smokers matched by propensity score using the Fine–Gray model.

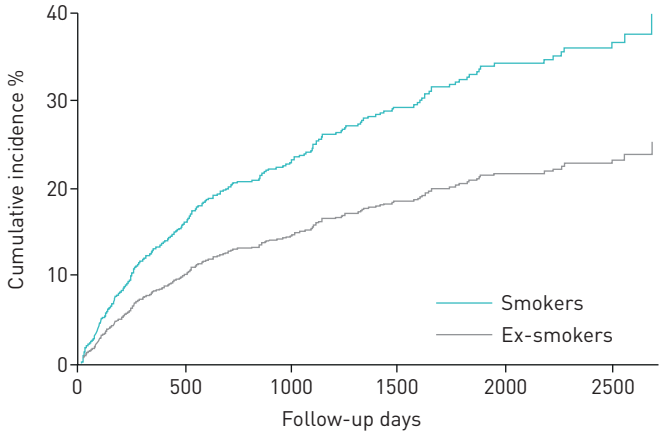

FIGURE 3 Cumulative incidence of the risk of admission to a psychiatric hospital with either depression, anxiety or bipolar disorder among consistent smokers and ex-smokers matched by propensity score using the Fine–Gray model.

population of consistent smokers and ex-smokers, and the significant associations persisted even after adjustment for former use of antidepressants.

Consistent smoking was associated with a 57% increased risk of prescription of antidepressants or all-cause mortality and a 38% increased risk of prescription of antidepressants alone. The latter might even underestimate the association since death was a frequent event in this population, and as expected, was more frequent among consistent smokers. A majority of both consistent smokers and ex-smokers had moderate to severe COPD based on spirometry, and approximately half of patients had one or more exacerbations of COPD in the past year at baseline.

We found an almost two-fold increased risk of admission to a psychiatric hospital with either depression, anxiety or bipolar disorder in patients with consistent smoking compared to ex-smokers with approximately same tobacco exposure and lung function.

One might suspect depressive COPD patients of being less likely to cease smoking due to anhedonia and therefore over-represented among consistent smokers. Therefore, we conducted sensitivity analyses with stratification by use of antidepressants 5 years prior to inclusion in the study to account for this; the signal was largely unchanged.

It is well established that people with mental disorders are more likely to smoke than those without mental disorder with reported rates two- to four-times higher. Despite increased smoking rates, people with mental disorders respond well to standard smoking cessation strategies [22], and cessation rates are equal to the general population [23].

If smoking cessation does reduce the incidence of mental depression among COPD patients, what might be the mechanism? Both smoking and depression are related to altered dopamine function, and the associations we found might in part be explained by normalisation of dopamine circuits, when a person permanently stops smoking. Depression is, apart from dysfunctional serotonin and norepinephrine circuits, associated with dopamine dysfunction and depressive patients have significantly lower dopamine transporter binding secondary to lower dopamine levels [24]. Smoking a cigarette leads to a rapid increase in plasma nicotine with subsequent binding to nicotinic cholinergic receptors in the brain, though persistent exposure to nicotine leads to desensitisation of nicotinic cholinergic receptors and development of tolerance to nicotine [25]. Importantly, a study using FDOPA positron emission tomography scan showed a lower dopamine synthesis capacity among smokers that normalised after 3-month smoking abstinence [26].

Strengths and limitations

To our knowledge, this is the first large study among COPD patients investigating the association between consistent smoking or consistent smoking abstinence and the risk of depression markers. The study was conducted on a large, well-defined, nationwide cohort of COPD patients with complete data available on prescription of medication and hospital admissions [17–20].

Despite these strengths, some limitations of the study should be considered: First, we only included patients who were consistent smokers or consistent ex-smokers during the study period. It would have been of great interest to analyse the use of antidepressants and admissions to psychiatric hospitals before and immediately after smoking cessation. However, we judged it necessary to exclude these patients as <10% of the observation time was after smoking cessation. We suspected a part of this skewness to be

caused by patients not being able physically to smoke during the last months of their life, which is hardly representative for the hypothesis tested. Second, although we did attempt to adjust and match for all known and possible confounders, residual confounding may very well be present and drive a part of the signal observed. This is an inert weakness of the design. However, we did try to address this by performing different analyses, and also by repeating all analyses after stratifying for previous use of antidepressants. Additionally, an interventional design is not possible for ethical reasons.

Third, although our databases are complete regarding most data, some variables were missing in some patients. A small minority of patients had missing data on smoking status. This could not be handled by imputation, as it was the main investigated risk variable. Nevertheless, patients with missing data on this or other variables may very well be a special group regarding the explored outcomes. Fourth, we did not have enough data and observation time on COPD patients who succeeded in smoking cessation, especially after cessation. Having such data would have qualified the conclusions further; this could be the scope of a future study on this important subject.

Conclusion

Consistent smoking among COPD patients is associated with an increased risk of using antidepressants and an increased risk of hospital admissions related to depression, anxiety or bipolar disorder. Possible explanations include an actual effect *via* the cerebral nicotine receptors and the influence on the dopamine system, or that smoking cessation merely is more likely among nondepressed, although the latter is somewhat contradicted by studies estimating the chance of smoking cessation in patients with and without psychiatric illnesses, and our results where stratified for previous use of antidepressants. Patients with COPD who smoke should always be encouraged to stop for several reasons; our study indicates that improving existing mood disorders and reducing the risk of novel mood disorders may be important reasons.

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