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Original Article

Interaction of Depression and Nicotine Addiction on the Severity of Chronic Obstructive Pulmonary Disease: A Prospective Cohort Study

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Abstract

Background: Depression and smoking decrease health status in Chronic Obstructive Pulmonary Disease (COPD), but the combined effect of the two factors is unknown. This study aimed to assess the interactive effects of depression and smoking on the severity of patients with COPD.

Methods: A prospective cohort study including 2,268 patients with COPD was conducted in seven rural communities from May 2008 to May 2012. The relationships between the BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index and depression and nicotine addiction were assessed. The product of depression and smoking was added to the logistic regression model to evaluate the multiplicative interaction and relative excess risk of interaction (RERI). The Attributable Proportion (AP) of interaction and the synergy index (S) was applied to evaluate the additive interaction of two factors.

Results: The severity of COPD in patients with depressive symptoms who never smoked was increased 1.74-fold and in smoking patients it increased by 6.08-fold. Highly addicted smokers with depressive symptoms had a nearly 40-fold increase in severity (all $P<0.001$). The increased values of the BODE index, HADS-D and Fagerström score also correlated positively ($P<0.001$). The co-presence of depressive symptoms and smoking significantly increased the BODE index by 11.99-fold with significant biological interactions, relative excess risk of interaction (RERI) was 12.12, the biological interactions were increased with increasing nicotine addiction.

Conclusions: Patients with depressive symptoms who also smoke have an increased risk of severity from COPD interaction effects. The risk for severity of COPD and depressive symptoms increased with increasing the severity of nicotine addiction.

Keywords: Chronic obstructive pulmonary disease, Smoking, Depression

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is mainly caused by smoking and different air pollutants, and is a progressive disease defined by a limitation of airflow that is at least irreversible (1) .COPD can cause systematic manifestations, resulting in substantial co-morbidity (2). Depression is one of the most common co-morbidities of patients with COPD (3), and is thought to be associated with worse health status in patients with COPD such that two patients with the same degree of lung function impairment have different health outcomes (4).

Cigarette smoking is the principal environmental risk factor for developing COPD(1), despite the disease, COPD smokers smoke more cigarettes per day than the healthy smokers, determined by

their greater nicotine dependence (5). Nicotine dependence is defined as addiction to nicotine and is considered a mental disorder by the Diagnostic and Statistical Manual of Mental Disorders (6). The pack-years is usually used to measure the extent of exposure to cigarette smoke for the smokers, however, it does not reflect other aspects of smoking behaviors such as depth of inhalation, number of puffs per cigarette, and age of onset of smoking(7). 39.7% of smokers with COPD showed high nicotine dependence, and smokers with high nicotine dependence had greater cumulative and current amounts of smoking (8). Therefore, nicotine dependence may increase the impact of smoking exposure due to altering the frequency or depth of smoke inhalation, even in COPD patients with the same pack-year history.

Cigarette smoking among individuals with COPD is not only known to worsen lung function (9), but also damage the quality of life (10). In addition, smoking confers a relative risk of mortality that is two times higher in COPD compared with the risk associated with smoking in other health conditions (11).

The severity of illness in patients with COPD is the result of interactions between many physiological, psychosocial factors and behavior risk factors (12). However, there is little understanding of these multivariate explanations of subjective health status in patients with COPD. There are no studies on the interaction of depression and smoking on severity in patients with COPD.

Therefore, our cohort study was a first research to explore the combined effects of smoking and depression on severity of patients with COPD. The primary aim of this cohort study was to examine the combined effects of depression and smoking on severity over a 4-year period in a Chinese primary care setting. A second aim was to examine the relationship between the BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index (13), nicotine addiction, and depressive symptoms. The third aim was to compare the effect of depressive symptoms and smoking on impaired health status.

Methods

Study population

The selection of patients had been previously described (14), briefly, from May 2008 to May 2012, 4020 patients with COPD met the criteria in seven rural communities were enrolled in a prospective observational study. Patients selected had to meet the criteria of COPD diagnosed by the standards of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) at baseline (1). The following exclusion criteria were used by the County People's Hospital: presence of fever, active tuberculosis, changes in radiographic images or medication in the 4 wk immediately preceding recruitment, primary diagnosis of asthma or obvious bronchiectasis, cystic fibrosis, interstitial lung disease, previous lung volume reduction surgery, lung transplantation and pneumonectomy; Uncontrolled or serious conditions that could potentially affect the spirometry test, and refusal to fill out psychological questionnaires were also excluded.

Ethics approval

The study protocol was approved by the Ethics Committee of Xuzhou Center for Disease Control and Prevention. All participants provided written informed consents.

Depression and anxiety

Depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS). This scale consists of 14 items. Seven items measure anxiety (HADS-A) and seven items measure depression (HADS-D). Scores ranging from 0–21 and scores of ≥8 on a subscale are taken as an indication of possible pathology (15). The Chinese version of the Hospital Anxiety and Depression Scale (HADS) has been developed and validated in previous studies (16). In the present study, patients who had a score more than or equal to 8 for depressive or anxious symptoms were defined as having depressive or anxious symptoms. Therefore, patients who had a score less than 8 for depressive or anxious symptoms were defined as not

having depressive symptoms or not having anxious symptoms.

Smoking status

Cigarette smoking status was obtained by self-report. Cigarette smoking was defined as having smoked at least 100 cigarettes during one's lifetime or smoking any amount for at least 6 months (17). Current smokers were those who had smoked at least 100 cigarettes during their lifetime and, at the time of the interview, reported smoking either every day or on some days. Never smokers were those who reported never having smoked 100 cigarettes during their lifetime. Questions on nicotine addiction were based on the Fagerström Test for Nicotine Dependence (FTND) (18). An FTND score of 0–3 was classed as mild, a score of 4–6 as moderate, and a score of ≥7 as high nicotine dependence (19).

Outcome measures

Assessment of COPD severity

The primary end point used to evaluate patient severity was the BODE index, calculated as previously described (13). Briefly, pulmonary function was assessed based on the standards set forth by the American Thoracic Society (ATS) (20). Dyspnea was measured according to the modified medical research council (mMRC) dyspnea scale (21), in which higher scores indicate more severe dyspnea. The six-min walking distance test (6MWD) was carried out according to ATS guidelines (20). Each of these BODE variables was assigned a specific index value, and from these the total score was calculated, ranging from 0 to 10 points, with a higher score indicating a greater severity. BODE scores were categorized as class 1 (score: 0 to 2), class 2 (score: 3 to 4); class 3 (score: 5 to 6); and class 4 (score: 7 to 10) (22). The BODE index is useful for the assessment of clinical course and stratification of severity of COPD (23).

Covariates

All participants completed questionnaires and underwent spirometry at baseline to determine relevant characteristics. The endpoint was recorded as the time of death, or loss to follow-up, or when data became incomplete or as the BODE index at end of follow up for patients with COPD. Methods for collecting demographic and sociological data have been previously reported (13). In this study, participants who had cooked two dinner equivalents per day for at least 6 months were defined as being exposed to coal and/or biomass smoke. Other patients were classified as not being exposed to coal and/or biomass smoke. The comorbidities were determined by the General Hospital's specialist outpatient medical records. Education was categorized into below high school, high school, or above high school education. The marital status assorted as married, divorce, widowed, solitary. Information was obtained on the amount and type of alcohol consumed during the previous year, and alcohol drinking was defined as the consumption of at least 30 g of alcohol per wk for one year or more (24). Passive smoking was defined as inhaling or being exposed to other people's smoking at home or at work for at least 15 min per day for no fewer than 3 days per wk (2, 5) continuing 6 month. Each volunteer's body height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) in light indoor clothing were measured. Body mass index (BMI; in kg/m^2) was calculated. BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5−24.0 kg/m^2) and overweight/obese (>24.0 kg/m^2) (26).

Statistical analysis

The computer-based analysis program SPSS version 13.0 was used for all statistical analyses. Differences in continuous variables were tested using the F-test or the *t* test, and differences in categorical variables were assessed using the Pearson χ^2 test. Possible associations between smoking, depressive symptoms and the BODE index were examined by Spearman correlation analysis. Multivariate logistic regression was used to analysis the relationship between depression and nicotine dependence on BODE index. The change value of BODE index was that the final BODE index score minus the baseline BODE index score. The BODE index which represented for health status was used dependent variable. The change value of

BODE index which was less than or equal to the mean change equal to 0, the change value of BODE index which was more than the average change equal to 1. The nicotine dependence was classified: an FTND score of 0–3 equal to 0, an FTND score of 4–6equal to 1, an FTND score of ≥7 equal to 2.

To estimate the biological interaction between depression (defined as ≥ 8) and nicotine dependence, we created three new variables: 1) nicotine dependence= yes and depression = no versus others; 2) nicotine dependence = no and depression = yes versus others; and 3) nicotine dependence = yes and depression = yes versus others (27, 28).

The relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (S) were used to estimate biological interactions (27). The RERI is the excess risk attributed to interaction relative to the risk without exposure. AP refers to the attributable proportion of disease caused by interaction in subjects with both exposures. S is the excess risk from both exposures when there is a biological interaction relative to the risk from both exposures without interaction. In the absence of additive interactions, RERI and AP are equal to 0(29). The current study refined the criteria as either a statistically significant RERI>0, AP>0, or S>1 to indicate biological interactions.

Results

General characteristics of participants at the baseline survey and 4-year follow-up

The 3,571 patients out of 4,020 patients who fulfilled the study criteria agreed to take part in our study. After 4 yr, 63.5% (2,268/3,571) completed the final analysis (Fig. 1). The average age of the final analyzed participants was 64.6 ± 14.1 yr. There were significance demographic differences between the four groups at baseline (Table 1). Notably, of the 3,571 participants who were initially enrolled in the study, 1,303 (36.5%) were not included in the final analysis, including 1281 (847 deaths included) who failed to complete the study and 22 who did not meet requirements. The general characteristics of those included and not included in the study at the final analysis included significant differences at baseline (Table 2).

Table 1: Characteristics of the COPD patients (n=2268)

	Total (n=2,268)	Neither smoking nor depression (n=884)	Only current smoking (n=543)	Only Depression (n=393)	Both smoking and depression (n=448)
Median of disease duration (yr)	18.0 ± 5.2	17.8 ± 5.1	18.0 ± 5.3	18.1 ± 5.4	18.2 ± 5.2
Male (n, %)	1,086(47.9)	420(47.5)	286(52.7)	179(45.5)	201(44.9)
*Age (yr)	61.6±13.3	59.9±13.4	61.6±13.1	61.7±13.5	61.8±13.4
Educated to high school level or beyond (n, %)	237(10.4)	140(15.8)	41(7.5)	29(7.4)	27(6.1)
Married (n, %)	1715(75.6)	783 (88.6)	369(68.0)	268(68.2)	295(65.8)
*Annual per capita income (Yuan)	6,830±290	7120±310	6,950±305	6,750±290	6,640±270
Passive smoking (n, %)	356 (15.7)	112(12.7)	123(22.7)	52(13.2)	69(15.4)
Having exposure to coal and/or biomass smoke (n, %)	864 (38.1)	324(36.6)	194(35.7)	169(43.0)	177(39.5)
Comorbidity (n, %)	676 (29.8)	208(23.5)	177(32.6)	132(33.6)	159(35.5)
HADS-A≥8 (n, %)	413 (18.2)	108(12.2)	119(21.9)	87(22.1)	99(22.1)
* BODE index	3.5±1.4	3.2±1.3	3.5±1.6	3.6±1.7	3.7±1.6
*6MWD (m)	352±57	392±54	351±61	345±58	341±62
MRC	1.7±1.2	1.5±1.0	1.9±1.3	1.9±1.1	2.0±1.2
*BMI (kg/m^2)	23.1±2.5	25.1±2.3	23.0±2.4	22.8±2.5	22.6±2.6
*FEV_1 (% predicted)	54.3±11.1	58.3±10.7	52.3±11.7	53.5±10.9	52.4±11.4

Compared with the participants who completed the study, those who dropped out were more often men, older, less educated, not married, had lower income, lower BMI, more likely to be smokers, more likely to be associated with coal and/or biomass smoke exposure, had a higher comorbidity rate, lower BODE index, higher rate of HADS-A and higher rate of HADS-D (P<0.001. Table 2).

Correlations between nicotine addiction and the BODE index, HADS-D and the BODE index, and nicotine addiction and HADS-D

At baseline, the correlations between nicotine addiction and BODE index, between HADS-D and BODE index, and between nicotine addiction and HADS-D were positive, with correlation coefficients of 0.71, 0.82, 0.86, respectively (P<0.001). The increased values of the BODE index, HADS-D and the Fagerström score were also positive correlations, with correlation coefficients of 0.75, 0.77, 0.81, respectively (P<0.001).

Change in the BODE index

At baseline, there were significant differences in BODE index scores between the four groups (Table 1). However, after four yr, the BODE index scores were significantly decreased in total and in all subgroups (Table 3, P<0.05). After adjusted for age, sex, education, annual per capita income, passive smoking, comorbidity, HADS-A,HADS-D and exposure to coal and/or biomass smoke, compared to neither smoking nor depression group, the BODE index scores of the only smoking group, the only depression group and the both smoking and depression group decreased 0.5 (95%CI:0.2-0.8), 0.4 (95%CI:0.1-0.7) and 0.7(95%CI:0.3-1.2) (P<0.001), respectively. The maximum decline occurred in both smokers and subjects with depressive symptoms. The decline of BODE index in the mildly, moderately and highly addicted nicotine groups was significant (F=85.44, P<0.001) (Fig. 2), and was seen accompany with nicotine addiction increased.

Table 2: Characteristics between follow-ups and drop-out patients at baseline

Parameters	follow-ups (n=2, 268)	drop-out (n=1, 303)
Male sex (n, %)	1,039 (45.8)	661 (50.7)
Age (yr)	62.2±8.4	65.5±7.8
Educated to high school level or beyond (n, %)	332 (14.6)	7 (0.5)
Married (n, %)	2,041 (90.1)	599 (46.0)
Annual per capita income (Yuan)	7,270±350	5350±320
BMI (kg/m^2)	24.4±2.5	21.1±2.7
Current smoking (n, %)	989 (43.6)	563 (43.2)
Passive smoking (n, %)	349 (15.4)	210 (16.1)
Having exposure to coal and/or biomass smoke (n, %)	841 (37.1)	515 (39.5)
Comorbid diseases (n, %)	510 (22.5)	517(39.7)
*BODE index	3.5±1.5	3.9±1.5
HADS-A≥8 (n,%)	389 (17.2)	294 (22.6)
HADS-D≥8 (n, %)	823(36.3)	576(44.2)

Table 3: Change of the COPD patients in BODE index after four yr (n=2268)

	Total	Neither smoking nor depression (n=884)	Only smoking (n=543)	Only Depression (n=393)	Both smoking and depression(n=448)
*BODE index					
Baseline	3.5±1.4	3.2±1.3	3.5±1.6	3.6±1.7	3.7±1.6
Final	4.2±1.5	3.5±1.4	4.2±1.6	4.4±1.6	4.7±1.7
ΔBODE index	0.7±0.5	0.3±0.3	0.8±0.5	0.7±0.6	1.0±0.5
T	11.20	2.48	4.52	4.03	5.47
P	<0.001	<0.001	<0.001	<0.001	<0.001

*Data are expressed as means ± SD. BODE: body mass index (B)/airflow obstruction(O)/dyspnea(D)/exercise capacity(E).T: paired t-test value

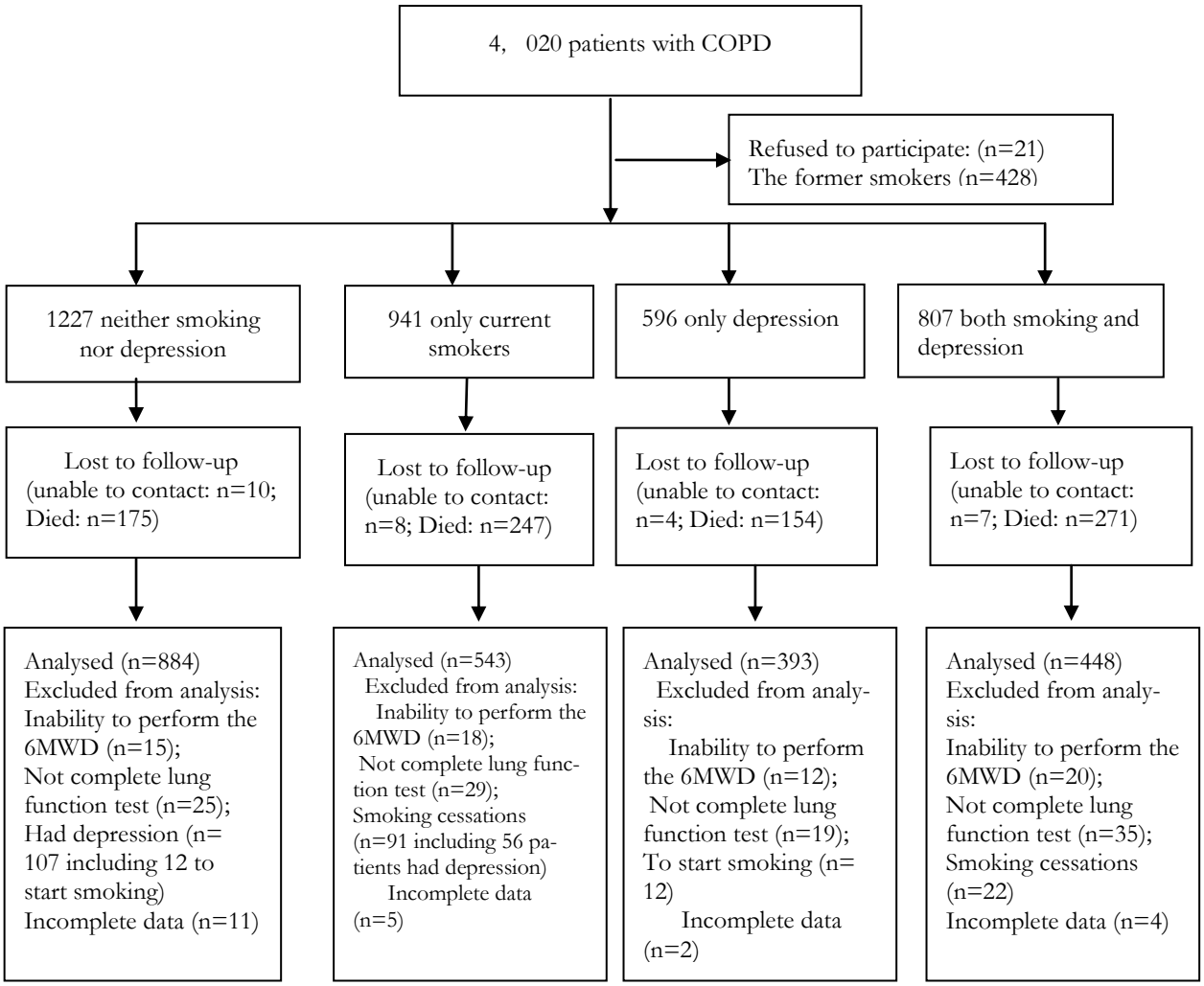

Fig. 1: Consort figure of the trail profile

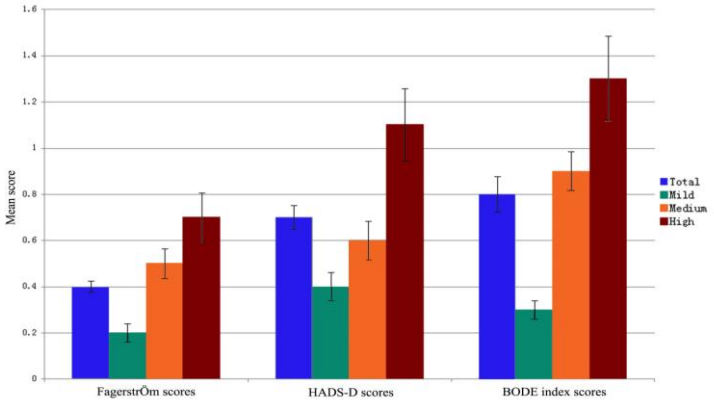

Fig. 2: Comparison of the change values of Fagerström, HADS-D and BODE index in total (n=991), mild (n=405), medium (n=351), high (n=235) nicotine dependence after 4 years.
Illustrations are expressed as means±standard errors. HADS, Hospital Anxiety and Depression Scale; HADS-D, HADS-depression. BODE: body mass index(B)/airflow obstruction(O)/dyspnea(D)/exercise capacity(E).

Biological interaction of smoking and depressive symptoms on severity of COPD

The results from the multiple logistic regression models are presented to assess interaction using a combined effects method, with the *P* value of the interaction term indicating statistical significance of multiplicative interactions (Table 4). Both smoking and depressive individuals had a significantly increased risk of reduced health status as measured by the BODE index compared with those who neither smoked nor had depression (OR: 11.99; 95% CI: 8.49–16.91; *P*<0.001). In addition, only current smokers with no depressive symptoms had a significantly higher risk of reduced health status as indicated by the BODE index compared with that in the neither smoking nor depression group (OR: 6.08; 95% CI: 4.35–8.77; *P*<0.001). Only depressive patients who never smoked also had reduced health status compared with that in the neither smoking nor depression group (OR: 1.74; 95% CI: 1.18–2.55; *P*<0.001). The reduced health status was greatest in the highly addicted nicotine group with greater depressive symptoms (OR: 39.95; 95% CI: 23.54–115.05; *P*<0.001).

Table 4: Odds ratios for the association between the nicotine addiction and severity by depressive symptom among patients with COPD

	Depressive symptom	ΔBODE index > 0.7	ΔBODE index ≤ 0.7	OR (95%CI)
Never smoked	<8	56	429	1
	≥8	75	324	1.74(1.18-2.55)
Smoker	<8	245	302	6.08(4.35-8.77)
	≥8	273	171	11.99(8.49-16.91)
Nicotine addiction (Mild)	<8	95	183	3.89(2.66-5.68)
	≥8	46	81	4.28(2.70-6.78)
Nicotine addiction (Medium)	<8	88	90	7.38(4.89-11.12)
	≥8	106	67	11.98(7.87-18.21)
Nicotine addiction (High)	<8	62	29	15.97(9.44-27.00)
	≥8	121	23	39.95(23.54-115.05)

Models were adjusted for age, sex, disease duration, marital status, income, education level, comorbidity, biomass smoke, the BODE index, depression and anxiety. *P* value (<0.001)

Sensitivity analysis

There was a strong additive interaction between current smoking and having depressive symptoms (RERI, 12.12; 95% CI: 5.41–19.16.) (Table 5). Therefore, the OR of increasing BODE index in current smoking patients with COPD who have depressive symptoms is 12.12 times higher as a result of the additive interaction between never smokers and no depression patients, with 84% of declining health status attributed to the interaction between smoking and depression. There was no interaction between mild nicotine addiction and depressive symptoms (RERI, −0.40; 95% CI: −0.72–0.43). This additive interaction between nicotine addiction and the depressive symptoms was increased with increasingly severe nicotine addiction. The largest interaction was seen with high nicotine addiction and depressive symptoms (RERI, 22.98; 95% CI: 15.67–52.48).

Discussion

The three main findings of this study were first, the combined interaction between cigarette smoking and depressive symptoms on severity of COPD appears to be increased by nicotine dependence, as nicotine dependence is strongly associated with both an increased odds ratio for the BODE index and depressive symptoms. Second, associations exist between the BODE index and nicotine addiction and depressive symptoms. Specifically, the links between changes in the BODE index and changes in nicotine addiction and in

depressive symptoms appear to be the positively correlated. Third, the severity of COPD in the only smoking patients is greater than in those only having depressive symptoms.

Table 5: Measures for estimation of the biological interaction between smoking and depression for the reducing of health status in patients with COPD

Measures of biological interaction	Estimate (95% CI)
Current smoking versus depression	
RERI	12.12(5.41–19.16)
AP	0.84(0.33–1.27)
S	12.36(4.14–20.26)
Mild versus depression	
RERI	-0.40(-0.72-0.43)
AP	-0.09(-0.16-0.27)
S	0.89(-0.12-1.43)
Medium versus depression	
RERI	3.83(1,61-5.57)
AP	0.32(0.09-0.77)
S	1.53(1.13-2.11)
High versus depression	
RERI	22.98(15.67-52.48)
AP	0.57(0.24-1.16)
S	2.49(1.68-4.51)

Reference group is never smoked.

In the present study, we found for the first time that there exists a combined effect between smoking and depression on severity of COPD. The BODE index decreased more in both smoking patients and in those with depressive symptoms than in only smoking patients or only having depressive symptoms patients. Not surprisingly, we also found that nicotine dependence is more strongly associated with the BODE index than current cigarette smoking.

The mechanisms through which smoking and depression have a combined effect on the BODE index are likely complex, involving biogenetic, psychological and environmental factors (5,30-32). These factors include genetic and neural connectivity variables that are common to both depression and smoking, smoking-induced neurobiological changes that might predispose to depression; the transient alleviation of depressive symptoms and psychotropic side effects with smoking, and increased smoking as part of an agitated mental state(5,30-32).

The status of both tobacco smoking and depression as risk factors for severity of COPD is supported by the evidence of shared pathways. Smoking dysregulates the striatal D2 receptor, which may play a shared role in both addiction and its effect on mood (33)? Smoking addiction, in common with other addictions, is mediated via the dopaminergic reward pathway, and dopamine has a key role in depression (34). Cigarette smoking has also been associated with raised levels of C-reactive protein, suggesting the stimulation of a chronic inflammatory state, which again, is described in both depression and COPD (35-37).

Our results show that smoking and depression both increase the severity of COPD, depression and nicotine addiction are all associated with the BODE index, the association between depression and nicotine addiction was also significant, and for the first time we found that the change in the BODE index had a better correlation with the change in nicotine addiction and the change in depressive symptoms. This may explain why depression was previously known to correlate with a higher prevalence of smoking and more intensive nicotine addictions than observed in healthy populations (38). A proportion of patients who develop COPD because of smoking show higher levels of depression than those of the general population. People depressed or have a history of depression are more likely to progress in their use of and dependence on nicotine (39, 40). Conversely, subjects with high levels of depressive tendencies (depression) can be a potential high-risk group susceptible to the development of nicotine dependence (41).

Our results also show that smoking increased the severity of COPD in the smoking patients more than in patients with depressive symptoms-only patients even after adjusting for the other confounders. Moreover, the severity of COPD increased in the highly nicotine addicted. That may explain why ventilation functions, especially the small airway functions, have already been damaged in smokers before any clinical manifestations.

These ventilation functions are positively correlated with smoking history and times (42). Conversely, the development of depression in chronic illness is related to loss of functionality (43). That depression increases the severity of COPD may be at least partly attributable to confounding by cigarette smoking and nicotine dependence (44). Nicotine addiction is likely to be the mechanism of this link. This finding has important and under-examined public health implications.

Although tobacco use may provide psychological relief for some individuals, primary health caregivers must persuade patients to stop smoking. Smokers with greater nicotine dependence find smoking cessation difficult. However, smoking status, and a history of depression are major determinants of mortality in primary health care (45).

Our study has certain limitations. First, we did not consider the effect of genetic factors and lifestyle on the severity of patients with COPD. Second, although we used a reliable and valid measure of depression, our measure was not a clinical diagnosis of a generalized depression disorder. Third, we could not adjust for other possible confounders, such as rehabilitation, exercising, and using beta agonists for therapy. Fourth, these findings were only derived from a Chinese cohort and need to be replicated in other ethnic populations. Fifth, this study was an epidemiological crowd research, not for the individual diagnosis, depressive symptoms and BODE index were only measured at baseline and final, the rate of change in depressive symptoms and BODE index might occur errors.

Conclusions

Despite these limitations, the strengths of the study include its prospective design, the use of a valid and reliable interview measure for HADS, and nicotine dependence; and being the first study to assess nicotine dependence in addition to smoking status in relation to COPD. In fully adjusted models, we estimated that 34–58% of the severity of COPD could be explained by an interaction between smoking and depressive symptoms. These findings support the notion that stopping smoking may reduce the severity of COPD in depressive patients. Given the difficulty in treatment of depression in certain COPD patients, recommendations to quit smoking may be an inexpensive and practical means of reducing severity from COPD. If the results are positive, quitting smoking may be an avenue for depressive patients with COPD to decrease the mortality rate. We believe that our results are significant for caregivers and public health policy makers.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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