Effects of Smoking, Depression, and Anxiety on Mortality in COPD Patients: A Prospective Study

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BACKGROUND: Smoking, depression, and anxiety increase the risk of death in patients with COPD, but the combined effect of these factors is unknown. We assessed the interactive effects of smoking, depression, and anxiety on mortality in patients with COPD. METHODS: We collected and analyzed data from 7,787 subjects with COPD, in 14 rural communities, from May 2008 to May 2012, and used logistic regression to evaluate the interactions and relative excess risk due to interaction (RERI). We applied the attributable proportion of interaction and the synergy index to evaluate the additive interactions of the factors. RESULTS: In our COPD subjects the interaction of current smoking and depression symptoms increased the death risk by 3.8-fold (odds ratio 3.78, 95% CI 2.51–5.05), with significant biological interactions (RERI 1.74, 95% CI 0.51−2.99, attributable proportion 0.48, 95% CI 0.13–0.85, synergy index 2.98, 95% CI 1.44–4.56). The biological interactions increased with increasing years or pack-years of smoking: for subjects with ≥ 30 years of smoking: RERI 1.80, 95% CI 1.05–2.75, attributable proportion 0.48, 95% CI 0.15–0.82, synergy index 2.85, 95% CI 1.75–3.96; for subjects with ≥ 40 pack-years of smoking: RERI 3.11, 95% CI 1.54–4.71, attributable proportion 0.60, 95% CI 0.31–0.91, synergy index 4.00, 95% CI 2.84–5.26. Similarly, the combined effect of current smoking and anxiety symptoms increased the death risk by 4.3-fold (odds ratio 4.27, 95% CI 95% CI 2.96–5.59), with significant biological interactions (RERI 1.51, 95% CI 0.31–2.74, attributable proportion 0.46, 95% CI 0.11–0.87, synergy index 2.89, 95% CI 1.31–4.51). The biological interactions also increased with increasing years or pack-years of smoking: for subjects with ≥ 30 years of smoking: RERI 1.41, 95% CI 0.45–2.43, attributable proportion 0.45, 95% CI 0.12–0.81, synergy index 2.88, 95% CI 1.24–5.98; for subjects with ≥ 40 pack-years of smoking: RERI 3.15, 95% CI 2.07–4.61, attributable proportion 0.55, 95% CI 0.21–0.94, synergy index 3.00, 95% CI 1.45–4.75. CONCLUSIONS: Smoking, depression, and anxiety are associated with higher risk of death in patients with COPD. The risk of death, depression, and anxiety increases with increasing duration of smoking (years) and cigarette pack-years. Chinese Clinical Trials Registration ChiCTR-TRC-12001958. *Key words: COPD; smoking; anxiety; depression; interaction; death.* [Respir Care 2014;59(1):54–61. © 2014 Daedalus Enterprises]

Introduction

COPD is a leading cause of morbidity and mortality, and is estimated to rank seventh in the worldwide disease burden, and the third most frequent cause of death.[1,2] Many studies[3-5] have shown that the causes of death in patients with mild COPD are predominantly cancer and cardiovas-

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cular disease, but as COPD severity increases, deaths due to non-malignant respiratory disease are increasingly common. In practice, the mortality of patients with COPD has been found to be predicted by air-flow limitation,[6] hypercapnia,[7] hypoxemia,[8] low exercise capacity,[9] smoking habits,[8,10] dyspnea,[11] low body mass index,[12] a high BODE (body mass index, obstruction, dyspnea, exercise capacity) index,[13,14] and exposure to biomass smoke.[15]

Two of the most common comorbidities of patients with COPD are depression and anxiety,[16] which increase mortality.[17-20]

Smoking significantly increased the cumulative incidence of COPD in a 25-year follow-up study.[21] The highest incidence for all stages of COPD was 35.5% in continuous smokers, whereas the incidence of COPD in never-smokers was only 7.8%. To the best of our knowledge, the present study is the first regarding the interaction of smoking, depression, anxiety, and mortality in patients with COPD.

Methods

Approval for this study was given by the ethics committee of the Xuzhou Center for Disease Control and Prevention and the Regional Ethical Vetting Board, Xuzhou, China. Written informed consent was obtained from all subjects.

Subjects

From May 2008 to May 2012, we enrolled and collected data from 7,787 subjects from 14 rural communities, and followed them until death or May 2012. The selection of subjects for this study was previously described.[22] The inclusion criteria included COPD diagnosed per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) at baseline.[23] The exclusion criteria included fever, active tuberculosis, changes in radiograph or medication in the 4 weeks immediately preceding recruitment, primary diagnosis of asthma or obvious bronchiectasis, cystic fibrosis, interstitial lung disease, previous lung-volume-reduction surgery, lung transplantation, pneumonectomy, uncontrolled or serious conditions that could potentially affect the spirometry, and refusal to fill out psychological questionnaires.

Smoking Status

Cigarette smoking history was obtained by self-report. Cigarette smoking was defined as having smoked at least 100 cigarettes during one's lifetime or had been smoking any amount for at least 6 months.[24] Current smokers were those who had smoked at least 100 cigarettes during their lifetime and, at the time of the interview, reported smoking

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QUICK LOOK

Current knowledge

Depression and anxiety reduce the quality of life and increase the risk of death in patients with COPD.

What this paper contributes to our knowledge

There was an interaction between smoking, depression, and anxiety and the risk death in patients with COPD. Depression plus anxiety increased the risk of death, which was greater than the simple summation of the risks attributable to never smoking and no depression or anxiety in isolation. The risk of death and depression and anxiety were increased with increasing duration of smoking.

either every day or some days. Former smokers were those who reported smoking at least 100 cigarettes during their lifetime but currently did not smoke. The amount of smoking was based on the number of cigarettes smoked per day, as a statistic. Smoking time (in years) was based on the start of smoking. Pack-years was calculated as the average amount smoked every day, divided by 20 (cigarettes to a pack), multiplied by the smoking time (years). Never-smokers were those who reported never having smoked 100 cigarettes during their lifetime.

Anxiety and Depression

Anxiety and depression were measured with the 14-item Hospital Anxiety and Depression Scale (HADS),[25] in which 7 items measure anxiety (HADS-A) and 7 items measure depression (HADS-D). The scores range from 0 to 21, and a score of ≥ 8 on a subscale is taken as an indication of possible pathology.[25] The Chinese version of HADS has been validated by previous studies.[26] In the present study, subjects who had a depression or anxiety score ≥ 8 were defined as having depression symptoms or anxiety symptoms, and subjects whose depression or anxiety scores were ≤ 8 were defined as without depression symptoms or without anxiety symptoms.

Covariates

All the subjects completed the questionnaires and underwent spirometry at baseline. The end point was death during the follow-up period. Collection of general characteristics was the same as previously reported.[22] In this study, subjects who had cooked 2 dinner equivalents per day for at least 6 months were defined as being exposed to

coal and/or biomass smoke.[27] Other subjects were classified as not being exposed to coal and/or biomass smoke.

Spirometry and bronchodilator response tests were carried out according to the American Thoracic Society guidelines.[28] GOLD COPD stage was per the updated GOLD guideline.[23] Dyspnea was measured with the modified Medical Research Council dyspnea scale.[29] The 6-min walk test was carried out according to the American Thoracic Society guidelines.[30]

The BODE index was calculated and used as previously described (a higher score indicates greater severity).[31]

Definition of End Point

Hospital discharge principal diagnoses, coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD 10), were used to identify end point events. The end point was death during the follow-up period.

Statistical Analysis

We used statistics software (SPSS 13.0, SPSS, Chicago, Illinois) for all calculations. Differences in continuous variables were calculated with the Student t test, and differences in categorical variables were calculated with the Pearson chi-square test. The associations between smoking, depression symptoms, anxiety symptoms, and death were determined with binary logistic regression. The results were stratified into smoking (never smoked vs formerly smoked, and never smoked vs currently smoking), depression (having depression symptoms vs not), or anxiety (having anxiety symptoms vs not), and were adjusted for age (continuous), sex (male or female), education level (less than high school, high school, or greater), marital status, comorbidities (yes or no), exposure to coal and/or biomass smoke (yes or no), and the BODE index (continuous). A cross-product interaction term was included in the logistic regression model to assess multiplicative interactions. Odds ratios and 95% CIs were calculated using the contrast statement in the statistics software. Variance was calculated using the Taylor series linearization method, which leads to an asymptotically unbiased estimate. Differences were deemed statistically significant when $P < .05$ via 2-tailed test.

Biological interactions of evaluation should be based on the sum of the scale, rather than multiplying the scale,[32,33] so we used 3 measures to estimate biological interactions: relative excess risk due to interaction (RERI), the attributable proportion due to interaction, and the synergy index. The RERI is the excess risk attributed to interaction relative to the risk without exposure. The attributable proportion refers to the attributable proportion of disease, which is caused by interaction in subjects with both ex-

posures. The synergy index 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 attributable proportion are equal to zero.[34] In the present study we refined the criteria as either a statistically significant RERI > 0, attributable proportion > 0, or synergy index > 1 to indicate biological interactions.

Results

General Characteristics of Subjects

The demographic and GOLD stage characteristics of the 7,787 subjects were described in a previous study.[22] The important characteristics for the present study are presented in Table 1.

The mean HADS-D score was 6.6 ± 4.3 and the mean HADS-A score was 6.7 ± 4.5. Over one third of the subjects (35.2%) had substantial depression symptoms, and one fifth (19.8%) had substantial anxiety symptoms. For the 7,787 subjects, the 1-year mortality was 151 (1.9%), the 2-year mortality was 351 (4.5%), the 3-year mortality was 447 (5.7%), and the 4-year mortality was 607 (7.8%) subjects. The mean follow-up time for those who died was 2.2 ± 1.3 years. The percentage of deaths was higher in subjects with depression symptoms (782/2,741, 28.5%) than in subjects without depression symptoms (774/5,046, 15.3%, chi-square 193.29, $P < .001$). The percentage of deaths was also higher in subjects with anxiety symptoms (476/1,541, 30.9%) than in subjects without anxiety symptoms (1,080/6,246, 17.3%, chi-square 142.94, $P < .001$). Survivors had a lower BODE index, lower rate of anxiety and depression, lower smoking rate, lower rate of comorbidity, shorter disease duration, younger age, higher education level, less exposure to coal and/or biomass smoke, and more partners than did the nonsurvivors (all $P < .001$). Sex and annual net household income were not significantly different among the groups (see Table 1).

Interaction of Smoking, Depression, Anxiety, and Death From COPD

Table 2 shows the multiple logistic regression results, which assess interaction with a combined effects method, with the P value of the interaction term indicating statistical significance of multiplicative interactions. Current smokers with depression symptoms had a significantly higher risk of death than those without depression symptoms who had never smoked (odds ratio 3.78, 95% CI 2.51–5.05). Former smokers with depression symptoms had a significantly higher risk of death than those who never smoked (odds ratio 3.58, 95% CI 3.25–3.92). The risk of death and depression symptoms increased with in-

Table 1. Subjects

	All Subjects $n = 7,787$	Lived $n = 6,231$	Died (All-Causes) $n = 1,556$	P
Disease duration, y	18 ± 5.2	16 ± 5.1	24 ± 6.5	$< .001$
Female, no. (%)	4,062 (52.2)	3,248 (52.1)	814 (52.3)	.93
Age, y	61.7 ± 13.1	59.5 ± 12.7	71.0 ± 13.5	$< .001$
Education $\geq$ high school, no. (%)	130 (1.6)	119 (1.9)	11 (0.7)	.02
Partner yes, no. (%)	5,136 (63.0)	4,749 (76.2)	387 (24.9)	$< .001$
Annual net household income, yuan	$17,830 \pm 2,280$	$17,930 \pm 2,310$	$16,870 \pm 2,470$	.12
Smoking status, no. (%)				
Current smoker	3,803 (48.8)	2,876 (46.2)	927 (59.6)	$< .001$
Former smoker	1,105 (14.2)	850 (13.6)	255 (16.4)	.004
Never smoked	2,879 (37.0)	2,506 (40.2)	373 (24.0)	$< .001$
Years of smoking, no. (%)				
1–29	743 (9.5)	584 (9.4)	159 (10.2)	.45
$\geq$ 30	4,165 (53.5)	3,141 (50.4)	1,024 (65.8)	$< .001$
Cigarette pack-years, no. (%)				
1–39	3,568 (45.8)	2,787 (44.7)	781 (50.2)	.004
$\geq$ 40	1,340 (17.2)	938 (15.1)	402 (25.8)	$< .001$
History of exposure to coal and/or biomass smoke, no. (%)	3,014 (38.8)	2,382 (38.2)	832 (53.5)	.001
Comorbidities, no. (%)	2,541 (32.6)	1,819 (29.2)	722 (46.4)	$< .001$
BODE index	3.7 ± 1.5	3.5 ± 1.4	5.9 ± 1.6	$< .001$
FEV_1, L	1.2 ± 0.6	1.26 ± 0.6	0.98 ± 0.7	$< .001$
Hospital Anxiety and Depression Scale score $\geq$ 8, no. (%)				
Anxiety domain	1,541 (19.8)	1,065 (17.1)	476 (30.6)	$< .001$
Depression domain	2,741 (35.2)	1,959 (31.4)	782 (50.3)	$< .001$

$\pm$ Values are mean $\pm$ SD.
BODE = body mass index, obstruction, dyspnea, exercise capacity

creasing duration of smoking and cigarette pack-years (see Table 2), but there was no multiplicative interaction of never-smoker and those without depression symptoms on the risk of death ($P = .46$).

Current smokers with anxiety symptoms had a significantly higher risk of death than did subjects without anxiety symptoms who had never smoked (odds ratio 4.27, 95% CI 2.96–5.59). Former smokers with anxiety symptoms had a significantly higher risk of death than those who never smoked (odds ratio 3.39, 95% CI 2.95–3.84). The risk of death and anxiety symptoms increased with increasing duration of smoking and pack-years (see Table 2), but there was no multiplicative interaction of never-smokers and anxiety symptoms on the risk of death ($P = .35$).

Sensitivity Analysis

Table 3 shows the RERI, attributable proportion, and synergy index interaction values. There was strong additive interaction between former or current smoker and depression symptoms (RERI 1.17, 95% CI 0.45–1.91, and 1.74, 95% CI 0.51–2.99, respectively). Therefore, the odds

ratio of death in current smokers with depression was 1.74 times higher as a result of the additive interaction between never-smoker and no depression symptoms. This additive interaction between smoking and depression symptoms was increased with a long duration of smoking (RERI 1.80, 95% CI 1.05–2.75) and a large number of pack-years (RERI 3.11, 95% CI 1.54–4.71).

The RERI derived from the relationship with anxiety symptoms was significantly lower than that derived from the relationship with depression symptoms. The highest RERI for death was for current smokers and anxiety symptoms. Only RERI, attributable proportion, and synergy index values were statistically significant in the anxiety symptoms versus current smoker analysis. In addition, the additive interaction between smoking and anxiety symptoms was also increased with a long duration of smoking (RERI 1.41, 95% CI 0.45–2.43) and a large number of pack-years of smoking (RERI 3.15, 95% CI 2.07–4.61). RERI, attributable proportion, and synergy index were higher in subjects who had a large number of pack-years of smoking plus anxiety symptoms, compared with subjects who had a large number of pack-years of smoking plus depression symptoms.

Table 2. Associations Between Death, Smoking, Depression, and Anxiety in Subjects With COPD*

Smoking Status	Depression Symptoms Score	Died (no.)	Lived (no.)	Odds Ratio	95% CI	P†
Never smoked	<8	248	1,833	1		.46
	≥8	125	673	1.35	1.02–1.68	
Former smoker	<8	127	588	1.57	1.23–1.93	
	≥8	128	262	3.58	3.25–3.92	
Current smoker	<8	398	1,852	1.57	1.16–1.99	
	≥8	529	1,024	3.78	2.51–5.05	
Smoked for 1–29 years	<8	93	439	1.54	1.25–1.85	
	≥8	66	145	3.33	3.03–3.65	
Smoked for ≥ 30 years	<8	433	2,000	1.57	1.21–1.95	
	≥8	591	1,141	3.79	2.84–4.75	
1–39 pack-years	<8	387	1,857	1.51	1.23–1.80	
	≥8	394	930	3.10	2.78–3.42	
≥ 40 pack-years	<8	139	582	1.74	1.31–2.19	
	≥8	263	356	5.43	4.71–6.16	
Smoking status	Anxiety Symptoms Score					
Never smoked	< 8	300	2,136	1		.35
	≥ 8	73	370	1.32	1.03–1.62	
Former smoker	< 8	190	715	1.85	1.25–2.47	
	≥ 8	65	135	3.39	2.95–3.84	
Current smoker	< 8	589	2,316	1.79	1.19–2.39	
	≥ 8	338	560	4.27	2.96–5.59	
Smoked for 1–29 years	< 8	118	486	1.70	1.20–2.21	
	≥ 8	41	98	2.95	2.20–3.71	
Smoked for ≥ 30 years	< 8	662	2,544	1.83	1.26–2.42	
	≥ 8	362	597	4.29	2.91–5.68	
1–39 pack-years	< 8	578	2,348	1.72	1.18–2.27	
	≥ 8	203	439	3.26	2.54–3.99	
≥ 40 pack-years	< 8	202	682	2.08	1.36–2.81	
	≥ 8	200	256	5.53	4.83–6.25	

* Adjusted for age, sex, disease duration, marital status, income, education level, comorbidity, biomass smoke exposure, BODE (body mass index, obstruction, dyspnea, exercise capacity) index, depression, and anxiety.
† Significance of interaction from weighted logistic regression model.

Discussion

In this prospective analysis we detected an interaction between smoking, depression, anxiety, and death in subjects with COPD. This suggests that the presence of depression and anxiety increases the risk of death, which is more than simple summation of the risks attributable to never smoking and no depression or anxiety occurring in isolation. The risk for death and psychological distress increased with increasing duration of smoking (years) and cigarette pack-years.

Although there is an ongoing debate about the association between depression and death in COPD,[35-37] many studies have found that depression is associated with an increased risk of death. Mykletun et al[19] reported that de-

pression was associated with a 1.52 times (95% CI 1.35–1.72) higher risk of death, after adjusting for confounders, than no depression, over a period of 3–6 years. We found a 1.35 times higher adjusted risk of death among depressed subjects who never smoked.

Patients with COPD experience losses in several areas of their lives. They may feel useless, experience reduced sexual activity, depend on others for their personal care, and lose interest in future projects.[38] Tobacco may provide psychological relief for some individuals.[39] Continuing smokers with COPD are more at risk of depression than those who quit.[40] A longitudinal cohort study showed that continuous smokers had a much steeper decline in lung function than those who stopped smoking.[41] We also found that with an increasing duration of smoking and the amount

Table 3. Interactions Between Smoking, Depression, Anxiety and Death in Subjects With COPD*

Comparison	Value	95% CI
Former smoking versus depression		
Relative excess risk due to interaction	1.17	0.45 to 1.91
Attributable proportion	0.43	0.12 to 0.75
Synergy index	3.02	1.64 to 4.41
Current smoking versus depression		
Relative excess risk due to interaction	1.74	0.51 to 2.99
Attributable proportion	0.48	0.13 to 0.85
Synergy index	2.98	1.44 to 4.56
1–29 years of smoking versus depression		
Relative excess risk due to interaction	0.66	−0.23 to 1.57
Attributable proportion	0.34	−0.09 to 0.81
Synergy index	3.44	2.25 to 4.71
≥ 30 years of smoking versus depression		
Relative excess risk due to interaction	1.80	1.05 to 2.75
Attributable proportion	0.48	0.15 to 0.82
Synergy index	2.85	1.75 to 3.96
1–39 pack-years of smoking versus depression		
Relative excess risk due to interaction	1.04	−0.26 to 2.36
Attributable proportion	0.38	−0.17 to 0.95
Synergy index	2.42	0.88 to 3.98
≥ 40 pack-years of smoking versus depression		
Relative excess risk due to interaction	3.11	1.54 to 4.71
Attributable proportion	0.60	0.31 to 0.91
Synergy index	4.00	2.84 to 5.26
Former smoking versus anxiety		
Relative excess risk due to interaction	0.48	−0.14 to 1.15
Attributable proportion	0.24	−0.07 to 0.57
Synergy index	1.98	0.83 to 2.89
Current smoking versus anxiety		
Relative excess risk due to interaction	1.51	0.31 to 2.74
Attributable proportion	0.46	0.11 to 0.87
Synergy index	2.89	1.31 to 4.51
1–29 years of smoking versus anxiety		
Relative excess risk due to interaction	0.45	−0.11 to 1.05
Attributable proportion	0.22	−0.22 to 0.69
Synergy index	1.80	0.78 to 2.84
≥ 30 years of smoking versus anxiety		
Relative excess risk due to interaction	1.41	0.45 to 2.43
Attributable proportion	0.45	0.12 to 0.81
Synergy index	2.88	1.24 to 5.98
1–39 pack-years of smoking versus anxiety		
Relative excess risk due to interaction	0.55	−0.17 to 1.25
Attributable proportion	0.27	−0.13 to 0.76
Synergy index	2.14	0.93 to 5.16
≥ 40 pack-years of smoking versus anxiety		
Relative excess risk due to interaction	3.15	2.07 to 4.61
Attributable proportion	0.55	0.21 to 0.94
Synergy index	3.00	1.45 to 4.75

* Reference group is never smoked.

of smoking, the number of deaths was increased. These results may be attributed to the interaction between de-

pression and smoking. Furthermore, there was an interaction between former smoking and depression, which may be due to short duration of quitting. Most of the former smokers quit only when they suffered from a serious condition. In addition, smoking cessation was reported to be associated with an increased rate of depression.[42] These results suggest that COPD patients should stop smoking as soon as possible.

Elevated anxiety in COPD patients is more common in current smokers than in nonsmokers.[43] Smoking is a common reason to explain the high association of anxiety with COPD. Tobacco use is widely acknowledged as the single most important environmental risk factor for the development of COPD,[28] and a high level of anxiety is a risk factor for starting to smoke.[44] A proportion of patients who develop COPD as a consequence of smoking show higher levels of anxiety than in the general population.[38] Taken together, it is likely that there is an interaction between current smoking and anxiety. In fact, our study shows that this interaction is increased with a long duration of smoking and a large number of pack-years.

Limitations

We did not consider the effect of genetic factors and lifestyle on death. Second, we did not systematically collect data on depression and anxiety during follow-up in the subjects who died. The depression/anxiety status in some subjects might have changed during the follow-up period. Third, although we used a reliable and valid measure of anxiety and depression, that measurement does not constitute a clinical diagnosis of anxiety and depression. Fourth, other confounders, such as hypoxemia, hypercapnia, and using beta agonists, could not be adjusted. Fifth, these findings were derived from a Chinese cohort and need to be replicated in other ethnic populations. Sixth, the end point of our study was death from COPD, and we analyzed the effect of smoking, depression, and anxiety on death. The treatment for COPD patients was not considered.

Conclusions

Our results are important for public health. In our fully adjusted model, 48–60% of the deaths in COPD subjects were explained by an interaction between smoking and depression symptoms, and 49–55% of the deaths of COPD subjects were explained by an interaction between smoking and anxiety symptoms. Our results suggest that quitting smoking may help depressed or anxious patients with COPD forestall death. Given the difficulty in the treatment of depression or anxiety in certain COPD patients, a recommendation to quit smoking may be an inexpensive and practical means of delaying death from COPD.

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