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Interaction of smoking and depression or anxiety on the mortality of COPD patients: a prospective study

Peian Lou, PhD, Xuzhou Center for Disease Control and Prevention, 142 West Erhuan Road, Xuzhou, Jiangsu Province, 221006, China.
E-mail:loupeian2004@yahoo.com.cn

Peipei Chen, PhD, Xuzhou Center for Disease Control and Prevention, 142 West Erhuan Road, Xuzhou, Jiangsu Province, Xuzhou, 221006, China.
E-mail: 71772690@qq.com

Pan Zhang, PhD, Xuzhou Center for Disease Control and Prevention, 142 West Erhuan Road, Xuzhou, Jiangsu Province, Xuzhou, 221006, China.
E-mail: xzzhangpan@126.com

Jiaxi Yu, PhD, Xuzhou Center for Disease Control and Prevention, 142 West Erhuan Road, Xuzhou, Jiangsu Province, Xuzhou, 221006,China.
E-mail: xzyjx007@163.com

Yong Wang, MD, Xuzhou Center for Disease Control and Prevention, 142 West Erhuan Road, Xuzhou, Jiangsu Province, China, Xuzhou, 221006, China. E-mail: xzcdc_wangyong@163.com

Na Chen, PhD, Xuzhou Center for Disease Control and Prevention, 142 West Erhuan Road, Xuzhou, Jiangsu Province, Xuzhou 221006, China.
E-mail: 147819560@qq.com

Lei Zhang, PhD, Xuzhou Center for Disease Control and Prevention, 142 West

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Erhuan Road, Xuzhou, Jiangsu Province, Xuzhou, 221006, China.

E-mail: 18905218811@189.cn

Hongmin Wu, MD, Department of Respiratory Medicine, Affiliated Hospital of Xuzhou Medical College, 99 West Huaiai Road, Xuzhou, Jiangsu Province, Xuzhou, 221006, China. E-mail: wuhongmin19870512@163.com

Jing Zhao, MD, Department of Respiratory Medicine, Affiliated Hospital of Xuzhou Medical College, 99 West Huaiai Road, Xuzhou, Jiangsu Province, Xuzhou, 221006, China. E-mail: 354551183@qq.com.

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Abstract

Background: Smoking, depression, and anxiety increase the risk of death in chronic obstructive pulmonary disease (COPD), but the combined effect of these factors is unknown. This study aimed to assess the interactive effects of smoking and psychological disorders on the death of patients with COPD.

Study Design： A cohort study which enrolled 7,787 participants in 14 rural communities was observed from **May, 2008 to May, 2012.**

Methods: Prospective data for 7,787 Chinese patients with COPD were analyzed. The product of smoking and psychological disorders 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: In COPD patients, **the interaction** of current smoking and depressive symptoms increased death risk by 3.8-fold (OR 3.78[95% CI 2.51-5.05]) with significant biological interactions (RERI 1.74 [0.51 –2.99]; AP 0.48 [0.13–0.85]; S 2.98 [1.44-4.56]). The biological interactions increased with increasing years or pack-years of smoking (years of smoking ≥ 30: RERI 1.80 [1.05–2.75]; AP 0.48 [0.15–0.82]; S 2.85[1.75–3.96]. pack-years of smoking ≥ 40: RERI 3.11 [1.54–4.71]; AP 0.60 [0.31–0.91]; S 4.00[2.84–5.26].). Similarly, **the combined effect** of current smoking and anxious symptoms increased death risk by 4.3-fold (OR 4.27[95% CI 2.96-5.59]) with significant biological interactions (RERI 1.51 [0.31 –2.74]; AP 0.46 [0.11–0.87]; S 2.89 [1.31-4.51]). The biological interactions also increased with increasing years or pack-years of smoking (years of smoking ≥ 30: RERI 1.41 [0.45–2.43]; AP 0.45 [0.12–0.81]; S 2.88[1.24–5.98]. pack-years of smoking ≥ 40: RERI 3.15 [2.07–4.61]; AP 0.55 [0.21–0.94]; S 3.00[1.45–4.75].).

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Conclusions: Smoking and psychological distress are associated with risk of death in patients with COPD. The risk for death and psychological distress increases with increasing duration of smoking (years) and cigarette pack-years.

Clinical Trial Registration: Chinese Clinical Trials Registration (**ChiCTR-TRC-12001958).**

Key words: chronic obstructive pulmonary disease; smoking; anxiety; depression; interaction; death;

Introduction

Chronic obstructive pulmonary disease (COPD) is a1eading cause of increased morbidity and mortality, and is estimated to rank seventh in the worldwide disease burden, in which it is 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 cardiovascular disease, but as COPD severity increases, deaths due to non-malignant respiratory disease are increasingly common. In practice, mortality of patients with COPD has been found to be predicted by airflow limitation,[6] hypercapnia,[7] hypoxemia,[8] low exercise capacity,[9] smoking habits,[8,10] dyspnea,[11] low body mass index, [12] a high BODE (B:body mass index; O:degree of airway obstruction; D:dyspnea; E:exercise capacity;) index,[13,14] and exposure to biomass smoke.[15]

Two of the most common co-morbidities of patients with COPD are depression and anxiety.[16] Depression and anxiety are repeatedly reported to increase mortality.[17-20]

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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, while the incidence of COPD in never smokers was only 7.8%.

To the best of our knowledge, there are no studies regarding the interaction of smoking and psychological disorders on mortality in patients with COPD. Therefore, the aim of this cohort study was to examine if there were combined effects of smoking and psychological disorders on mortality in patients with COPD in a 4-year period in Chinese primary care.

Methods

Study population

Ethical approval for the 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 participants.

From May 2008 to May 2012, a total of 7,787 participants from 14 rural communities were enrolled in the study and followed until either the time of death or to May 2012. The selection of patients for this study has been previously described.[22] here patients had to meet the criteria of COPD diagnosed by the standards set forth by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) at baseline.[23] Exclusion criteria included the presence of fever, active tuberculosis, changes in radiographic images 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 test, and refusal to fill out psychological questionnaires.

Smoking status

Cigarette smoking **history** was obtained by self-report. Cigarette smoking was

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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 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 (cigarettes/day) as a statistic. Smoking time (years) was based on the start of smoking. The total dose smoked (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 using the HADS.[25] This scale consists of 14 items. Seven items measure anxiety (HADS-A) and seven items measure depression (HADS-D). The scores range from 0–21, and scores of ≥8 on a subscale should be taken as an indication of possible pathology.[25] The Chinese version of HADS has been developed and validated by previous studies.[26] 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 symptoms (HDS) or having anxious symptoms (HAS). Therefore, the patients who had a score less than 8 for depressive or anxious symptoms were defined as not having depressive symptoms (NHDS) or not having anxious symptoms (NHAS).

Covariates

All participants completed questionnaires and underwent spirometry at baseline to

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determine relevant characteristics. The endpoint was recorded in the death of patients with COPD. Collection of general characteristics was the same as previously reported.[22] In this study, participants 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 patients were classified as not being exposed to coal and/or biomass smoke.

Spirometry and bronchodilator response tests were carried out according to standardized guidelines by the American Thoracic Society.[28] GOLD stages were defined as described in the updated GOLD.[23] Dyspnea was measured using the modified Medical Research Council dyspnea scale (MRC).[29] The 6-minute walking distance (6MWD) test was carried out according to American Thoracic Society guidelines.[30]

The BODE index is a multidimensional index comprising body mass index (BMI), the degree of airway obstruction (FEV_1pre), functional dyspnea (MRC), and exercise capacity (6MWD). For calculation of the BODE index, we used an empirical model as previously described (higher scores indicate greater severity).[31]

Definition of endpoints

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

Statistical analysis

The computer-based analysis program SPSS version 13.0 was used for all calculations. Differences in continuous variables were tested using the Student's t-test, and differences in categorical variables were assessed using Pearson's χ^2 test. The associations between smoking, depressive symptoms, or anxious symptoms and the death of patients with COPD were determined using binary logistic regression. The results were stratified into smoking (never smoked versus formerly smoked, and never smoked versus currently smoking), depression (having depressive symptoms versus not), or anxiety (having anxiety symptoms versus not), and were adjusted for age

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(continuous), sex (males or females), educational level (less than high school, high school, or greater), marital status, co-morbidity (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 (ORs) and 95% confidence intervals (CIs) were calculated using the contrast statement in SPSS13.0. Variance was calculated using the Taylor series linearization method, which leads to an asymptotically unbiased estimate. All associations reported were statistically significant (P<.05) using two-tailed tests.

Biological interactions of evaluation should be based on the sum of the scale rather than multiplying the scale.[32, 33] Therefore, we used three measures to estimate biological interactions: relative excess risk due to interaction (RERI); the attributable proportion due to interaction (AP); and the synergy index (S). The RERI is the excess risk attributed to interaction relative to the risk without exposure. AP refers to the attributable proportion of disease, which is caused by interaction in participants 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.[34] 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

The demographic characteristics of the 7,787 participants and disease severity according to the GOLD stage have been described in a previous study.[22] Characteristics of our study sample (4,062 women and 3,725 men) overall and according to their vital status 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 patients (35.2%) tested above the standard cut-off score and was classified as having substantial depressive symptoms, and one fifth of patients

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(19.8%) had substantial anxious symptoms. For the 7787 patients, 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%) patients, mean length of follow up for the deaths was 2.2±1.3 years**.** The percentage of deaths was higher in HDS patients (782/2,741=28.5%) than that in NHDS patients (774/5,046=15.3%; chi square=193.29; P＜0.0001). The percentage of deaths was also higher in HAS patients (476/1,541=30.9%) than that in NHAS patients (1,080/6,246=17.3%; chi square=142.94; P＜0.0001). Survivors had a lower BODE index, lower rate of anxiety and depression, lower smoking rate, lower rate of co-morbidity, shorter disease duration, younger age, higher education levels, lower exposing to coal and/or biomass smoke history**,** and more partners than did nonsurvivors (All P ＜ 0.001). Gender and annual net household income were not significantly different among the groups (see Table 1.).

Biological interaction of smoking and psychological distress on death from COPD

Results from the multiple logistic regression models adjusted for age, sex, education level, income, disease duration, partner status, coal/biomass exposure, and co-morbidity and the BODE index are shown in Tables 2. The results are presented to assess interaction using a combined effects method, with the P value of the interaction term indicating statistical significance of multiplicative interactions. Current smoking individuals with HDS had a significantly increased risk of death compared with those with NHDS who had never smoked (OR: 3.78; 95% CI: 2.51–5.05). In addition, former smokers with depressive symptoms had a significantly higher risk of death compared with that in the never smoking group (OR: 3.58; 95% CI: 3.25–3.92). The risk for death and HDS increased with increasing duration of smoking and cigarette

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pack-years (see Table 2.). However, there was no multiplicative interaction of never smokers and NHDS on increasing the risk of death (P=0.46).

Current smoking patients with HAS had a significantly increased risk of death compared with that for individuals with NHAS who had never smoked (OR: 4.27; 95% CI: 2.96–5.59). In addition, former smokers with anxious symptoms had a significantly higher risk of death compared with that in the reference group (OR: 3.39; 95% CI: 2.95–3.84). The risk for death and HAS increased with increasing duration of smoking and cigarette pack-years (see Table 2.). However, there was no multiplicative interaction of never smokers and anxious symptoms on increasing the risk of death (P=0.35).

Sensitivity analysis

RERI, AP, and S were calculated as measures of additive interaction and are presented in Tables 3. There was strong additive interaction between former or current smokers and HDS (RERI, 1.17; 95% CI: 0.45–1.91 and 1.74; 95% CI: 0.51–2.99, respectively). Therefore, the OR of death in current smoking patients with COPD who have HDS is 1.74 times higher as a result of the additive interaction between never smokers and NHDS. This additive interaction between smoking and HDS was increased with a long duration of smoking (RERI, 1.80; 95% CI: 1.05–2.75) and a large number of pack-years of smoking (RERI, 3.11; 95% CI: 1.54–4.71).

RERI derived from the relation with HAS was significantly lower than that derived from the relation with HDS. The highest RERI for death was observed for current smokers and HAS. Only RERI, AP, and S values were statistically significant in the HAS versus current smoker analysis. In addition, the additive interaction between smoking and HAS 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%

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CI: 2.07–4.61). RERI, AP, and S were higher in patients who had a large number of pack-years of smoking with HAS analysis compared with patients who had a large number of pack-years of smoking with HDS analysis.

Discussion

In this prospective analysis, we detected an interaction between smoking and psychological disorders for death in patients with COPD. This suggests that the co-presence of both risk factors confers an increased risk of death, which is more than simple summation of the risks attributable to never smoking and no psychological disorders 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 consistently found that depression is associated with an increased risk of death. Among these studies, Mykletun *et al.* [19] reported that depression was associated with a 1.52 times (95% CI: 1.35–1.72) higher risk of death after adjusted confounders than no depression over a period of 3–6 years. In support of these findings, we also found a 1.35 times higher adjusted risk of death among depressive patients 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 of smoking, the number of deaths was increased. These results may be attributed to the interaction between depression 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 were suffer from serious condition. In

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addition, smoking cessation was reported to be associated with an increased rate of depression.[42] These results suggested that COPD patients should stop smoking as earlier as possible.

Greater levels of anxiety in COPD patients are more common in current smokers than those 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 high levels of anxiety have been identified as a risk factor for people starting to smoke.[44] A proportion of patients who develop COPD as a consequence of smoking show higher levels of anxiety than those of the general population.[38] Taken together, it is likely that there is an interaction between current smoking and anxiety. In fact, our study showed that this interaction was increased with a long duration of smoking and a large number of pack-years of smoking.

Our study has certain limitations. First, we did not consider the effect of genetic factors and lifestyle on death. Second, depression/anxiety levels during follow-up were not systematically collected in patients who died. The depression/anxiety status in some patients might also have changed during the follow-up period. Third, although we used a reliable and valid measure of anxiety and depression, our measure was not a clinical diagnosis of a generalized anxiety and depression disorder. Fourth, other confounders, such as hypoxemia, hypercapnia, and using beta agonists for therapy, could not be adjusted. Fifth, these findings were only derived from a Chinese cohort and need to be replicated in other ethnic populations. Sixth, the endpoint of our study is death from COPD, and we analyzed the effect of both smoking and psychological disorders on this endpoint. The treatment for COPD patients is not considered

Conclusions

Despite these limitations, we believe that our results have a large significance for public health. In fully adjusted models, we estimated that 48-60% of the death of COPD patients can be explained by an interaction between smoking and HDS, 49-55% of the death of COPD patients can be explained by an interaction between smoking and HAS. Our results suggested that quitting smoking may be an

avenue for depressive or anxious patients with COPD to decrease death. Given the difficulty in treatment of depression or anxiety in certain COPD patients, recommendations to quit smoking may be an inexpensive and practical means of reducing death from COPD.

Declarations:

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Conflict of interest: The authors have no conflict of interest. The present paper is not published or presented before (including abstract, or in the relevant meeting).

Acknowledgments: PL participated in writing the manuscript. YN conceived the study, participated in the design of the study, wrote the paper, and was involved in data collection and analysis. PC carried out the literature search and wrote the manuscript. PZ and JY conceived the study, participated in the design of the study, and wrote the manuscript. NZ and NC contributed to the conception of the study, participated in the study design, and contributed to manuscript drafts. LZ, HW, and JZ were lead authors in the original review, contributed to the conception of the study, participated in the study design, and contributed to manuscript drafts. All authors read and approved the final manuscript.

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Table 1. Characteristics of the COPD patients (n=7,787)

Variable	All patients	Survivors (6231)	All-cause mortality(1556)	*p* value[a]
Median of disease duration (years)	18 ± 5.2	16 ± 5.1	24 ± 6.5	0.000
Female	4062 (52.2)	3248(52.1)	814(52.3)	0.93
Age (year)	61.7±13.1	59.5±12.7	71.0±13.5	0.000
Educational levels of high school and above	130 (1.6)	119 (1.9)	11 (0.7)	0.015
Partner yes	5136 (63.0)	4749(76.2)	387 (24.9)	0.000
Annual net household income (Yuan)	17,830±2,280	17,930±2,310	16,870±2,470	0.119
Smoking status				
Current smoker	3803(48.8)	2876(46.2)	927(59.6)	0.000
Former smoker	1105 (14.2)	850 (13.6)	255(16.4)	0.0037
Never smoked	2879 (37.0)	2506(40.2)	373(24.0)	0.000
Duration of smoking (years)				
1–29	743(9.5)	584 (9.4)	159 (10.2)	0.448
≥30	4165(53.5)	3141 (50.4)	1024 (65.8)	0.000
Cigarette pack-years				
1–39	3568 (45.8)	2787 (44.7)	781(50.2)	0.004
≥40	1340 (17.2)	938 (15.1)	402 (25.8)	0.000
Exposure to coal and/or biomass smoke history	3014 (38.8)	2382 (38.2)	832 (53.5)	0.001
Comorbidity	2541 (32.6)	1819(29.2)	722 (46.4)	0.000
BODE index	3.7±1.5	3.5±1.4	5.9±1.6	0.000
FEV1(liters)	1.2±0. 6	1.26±0. 6	0.98±0. 7	0.000

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HADS-A≥8	1541(19.8)	1,065 (17.1)	476 (30.6)	0.000
HADS-D≥8	2741 (35.2)	1,959(31.4)	782 (50.3)	0.000

HADS：Hospital Anxiety and Depression Scale：HADS-A：HADS—anxiety；HADS-D：HADS—depression；BODE index：body mass index, degree of airway obstruction, dyspnea and exercise capacity; FEV1: forced expiratory volume in one second.

Data are presented as means ± SD or n (%); *P value represents differences in means±SD or proportions using Student t test or Pearson χ^2 test.

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Table 2: Odds ratios for the association between smoking and death by psychological distress among patients with COPD

Smoking status	Depressive symptom	Death	Survivor	OR (95%CI)	P
Never smoked	<8	248	1833	1	0.46
	≥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	1852	1.57(1.16-1.99)	
	≥8	529	1024	3.78(2.51-5.05)	
1–29 years	<8	93	439	1.54(1.25-1.85)	
	≥8	66	145	3.33(3.03-3.65)	
≥30 years	<8	433	2000	1.57(1.21-1.95)	
	≥8	591	1141	3.79(2.84-4.75)	
1–39 pack-years	<8	387	1857	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	Anxious symptom				
Never smoked	<8	300	2136	1	0.35
	≥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	2316	1.79(1.19-2.39)	
	≥8	338	560	4.27(2.96-5.59)	
1–29 years	<8	118	486	1.70(1.20-2.21)	
	≥8	41	98	2.95(2.20-3.71)	
≥30 years	<8	662	2544	1.83(1.26-2.42)	

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	≥8	362	597	4.29(2.91-5.68)
1–39 pack-years	<8	578	2348	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)

Models were adjusted for age, sex, disease duration, marital status, income, education level, co-morbidity, biomass smoke, the BODE index, depression and anxiety. *P value represents significance of interaction from weighted logistic regression model.

Table 3: Measures for estimation of the biological interaction between smoking

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and psychological distress for the risk of death in patients with COPD

Measures of biological interaction	Estimate (95% CI)
Former smoking versus depression	
RERI	1.17(0.45 -1.91)
AP	0.43(0.12–0.75)
S	3.02(1.64–4.41)
Current smoking versus depression	
RERI	1.74(0.51–2.99)
AP	0.48(0.13–0.85)
S	2.98(1.44–4.56)
1–29 years of smoking versus depression	
RERI	0.66(-0.23–1.57)
AP	0.34(-0.09–0.81)
S	3.44(2.25–4.71)
≥30 years of smoking versus depression	
RERI	1.80(1.05–2.75)
AP	0.48(0.15–0.82)
S	2.85(1.75–3.96)
1–39 pack-years of smoking versus depression	
RERI	1.04(–0.26–2.36)
AP	0.38(–0.17–0.95)
S	2.42(0.88–3.98)
≥40 pack–years of smoking versus depression	
RERI	3.11(1.54–4.71)
AP	0.60(0.31–0.91)
S	4.00(2.84–5.26)
Former smoking versus anxiety	
RERI	0.48(–0.14–1.15)

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AP	0.24(–0.07–0.57)
S	1.98(0.83–2.89)
Current smoking versus anxiety	
RERI	1.51(0.31–2.74)
AP	0.46(0.11–0.87)
S	2.89 (1.31–4.51)
1–29 years of smoking versus anxiety	
RERI	0.45(–0.11–1.05)
AP	0.22(–0.22–0.69)
S	1.80(0.78–2.84)
≥30 years of smoking versus anxiety	
RERI	1.41(0.45–2.43)
AP	0.45(0.12–0.81)
S	2.88(1.24–5.98)
1–39 pack–years of smoking versus anxiety	
RERI	0.55(–0.17–1.25)
AP	0.27(–0.13–0.76)
S	2.14(0.93–5.16)
≥40 pack–years of smoking versus anxiety	
RERI	3.15(2.07–4.61)
AP	0.55(0.21–0.94)
S	3.00(1.45–4.75)

Reference group is never smoked