Independent Effect of Depression and Anxiety on Chronic Obstructive Pulmonary Disease Exacerbations and Hospitalizations

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Rationale: **Depression and anxiety are significant comorbid and potentially modifiable conditions in chronic obstructive pulmonary disease (COPD), but their effects on exacerbations are not clear.**
Objectives: **To investigate the independent effect of depression and anxiety on the risk of COPD exacerbations and hospitalizations.**
Methods: **A multicenter prospective cohort study in 491 patients with stable COPD in China. Multivariate Poisson and linear regression analyses were used, respectively, to estimate adjusted incidence rate ratios (IRRs) and adjusted effects on duration of events.**
Measurements and Main Results: **Depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS) at baseline. Other measurements included sociodemographic, clinical, psychosocial, and treatment characteristics. Patients were then monitored monthly for 12 months to document the occurrence and characteristics of COPD exacerbations and hospitalizations. Exacerbation was determined using both symptom-based (worsening of ⩾1 key symptom) and event-based definitions (⩾1 symptom worsening plus ⩾1 change in regular medications). A total of 876 symptom-based and 450 event-based exacerbations were recorded, among which 183 led to hospitalization. Probable depression (HADS depression score ⩾ 11) was associated with an increased risk of symptom-based exacerbations (adjusted IRR, 1.51; 95% confidence interval [CI], 1.01–2.24), event-based exacerbations (adjusted IRR, 1.56; 95% CI, 1.02–2.40), and hospitalization (adjusted IRR, 1.72; 95% CI, 1.04–2.85) compared with nondepression (score ⩽ 7). The duration of event-based exacerbations was 1.92 (1.04–3.54) times longer for patients with probable anxiety (HADS anxiety score ⩾ 11) than those with no anxiety (score ⩽ 7).**
Conclusions: **This study suggests a possible causal effect of depression on COPD exacerbations and hospitalizations. Further studies are warranted to confirm this finding and to test the effectiveness of antidepressants and psychotherapies on reducing exacerbations and improving health resource utilizations.**

Keywords: chronic obstructive pulmonary disease; exacerbation; depression; anxiety; risk factor

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Depression and anxiety are significant comorbid and potentially modifiable conditions in chronic obstructive pulmonary disease, but their effects on exacerbations are not clear.

What This Study Adds to the Field

This study suggests a possible causal association between depression and chronic obstructive pulmonary disease exacerbation and hospitalization. Interventional trials appear to be warranted to evaluate the effectiveness of antidepressants and psychotherapies on reducing exacerbations.

Exacerbation is an important adverse event in the progression of chronic obstructive pulmonary disease (COPD). It is the most common cause of death (1), hospital admission (1), and increased health care cost (2). Many exacerbations are treated at home and not serious enough to warrant hospital admissions (3), although they may still have negative impacts on lung function (4) and health status (5). Guidelines emphasize the importance of treatment to reduce both frequency and severity of COPD exacerbation (6). Thus, the determinants of both frequency and severity of COPD exacerbation need to be studied (7).

Although a number of studies have investigated risk factors of COPD exacerbation and hospitalization, few have focused on psychological disorders (8, 9). They deserve more attention, however, given that depression and anxiety are significant comorbid conditions in COPD (10, 11) and are potentially modifiable. Increasing evidence suggests that depression and anxiety may have direct impact on health (12–14) rather than merely being consequences or markers of disease severity. Negative impacts of depression have been established for chronic diseases such as coronary artery disease, diabetes mellitus, and hypertension (15–18), but poorly studied in COPD. Although the association between psychological disorders and hospital readmission have been examined among admitted patients with COPD (8, 9), very few studies have investigated the effects of depression (19) and anxiety on the risk of COPD exacerbation in patients with stable COPD and it remains to be shown if the effect is independent of disease severity.

The main objective of this study was to investigate the independent effect of depression and anxiety on the risk of COPD exacerbations and hospitalizations in a population of patients with COPD in China. We hypothesized, *a priori*, that depression and anxiety identified in patients with stable COPD are associated with an increased risk of exacerbations and hospitalizations in the following year.

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METHODS

This is a prospective cohort study with a 12-month follow-up period, conducted from August 2004 to June 2006 in respiratory departments of 10 general hospitals in Beijing, China. The study protocol was approved by the research ethics boards responsible for all participating hospitals and McGill University Health Center, and written informed consent was obtained from all participants.

Study Population

To be eligible, patients had to meet the following criteria at baseline: (*1*) age of 30 years or older; (*2*) physician-diagnosed COPD; (*3*) post-bronchodilator FEV_1/FVC ratio of less than 0.7 and FEV_1 of less than 80% of predicted value; (*4*) no fever, no worsening of respiratory symptoms, and no medication change within 4 weeks before recruitment; (*5*) no primary diagnosis of asthma; (*6*) no previous lung volume reduction surgery, lung transplantation, or pneumonectomy; and (*7*) expected survival $\geq$ 6 months. In each center, 40 to 60 patients were recruited, at least one-third of whom were females; 40% of patients had Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II disease (FEV_1%: 50–79), 40% had stage III disease (FEV_1%: 30–49), and 20% had stage IV COPD (FEV_1% $<$ 30).

Measurement of Exposures and Confounders

All interviewers (2 clinicians, 2 physiotherapists, and 10 respiratory nurses) were trained to administer the structured questionnaires in the same manner. They were also blinded to the patients' psychological status during the follow-up.

Depression and anxiety were assessed at baseline using the Hospital Anxiety and Depression Scale (HADS) (20). It is a validated screening tool for symptom severity and cases of depression and anxiety in both hospitalized and primary care patients (21) with chronic diseases, including COPD (8, 9), and in the general population (21). The HADS consists of seven items for depression (HAD-D) and seven items for anxiety (HAD-A). The scores range from 0 to 21 for each subscale, with a score of 0–7 denoting a noncase, 8–10 a possible case, and 11 or higher a probable case (20). The Mandarin-Chinese HADS was also translated and validated in our population (unpublished data).

Age, sex, education level, current employment, marital status, living alone, smoking status (current-, ex- or never-smoker), cumulative smoking (pack-years), body mass index (BMI; weight/height^2), the number of exacerbations in the previous year, whether there was a hospital admission for the most recent exacerbation, and the number of years for physician-diagnosed COPD were assessed at baseline based on the patient's report.

Spirometry and bronchodilator response tests were performed by trained professionals according to American Thoracic Society (ATS) standardized guidelines (22). Dyspnea was assessed using the 5-grade Medical Research Council dyspnea scale (23). Daily productive cough was defined as cough and bringing up phlegm for more than 4 days per week and for 3 consecutive months or more in the previous year. Daily wheeze was defined as the chest sounding wheezy or whistling for most days or nights during a week when having cold or occasionally apart from the cold. These were assessed using the modified ATS-DLD-78 questionnaire (24).

Exercise capacity was measured using the six-minute-walk test (6MWT) following the ATS guideline (25). Health-related quality of life (HRQL) was measured using the validated Mandarin-Chinese St. George's Respiratory Questionnaire (SGRQ) (26). The SGRQ contains three subscales (symptom, activity, and impact), and the total score varies from 0 to 100, with higher score indicating worse health status (27).

Self-efficacy was measured by the standardized COPD Self-Efficacy Scale (CSES) (28), which measures how confident patients are that they can manage breathing difficulty or avoid breathing difficulty in various situations in COPD (i.e., negative affect, intense emotional arousal, physical exertion, weather/environmental, and behavioral risk factors). It contains 34 items and answers were scored on a 5-point scale ranging from 1 (very confident) to 5 (not at all confident) in being able to deal with different situations. Perceived social support was measured using a standardized Personal Resource Questionnaire (PRQ2000) (29), which consists of 15 items and assesses the extent to which the individual (*1*) has an indication of being valued, (*2*) is an integral part of a group, (*3*) provides for attachment/intimacy, (*4*) has the opportunity for nurturance, and (*5*) has available informational, emotional, and material help. Answers were scored on a 7-point scale ranging from 1 (strongly disagree) to 7 (strongly agree). The Mandarin-Chinese COPD self-efficacy scale and PRQ2000 were translated and validated in our study population (unpublished data).

Significant comorbidities associated with COPD exacerbation and hospitalization were identified from the literature (30–33); these included myocardial infarction, congestive heart failure, ischemic heart disease, coronary artery disease, hypertension, stroke, diabetes mellitus, cancer, and chronic renal insufficiency. These were assessed systematically in each patient using a questionnaire developed for this study.

Treatment profile was assessed using a structured questionnaire developed for this study. Patients were asked whether or not they used long-acting β_2-agonist, inhaled corticosteroid, combined long-acting β_2-agonist and inhaled corticosteroid, long-acting anticholinergic and oral mucolytics at baseline, and whether they had influenza and pneumococcal vaccination, participated in a pulmonary rehabilitation program and had received a prescription of long-term oxygen therapy (LTOT) in the previous year. LTOT was defined as daily use of oxygen at home for more than 9 months in the previous year. Participating hospitals were dichotomized as being university affiliated or non–university affiliated to account for the potential differences in level of health care and COPD management.

Exacerbations and Hospitalizations

Patients were monitored monthly by telephone for 12 months to document the occurrence and characteristics of COPD exacerbations and hospitalizations. At each telephone contact, a short questionnaire was administered to assess the change in respiratory symptoms and medical interventions in the past month. Patients were also encouraged to report to their attending physicians and research nurses whenever they experienced symptom worsening. A symptom-based exacerbation was confirmed if, for at least 48 hours, patients experienced a worsening of at least one of three key symptoms (increased sputum amount, changed sputum color or purulence, and increased dyspnea). An event-based exacerbation was confirmed if patients experienced at least one key symptom worsening plus a change in at least one of three medications (antibiotics, corticosteroid, and bronchodilator). The end of an exacerbation episode was determined when patients' symptoms improved and returned to their pre-episode status for at least 3 days, or when the symptoms improved and remained stable for at least 3 days. This criterion was also used to distinguish relapse (symptom fluctuation in the same episode) from the recurrence of exacerbations. The start and the end date of each event-based exacerbation and hospital admission were recorded on the basis of a follow-up questionnaire and hospital chart, respectively.

Statistical Analyses

Data analyses were performed using SAS version 9.1.2 (SAS Institute, Inc., Cary, NC). The level of significance was set at $P < 0.05$. The primary outcomes were the rates of exacerbations and hospitalizations, calculated as the total number of exacerbations and hospitalizations divided by the total number of follow-up time free of the corresponding events. Multivariate Poisson regression with overdispersion correction (i.e., SAS PROC GENMOD) was used to estimate the adjusted incidence rate ratios (IRRs). Overdispersion accounts for the within-patient clustering of outcomes. That is, the number of exacerbations and hospitalizations within a patient was assumed to follow the Poisson distribution, and the variability in the event rate between patients was estimated and accounted for using an overdispersion parameter (34). The 95% confidence interval (CI) surrounding the rate ratio was based on the sum of within- and between-subject variability, rather than only on the within-subject variability that would be used with the standard Poisson approach (34). We considered multiple approaches to adjust for clustering of outcomes by hospital. Given the relatively small number of hospitals, numbers of patients per hospital, and the intraclass correlation coefficients in hospital level (intraclass correlation coefficient = 0.08, 0.004,

and 0.001 for symptom-based exacerbation, event-based exacerbation, and hospitalization, respectively), we decided to adjust for hospital using hospital-level covariates rather than generalized estimating equations or random effects models. The hospital type (i.e., university-affiliated or non–university-affiliated hospital) was adjusted in the final multivariate model because this approach resulted in similar effect estimates (i.e., changes less than 10%) and did not change our conclusions compared with adjusting individually for the 10 participating hospitals. The secondary outcomes were the overall lengths (i.e., the cumulative number of days) of exacerbations and hospitalizations over the follow-up period. Due to the skewed distributions, these outcomes underwent natural logarithmic transformation. Multivariate linear regression (i.e., SAS PROC REG) was used to estimate the adjusted effects of depression and anxiety on the cumulative number of days of exacerbations and hospitalizations. The reported parameters are back transformed and represent the proportional increase in overall length of exacerbation and hospitalization relative to the reference category. Testing for linear trends was conducted by assigning the median score to each exposure category, and representing the exposure categories in the model with recoded ordinal variables. For instance, the median value of 3.5, 9, and 16 were assigned to no depression/anxiety, possible depression/anxiety, and probable depression/anxiety categories, respectively, and considered as a continuous variable in the Poisson regression model to obtain the *P* value for the corresponding regression coefficient.

A priori causal reasoning was used to guide confounder evaluation (35, 36). Potential risk factors for COPD exacerbation and hospitalization were identified from a comprehensive literature review. Studies were searched from MEDLINE, EMBASE, and the Cochrane Library from 1980 to 2007, using the key words "COPD," "exacerbation/hospitalization/admission," and "risk factor/determinant/cause." The causal relationships of each risk factor with outcome (exacerbation and hospitalization), exposure (depression and anxiety) and other risk factors were then presented in Directed Acyclic Graphs (35, 36). Additional details and the Directed Acyclic Graph used in this study for confounding evaluation are provided in the online supplement. Briefly, "these graphs link variables by arrows that represent direct causal effects (protective or causative) of one variable on another. As causes precede their effects, these graphs are acyclic: one can never start from one variable and, following the direction of the arrows, end up at the same variable" (36). The confounders for each association under study were identified and adjusted in multivariate analyses, except for those with low variability (e.g., less than 3% subjects participated in pulmonary rehabilitation). The interactions between psychological status (i.e., depression and anxiety) and disease severity (based on FEV_1%) were tested in the multivariate models.

Multiple imputation (Markov chain Monte Carlo method) (37, 38) was used to impute the 41 missing values of baseline six-minute-walk distance (6MWD) (20 with contraindications for 6MWT and 21 with unknown reasons), using other baseline characteristics (e.g., age, sex, FEV_1%, baseline respiratory symptoms, psychosocial status, and treatment profile). SAS PROC MI procedure was used to create multiple imputed datasets, and SAS PROC MIANALYZE procedure was used to combine results after analysis (SAS Institute). The incomplete values for the length of exacerbations (146 exacerbations) and hospitalizations (31 admissions) were also imputed using baseline characteristics (e.g., age, sex, living alone, marital status, FEV_1%, respiratory symptoms, psychosocial status) and exacerbation characteristics (e.g., symptoms worsening, treatment profile such as use of systemic corticosteroid, use of oxygen, noninvasive ventilation, hospitalization cost).

RESULTS

A total of 491 eligible patients were included in the analyses. The mean follow-up time was 373 (SD, 65) days (median, 369 d). Forty patients (8.0%) dropped out before the end of follow-up due to death (n = 16), severe comorbidity (n = 1), losing contact (n = 13), withdrawal (n = 9), and other reasons (n = 1).

As shown in Table 1, 112 (22.8%) patients were suspected of having depression at baseline, including 68 possible cases (13.8%) and 44 probable cases (9.0%). Forty-seven (9.6%) patients were suspected of having anxiety, including 22 possible cases (4.5%) and 25 probable cases (5.1%). Table 1 shows that depressed patients had a higher proportion of concurrent anxiety; were less likely to be married; had a lower level of education, lower FEV_1, FVC, and FEV_1/FVC ratio; and had more severe dyspnea ($\geq$ grade 4) and a shorter 6MWD as compared with nondepressed patients. Depressed patients also had more past exacerbation and hospitalization. Finally, they had lower levels of self-efficacy and social support, and worse HRQL. Similar results were found for anxious compared with nonanxious patients with respect to comorbid depression, 6MWD, dyspnea, self-efficacy, social support, and HRQL.

As shown in Table 2, a total of 876 symptom-based exacerbations and 450 event-based exacerbations were recorded over the 1-year follow-up period, among which 183 (40.7% event-based exacerbations) led to hospitalization. The overall symptom-based exacerbation rate was 1.95/person-year (95% CI, 1.83–2.07), the event-based exacerbation rate was 1.02/person-year (95% CI, 0.93–1.11), and the hospitalization rate was 0.44/person-year (95% CI, 0.38–0.50).

Table 3 shows that depressed patients had more mortality, symptom-based exacerbations, event-based exacerbations, and hospitalizations, and longer hospital stay as compared with nondepressed patients. Anxiety was associated with more frequent symptom-based exacerbation and longer hospital stay ($P < 0.05$).

Table 4 shows an overall trend toward increased risk of exacerbations and hospitalizations in relation to depression. Probable depression (HADS-D score $\geqslant$ 11) was significantly associated with an increased risk of symptom-based exacerbations (adjusted IRR, 1.51; 95% CI, 1.01–2.24; *P* value for trend = 0.02), event-based exacerbations (adjusted IRR, 1.56; 95% CI, 1.02–2.40; *P* value for trend = 0.03), and hospitalization (adjusted IRR, 1.72; 95% CI, 1.04–2.85; *P* value for trend = 0.03) as compared with nondepression (HADS-D score $\leqslant$ 7), after adjusting for known confounders. These effects were after adjustment for FEV_1% (every 10% increase: 0.91 [0.84–0.97], 0.91 [0.83–0.98], and 0.79 [0.70–0.89] for symptom-based exacerbation, event-based exacerbation, and hospitalization, respectively), MRC dyspnea (every 1 grade increase: 1.11 [0.99–1.24], 1.03 [0.91–1.17], and 0.88 [0.74–1.04], respectively), and 6MWD (every 50-m increase: 1.04 [0.99–1.09], 0.94 [0.88–0.99] and 0.95 [0.87–1.04], respectively). Other significant covariates were as follows: worse self-efficacy score ($\geqslant$96 vs. <96) (1.51, 1.19–1.91), living alone (0.62, 0.39–0.99), and being recruited and monitored in a university-affiliated hospital (0.76, 0.60–0.96) for symptom-based exacerbation; worse self-efficacy score (1.41, 1.06–1.87) and past exacerbation (1.34, 1.04–1.73) for event-based exacerbation; and hospitalization for the most recent exacerbation (2.95, 2.01–4.37), age (every one year older) (1.02, 1.00–1.04), and LTOT (1.73, 1.11–2.72) for hospitalization. Other confounders and the interaction terms between depression categories and disease severity (FEV_1% $\geqslant$ 30 vs. FEV_1% < 30) were found to be not statistically significant (i.e., *P* values > 0.1). No significant effect was found for anxiety, and the estimates of disease severity, other covariates, and interaction terms were very similar to those estimated from the multivariate models for depression (unpublished data).

Table 5 shows that, among patients with at least one exacerbation, the overall length of exacerbation was 1.92 times longer (95% CI, 1.04–3.54) for patients with probable anxiety (HADS-A $\geqslant$ 11) than those with no anxiety (HADS-A $\leqslant$ 7) after adjusting for known confounders. Among patients with at least one hospitalization, the overall length of hospitalization is estimated to be 2.45 times longer (95% CI, 0.76–7.87) for patients with probable depression (HADS-D $\geqslant$ 11) and 1.99 times longer (95% CI, 0.59–6.72) for patients with probable anxiety

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY POPULATION ACCORDING TO DEPRESSION AND ANXIETY STATUS (n = 491)

	No Depression (HADS-D ⩽ 7) (n = 379)	Depression* (HADS-D ⩾ 8) (n = 112)	Difference† in Means or Proportions (95% CI)	No Anxiety (HADS-A ⩽ 7) (n = 444)	Anxiety* (HADS-A ⩾ 8) (n = 47)	Difference† in Means or Proportions (95% CI)
HADS total score, mean (SD)	5.1 (3.7)	16.8 (6.4)	12.7 (10.7, 12.6)‡	6.3 (4.5)	22.0 (6.1)	15.7 (14.2, 17.2)‡
Comorbid anxiety, n (%)	11 (2.9)	36 (32.1)	29.2% (20.4, 38.0)‡	NA	NA	NA
Comorbid depression, n (%)	NA	NA	NA	76 (17.1)	36 (76.5)	59.4% (46.8, 72.0)‡
Age, yr, mean (SD)	65.2 (10.7)	67.0 (10.7)	1.8 (−0.5, 4.1)	65.6 (10.7)	65.7 (10.6)	0.1 (−3.1, 3.2)
Male sex, n (%)	264 (69.6)	74 (66.0)	−3.6% (−13.5, 6.3)	307 (69.1)	31 (65.9)	−3.2% (−16.7, 12.7)
Currently married, n (%)	343 (90.5)	92 (82.2)	−8.3% (−16.0, −0.6)‡	396 (89.2)	39 (82.9)	−6.2% (−17.3, 4.9)
Currently retired or disabled, n (%)	277 (73.1)	84 (75)	1.9% (−7.2, 11.0)	327 (73.6)	34 (72.3)	−1.3% (−14.7, 12.1)
High school or above, n (%)	260 (68.6)	58 (51.8)	−16.8% (−27.1, −6.4)‡	292 (65.8)	26 (55.4)	−10.4% (−25.3, 4.4)
BMI, kg/m^2, mean (SD)	24.0 (4.2)	23.8 (4.3)	−0.2 (−1.1, 0.7)	23.8 (4.2)	23.9 (4.2)	0.1 (−1.2, 1.3)
Cumulative smoking, pack-years, mean (SD)	26.2 (28.9)	28.9 (30.4)	2.7 (−3.5, 8.9)	26.6 (29.1)	28.9 (31.1)	2.2 (−6.6, 11.1)
Spirometric values (post-BD), mean (SD)						
FEV_1, L	1.20 (0.48)	1.05 (0.41)	−0.15 (−0.24, −0.04)‡	1.17 (0.47)	1.11 (0.43)	−0.06 (−0.20, 0.08)
FEV_1, % of predicted value	48.2 (15.8)	45.7 (16.4)	−2.5 (−5.9, −0.8)	47.8 (15.9)	46.0 (15.8)	−1.8 (−6.6, 3.0)
FVC, L	2.38 (0.82)	2.23 (0.70)	−0.15 (−0.32, −0.01)‡	2.36 (0.81)	2.28 (0.69)	−0.08 (−0.32, 0.16)
FVC, % of predicted value	75.9 (19.1)	75.5 (21.2)	−0.4 (−4.6, 3.7)	75.9 (19.7)	75.5 (19.1)	−0.4 (−6.4, 5.6)
FEV_1/FVC	0.50 (0.10)	0.47 (0.10)	−0.03 (0.05, −0.01)‡	0.49 (0.19)	0.48 (0.10)	−0.01 (−0.04, 0.02)
Severe COPD (FEV_1% < 30), n (%)	55 (14.5)	21 (18.7)	4.2% (−3.8, 12.2)	66 (14.8)	10 (21.2)	6.4% (−5.7, 18.5)
6MWD§, m, mean (SD)	402.7 (129.9)	320.5 (138.3)	−82.2 (−111.7, −52.7)‡	389.5 (134.4)	333.0 (143.0)	−56.5 (−101.1, −12.0)‡
MRC dyspnea grade ⩾ 4, n (%)	72 (19.0)	51 (45.5)	26.5% (16.5, 36.5)‡	101 (22.7)	22 (46.8)	24.1% (9.3, 38.9)‡
Exacerbations in past year ⩾ 1, n (%)	308 (81.2)	99 (88.3)	7.1% (0.01, 14.2)‡	366 (82.4)	41 (87.2)	4.8% (−5.3, 14.9)
Hospital admission for the last exacerbation, n (%)	173 (45.6)	64 (57.1)	11.5% (1.0, 21.9)‡	211 (47.5)	26 (55.3)	7.8% (−7.1, 22.7)
COPD diagnosis ⩾ 5 yr, n (%)	102 (26.9)	40 (35.7)	8.8% (1.1, 18.7)‡	127 (28.6)	15 (31.9)	3.3% (−10.6, 17.2)
Significant comorbidities ⩾ 1, n (%)	194 (51.2)	67 (59.8)	8.6% (−1.7, 19.0)	236 (53.1)	25 (53.1)	0.0% (−15.0, 15.0)
CSES score, mean (SD)‖	90.5 (21.8)	111.2 (22.5)	20.7 (16.1, 25.4)‡	93.0 (22.4)	116.8 (23.6)	23.8 (17.0, 30.6)‡
PRQ score, mean (SD)‖	85.8 (9.5)	75.6 (13.7)	−10.2 (−12.5, −7.9)‡	84.3 (10.6)	75.1 (15.2)	−9.2 (−12.6, −5.9)‡
SGRQ total and subscore, mean (SD)‖						
Total	41.6 (16.6)	62.3 (17.5)	20.7 (17.1, 24.3)‡	44.1 (17.5)	61.3 (18.7)	23.2 (17.9, 28.5)‡
Symptom	59.2 (17.9)	70.3 (19.5)	11.1 (7.3, 15.0)‡	60.7 (18.5)	71.2 (19.4)	10.5 (4.8, 16.0)‡
Activity	51.3 (20.2)	72.5 (19.6)	21.2 (16.9, 25.4)‡	54.1 (20.9)	74.8 (23.3)	20.7 (14.2, 27.0)‡
Impact	30.4 (19.8)	53.9 (20.7)	23.5 (19.3, 27.7)‡	33.0 (20.6)	61.7 (20.8)	28.7 (22.4, 34.9)‡
Treatment profile, n (%)						
LABD¶	173 (45.6)	54 (48.2)	2.4% (−8.0, 12.9)	212 (47.7)	15 (31.9)	−15.8% (−29.9, −1.7)‡
ICS	109 (28.7)	48 (38.3)	9.5% (−0.5, 19.6)	137 (30.9)	15 (31.9)	1.0% (−12.9, 15.0)
Mucolytics	191 (50.5)	58 (51.7)	1.3% (−9.2, 11.7)	229 (51.7)	20 (42.5)	−9.1% (−24.0, 5.7)
Influenza vaccine in the past year	130 (34.3)	33 (38.9)	−0.5% (−10.4, 9.5)	150 (33.8)	18 (38.2)	4.4% (−10.1, 19.0)
LTOT in the past year	24 (6.3)	10 (8.9)	2.6% (−3.2, 8.4)	31 (6.9)	3 (6.3)	−0.6% (−7.9, 6.7)
Traditional Chinese medicine	191 (50.5)	57 (50.9)	0.4% (−10.1,10.9)	225 (50.7)	23 (48.9)	−1.8% (−16.8, 13.1)

Definition of abbreviations: BD = bronchodilator; BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CSES = COPD-specific self-efficacy; HADS = Hospital Anxiety and Depression Scale; HADS-D = HADS-Depression; HADS-A = HADS-Anxiety; ICS = inhaled corticosteroid; LABD = long-acting bronchodilator; LTOT = long-term oxygen therapy; MRC = Medical Research Council; NA = not applicable; PRQ = Perceived Resource Questionnaire; SGRQ = St. George's Respiratory Questionnaire.

* Possible depression (8 ⩽ HADS-D ⩽ 10) and probable depression (HADS-D ⩾ 11) were combined and referred to as depression (HADS-D ⩾ 8). Possible anxiety (8 ⩽ HADS-A ⩽ 10) and probable anxiety (HADS-A ⩾ 11) were combined and referred to as anxiety (HADS-A ⩾ 8).

† Differences (95% CI) in mean values (for continuous variables) and in proportions (for categorical variables) between patients with and without psychological disorders.

‡ P value < 0.05. Unpaired two-tailed t test was used for continuous variable (compare two means); χ^2 test was used for categorical variables (compare percentages).

§ On the basis of 450 patients who completed a six-minute-walk test.

‖ A higher CSES score indicates worse self-efficacy. A higher PRQ score indicates better perceived social support. A higher SGRQ score indicates worse health-related quality of life.

¶ LABD includes long-acting β_2-agonist and long-acting anticholinergic.

(HADS-A ⩾ 11) compared with those without corresponding disorders, but these associations were statistically insignificant.

DISCUSSION

The main finding of this study is that depression identified in patients with stable COPD was significantly associated with a higher risk of exacerbations and hospitalizations after adjusting for known confounders. This effect was adjusted for disease severity and showed a significant dose–response trend. Secondary analyses show that anxiety identified in stable COPD was significantly associated with increased overall length of event-based exacerbations in patients with at least one exacerbation. Univariate analyses show an overall worse health profile (e.g., disease severity, quality of life, and psychosocial status) in patients who had comorbid depression and anxiety as compared with those who did not.

To our knowledge, this is the first report of the possible causal association between depressive symptoms and exacerbations and hospitalizations in stable COPD, with an *a priori*

TABLE 2. TOTAL NUMBER AND OVERALL RATE OF EXACERBATIONS AND HOSPITALIZATIONS

Exacerbations and Hospitalizations	
Symptom-based exacerbations (≥1 key symptom)	
No. of exacerbations	876
No. of patients with ≥1 exacerbation	306
Overall rate (95% CI)	1.95/person-year (1.83–2.07)
Event-based exacerbations (≥1 key symptom plus ≥1 medication)	
No. of exacerbations	450
No. of patients with ≥1 exacerbation	231
Overall rate (95% CI)	1.02/person-year (0.93–1.11)
Hospitalizations due to COPD exacerbations	
No. of hospitalizations	183
No. of patients with ≥1 hospitalization	108
Overall rate (95% CI)	0.44/person-year (0.38–0.50)

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease.

hypothesis. Our finding is consistent with a recent study (19) in which frequent exacerbators (≥3) had a worse depression score than infrequent exacerbators (<3) (P for χ^2 test = 0.03). However, the effect estimate for depression was not provided and the multivariate analysis (e.g., confounding evaluation and model selection) was not described in that study. A few previous studies have investigated psychological risk factors of COPD hospitalization (8, 9, 39–42) but were unable to find an increased risk of hospitalization in association with depression. On the other hand, we were not able to find solid evidence supporting the significant association between anxiety and hospitalization that was reported in a previous study (8). These inconsistencies may be due to the different study populations, because most previous studies were conducted in admitted patients. Moreover, most previous studies were open to methodologic limitations. For instance, the outcome events were measured before or at the same time as psychological measures (40, 41), seasonal confounding was not controlled (8, 9), different follow-up times (39) or early dropouts (9) were not taken into consideration, sedative consumption was used as the marker of psychological disorders (42), and model selection was based on an automatic data-driven approaches (8, 9, 39–42).

Selection bias was unlikely to be responsible for the significant association between depression and COPD exacerbation in this study. Although differential loss to follow-up was possible because patients who withdrew earlier (n = 40) had more severe COPD ($FEV_1\% < 30\%$) and were more depressed (HADS-D ≥ 8) than those who completed the entire follow-up period, this would only lead to an underestimation of the association between depression and exacerbation. On the other hand, this potential bias may explain the weak and statistically insignificant effect of anxiety.

A comprehensive confounding evaluation was performed using the causal diagram approach (35, 36). This approach has been considered to be a more appropriate strategy compared

TABLE 3. CLINICAL OUTCOMES OF PATIENTS WITH STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE ACCORDING TO DEPRESSION AND ANXIETY STATUS (n = 491)

Clinical Outcomes	No Depression (*n = 379*)	Depression* (*n = 112*)	*P* Value†	No Anxiety (*n = 444*)	Anxiety* (*n = 47*)	*P* Value†
Mortality						
No. (%) of deaths over 1 year	7 (1.8)	9 (8.0)	0.001	13 (2.9)	3 (6.4)	0.20
Time to death for deceased patients						
Mean (SD), d	254 (102.6)	187 (73.5)	0.15	226 (97.4)	172 (38.2)	0.36
Median (IQR), d	236 (152–334)	191 (128–263)	0.38	236 (131–282)	191 (128–197)	0.38
Exacerbations						
No. (%) of patients with symptom-based exacerbations						
0	152 (40.1)	33 (29.5)	0.04	169 (38.1)	16 (34.0)	0.003
1	82 (21.6)	28 (25.0)		99 (22.3)	11 (23.4)	
≥2	145 (38.3)	51 (45.5)		176 (39.6)	20 (42.6)	
No. (%) of patients with event-based exacerbations						
0	212 (55.9)	48 (42.9)	0.003	240 (54.0)	20 (42.6)	0.35
1	92 (24.3)	36 (32.1)		114 (25.7)	14 (29.8)	
≥2	75 (19.8)	28 (25.0)		90 (20.2)	13 (27.6)	
Overall length of event-based exacerbations for exacerbated patients (n = 304) over 1 year						
Mean (SD), d	20.4 (14.4)	24.6 (23.9)	0.14	20.7 (16.1)	27.4 (25.0)	0.07
Median (IQR), d	15 (10–29)	17 (10–26)	0.05	15 (10–28)	17.5 (10–40)	0.14
Hospitalizations						
No. (%) of patients with hospitalization						
0	304 (80.2)	79 (70.5)	0.03	348 (78.4)	35 (74.5)	0.11
1	46 (12.1)	17 (15.2)		56 (12.6)	7 (14.9)	
≥2	29 (7.7)	11 (14.3)		40 (9.0)	5 (10.6)	
Overall length of hospital stay for admitted patients (n = 101) over 1 year						
Mean (SD), days	25.6 (18.7)	37.7 (36.9)	0.05	26.9 (21.3)	49.1 (48.2)	0.03
Median (IQR), days	19 (13–34)	26 (14–44)	0.39	20 (13–35)	36.5 (25–49)	0.39
No. (%) of patients with ≥1 exacerbations requiring systemic corticosteroid use	37 (9.8)	9 (8.0)	0.57	40 (9.0)	6 (12.8)	0.40

Definition of abbreviation: IQR = interquartile range.

* Possible depression (8 ≤ Hospital Anxiety and Depression Scale–Depression [HADS-D] ≤ 10) and probable depression (HADS-D ≥ 11) were combined and referred to as depression (HADS-D ≥ 8). Possible anxiety (8 ≤ HADS-Anxiety [HADS-A] ≤ 10) and probable anxiety (HADS-A ≥ 11) were combined and referred to as anxiety (HADS-A ≥ 8).

† Unpaired two-tailed *t* test was used for continuous variable (compare two means); Wilcoxon sum rank test was used for continuous variable (compare two medians); χ^2 test was used for categorical variables (compare percentages).

TABLE 4. ADJUSTED ASSOCIATIONS BETWEEN PSYCHOLOGICAL DISORDERS AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATIONS AND HOSPITALIZATIONS (n = 491)

		Adjusted* Incidence Rate Ratio (*95% CI*)		
	No. of Patients	Exacerbation (symptom-based)	Exacerbation (event-based)	Hospitalization
No depression (HADS-D ⩽ 7)	379	1 (reference)	1 (reference)	1 (reference)
Possible depression (8 ⩽ HADS-D ⩽ 10)	68	1.32 (0.97, 1.80)	1.30 (0.90, 1.87)	1.37 (0.87, 2.16)
Probable depression (HADS-D ⩾ 11)	44	1.51 (1.01, 2.24)	1.56 (1.02, 2.40)	1.72 (1.04, 2.85)
P value for trend†		0.02	0.03	0.03
No anxiety (HADS-A ⩽ 7)	444	1 (reference)	1 (reference)	1 (reference)
Possible anxiety (8 ⩽ HADS-A ⩽ 10)	22	0.86 (0.51, 1.46)	1.11 (0.63, 1.96)	0.84 (0.38, 1.85)
Probable anxiety (HADS-A ⩾ 11)	25	1.47 (0.97, 2.27)	1.26 (0.78, 2.03)	1.63 (0.88, 3.03)
P value for trend†		0.90	0.31	0.22

Definition of abbreviations: CI = confidence interval; HADS = Hospital Anxiety and Depression Scale; HADS-A = HADS-Anxiety; HADS-D = HADS-Depression.

* Adjusted for age, sex, current smoking, marital status, education level, current employment, living alone (for exacerbation only), FEV_1%, Medical Research Council dyspnea score, six-minute-walk distance, social support, chronic obstructive pulmonary disease–specific self-efficacy, significant comorbidities, hospital type, use of long-acting bronchodilator and inhaled corticosteroid, long-term oxygen therapy (for hospitalization only), past event-based exacerbation (for exacerbation only), and past hospitalization (for hospitalization only).

† *P* value of testing for linear trend.

with more traditional methods such as those based on stepwise regression and the change-in-estimation approach (43–45). It allows for consideration of interrelationships between multiple covariates, it avoids unnecessary or harmful adjustment that may result from conventional strategies, it explicitly reveals the causal assumptions between variables that were implied but obscured in most studies based on data-driven approaches, and it is also mathematically rigorous while being a qualitative and simple way to approach causal inference from observational data (35, 36). On the basis of our causal diagram, the only unmeasured known confounder was hypoxemia. However, because hypoxemia at rest is the major clinical indication for the prescription of LTOT, most of the confounding of hypoxemia was controlled by adjusting for the use of LTOT in the multivariate model. Seasonal confounding was not a problem in this longitudinal study, which covered periods of 12 months. As with any model, however, there can be no guarantee that our causal diagram is correct or that other models could not be put forward. However, this approach allows us to make our causal assumptions explicit.

Due to the heterogeneous nature of COPD exacerbation and the lack of a reliable biomarker, the precise definition of an exacerbation is difficult and controversial. We used both a symptom-based (relying on respiratory symptoms alone) (46) and an event-based definition (sustained symptoms worsening plus a necessary change in regular medication) (47). Because of expected poor compliance to the diary card approach in this less-educated study population, a monthly follow-up using a standardized questionnaire was used to reduce the chances of underreporting and inaccurate recall. However, patients might not recall mild symptom worsening in the past month. The possible impact could be bidirectional. Depressed patients may have heightened awareness of physical symptoms (48, 49) and thus be less likely to miss mild symptom worsening compared with nondepressed patients. On the other hand, depressed patients may be even less likely to report symptom change due to reduced motivation or mobility (4). However, inaccurate recall is more likely to affect symptom-based exacerbation. The fact that the depression was consistently associated with symptom-based, event-based and hospitalized exacerbations reinforces our finding.

The HADS is a widely used screening tool for depression and anxiety (21) in patients with chronic disease, including COPD (8, 9). Our Chinese (Mandarin) translation of HADS was accepted by the original publisher (NFER-Nelson, London,UK; personal communication) and validated in the study population (unpublished data). The established cutoff points for possible and probable cases were adopted from the literature (20), which

TABLE 5. ASSOCIATIONS BETWEEN PSYCHOLOGICAL DISORDERS AND THE OVERALL LENGTH (CUMULATIVE NUMBER OF DAYS) OF EVENT-BASED EXACERBATIONS AND HOSPITALIZATIONS AMONG EXACERBATED (EVENT-BASED) PATIENTS (n = 231) AND ADMITTED PATIENTS (n = 108)

	Exacerbation		Hospitalization	
	No. of Patients	Adjusted* Ratio† (days/reference days)	No. of Patients	Adjusted* Ratio† (days/reference days)
No depression (HADS-D ⩽ 7)	167	1 (reference)	75	1 (reference)
Possible depression (8 ⩽ HADS-D ⩽ 10)	37	0.91 (0.56, 1.50)	16	1.29 (0.54, 3.03)
Probable depression (HADS-D ⩾ 11)	28	1.00 (0.54, 1.84)	17	2.45 (0.76, 7.87)
P value for trend‡		0.91		0.13
No anxiety (HADS-A ⩽ 7)	204	1 (reference)	96	1 (reference)
Possible anxiety (8 ⩽ HADS-A ⩽ 10)	13	1.13 (0.43, 2.96)	4	1.40 (0.27, 7.39)
Probable anxiety (HADS-A ⩾ 11)	15	1.92 (1.04, 3.54)	8	1.99 (0.59, 6.72)
P value for trend‡		0.06		0.27

Definition of abbreviations: HADS-D = Hospital Anxiety and Depression Scale–Depression; HADS-A = Hospital Anxiety and Depression Scale–Anxiety.

* Adjusted for age, sex, marital status, current employment, current smoking, FEV_1%, dyspnea, six-minute-walk distance, social support, chronic obstructive pulmonary disease–specific self-efficacy, significant comorbidities, hospital type, use of long-acting bronchodilator and inhaled corticosteroid, long-term oxygen therapy (for hospitalization only), past exacerbation (for exacerbation only), and past hospitalization (for hospitalization only).

† The original analyses are on natural log scale. The reported parameters are back transformed and represent the proportional increase in overall length of exacerbation and hospitalization relative to the reference category. For instance, the ratio of 1.92 means that the overall length of exacerbation is estimated to be 1.92 times longer for patients with probable anxiety (HADS-A ⩾ 11) than those with no anxiety (HADS-A ⩽ 7).

‡ *P* value of testing for linear trend.

allows us to examine the dose–response effect of depression and anxiety symptoms. The misclassification between categories, if any, would be nondifferential and would only bias the results toward the null.

Despite the control of known confounders, we cannot rule out the possible impact of unknown confounders. The relatively small number of patients with anxiety is another limiting factor. A longer follow-up period and more frequent measure of psychological status would have been useful. In contrast to our *a priori* hypotheses, we did not find significant associations between depression and overall length of event-based exacerbations and hospitalizations in secondary analyses. This may be due to the subgroup chosen for these analyses (i.e., patients who had at least one event-based exacerbation or hospitalization). In addition, although we have imputed the missing length of outcome events, the residual impact of the missing data may still exist.

A few possible mechanisms might explain the effect of depression on COPD exacerbation:

1. Depressed subjects may have changes in major immune cell classes (12–14), which may be responsible for the susceptibility to environmental triggers of COPD exacerbation (e.g., virus/bacteria infection and air pollutants).
2. Many patients with chronic diseases (e.g., COPD) are able to adapt to chronic symptoms (e.g., dyspnea). However, having comorbid depression may interfere this adaptation process and is related to increased awareness and focus on physical symptoms (18, 49). Therefore, depressed patients with COPD may be more sensitive to or report more respiratory symptoms change. This could also lead to more frequent doctor visits and an increased opportunity for pharmacologic prescription (18, 40).
3. Depressed patients may have lower self-confidence and a feeling of hopelessness (50). They may have suboptimal disease control due to poor self-care strategies and adherence to medications (48, 49). These patients tend to be vulnerable when exposed to a trigger of COPD exacerbation.

In conclusion, this study suggested a possible causal relationship between depression and the risk of COPD exacerbation and hospitalization. Thus, better detection and treatment of depression in patients with COPD may result in improved clinical outcomes and health resource utilization. Intervention trials to investigate the effect of antidepressants and psychotherapies on COPD exacerbations appear to be warranted. Pathophysiologic studies are also necessary to understand the underlying disorders that increase the risk of exacerbations and plan interventions more efficiently.

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