Systematic Review and Meta-Analysis of Psychological Distress and Acute Exacerbation of Chronic Obstructive Pulmonary Disease and Consequences

Prasert Kham-ai ▼ Karen Heaton ▼ Chunhong Xiao ▼ Pariya Wheeler

Background: People with chronic obstructive pulmonary disease (COPD) occasionally develop acute exacerbation of COPD—a potentially fatal condition. Psychological distress was associated with acute exacerbation of COPD. However, the evidence on the effect of psychological distress on acute exacerbation of COPD remains unclear.

Objective: The aim of this study was to explore the influence of psychological distress on acute exacerbation of COPD and its consequences.

Methods: The current review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines using three databases (PubMed, CINAHL, and PsyINFO) that were searched to identify relevant articles. Pooled risk ratios and 95% confidential interval were calculated from the included studies' data with random-effect methods to estimate the effect of psychological distress on acute exacerbation of COPD and its consequences.

Results: Nineteen articles were included in the review. Most revealed that psychological distress was significantly associated with increased risk of acute exacerbation of COPD and its consequences. The meta-analyses showed that psychological distress increased risk of acute exacerbation of COPD, COPD-related hospitalization, and death.

Conclusion: Psychological distress had negative effects on acute exacerbation of COPD and its consequences. The results of the meta-analyses show that persons with COPD and psychological distress had a greater risk of acute exacerbation of COPD, hospitalization, and death.

Key Words: chronic obstructive • death • emotional distress • exacerbation of chronic disease • hospitalization • psychological • pulmonary disease • stress

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Chronic obstructive pulmonary disease (COPD) is a respiratory condition that affects 200 million people worldwide (European Respiratory Society, 2017) and causes millions of deaths each year (Celli & Wedzicha, 2019). The global prevalence of COPD rose from 11.7% in 2010 to 13.1% in 2019 (Adeloye et al., 2015; Blanco et al., 2019). Individuals with COPD have progressive respiratory tract inflammation associated with an increased inflammatory response after exposure to noxious particles or gases (Terzikhan et al., 2016). Consequently, people with COPD experience persistent restricted airflow and difficulty breathing and present with respiratory symptoms, including dyspnea and cough with or without sputum production. They also may experience periods of acute worsening of respiratory symptoms called acute exacerbations of COPD (AECOPD; Singh et al., 2019). AECOPD can lead to many serious consequences related to lung function decline, including decreased physical activity, poorer health-related quality of life, and even increased mortality (Ritchie & Wedzicha, 2020). AECOPD is also a common cause of hospitalization (Serra-Picamal et al., 2018). From the perspective of individuals with COPD, exacerbations and hospitalization because of exacerbations were the most critical consequences of COPD (Zhang et al., 2018). Furthermore, AECOPD has a substantial burden on healthcare systems (Hurst et al., 2020).

Psychological Distress and AECOPD

In most cases, AECOPDs are triggered or worsened by respiratory infections or environmental factors such as air pollution and outdoor weather (Ritchie & Wedzicha, 2020). However,

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a considerable portion (16%) of persons with COPD perceived psychological distress as triggering AECOPD (Werchan et al., 2019). It has been revealed that worsening COPD symptoms were significantly associated with psychological distress (Mathew et al., 2019). Psychological distress can trigger COPD symptoms by increasing basal cholinergic tone and/or vagal variations, which can lead to airway constriction (Liccardi et al., 2018). Another link is that psychological distress can impair the immune systems of people with COPD, consequently predisposing them to infections that trigger AECOPD (Pumar et al., 2014).

Although prior studies have revealed an association between AECOPD and psychological distress, the evidence of the influence of psychological distress on AECOPD remains inconclusive because the association between these two variables can be bidirectional and the significance and magnitude of the relationship varies from study to study (Atlantis et al., 2013). Furthermore, the effect of psychological distress on AECOPD is unclear as in some studies, individuals with COPD who had psychological distress had a greater chance of experiencing AECOPD (Huang et al., 2021) and had increased risk of COPD-related hospitalization (Han et al., 2021), whereas some longitudinal studies showed that the occurrence of AECOPD was not significantly associated with psychological distress (Montserrat-Capdevila et al., 2017; Xu et al., 2008). Analyzing existing longitudinal research studies and quantitatively consolidating the research related to the influence of psychological distress on AECOPD to understand the effect of psychological distress on AECOPD and its consequences is important.

This study aimed to explore the longitudinal effect of psychological distress on AECOPD and its consequences. All longitudinal studies that examined the influence of psychological distress on AECOPD and the consequences of AECOPD were included. Meta-analyses were performed to quantitatively synthesize the data and estimate pooled significance and magnitude of the effect of psychological distress on AECOPD and/or its consequences over time.

METHODS

Design

The current systematic review and meta-analysis were conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Page et al., 2021), which consist of a 27-item checklist and the adopted flowchart (see Supplemental Digital Content, Appendix 5, http://links.lww.com/NRES/A496).

Search Strategy

The literature search was conducted using research databases PubMed, CINAHL, and PsyINFO without date limitations to identify all relevant published articles. The key words used for the search were ("Psychological Distress" OR (emotion* OR mental* OR psycholog*) AND (distress*) OR "anxiety" OR "depression") AND ("Pulmonary Disease, Chronic Obstructive" OR COPD) AND (longitudinal OR prospective).

Inclusion/Exclusion and Eligibility Criteria The included studies needed to meet the PECO statement (P = Population/patient; E = Exposure; C = Comparison; O = Outcome) and meet the following eligibility criteria: (a) examined the influence of psychological distress with AECOPD and/or its consequences on the same group of individuals over an extended period; (b) included individuals with COPD (Population); (c) evaluated psychological distress as the exposure at baseline (Exposure); (d) compared prevalence of AECOPD and/or its consequence occurrences between participants who had psychological distress and those who did not (Comparison); (e) reported AECOPD or the consequences of AECOPD as the outcome (Outcome); (f) used validated and reliable measures to determine psychological distress exposure; and (g) had a duration of at least 1 year during which the outcome variables were assessed.

The term *psychological distress* refers to emotional suffering, including depression or anxiety, evaluated by questionnaires or specific diagnoses but does not include suicide. Consequences of AECOPD refer to adverse outcomes related to lung function decline, including COPD-related emergency department (ED) visits, hospitalizations, and mortality. Articles were excluded if they were not written in English or their full-text versions were not available.

Two researchers performed the literature search separately and completed it by February 28, 2022. All the articles initially found by the two researchers (P. K. and C. X.) were pooled together after reviewing titles and abstracts for comprehensive review and quality assessment. The two researchers independently reviewed full-text versions of the included articles and assessed their quality. Publications that met eligibility criteria and had at least "fair quality" based on the Newcastle–Ottawa Scale (NOS) quality assessment for cohort studies (Wells et al., 2021) were selected (see Supplemental Digital Content, Appendix 1, http://links.lww.com/NRES/A496). Articles selected by both researchers were automatically included in the study, whereas those chosen by neither were excluded. Finally, the two researchers collaboratively determined eligibility of the remaining articles where there were differing reviewer assessments. Table 1 summarizes the characteristics of included studies, including the author(s), country, type of psychological distress, measure of psychological distress, outcome of study, sample size, and main relevant results.

Statistical Analyses

When a group of studies was sufficiently homogeneous in terms of independent variables, outcome variables, measurements used to evaluate psychological distress, and period of time to measure the longitudinal outcomes, meta-analyses were

TABLE 1. Characteristic of Included Studies

Study	Country	Type of psychological distress	Measure	Outcome of study	Sample size	Follow-up (months)	Main relevant result
Almagro et al. (2002)	Spain	Depression	Yesavage scale	Mortality	129	24	Depression was significantly associated with increased mortality rate (a*OR* = 3.60, 95% CI [1.50, 8.65]).
Blakemore et al. (2019)	United Kingdom	Depression	HADS	ED visit	355	12	Patients with COPD with scores with depression were associated with increased odds of attending ED (*OR* = 2.78, 95% CI 1.55, 4.99) or having an emergency admission (*OR* = 2.63, 95% CI [1.48, 4.66]).
Coventry et al. (2011)	United Kingdom	Depression and/or anxiety	HADS	Readmission	79	12	Depression was significantly associated with increased readmission rate (*OR* = 1.30, 95% CI [1.06, 1.60]).
Dueñas-Espín et al. (2016)	Greece	Depression or anxiety	HADS	Physical activity	236	12	Patients with COPD with depression performed 81 fewer steps/day for each extra point on the HADS-D score (β = –81, 95% CI [–149, –12). Anxiety was not significantly associated with physical activity.
Fan et al. (2007)	United States	Depression	BDI	Hospitalization, mortality	603	36	Patients with COPD with depression had an increased risk of respiratory hospitalization in unadjusted analysis compared with patients without depression (*OR* = 2.26, 95% CI [1.30, 3.93]). Depressive symptoms were not associated with hospitalization in adjusted analyses. The prevalence rate of COPD-related hospitalization of patients with (29.9%) and without (24.8%) depression were not significantly different (*p* = .16).
Frei et al. (2014)	Switzerland	Depression, anxiety	HADS	Health status	408	24	Depression (coefficient [β] = –9.0, 95% CI [–13.5, –4.5]) and anxiety (β = 5.5, 95% CI [–10.3, –0.8]) were significantly associated with decreased health status.
Han et al. (2021)	Korea	Depression	CES-D	Hospitalization	10,180	12	Multiple hospital admissions were significantly more common among patients with COPD with depression (14%) than among patients with COPD without depression (5.8%, *p* < .001).
Huang et al. (2021)	China	Depression or anxiety	SAS, SDS	AECOPD	504	18	Anxiety and depression were significantly associated with AECOPD (a*OR* = 1.6, 95% CI [1.1, 2.3]).
Ito et al. (2012),	Japan	Depression	CES-D	AECOPD, hospitalization	131	12	Depression was significantly associated with AECOPD and hospitalization (RR = 4.88, 95% CI [1.37, 17.4], and RR = 14.8, 95% CI [3.07, 70.09], respectively).

(continues)

TABLE 1. Characteristic of Included Studies, Continued

Study	Country	Type of psychological distress	Measure	Outcome of study	Sample size	Follow-up (months)	Main relevant result
Laurin et al. (2009)	Canada	Psychiatric disorder	Structured interview	AECOPD	116	24	Patients with COPD with psychological disorder had a significantly greater risk of AECOPD compared with those without psychological disorder in both unadjusted (RR = 1.63, 95% [1.10, 2.42]) and adjusted (aRR = 1.56, 95% CI [1.02, 2.37]) analyses.
Lou et al. (2014)	China	Depression, and/or anxiety	HADS	Mortality	7,787	12	The percentage of deaths was higher in subjects with depression than in subjects without depression (28.5% vs 15.3%, $\chi^2 = 193.29$, $p < .001$). The percentage of deaths was also higher in subjects with anxiety (476/1,541, 30.9%) than in subjects without anxiety (30.9% vs. 17.3%, $\chi^2 = 142.94$, $p < .001$).
Lou et al. (2016)	China	Depression	HADS	Severity of COPD	2,268	48	Depression was significantly associated with COPD severity (*OR* = 1.74, 95% CI [1.18, 2.55]).
Montserrat-Capdevila et al. (2017)	Spain	Depression, and/or anxiety	HADS	AECOPD	512	24	Anxiety and depression were strongly associated with moderate–severe frequent exacerbation in the crude analysis (*OR* = 2.28, 95% CI [1.17, 4.42]). After controlling for confounders, anxiety and depression were not significantly associated with frequent exacerbation (a*OR* = 1.57, 95% CI [0.77, 3.22]).
Montserrat-Capdevila et al. (2018)	Spain	Depression, and/or anxiety	HADS	Hospitalization	512	24	Patients with COPD with depression or anxiety had a significantly higher hospitalization rate (17.5%) than those without (6.5%, $p = .003$).
Ng et al. (2007)	Singapore	Depression	HADS	Hospitalization, mortality, QOL	376	12	Depression *was not* significantly associated with hospitalization (HR = 1.16, 95% CI [0.88, 1.53]; aHR = 0.93, 95% CI [0.68, 1.28]). Depression was significantly associated with mortality (HR = 2.27, 95% CI [1.33, 3.87]; aHR = 1.93, 95% CI [1.04, 3.58]). Patients with COPD with depression had poorer QOL score compared to those without depression (51.9 vs 38.8, $p < .001$).
Stage et al. (2005)	Denmark	Depression	ICD-10	Mortality	49	26	Depression was significantly associated with decreased mortality (aHR = 0.27, 95% CI [0.09, 0.84]).

(continues)

TABLE 1. Characteristic of Included Studies, Continued

Study	Country	Type of psychological distress	Measure	Outcome of study	Sample size	Follow-up (months)	Main relevant result
Xu et al. (2008)	China	Depression, and/or anxiety	HADS	AECOPD, hospitalization	491	12	Depression was associated with an increased risk of AECOPD (aIRR = 1.56, 95% CI [1.02, 2.40]) and hospitalization (aIRR = 1.72, 95% CI [1.04, 2.85]]). Anxiety was not significantly associated with AECOPD aIRR = 1.26, 95% CI [0.78, 2.03]) or hospitalization aIRR = 1.63, 95% CI [0.88, 3.03]).
Yohannes et al. (2017)	United Kingdom	Depression	CES-D	AECOPD	2,059	36	Depression was significantly associated with moderate–severe AECOPD (*OR* = 1.18, 95% CI [1. 07, 1.30]) and severe AECOPD (*OR* = 1.36, 95% CI [1.09, 1.69]).
Zohal et al. (2020)	Iran	Depression or anxiety	HADS	Hospitalization	128	12	Depression and anxiety (*OR* = 1.17, 95% CI [1.01, 4.8]) scores were significantly associated with increased hospitalization for depression (*OR* = 1.21, 95% CI [1.12, 3.7]) and for anxiety (*OR* = 1.17, 95% CI [1.01, 4.8]).

Note. a*OR* = adjusted odds ratio; CI = confidence interval; HADS = Hospital Anxiety and Depression Scale; ED = emergency department; COPD = chronic obstructive pulmonary disease; *OR* = odds ratio; HADS-D = Hospital Anxiety and Depression Scale for depression; BDI = Beck Depression Inventory for depression; CES-D = Center for Epidemiologic Studies Depression Scale; SAS = self-rating anxiety scale; SDS = self-rating depression scale; AECOPD = acute exacerbation of chronic obstructive pulmonary disease; RR = relative risk; aRR = adjusted relative risk; QOL = quality of life; HR = hazard ratio; aHR = adjusted hazard ratio; ICD-10 = International Classification of Diseases, 10th Revision; aIRR = adjusted incidence rate ratio.

performed to estimate the pooled longitudinal effect of psychological distress on AECOPD and/or its consequences. Pooled risk ratios (RRs) and 95% confidence interval (CI) were calculated using the number of events (having/not having psychological distress and having/not having AECOPD and/or its consequences) from the included studies' data with random-effect methods to estimate the effect of psychological distress on AECOPD and its consequences.

Adjusted measures of relative effect (i.e., odds ratio [*OR*], RR, hazard ratio [HR], incidence rate ratio) after controlling for the confounders from the included studies were used to calculate the pooled measures of relative effect to estimate potential direct effect of psychological distress on AECOPD or its consequences. Chi-square and I^2 were also calculated to examine the heterogeneity of the included studies. All the analyses were performed using ReviewManager (RevMan Version 5.4; The Cochrane Collaboration, 2020).

RESULTS

Overall, 895 studies were found from the literature search: 506 from PubMed, 247 from CINAHL, and 142 from PsycINFO. After removing duplicates, 671 articles were screened by titles and abstracts for relevance using the inclusion criteria. This yielded 52 articles, which were assessed for quality based on the NOS for cohort studies and reviewed in detail for reporting the potential effect of psychological distress on AECOPD and its consequences. Thirty-three publications were excluded in this stage. Most (n = 17) were excluded because they did not examine the influence of psychological distress on AECOPD and/or its consequences. Six were excluded because the population of interest was not individuals with COPD or included individuals with other chronic respiratory illnesses. Five studies were excluded because of the lack of a comparison group. Two studies were excluded because the follow-up period was too short (only 4 and 8 weeks). One study was excluded because of the lack of clarity in evaluating psychological distress, and another was excluded because the participants were evaluated for psychological distress while having AECOPD. Finally, one study was excluded because the full-paper version was not published in English.

As a result, 19 articles were included in the review. Of these studies, seven addressed the influence of psychological distress on AECOPD prevalence, whereas the remaining studies explained the influence of psychological distress on AECOPD and its consequences, including COPD-related hospitalization (n = 7), COPD-related mortality (n = 4), general health outcomes (n = 4), and ED visits (n = 1). All included studies were either fair or good quality based on the NOS for cohort studies.

Qualitative Synthesis

The included studies were from 12 different countries including Switzerland (Frei et al., 2014), China (Huang et al., 2021;

Lou et al., 2014, 2016; Xu et al., 2008), Korea (Han et al., 2021), Spain (Almagro et al., 2002; Montserrat-Capdevila et al., 2017, 2018), Greece (Dueñas-Espín et al., 2016), the United Kingdom (Blakemore et al., 2019; Coventry et al., 2011; Yohannes et al., 2017), Singapore (Ng et al., 2007), Canada (Laurin et al., 2009), the United States (Fan et al., 2007), Iran (Zohal et al., 2020), Denmark (Stage et al., 2005), and Japan (Ito et al., 2012). Almost all studies examined depression and/or anxiety as the independent variables and used patient-reported outcome measures to evaluate these variables. The outcome variables of the included studies were AECOPD prevalence, COPD-related ED visits, COPD-related hospitalization, mortality, physical status, physical activity, health status, the severity of COPD, and quality of life. The sample size of the studies ranged from 49 to 10,180. The average follow-up length was 20 months (see Table 1).

Psychological Distress and AECOPD The effect of psychological distress on AECOPD was inconsistent. Some studies showed that psychological distress was a risk factor for AECOPD (Huang et al., 2021; Ito et al., 2012; Montserrat-Capdevila et al., 2018; Ng et al., 2007), whereas some showed that psychological distress was not a significant predictor for AECOPD (Fan et al., 2007; Xu et al., 2008). However, when separately analyzing subtypes of psychological distress (depression and anxiety), we found that most identified depression as a predictor of AECOPD (Huang et al., 2021; Ito et al., 2012; Montserrat-Capdevila et al., 2017, 2018; Ng et al., 2007).

Psychological Distress and AECOPD Consequences Four consequences were found from the included studies—COPD-related hospitalization, COPD-related ED visit, mortality, and general consequences. The effect of psychological distress on hospitalization was inconsistent. Most studies showed that depression (Blakemore et al., 2019; Coventry et al., 2011; Han et al., 2021; Montserrat-Capdevila et al., 2018; Zohal et al., 2020) and anxiety (Montserrat-Capdevila et al., 2018; Zohal et al., 2020) were significant predictors for COPD-related hospital admission. However, some studies controlling for covariates suggested that depression (Fan et al., 2007; Ng et al., 2007; Xu et al., 2008) and anxiety (Montserrat-Capdevila et al., 2018; Xu et al., 2008) did not significantly affect COPD-related hospital admission rates.

Only one study revealed the potential effect of psychological distress on COPD-related ED visits. Blakemore et al. (2019) reported that depression was a predictor of emergency care as it was found that those with depression had a significantly increased chance to visit the ED in the follow-up year (*OR* = 4.56, 95% CI [1.96, 10.6]).

Most studies showed that depression was a predictor of increased mortality (Fan et al., 2007; Lou et al., 2014; Ng et al., 2007). However, a study by Stage et al. (2005) reported a contrary result, showing that individuals with COPD who met the International Classification of Diseases, 10th Revision (ICD-10) criteria for depression had a significantly lower mortality risk compared to those who did not meet the criteria (adjusted HR = 0.27, 95% CI [0.09, 0.84]).

Psychological distress influenced general consequences of AECOPD as well; depression was significantly related to poorer health status (Frei et al., 2014; Ng et al., 2007), increased COPD severity (Lou et al., 2016), lower physical activity (Dueñas-Espín et al., 2016), and poorer quality of life (Ng et al., 2007). Anxiety was also significantly associated with poorer health status (Frei et al., 2014). However, anxiety was not significantly associated with physical activity (Dueñas-Espín et al., 2016).

Quantitative Analysis

When considering the homogeneity of the included studies in terms of independent variables, outcome variables, measurements used to evaluate psychological distress, and period to measure the longitudinal outcomes, we performed meta-analyses using data from some studies to estimate the pooled longitudinal effect of psychological distress on AECOPD and its consequences, including COPD-related hospitalization, and mortality. Furthermore, we found that some studies categorized psychological distress into several types (e.g., anxiety, depression, or anxiety or depression) and analyzed their effects separately. Therefore, we included these subanalyses as subgroups in the meta-analyses.

Longitudinal Effect of Psychological Distress on AECOPD Based on the event-based definition of AECOPD—which includes persons whose conditions have changed enough to require a change in treatment (Kim & Aaron, 2018)—individuals with COPD visiting the ED could be considered to have AECOPD. As a result, we included a study that addressed the effect of psychological distress on ED visits in this meta-analysis. Meta-analyses were performed to quantitatively estimate the effect of psychological distress on the incidence of AECOPD. The pooled RRs were calculated from 11 different subgroups from seven studies (some reported more than one type of psychological distress). The meta-analysis showed that individuals with psychological distress had a 32% greater risk of experiencing AECOPD (pooled RR = 1.32, 95% CI [1.234, 1.40], $p < .001$) compared to those without psychological distress, with acceptable heterogeneity ($\chi^2 = 14.65$, $p = .40$, $I^2 = 4\%$) indicating that the findings from included studies were consistent (Figure 1).

Longitudinal Effect of Psychological Distress on COPD-Related Hospitalization The meta-analysis of 10 different subgroups from five studies showed that individuals with COPD and psychological distress had a 50% greater risk of experiencing COPD-related hospitalization (pooled RR = 1.50, 95% CI [1.25, 1.81], $p < .001$) compared to those

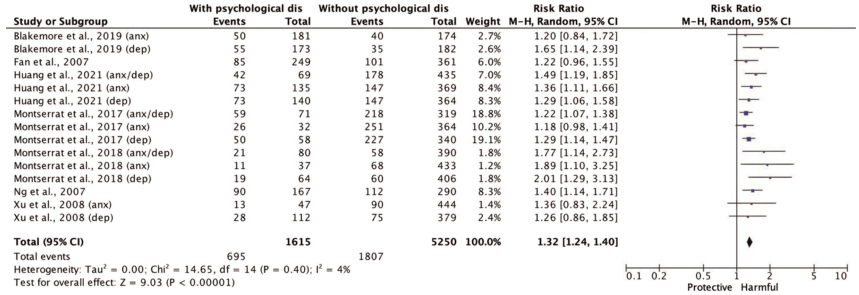

FIGURE 1. Risk ratio of having AECOPD among patients with COPD with psychological distress compared to those without psychological distress. COPD = chronic obstructive pulmonary disease; AECOPD = acute exacerbations of COPD.

without psychological distress, with acceptable heterogeneity ($\chi^2 = 13.41$, $p = .15$, $I^2 = 33\%$; Figure 2).

Longitudinal Effect of Psychological Distress on Mortality

The meta-analysis of five different subgroups from three included studies showed that individuals with COPD and psychological distress had a 72% greater risk of death (pooled RR = 1.72, 95% CI [1.50, 1.97], $p < .001$) compared to those without psychological distress, with moderate heterogeneity ($\chi^2 = 12.40$, $p = .03$, $I^2 = 60\%$; Figure 3). This heterogeneity might be from significant disparity in sample sizes among the studies included in this analysis; one included study was conducted with only 49 participants and had a contradictory result.

Potential Independent Effect of Psychological Distress on AECOPD and Its Consequences

We estimated the independent effect of psychological distress on AECOPD and its consequences by performing a meta-analysis using adjusted measures of relative effect from the included studies that controlled for the confounders. Even though the measures of relative effects (i.e., *OR*, RR, HR, incidence rate ratio) reported in the included studies were different, we found that the *OR* was the most frequently used. As a result, we calculated the pooled *OR* from the studies that controlled for confounders to estimate the potential independent effect of psychological distress on AECOPD and its consequences.

Potential Independent Effect of Psychological Distress on AECOPD Only three subgroups from two studies were available to perform a meta-analysis. The results showed that people with COPD and psychological distress had two times the odds of experiencing AECOPD compared to those without psychological distress (pooled *OR* = 2.04, 95% CI [1.43, 2.93], $p < .001$), with acceptable heterogeneity ($\chi^2 = 0.30$, $p = .86$, $I^2 = 0\%$; Appendix 2, http://links.lww.com/NRES/A496).

Potential Independent Effect of Psychological Distress on COPD-Related Hospitalization This meta-analysis was performed using three studies. We found that individuals with COPD who had psychological distress had 1.4 times the odds of COPD-related hospitalization (pooled *OR* = 1.36, 95% CI [1.03, 1.64], $p = .001$), with acceptable heterogeneity ($\chi^2 = 1.50$, $p = .45$, $I^2 = 0\%$; Appendix 3, http://links.lww.com/NRES/A496).

Potential Independent Effect of Psychological Distress on Mortality Three subgroups from two studies were available for meta-analysis. The results indicated that people with COPD and psychological distress had almost three times the odds of mortality compared to those without psychological distress (pooled *OR* = 2.77, 95% CI [1.50, 8.64], $p < .001$) with acceptable heterogeneity ($\chi^2 = 0.81$, $p = .67$, $I^2 = 0\%$; Appendix 4, http://links.lww.com/NRES/A496).

DISCUSSION

This systematic review showed that psychological distress tended to have a negative effect on AECOPD (Huang et al., 2021; Ito et al., 2012; Montserrat-Capdevila et al., 2018; Ng et al., 2007) and its

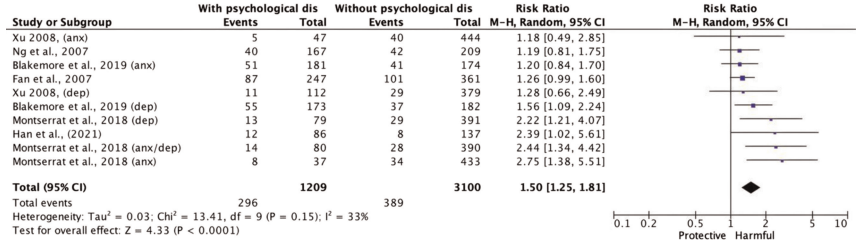

FIGURE 2. Risk ratio of hospitalization among patients with COPD with psychological distress compared to those without psychological distress. COPD = chronic obstructive pulmonary disease.

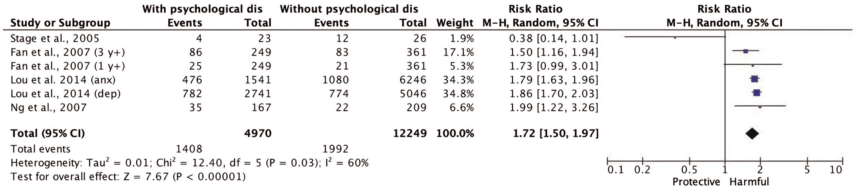

FIGURE 3. Risk ratio of mortality among patients with COPD with psychological distress compared to those without psychological distress. COPD = chronic obstructive pulmonary disease.

consequence (Blakemore et al., 2019; Coventry et al., 2011; Han et al., 2021; Montserrat-Capdevila et al., 2018; Zohal et al., 2020). However, there was some contrasting evidence, with some studies reporting that psychological distress was not a significant predictor for AECOPD (Fan et al., 2007; Xu et al., 2008) and its consequences—especially studies that performed adjusted analyses controlling for the relevant covariates—such as gender, age, and smoking (Fan et al., 2007; Montserrat-Capdevila et al., 2018; Ng et al., 2007; Xu et al., 2008). The results substantiate the need to control confounders when exploring the independent effect of psychological distress on AECOPD and its consequences. The results also imply that psychological distress may directly and indirectly affect AECOPD and its consequences. As a result, it is critical to investigate how mediating factors influence the influence of psychological distress on AECOPD and its consequences, as well as the mediating effect of psychological distress on these variables of interest.

The included studies were from 12 different countries, suggesting the effect of psychological distress on AECOPD and its consequences is an issue affecting individuals with COPD worldwide, with most researchers focused on the longitudinal effect of depression and/or anxiety. When comparing the effects of depression and anxiety on AECOPD and its consequences, depression appears to have a more consistent influence than anxiety. To date, there is no known study investigating why depression appears to exert a more pronounced effect on AECOPD compared to anxiety. However, a study by Lu et al. (2013) provided valuable insights into the potential underlying mechanism elucidating the influence of depression on AECOPD.

Lu et al. (2013) found that increased interleukin-6, increased C-creative protein, and depressive symptoms were independently associated with decreased FEV1% predicted and FEV1/FVC% predicted after adjusting for smoking status, body mass index, and number of chronic inflammatory diseases. These findings suggest that the proinflammatory cytokines may play a significant role in connecting depression and increased respiratory symptoms in people with COPD. Further research focusing specifically on the effect of depression on AECOPD and its consequences is needed.

The current analysis also revealed the increased heterogeneity of results when including a study that used ICD-10 criteria (Stage et al., 2005) alongside other studies using standard patient-reported measures in the meta-analysis. This finding may stem from the distinct methods and approaches employed to detect psychological distress. ICD-10 criteria involve assessing symptoms and comparing them to specific diagnostic criteria outlined by the World Health Organization (2003). This approach is used in clinical settings to diagnose mental health disorders based on standardized guidelines. In contrast, standard patient-reported measures, such as the Kessler Psychological Distress Scale, involve individuals answering questions based on their subjective experiences and feelings. The responses are then scored to estimate the severity or likelihood of psychological distress (Kessler et al., 2002). The use of ICD-10 criteria tends to provide a more objective and specific approach compared to standard patient-reported measures—which may account for this unique finding.

Besides estimating the longitudinal effect of psychological distress on AECOPD and its consequences using the number of events from the included studies to calculate pooled RR, we also performed meta-analyses using adjusted *OR* reported by the included studies to estimate the potential independent effect of psychological distress on AECOPD and its consequences. However, with limited information on the diversity of relative effects measures, we could not estimate the potential independent effect of psychological distress on hospitalization; this may need further research.

Limitations

All the meta-analyses in this study yielded acceptable heterogeneities, indicating that the results of the analyses are consistent. However, the review is limited by several factors. First, the review is over 1 year old; thus, more recent literature that affects the conclusions presented here may be available. Second, only three databases were searched, potentially omitting relevant studies that may have been present in other databases or sources. Last, a research librarian was not used to establish search terms, potentially leading to a narrower scope of relevant studies being included in this review.

Additional limitations are inherent in secondary data analysis. First, the analysis might raise a concern about selection bias as we excluded several studies from the quantitative analysis process to increase the homogeneity of the included studies so we could perform meta-analyses. Furthermore, some studies did not report the details (number of events) or the

measures of relative effects of insignificant results. The results of the meta-analyses in this study do not reflect those missing data.

Another limitation is that the included studies used different measures of relative effects. Thus, we could not estimate the pool relative effects of psychological distress on AECOPD and its consequences from all included studies using the precalculated relative effects. Instead, we had to estimate the pool RR using the number of events because most included studies reported this information in detail. We could not estimate the potential independent effect of psychological distress on some variables of interest—even if many studies reported adjusted measures of relative effect. Also, it is essential to acknowledge that COPD severity and frequency of exacerbations for the participants in the included studies were not considered. This is because most reviewed studies did not address these clinical factors.

Another limitation of this review is the absence of comprehensive data on the timing of AECOPD in the reviewed studies. Although the included studies followed subjects for a minimum of 1 year, the specific time frame from baseline to the occurrence of AECOPD events was not consistently reported, hindering the ability to determine if there was an increased risk within a particular period, such as the next year, 2 years, or longer.

Conclusion

The results of the meta-analyses show that patients with COPD with psychological distress had a greater risk of AECOPD, hospitalization, and death. In addition, the effect of depression on AECOPD and its consequences was more consistent than the effects of anxiety. Psychological distress appears to have independent negative effects on AECOPD COPD-related hospitalization and mortality among individuals with COPD.

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