Review Article

Association between Chronic Obstructive Pulmonary Disease and Dementia: Systematic Review and Meta-Analysis of Cohort Studies

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Keywords

Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a common disease among the elderly, which has been linked to cognitive decline. However, the relationship between COPD and dementia remains unclear. **Summary:** We conducted a systematic literature review by searching databases such as Pubmed, Embase, EBSCO, and Cochrane Library (from inception to April 18, 2018) for studies on COPD that also investigated the prevalence of dementia. We found 3 cohort studies including a total of 39,392 COPD patients. Then we applied the Newcastle-Ottawa Scale to evaluate the risk of bias. **Key Messages:** COPD patients faced a higher risk of dementia (HR 1.46; 95% CI 1.22–1.75; $p < 0.001$). Subgroup analysis on gender determined that the association between COPD and dementia was stronger in male patients (HR 1.49, 95% CI 1.20–1.86, $p < 0.001$) than in female patients (HR 1.41, 95% CI 1.27–1.57, $p < 0.001$). A subset study of patients aged >65 years revealed that the HR was greater for patients aged ≥75 years (HR 1.46, 95% CI 1.07–2.00, $p = 0.02$) than for those aged 65–74 years (HR 1.40, 95% CI 1.28–1.53, $p < 0.001$). The cohort studies included were from similar population-based databases, suggesting possible regional limitations and publication bias.

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Dementia

Introduction

Dementia is the fourth leading cause of death among the elderly, following cancer, heart disease, and cerebrovascular disease [1]. Dementia-related mortality rates have been reported to range from 0.8 to 27% worldwide [2]. Dementia is a progressive neurocognitive disease. In the absence of any disease-modifying treatment, increasing focus has been placed on primary prevention (to reduce the risk of development) and early intervention (to slow progression) therapies. A better understanding of the risk factors of dementia is crucial to improving therapeutic interventions. In addition to a number of well-described cardiovascular risk factors, there is a growing body of evidence which suggests a link between COPD and the development of dementia. The first report on cognitive impairment in COPD patients was published in 1982 [3]. Since that time, numerous studies have documented a relationship between COPD and cognitive and psychological dysfunctions [4–6]. Dementia has also been associated with age, obesity, genetics, education, smoking, alcohol, cerebral trauma, mid-life hypertension, stroke, diabetes, hyperlipidemia, myocardial infarction, and heart failure [7–11].

Very little previous research has investigated a direct relationship between COPD and dementia. Furthermore, to the best of our knowledge, no previous study has determined whether COPD represents prodromal symptoms or acts as an independent risk factor of dementia among the elderly. In this work, we conducted a meta-analysis of previous studies with the primary objective of assessing the risk of dementia in patients with COPD, which we believe is the most salient aspect of current research. We also sought to determine whether further studies on the potential link between COPD and dementia are warranted and to provide guidance if that is the case.

Materials and Methods

Search Strategy

A thorough search was conducted on the PubMed, Web of Science, EBSCO, Embase, Cochrane Library, CNKI (China National Knowledge Infrastructure), and WanFang databases using the following keywords: "(Chronic Obstructive Pulmonary Disease OR COPD OR Chronic Obstructive Airway Disease OR COAD OR Chronic Airflow Obstructions OR Chronic Obstructive Lung Disease) AND (Dementia)." No language limitations were imposed, and the search period was from inception of the database to April 18, 2018. An initial screening of studies using the aforementioned keywords was independently performed by 3 researchers (Y. Wang, X. Li, and B. Wei) based on title, abstract, and keywords. In case of disagreement, a fourth person (T.-H. Tung) decided whether to include or exclude the study. For those papers lacking necessary data, attempts were made to contact the original authors. In the event that information on the prevalence of dementia was unavailable, the study was excluded.

Study Selection

The inclusion criteria for studies was as follows. (1) They employed a cohort study design. (2) They adopted a defined outcome of dementia, as reported by physicians using International Classification of Diseases (ICD) codes. (3) They compared an exposure group that comprised individuals who were clinically diagnosed with COPD and who were followed until a diagnosis of dementia was made, death, or the end of the study period with a control group that comprised subjects without a history of COPD or dementia. (4) They reported results which included a hazard ratio (HR) with a 95% confidence interval (CI) or raw data which was available for conversion. Cross-sectional or case-control studies that could not be used
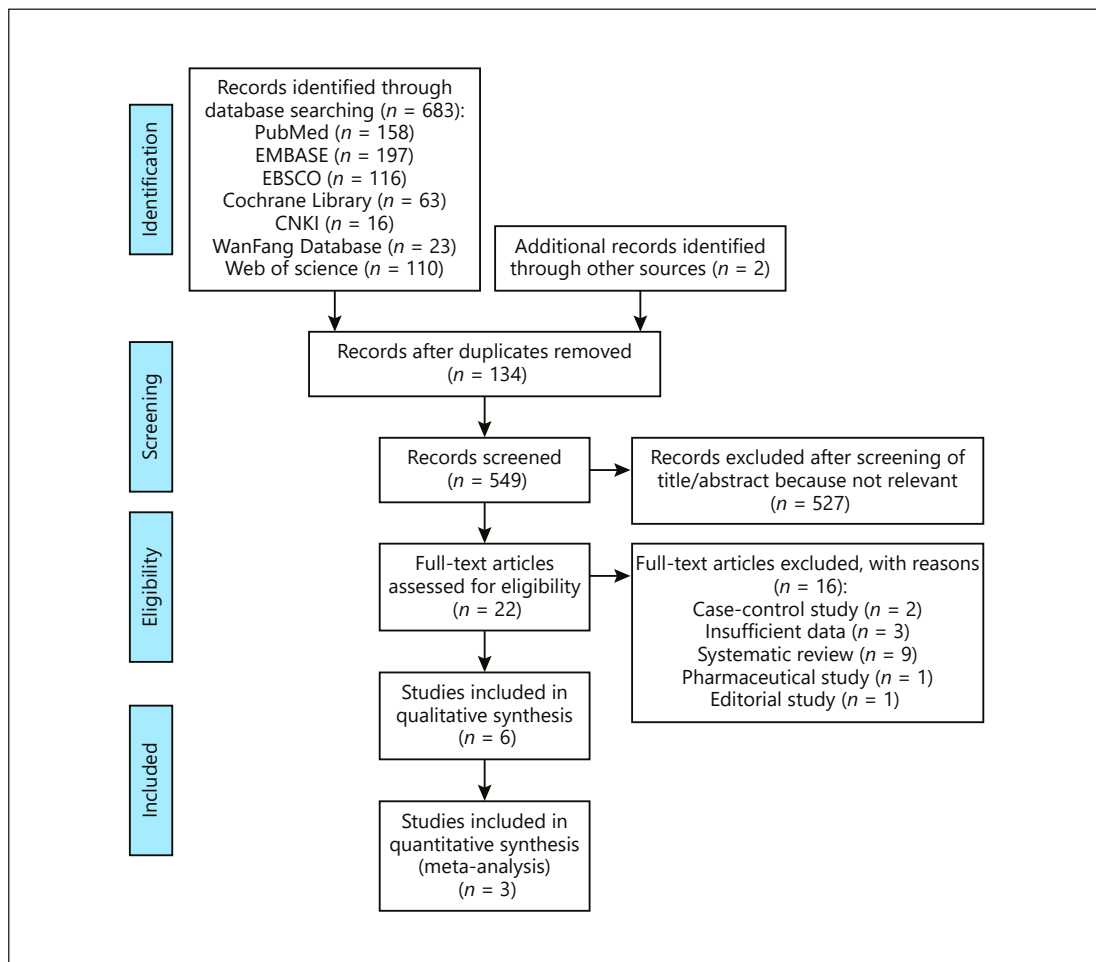
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Fig. 1. Flowchart of the article selection. CNKI, China National Knowledge Infrastructure.

to assess the causal relationship between COPD and dementia were excluded. We also excluded conference abstracts, editorials, and systematic reviews that provided limited information. We reviewed the full text of all articles which appeared to be related to COPD and dementia.

Data Extraction

The following data were extracted from the included studies: first author, year of publication, region, database, study duration, research design, inclusion criteria, type of participants, comparisons, outcomes, and risk estimates. We also adopted the Newcastle-Ottawa Scale, which considers the selection of study groups, comparability, and outcome assessment in evaluating the quality of cohort studies.

Statistical Methods

Review Manager 5.3 was used to perform the meta-analysis. The risk of outcome was presented as an HR with a 95% CI. We also used inconsistency statistics. The statistic describes the percentage of variation across studies due to heterogeneity rather than chance alone. A value ≥50% represents substantial heterogeneity. The current meta-analysis was based on a random-effects model due to the expectation of considerable clinical heterogeneity.

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Subgroup analysis was subsequently employed to analyze associations between dementia and COPD in various groups of people. We divided the studies into a male and female group by origins, and into a group of <65-yearolds, 65- to 74-year-olds, and ≥75-year-olds by origins. The third study was only excluded from the age-related subgroup analysis due to the unclear classification of age.

Results

Description of Studies Selected for Inclusion

A total of 683 studies were identified in the combined search from which we removed 134 duplicate studies. After reviewing the titles and abstracts, a further 527 studies were excluded. This left 22 eligible studies, of which 19 were selected for a full review. All of the reviewed articles were full-text publications [6, 12–29]. 16 articles were excluded for the following reasons: they employed a case-control study design [28, 29]; they contained insufficient data [20–22]; they involved a systematic review [6, 12–19]; they comprised a pharmaceutical study [23]; or they had been published as an editorial [24] (Fig. 1).

After excluding unrelated studies and studies that did not meet our inclusion criteria, 3 prospective cohort studies were available for our meta-analysis. Key details of these studies are summarized in Table 1, including diagnostic criteria and characteristics of exposure groups and control groups. The 3 cohort studies measured the rate of dementia among individuals with COPD during the tracking period. All studies were conducted in Taiwan, ROC and were written in English [25–27].

All 3 of the cohort studies used an exposure group in the National Health Insurance Research Database; however, they varied in terms of the period in which diagnoses were made [25–27]. None of the participants included in control groups had a history of COPD. Two of the studies only included patients over 40 years old [25, 27], whereas the third study included patients over 20 years old [26]. The same outcome measures (i.e., diagnoses made in accordance with ICD-9-CM codes) were employed by all 3 studies.

Methodologic Quality of Included Reviews

One study achieved a moderate Newcastle-Ottawa Scale quality score of 7, and two achieved high scores of 8, as shown in Table 2.

Association between COPD and Dementia

All 3 of the studies included in this meta-analysis reported a significant association between COPD and dementia. The first study, by Yeh et al. [25], included 10,260 patients with COPD and asthma and 20,513 control subjects. In that research, the COPD and asthma group had a higher risk of neurodegenerative diseases, wherein the risk of dementia was 1.43× higher than that of non-COPD patients (HR 1.43, 95% CI 1.29–1.59). The second study, by Liao et al. [26], followed up 8,640 COPD patients and 17,280 control subjects and reported that COPD increased the risk of dementia (Alzheimer's disease or Parkinson's disease) (HR 1.74, 95% CI 1.55–1.95). The third study was conducted by Liao et al. [27] and included 20,492 COPD patients and 40,765 control subjects. In that research, COPD was found to be associated with a higher risk of dementia after comorbidities were adjusted for (HR 1.27, 95% CI 1.20–1.34). Moreover, the association was stronger among patients who experienced a higher frequency of acute COPD exacerbation events.

Significant associations were shown in Figure 2. The funnel plot in Figure 3 gave no indication of serious publication bias.

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Table 1. Characteristics of included studies

First author, year of publication, region, database	Research design	Inclusion criteria/ type of participant	Study subjects		Outcome measures		HR/OR (95% CI)
			exposed group	control group	number of exposed group events	number of control group events	
Yeh [25], 2017, Taiwan, ROC, NHIRD, 2000–2010	cohort study	aged >40 years without a history of PD (ICD-9-CM 332), dementia (ICD-9-CM 332)	patients with COPD (ICD-9-CM codes: 491, 492, 496) n = 10,260	patients without COPD n = 20,513	11.1/per 1,000 person-years	8.81/per 1,000 person-years	1.43 (1.29–1.59)
Liao [26], 2015, Taiwan, ROC, NHIRD, 2002–2011	cohort study	aged >40 years without of a history of AD (ICD-9-CM 331) or PD (ICD-9-CM 332).	patients with COPD (ICD-9-CM codes: 490–492, 496) n = 8,640	patients without COPD n = 17,280	522/per 10,000 person-years	706/per 10,000 person-years	1.74 (1.55–1.95)
Liao [27], 2015, Taiwan, ROC, NHIRD, 1998–2008	cohort study	aged >20 years without a history of dementia (ICD-9-CM 290, 294.1, 331.0)	patients with COPD (ICD-9-CM code: NA) n = 20,492	patients without COPD n = 40,765	13.2/per 1,000 person-years	9.11/per 1,000 person-years	1.27 (1.20–1.34)

NHIRD, National Health Insurance Research Database; COPD, chronic obstructive pulmonary disease; AD, Alzheimer's disease; PD, Parkinson's disease; ICD-9-CM, international classification of diseases-9-clinical modification.

Table 2. Quality assessment of included cohort studies

First author, year	Selection				Comparability		Outcome			score
	representative of exposed cohort	selection of nonexposed cohort	ascertainment of exposed	demonstration that outcome of interest was no present at start of study	control for important cohort	additional factors	assessment of outcome	follow-up	adequacy of follow-up	
Yeh [25], 2017	yes	yes	yes	yes	yes	no	yes	yes	no	7
Liao [26], 2015	yes	yes	yes	yes	yes	yes	yes	yes	no	8
Liao [27], 2015	yes	yes	yes	yes	yes	no	yes	yes	yes	8

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Study or subgroup	log[Hazard ratio]	SE	Weight	Hazard ratio IV, random, 95% CI	Hazard ratio IV, random, 95% CI
Liao et al. [26], 2015	0.5539	0.059	31.9%	1.74 [1.55, 1.95]	
Liao et al. [27], 2015	0.239	0.0289	35.4%	1.27 [1.20, 1.34]	
Yeh et al. [25], 2017	0.3577	0.0526	32.7%	1.43 [1.29, 1.59]	
Total (95% CI)			100.0%	1.46 [1.22, 1.75]	

Heterogeneity Tau^2 = 0.02; χ^2 = 23.94, df = 2 (p < 0.00001); I^2 = 92%
Test for overall effect: Z = 4.12 (p < 0.0001)

0.5   0.7   1   1.5   2
Favours control   Favours COPD

Fig. 2. Meta-analysis of the risk of dementia in all people with COPD. CI, confidence interval; SE, standard error.
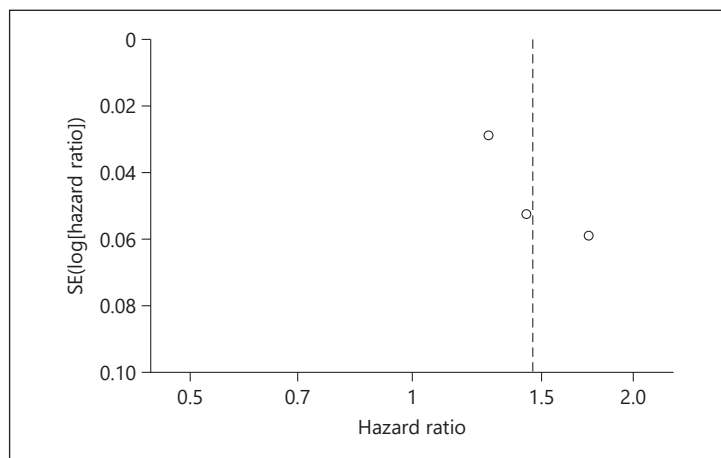

Fig. 3. Funnel plot of publication bias of the cohort study.

Considerable heterogeneity was observed across studies (p < 0.001, 92%), indicating a very high degree of variation. Meta-analysis using a random-effects model revealed an increased risk of dementia among patients with COPD (HR 1.46, 95% CI 1.22–1.75).

To identify which factors were primarily responsible for the heterogeneity we observed, we also conducted subgroup analysis according to gender and age. Subgroup analysis by gender indicated that COPD was significantly associated with dementia (HR 1.49, 95% CI 1.20–1.86, p < 0.001) among male patients. Similar results were obtained for female patients (HR 1.41, 95% CI 1.27–1.57, p < 0.001) (Fig. 4). Among patients aged <65 years, no significant correlation was observed between COPD and dementia (HR 1.80, 95% CI 1.00–3.22, p = 0.05); however, COPD was significantly associated with dementia in older patients. The HR for patients aged 65–74 years was 1.40 (95% CI 1.28–1.53, p < 0.001), and the HR for patients aged ≥75 years was 1.46 (95% CI 1.07–2.00, p = 0.02) (Fig. 5).

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to examine associations between COPD and dementia. Our results indicate that patients with COPD face an increased risk of dementia.

Subgroup analysis by age revealed a significant correlation between COPD and dementia among patients over 65 years old. COPD was not a risk factor for dementia among patients
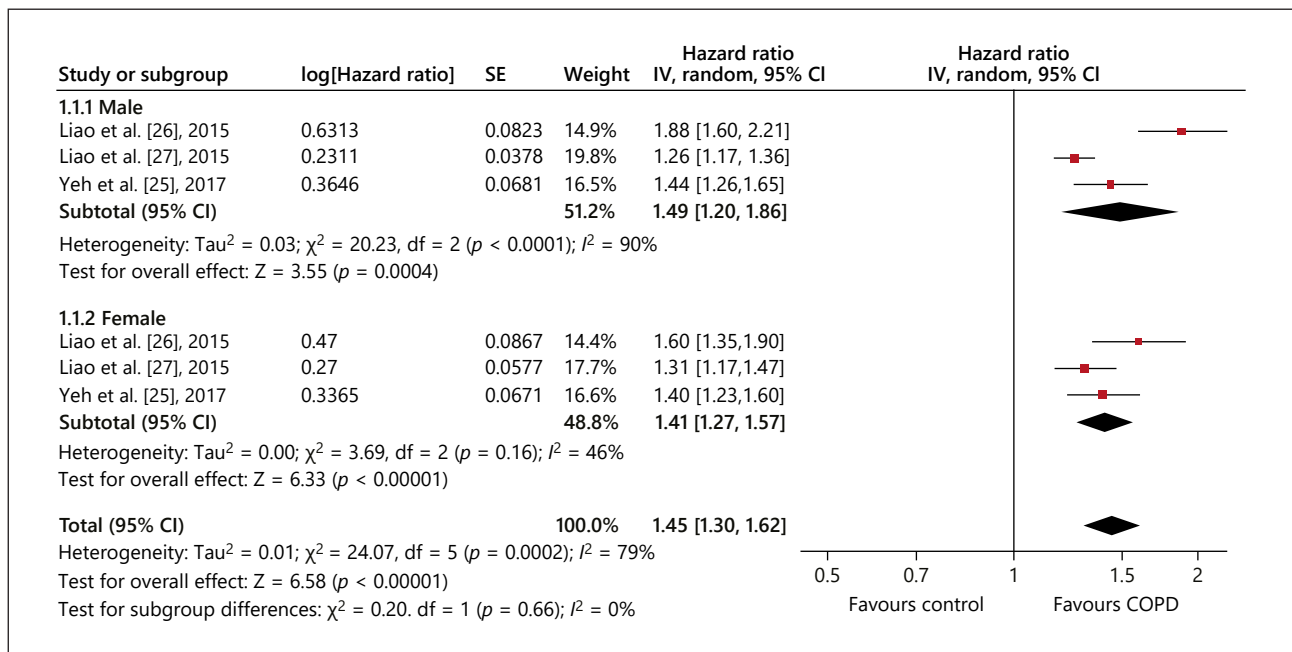
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Fig. 4. Subgroup analysis by gender evaluating the risk of dementia in all people with COPD. CI, confidence interval; SE, standard error.
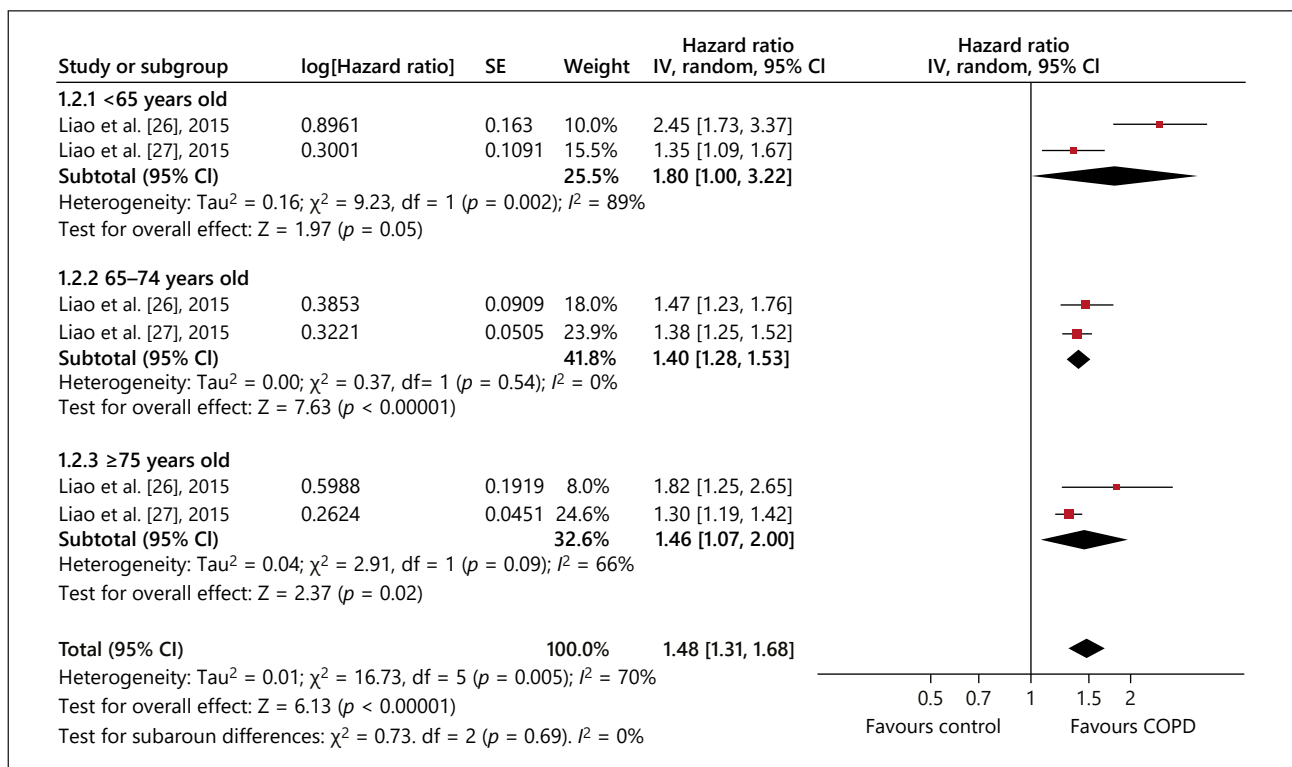

Fig. 5. Subgroup analysis by age group evaluating the risk of dementia in all people with COPD. CI, confidence interval; SE, standard error.

younger than 65 years old. Subgroup analysis did not reveal a significant difference in the risk of dementia between males and females.

These findings suggest that COPD treatment and prevention of COPD exacerbation are important in reducing the risk of dementia. Nonetheless, additional research will be required to identify the types of treatment which are capable of slowing the progression of dementia among individuals with COPD.

Dementia is a multifactorial disease which has been linked to age, obesity, genetics, education, smoking, alcohol, cerebral trauma, mid-life hypertension, stroke, diabetes, hyperlipidemia, myocardial infarction, and heart failure [7–11]. From a clinical perspective, COPD can lead to hypoxemia and pulmonary encephalopathy, which can have a substantial impact on brain dysfunction [30] and therefore COPD may lead to dementia. COPD has been associated with cognitive decline [13]; however, there does not appear to be any direct evidence of a relationship between COPD and dementia. COPD was first linked to neuropsychological deficit in the early 1980s [31]. A number of researchers have invoked hypoxia to explain the connection between pulmonary failure and brain dysfunction [32]. However, other studies have reported that multiple factors contribute to dementia, including systemic inflammation [30, 33], hypercapnia [34], oxidative stress, and hypoperfusion [35, 36]. Shared risk factors, such as age, smoking, and obesity also contribute, as do commonly associated diseases, such as cerebral disorder, diabetes mellitus, and previous stroke [7–11].

In this study, we addressed the lack of research on the relationship between COPD and dementia with the aim of identifying a causal relationship. We included cohort studies and excluded cross-sectional and case-control studies to increase the strength of the evidence. From a practical perspective, it would not be possible to randomly distribute individuals into the categories "with COPD" and "without COPD;" therefore, randomized controlled trials were excluded from this research. Only cohort studies can be used to detect the effects of long-term COPD (including effects that vary according to disease severity), which may play an important role in the development of dementia.

There were a number of limitations that may have influenced the precision of our metaanalysis. (1) We only identified a few relevant cohort studies, and all of them were conducted in Taiwan, ROC. Therefore, there is no way to determine whether the risk of dementia differs among COPD patients in other parts of the world. (2) We were unable to conduct subgroup analysis based on comorbidities or the severity of COPD, due to the fact that the included studies did not provide adequate data for this type of subgroup analysis. This reduced the strength of evidence which indicated an association between COPD and dementia. (3) Diagnostic methods varied among the studies included in our meta-analysis. (4) Variations in matched comorbidities and variables may have introduced bias.

Conclusions

Results from this meta-analysis revealed that the risk of dementia was higher among patients with COPD than among patients without COPD. However, our research findings could be strengthened through the inclusion of new evidence (e.g., data from different regional areas) to clarify whether a factor such as geographical bias influenced our results. Future meta-analyses which include additional studies could also improve the quality and reliability of findings.

Disclosure Statement

Ying Wang, Xiaotong Li, Biying Wei, Tao-Hsin Tung, Ping Tao, and Ching-Wen Chien declare that they do not have any conflicts of interest.

Funding Sources

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