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Association between chronic obstructive pulmonary disease and mild cognitive impairment and dementia risk: A systematic review and meta-analysis

COPD and MCI and Dementia risk

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Abstract

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a common public health issue that has been linked to cognitive dysfunction.

AIM

The current meta-analysis was performed to investigate the relationship between COPD and a risk of mild cognitive impairment (MCI) and dementia.

METHODS

A comprehensive literature search of the PubMed, Embase, Google Scholar and Cochrane Library electronic databases was conducted. Odds ratios (OR) and Mean Differences (MD) with 95% confidence intervals (CIs) using random or fixed effect models were used to calculate pooled estimates. Studies that met the inclusion criteria were assessed for quality using the Newcastle Ottawa Scale.

RESULTS

Twenty-seven studies met all the inclusion criteria. Meta-analysis yielded a strong association between COPD and increased risk of MCI incidence (OR=2.11, 95%CI: 1.32-3.38). It also found a borderline trend for increased dementia risk in COPD patients (OR=1.16, 95%CI: 0.98-1.37). Pooled hazard ratios using adjusted confounders also showed a higher incidence of MCI (HR=1.22, 95%CI: -1.18 to -1.27) and dementia (HR=1.32, 95%CI: -1.22 to -1.43) in COPD patients. A significant lower MMSE score in COPD patients was noted (MD=-1.68, 95%CI: -2.66 to -0.71).

CONCLUSION

Our findings revealed an elevated risk for the occurrence of MCI and dementia in COPD patients. Proper clinical management and attention are required to prevent and control MCI and dementia incidence in COPD patients.

Key Words: Mild cognitive impairment; Chronic obstructive pulmonary disease; Dementia; Meta-analysis

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Core Tip: Chronic obstructive pulmonary disease (COPD) is a common public health issue that has been linked to cognitive dysfunction. The current meta-analysis was performed to investigate the relationship between COPD and mild cognitive impairment (MCI) and dementia risk. Twenty-seven studies met all the inclusion criteria. Meta-analysis yielded a strong association between COPD and increased risk of MCI incidence (OR=2.11, 95%CI: 1.32-3.38). Our findings revealed an elevated risk for the occurrence of MCI and dementia in COPD patients. Proper clinical management and attention is required to prevent and control MCI and dementia incidence in COPD patients.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive multicomponent lung disease that occurs more commonly in the elderly [1]. It is characterised by a partially irreversible chronic obstruction of lung airflow resulting in an abnormal decrease in blood oxygen levels, potentially leading to cognitive dysfunction [2]. Various studies have estimated that the prevalence of cognitive impairment in COPD patients ranges from 16% to 57% [3,4]. A prior review of 17 individual studies by Yohannes *et al.* (2017) [5] showed that 32% of COPD patients showed some sign of cognitive dysfunction, with no less than 25% of patients showing at least mild cognitive impairment (MCI).

Cognitive impairment in COPD patients may compromise an individual's capability to self-care and adhere to treatment regimens, making the relationship between COPD and cognitive impairment important for devising therapeutic approaches for COPD [6,7].
1 Some studies have focused on the relationship between COPD and neurologic function, but with inconsistent conclusions[8]. Data based on the Atherosclerosis Risk in Communities (ARIC) study showed that reduced lung function was associated with poor cognitive performance and higher risk of dementia hospitalization[9]. Data based on Taiwanese National Health Insurance Research Database showed that COPD patients exhibited a 1.27-fold higher risk of developing dementia[10].

To our knowledge, there has only been one published meta-analysis investigating the statistical association of COPD with cognition dysfunction. Zhang *et al.*(2016) [11] concluded that COPD patients had elevated risk of cognitive dysfunction. Similarly, only one single meta-analysis has looked at the relationship between COPD and dementia. Pooling data from three studies, Wang *et al.* (2019) [12] showed that COPD patients faced a higher risk of developing dementia. However, these important clinical questions have not been investigated in a more thorough and conclusive manner. As
6 such, we conducted a comprehensive systematic review and meta-analysis to investigate the association between COPD and the risk of MCI and dementia.

MATERIALS AND METHODS

Search strategy

Our meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [13]. We conducted a comprehensive search using PubMed, Embase, Google Scholar, and Cochrane Library online databases for articles published prior to 31st March 2021. The following key terms were used: "Chronic Obstructive Pulmonary Disease" OR "COPD" OR "Chronic Obstructive Airway Disease" OR "COAD" AND "Mild Cognitive impairment" OR "MCI" OR "Cognitive dysfunction" OR "Cognitive decline" AND "Dementia". Studies

cited by articles that met the inclusion criteria were manually searched to identify additional eligible studies. Study eligibility was not restricted based on language, sex, or publication year. Systematic reviews, conference abstracts, and editorials were excluded due to insufficient data presentation details.

Eligibility criteria

Inclusion criteria:

We included studies that (a) investigated the association between COPD and a risk of MCI or dementia, (b) adopted a definite outcome of cognitive impairment or dementia in COPD and non-COPD subjects, (c) reported raw values necessary to calculate odds ratios (OR) or hazard ratios (HR) for the incidence of cognitive impairment or dementia, (d) contained case controls, were prospective or retrospective cohort studies, or had a cross-sectional design, (e) compared the association between COPD and non-COPD patients.

Exclusion criteria:

We excluded studies that (a) did not report relevant outcomes (b) or did not have accessible full text manuscripts.

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Data collection and analysis

All eligible studies were separately screened by two reviewers to determine whether they met inclusion criteria. Screening was first conducted at the abstract content level, with relevant studies further investigated at the full-text level. 2 Articles published in languages other than English were machine-translated using Google Translate, with the translated version reviewed. The following information was extracted from the included studies for summarization and analysis: author, year, study design type, group investigated, sample size, diagnostic criteria for COPD, adjusted confounder for calculating pooled ratio, MCI prevalence, dementia prevalence, and scales used for cognitive assessment.

Quality assessment

Study quality was assessed independently by two separate reviewers ⁵ using the Newcastle-Ottawa Scale (NOS) ¹⁴, which examined three components: selection, comparability, and ascertainment of outcome. Disagreements ² were resolved through discussion.

Publication bias

Publication bias was assessed using Funnel plot analysis and Egger's regression test ² [15,16].

Statistical analysis

Mean differences (MD) with 95% confidence intervals (CIs) were calculated for continuous outcomes. For categorical outcomes, Odds ratios (ORs) and hazard ratios (HRs) with 95% CIs ² was calculated to estimate pooled findings. Heterogeneity between studies (measurable heterogeneity) was evaluated using I^2 statistics. If I^2 values >50%, a random-effects model was applied, while if I^2 values were <50%, a fixed-effect model was applied. Statistical analyses were performed using Review Manager software (Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration 2014).

RESULTS

Literature search

Preliminary screening of PubMed, EMBase, Google Scholar, and Cochrane Library databases yielded 234 results (Figure 1). Review of article title and abstract resulted in 72 remaining studies. Full-text review further excluded 45, leaving 27 studies ^{3,4,10,17-40} that were ultimately included in the meta-analysis.

Properties and characteristics of included studies

Relevant study data, including the diagnostic criteria for COPD, sample size, and disease assessment scales for all 27 included studies ^{3,4,10,17-40} can be found ² in Table 1.

The included studies were published between 1996 and 2020, and study sample sizes ranged from 20 to 243,420 subjects. Ten studies [17,19–22,28,29,34,35,39] were case control studies, 10 were cross-sectional studies [3,4,24–26,32,36–38,40], four were prospective cohort studies [18,27,30,31], and three were retrospective cohort studies [10,23,33]. Seventeen studies [4,17–22,25,31,32,34–40] reported cognitive impairment data based on the Mini-Mental State Examination (MMSE) scoring system. Twenty-two studies used GOLD criteria, three studies [10,23,33] reported ICD-9 CM criteria, and 2 studies [3,26] followed standardized guidelines for COPD diagnosis. The quality score was high in 12 studies and medium in 7 studies and low in 6 studies (Supplementary Table-S1). The assessment criteria involving NOS uses three broad criteria: selection, comparability and exposure, where the selection defines and analyses the cases and control subjects included in the study, comparability defines the matching or comparison of cases and control subjects for better empirical investigation and exposure determines whether the study was conducted in a blinded or unbiased manner along with the response of the subjects.

Association of COPD with MCI risk

Ten studies [3,18,19,24,26–29,33,37] detailing 71,174 COPD patients and 22,082 control subjects investigated the association of COPD with MCI risk. Our meta-analysis indicated a strong association between COPD and increased MCI incidence risk (OR=2.11, 95% CI: 1.32 to 3.38). A significant degree of heterogeneity was observed (I^2 : 99%). Using a random effects model, we demonstrate that COPD patients are 1.26 times more susceptible to MCI compared to non-COPD controls (**Figure 2**).

Adjusted hazard ratios for MCI risk in COPD patients

Pooling adjusted hazard ratios from four studies [3,18,27,28] investigating the relationship between COPD and MCI incidence revealed a significant association (HR=1.22, 95% CI: -1.18 to -1.27; I^2 : 26%) (**Figure 3**).

Association of COPD with the risk of Dementia

Seven studies, [10,18,23,24,27,28,30] involving 108,606 COPD patients and 347,939 control subjects, investigated the relationship between COPD and dementia risk. Pooling these data showed a borderline trend for increased dementia risk in COPD patients compared

to non-COPD control patients (OR=1.16, 95%CI: 0.98 to 1.37). A high degree of heterogeneity was observed (I^2 : 94%). Our meta-analysis shows that COPD patients are more susceptible to dementia (**Figure 4**).

Adjusted hazard ratios for dementia risk in COPD patients

Pooling adjusted hazard ratios from six studies [10,18,23,27,28,30], investigating the relationship between COPD and dementia incidence revealed a significant association (HR=1.32, 95%CI: -1.22 to -1.43; I^2 : 99%) (**Figure 5**).

MMSE score in COPD and non-COPD patients

Seventeen studies, [4,17–22,32,35–40,25,31,34] involving 1,392 COPD patients and 5,097 control subjects, reported mean Mini-Mental State Examination (MMSE) score data for both COPD and non-COPD patients. Pooling these results showed a significant lower MMSE score in COPD patients compared to controls (MD=-1.68, 95%CI: -2.66 to -0.71] (**Figure 6**). A high degree of heterogeneity among these seventeen studies was observed (I^2 : 96%).

Publication bias

Egger's tests did not show any significant publication biases for the examined comparisons. Figure 7 (a-e) shows the funnel plot of the studies included in each comparison. However, no significant publication biases were observed for the association of COPD with risk of (a) MCI, (b) dementia, (c) MCI risk in COPD patients, (d) Dementia risk in COPD patients, and (e) Comparison of MMSE score between COPD and control groups.

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DISCUSSION

This study is the first systematic review and meta-analysis examining the association between COPD and the risk of MCI and dementia. We found that patients with COPD are 2.11 times more susceptible to MCI and 1.16 times more susceptible to dementia.

Moreover, lower MMSE scores were observed in COPD patients, indicating greater cognitive impairment.

COPD-associated neurological impairment and dementia put a great burden on the patients and the healthcare system. In particular, declining cognition leads to COPD patients requiring more assistance for daily activities [41]. Our analysis was performed based on the reported adjustments within individual studies for confounding factors such as age, sex, smoking, body mass index, education level, diabetes mellitus, and previous history of stroke or cardiovascular disease [10,23,27,28,30]. Studies by Thakur *et al.* (2010) [33], Singh *et al.* (2013) [26], and Martinez *et al.* (2014) [24] reported data as odds ratios for adjusted confounders and therefore were not included in the calculations for pooled incidence for MCI or dementia.

From a clinical approach, COPD can lead to pulmonary encephalopathy, hypoxemia, and inflammation, all of which may impact brain function [42]. Indeed, COPD patients exhibit a unique neurophysiological profile stemming from neurotoxicity featuring deficits of attention, motor, memory, and cognitive domain executive function [4]. Interestingly, the relationship between COPD and dementia persists even after accounting for the presence of vascular disease, suggesting that COPD is an independent predictor of dementia.

Our findings are consistent with previous literature[5,11,12,42,43]. However, the available literature on the relationship between dementia and COPD remains limited, as only seven studies were found for this meta-analysis. Our study also had several other limitations. The included studies were of different designs, which may be one of the leading causes of heterogeneity. Additional sources of heterogeneity may include different geographical population, variation in the diagnostic criteria of COPD, diversity in the factors undertaken for the multivariate analysis of each included studies. The included studies also lacked long-term follow-up data, as well as data that would facilitate subgroup analysis based on co-morbidities, age, and gender factors. Finally, different studies varied in how they assessed and diagnosed COPD and cognitive impairment.

CONCLUSION

Our meta-analysis revealed an elevated risk for MCI and dementia in COPD patients. Proper clinical management and attention is necessary to prevent or mitigate the incidence of MCI and dementia in COPD patients.

ARTICLE HIGHLIGHTS

Research background

Chronic obstructive pulmonary disease (COPD) is a common public health issue that has been linked to cognitive dysfunction. No clear evidences are available for the relationship between COPD and mild cognitive impairment (MCI) and dementia risk.

Research motivation

To our knowledge, there has only been one published meta-analysis with limited number studies investigating the statistical association of COPD with cognition dysfunction.

Research objectives

The current meta-analysis was performed to investigate the relationship between COPD and MCI and dementia risk.

Research methods

A comprehensive search using PubMed, EMbase, Google Scholar, and Cochrane Library online databases for articles published prior to 31st March 2021.

Research results

Twenty-seven studies met all the inclusion criteria. Meta-analysis yielded a strong association between COPD and increased risk of MCI incidence. It also found a

borderline trend for increased dementia risk in COPD patients. A significant lower MMSE score in COPD patients was noted.

Research conclusions

Our findings revealed an elevated risk for the occurrence of MCI and dementia in COPD patients. Proper clinical management and attention is required to prevent and control MCI and dementia incidence in COPD patients.

Research perspectives

Further large prospective observational studies are needed to strengthen the evidence on this important subject.

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