Association of non-obstructive dyspnoea with all-cause mortality and incident chronic obstructive pulmonary disease: a systematic literature review and meta-analysis

Yuyan Hou, Fan Wu, Huanhuan Fan, Haiqing Li, Binwei Hao, Zhishan Deng, Xiaoyan Lu, Yumin Zhou, Pixin Ran

ABSTRACT
Background Controversy exists regarding the association between non-obstructive dyspnoea and the future development of chronic obstructive pulmonary disease (COPD) and mortality. Therefore, we aimed to evaluate the association of non-obstructive dyspnoea with mortality and incident COPD in adults.

Methods We searched PubMed, Embase, and Web of Science to identify studies published from inception to 13 May 2023. Eligibility screening, data extraction, and quality assessment of the retrieved articles were conducted independently by two reviewers. Studies were included if they were original articles comparing incident COPD and all-cause mortality between individuals with normal lung function with and without dyspnoea. The primary outcomes were incident COPD and all-cause mortality. The secondary outcome was respiratory disease-related mortality. We used the random-effects model to calculate pooled estimates and corresponding 95% confidence interval (CI). Heterogeneity was determined using the I² statistic.

Results Of 6486 studies, 8 studies involving 100,758 individuals fulfilled the inclusion and exclusion criteria and were included in the study. Compared with individuals without non-obstructive dyspnoea, individuals with non-obstructive dyspnoea had an increased risk of incident COPD (relative risk: 1.41, 95% CI: 1.08 to 1.83), and moderate heterogeneity was found (p=0.079, I²=52.2%). Individuals with non-obstructive dyspnoea had a higher risk of all-cause mortality (hazard ratio: 1.21, 95% CI: 1.14 to 1.28, I²=0.0%) and respiratory disease-related mortality (hazard ratio: 1.52, 95% CI: 1.14 to 2.02, I²=0.0%) than those without.

Conclusions Individuals with non-obstructive dyspnoea are at a higher risk of incident COPD and all-cause mortality than individuals without dyspnoea. Further research should investigate whether these high-risk adults may benefit from risk management and early therapeutic intervention.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Previous studies have explored the association between non-obstructive dyspnoea and incident chronic obstructive pulmonary disease (COPD), but they have yielded inconsistent results. A pooled analysis of the association of non-obstructive dyspnoea with incident COPD and mortality has not been performed.

WHAT THIS STUDY ADDS
⇒ In individuals with normal spirometry, the presence of dyspnoea was associated with higher risks of incident COPD and all-cause mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ In this review, we found that non-obstructive dyspnoea is related to an increase in incident COPD and mortality. This indicates that this type of individual can be considered as a special clinical subtype of pre-COPD, which has guiding significance for early screening, follow-up, and management.

INTRODUCTION
Chronic obstructive pulmonary disease (COPD) is a multifaceted pulmonary ailment distinguished by persistent respiratory symptoms, including dyspnoea, cough, expectoration, and/or exacerbation. The Global Burden of Disease study 2017 indicated that COPD is the third leading cause of death and disability worldwide. To reduce the disease burden caused by COPD, the goal of COPD treatment has shifted from the treatment of advanced COPD to the identification, management, and intervention of early COPD or pre-COPD. Accurate and early identification of individuals at risk of COPD, also known as pre-COPD, is the foundation for effective management.
Dyspnoea is the subjective experience of lack of air or breathing discomfort.\(^5\,^6\,^7\) We usually use the modified Medical Research Council (mMRC) Dyspnoea Scale to quantify dyspnoea severity.\(^8\) Dyspnoea is the main symptom of COPD, but some individuals with normal lung function also have dyspnoea (non-obstructive dyspnoea).\(^9\,^10\) Previous studies have explored the association between non-obstructive dyspnoea and incident COPD, but they have yielded inconsistent results.\(^9\,^11\,^12\) Using data from the European Community Respiratory Health Survey, De Marco et al found that dyspnoea was not associated with incident COPD when lung function was normal.\(^13\) In 2018, Kalhan et al reached the same conclusion.\(^10\) However, other studies have produced mixed results.\(^11\,^12\) Therefore, whether normal lung function with dyspnoea is associated with COPD development remains controversial. Many studies have found that individuals with non-obstructive dyspnoea are at a higher risk of all-cause mortality than those with normal lung function without dyspnoea.\(^13\,^14\,^15\)

To our knowledge, a pooled analysis of the association of non-obstructive dyspnoea with incident COPD and mortality has not been performed. To accurately identify individuals with pre-COPD, an up-to-date synthesis of data from existing studies is needed to quantitatively evaluate these associations. Bearing this in mind, we aimed to perform a comprehensive systematic review and meta-analysis to assess the association of non-obstructive dyspnoea with incident COPD and mortality.

METHODS

Data sources and search strategy

In this systematic review and meta-analysis, two reviewers (YH and HF) independently performed a comprehensive search of Embase, Web of Science, and PubMed to identify studies published from inception to 13 May 2023, with the following search terms: ‘dyspnoea’, ‘shortness of breath’, ‘normal lung function’, ‘normal pulmonary function’, ‘normal spirometry’, ‘without airflow obstruction’, ‘without airflow limitation’, ‘preserved lung function’, ‘preserved pulmonary function’, and ‘preserved spirometry’. The references of relevant studies were also manually checked to identify other potentially related studies. Online supplemental material 1 shows the search details used for all of the databases. The Preferred Reporting Items for Systematic reviews and Meta-Analyses statement was followed in the conduct and reporting of this study.\(^16\)

The protocol is registered in the International Prospective Register of Systematic Reviews (registration number: CRD 42023395192). The abstract of this study was previously presented at the 27th congress of the Asian Pacific Society of Respirology.\(^17\)

Study selection

Two reviewers (YH and HF) independently reviewed the studies. Discussions or consultations with a third researcher (FW) were used to resolve any disagreements or uncertainties. For primary inspection, the titles and abstracts were screened. Studies were mainly excluded due to the analysis of obstructive dyspnoea and the presence of data that could not be extracted. The second inspection involved full-text review and article selection based on the inclusion and exclusion criteria. Studies were included if they (1) provided data to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality and respiratory-related mortality, or relative risks (RRs) and 95% CIs for COPD development, in individuals with non-obstructive dyspnoea compared with individuals with normal lung function without dyspnoea; (2) were independent studies; and (3) were prospective cohort studies or retrospective cohort studies. Studies that replicated previously published research data were not considered independent. Exclusion criteria include (1) acute dyspnoea or dyspnoea with a clear cause; (2) failure to clearly state that the included subjects have normal pulmonary function; (3) repeated studies; (4) only meeting abstracts; and (5) no study endpoints of interest were reported.

The primary endpoints of the study were COPD development and all-cause mortality. The secondary endpoint was respiratory disease-related mortality. This review adopted the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition of COPD.\(^1\) A postbronchodilator forced expiratory volume in 1 s (FEV\(_1\))/forced vital capacity (FVC) ratio of \(<0.70\) was the preferred definition of COPD. Previous studies have shown that prebronchodilator lung function and postbronchodilator lung function have the same ability to assess the risk of long-term mortality.\(^18\) Therefore, studies using a prebronchodilator FEV\(_1\)/FVC of \(<0.70\) to define COPD were also considered for inclusion in this study. Dyspnoea was defined by self-reporting in survey-based studies or studies using the mMRC Dyspnoea Scale Questionnaire, with a minimum rating of \(\geq1\), or even \(\geq2\).\(^8\)

Data extraction and risk-of-bias assessment

The data included first author, year of publication, region, study design, sample size, age of study participants, follow-up period, dyspnoea definition, normal lung function definition, COPD definition, RRs and 95% CIs, and HRs and 95% CIs, which were extracted and entered by two independent reviewers (YH and HF). Two reviewers independently checked the accuracy of the extracted information. The Newcastle Ottawa Scale (NOS) score ranges from 0 to 9 (9 being the best quality) with a total score of \(\geq7\) being considered good quality.\(^19\) Two reviewers (YH and HF) independently conducted the risk-of-bias assessment based on the NOS score, including the selection of the cohort study, comparability of the study, and outcome of the study. Any divergences were settled by discussion or by consulting a third researcher (FW).
Data synthesis and statistical analysis

To describe the outcome of incident COPD, we used RRs and 95% CIs for quantitative synthesis. The calculation formula (RR=OR ÷ [(1 – p0) + (p0×OR)]) was employed to convert ORs to RRs in instances where ORs were used in the studies. The p0 is the incidence of results of interest in the reference group. We used HRs and 95% CIs in our quantitative synthesis to depict the results of mortality due to all causes and respiratory diseases. From the eligible studies, we preferentially extracted and used the results of multiple-factor adjustment. However, we also used single-factor uncorrected results when only the results without multiple-factor correction were found in the study. To calculate the pooled effect sizes and 95% CIs, we used the random-effects model based on the fact that these studies were conducted in a variety of settings and among different populations. Heterogeneity was determined using the I² statistic. Values of 0%–24% represented no heterogeneity, 25%–49% were considered low heterogeneity, 50%–74% were considered moderate heterogeneity, and values of ≥75% indicated substantial heterogeneity. If the number of included studies reached ≥10, we planned to perform a funnel plot analysis by plotting the ORs of the individual studies against their variance to detect the risk of publication bias. Egger’s test was also used to assess the funnel plot asymmetry for incident COPD, all-cause mortality, and respiratory mortality with at least 10 studies included. Further subgroup analyses were planned to examine crucial variables that might affect incident COPD and mortality, and to assess sources of heterogeneity. The planned subgroups included smoking status, follow-up year, baseline age, and sex. We used Stata/SE V.15.1 (Statacorp LP, College Station, TX, USA) to conduct this meta-analysis. A p-value of <0.05 was considered statistically significant, and all statistical tests were two-sided.

RESULTS

Search results and study characteristics

As shown in figure 1, the flow diagram represents the systematic selection and search process. Of the 6479 studies identified on PubMed, Embase, and Web of Science, as well as the seven additional studies from previous meta-analyses and systematic reviews (online supplemental material 2), 5214 studies remained after duplicate removal. After checking the titles and abstracts, 16 articles remained eligible for full-text reading. We ultimately included eight studies that fulfilled the inclusion criteria.
and exclusion criteria. The reasons for exclusion included not distinguishing participants with normal lung function, unavailable full texts, and not reporting the outcome of interest.

Table 1 shows the characteristics of the included studies. A total of 100,758 individuals were included in the meta-analysis. The average follow-up period was more than 5 years. With the exception of one study, which was a retrospective study, all studies were prospective studies. All individuals included in this review were from the general population. One study recruited only women, whereas all other studies included both men and women. All studies were published between 2005 and 2023. This review included six studies with a prebronchodilator FEV1/FVC of <0.70 as the main definition of COPD, one study with a postbronchodilator FEV1/FVC of <0.70 and an FEV1 of ≥80% predicted value as the main definition of COPD, and one study with a physician-based diagnosis of COPD as the main definition of COPD. Six studies with mMRC scores of ≥1 as the main definition of dyspnoea, one study with an mMRC score of ≥2 as the main definition of severe dyspnoea, and one study with self-reported breathing difficulties as the main definition of dyspnoea were included. Table 2 presents the results based on the NOS scores of the included studies. The included studies scored 7–9 on the NOS, indicating good methodological quality.

**Association between non-obstructive dyspnoea and incident COPD**

Four studies involving 12,273 individuals examined the association between non-obstructive dyspnoea and incident COPD. All four of these studies adjusted for multiple confounding factors. The results were presented as RRs and 95% CIs in one study, and as ORs and 95% CIs in the remaining three studies. We accounted for the incidence of COPD by converting the OR to the RR. Compared with normal lung function without dyspnoea, the pooled analysis identified a higher risk of incident COPD in individuals with non-obstructive dyspnoea (RR: 1.41, 95% CI: 1.08 to 1.83, p=0.011) with moderate heterogeneity (I²=52.2%, Tau²=0.044, p=0.079) (figure 2). Fewer than 10 studies were included, which was not sufficient to evaluate publication bias.

**Association between non-obstructive dyspnoea and all-cause mortality/respiratory disease-related mortality**

Three studies involving 88,485 individuals examined the association between non-obstructive dyspnoea and all-cause mortality. Multiple confounders were adjusted for in all studies, and the results were presented as HRs and 95% CIs. In individuals with normal spirometry, the presence of dyspnoea was associated with a higher risk of all-cause mortality (HR: 1.21, 95% CI: 1.14 to 1.28, p=0.001) with no heterogeneity (I²=0.0%, Tau²=0.000, p=0.618) compared with individuals without dyspnoea. The association between non-obstructive dyspnoea and respiratory disease-related mortality was examined in two studies. Compared with individuals with normal lung function without dyspnoea, individuals with non-obstructive dyspnoea had a higher risk of respiratory disease-related mortality (HR: 1.52, 95% CI: 1.14 to 2.02), with no heterogeneity (I²=0.0%, Tau²=0.000, p=0.340) (figure 3). Only eight studies met the inclusion requirements and therefore we did not evaluate publication bias.

**Subgroup analysis**

As a result of the limited number of studies included, the subgroup analysis was not conducted.

**DISCUSSION**

To the best of our knowledge, this systemic review and meta-analysis is the first to quantitatively synthesise current evidence on the prognosis of non-obstructive dyspnoea and respiratory health in adults. In this comprehensive meta-analysis of eight studies involving more than 100,000 participants, a major finding emerged. In individuals with normal spirometry, the presence of dyspnoea was associated with higher risks of incident COPD and all-cause mortality.

The GOLD Report in 2001 proposed an ‘at risk’ stage (GOLD stage 0), which only included the respiratory symptoms of chronic cough and sputum production. However, not all individuals with normal lung function and respiratory symptoms will develop COPD, and thus GOLD 0 was delisted from the 2006 GOLD classification. In 2021, Han et al proposed the concept of pre-COPD, meaning that individuals are at high risk of COPD, including non-obstructive dyspnoea. According to data from the European Community Respiratory Health Survey II, De Marco et al found that non-obstructive dyspnoea was not associated with incident COPD in young adults. However, Lindberg et al observed conflicting results. Substantial controversy followed these discordant results regarding the important, but yet unsolved, puzzle of whether individuals with normal lung function with dyspnoea are more likely to develop incident COPD than those without dyspnoea. Moreover, whether dyspnoea should be considered as one of the specific definitions of pre-COPD is unclear. In this review, we found that non-obstructive dyspnoea is related to an increase in incident COPD and mortality. This indicates that this type of individual can be considered as a special clinical subtype of pre-COPD, which has guiding significance for early screening, follow-up, and management. Notably, individuals with non-obstructive chronic bronchitis, emphysema, airway remodelling, and small airway disease are among the pre-COPD population. Therefore, comprehensive evaluation is needed when managing the pre-COPD population.

Our study did not perform a subgroup analysis because the number of relevant studies was small and the minimum requirements were not met. Lindberg et al found that dyspnoea is a significant risk factor for incident COPD...
<table>
<thead>
<tr>
<th>Study</th>
<th>Regions (country)</th>
<th>Study design</th>
<th>Dyspnoea definition</th>
<th>Normal lung function definition</th>
<th>COPD definition</th>
<th>Sample size (% men)</th>
<th>Age, year</th>
<th>Follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindberg 2005</td>
<td>Norrbotten, Sweden</td>
<td>Prospective cohort</td>
<td>mMRC≥1</td>
<td>Pre-BD FEV₁/FVC≥0.70</td>
<td>Pre-BD FEV₁/FVC&lt;0.70 and FEV₁&lt;80% predicted</td>
<td>1109 (51.8%)</td>
<td>Born in 1919 to 1920, 1934 to 1935, and 1949 to 1950</td>
<td>10</td>
</tr>
<tr>
<td>de Marco 2007</td>
<td>Europe</td>
<td>Prospective cohort</td>
<td>mMRC≥1</td>
<td>Pre-BD FEV₁/FVC≥0.70</td>
<td>Pre-BD FEV₁/FVC&lt;0.70</td>
<td>4856 (48.8%)</td>
<td>20–44</td>
<td>8.9 (min-max: 5.8–11.4)</td>
</tr>
<tr>
<td>Kalhan 2018</td>
<td>Birmingham, Chicago, Minneapolis, and Oakland, America</td>
<td>Prospective cohort</td>
<td>mMRC≥1</td>
<td>Pre-BD FEV₁/FVC≥0.70</td>
<td>Pre-BD FEV₁/FVC&lt;0.70</td>
<td>2724 (57.1%)</td>
<td>18–30</td>
<td>30</td>
</tr>
<tr>
<td>Çolak 2019</td>
<td>Danish</td>
<td>Prospective cohort</td>
<td>mMRC≥1</td>
<td>Pre-BD FEV₁/FVC≥0.70</td>
<td>Pre-BD FEV₁/FVC&lt;0.70</td>
<td>83889 (45.0%)</td>
<td>20–100</td>
<td>8.8 (range up to 14.4)</td>
</tr>
<tr>
<td>Opina 2019</td>
<td>Memphis and Pittsburgh, America</td>
<td>Prospective cohort</td>
<td>mMRC≥1</td>
<td>Pre-BD FEV₁/FVC≥0.70</td>
<td>Pre-BD FEV₁/FVC&lt;0.70</td>
<td>104 (50%)</td>
<td>70–79</td>
<td>13</td>
</tr>
<tr>
<td>Engel 2022</td>
<td>Australia</td>
<td>Retrospective cohort</td>
<td>Self-reported breathing difficulties</td>
<td>No physician-based diagnosis of COPD</td>
<td>Physician-based diagnosis of COPD</td>
<td>3584 (0%)</td>
<td>47.6 (SD 1.5)</td>
<td>23</td>
</tr>
<tr>
<td>Lee 2022</td>
<td>Singapore</td>
<td>Prospective cohort</td>
<td>mMRC≥1</td>
<td>Pre-BD FEV₁/FVC≥0.70</td>
<td>Pre-BD FEV₁/FVC&lt;0.70</td>
<td>3465 (36.9%)</td>
<td>65.7</td>
<td>11</td>
</tr>
<tr>
<td>Wassim 2023</td>
<td>The USA</td>
<td>Prospective cohort</td>
<td>More severe dyspnoea: mMRC≥2</td>
<td>Post-BD FEV₁/FVC≥0.70 and FEV₁≥80% predicted</td>
<td>Post-BD FEV₁/FVC&lt;0.70</td>
<td>1027</td>
<td>45–80</td>
<td>10.1</td>
</tr>
</tbody>
</table>

BD, bronchodilator; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, modified Medical Research Council Dyspnoea Scale; SD, standard deviation.
## Table 2  Newcastle–Ottawa Scale scores and quality assessment of all studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection (stars awarded)</th>
<th>Comparability (stars awarded)</th>
<th>Outcome (stars awarded)</th>
<th>Quality (total stars awarded)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Representativeness</td>
<td>Selection</td>
<td>Ascertainment</td>
<td>Outcome</td>
</tr>
<tr>
<td>Lindberg et al 200511</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>de Marco et al 20079</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Kalhan et al 201810</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Çolak et al 201914</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Opina et al 201915</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Engel et al 202212</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Lee et al 202213</td>
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<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Wassim et al 2023</td>
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<td>*</td>
</tr>
</tbody>
</table>

In the NOS score, except for comparability, which can be rated up to 2 stars, the other items can be rated up to 1 star, with a full score of 9 stars. Higher scores indicate higher quality research.
Whether dyspnoea demonstrate sex differences remains unknown. Knowledge in this area is still lacking, and further studies are needed to enhance our understanding of dyspnoea with COPD. Dyspnoea has various causes, and therefore further etiological investigations are necessary. In individuals with normal spirometry, dyspnoea may be caused by exercise or physical activity, pulmonary infection, inflammatory lung diseases, pulmonary embolism, pulmonary allergic reaction, cardiovascular disease, anaemia or even psychological factors (anxiety or panic). Therefore, clinicians should screen and exclude dyspnoea caused by other diseases and psychological factors before managing individuals with non-obstructive dyspnoea with pre-COPD to avoid delayed management.

At present, no clear evidence indicating that drugs can alter COPD progression is available. Our study focused on identifying high-risk individuals who retained normal lung function, increasing attention to non-obstructive dyspnoea, strengthening follow-up and lung function testing, and even drug therapy to allow patients to benefit from early treatment. Early

**Figure 2**  Forest plot of the risk of incident chronic obstructive pulmonary disease in individuals with non-obstructive dyspnoea compared with individuals without non-obstructive dyspnoea. Larger boxes indicate studies with larger sample sizes and larger weight. The combined effect size estimate takes into account both the individual study estimates and their respective weights. The pooled effect size estimate, indicated by the diamond at the bottom of the forest plot, provides an overall summary of the effect across all included studies. RR, relative risks

**Figure 3**  Forest plot of the risk of all-cause mortality and respiratory mortality in individuals with non-obstructive dyspnoea compared with individuals without non-obstructive dyspnoea. Larger boxes indicate studies with larger sample sizes and larger weight. The combined effect size estimate takes into account both the individual study estimates and their respective weights. The pooled effect size estimate, indicated by the diamond at the bottom of the forest plot, provides an overall summary of the effect across all included studies.

<table>
<thead>
<tr>
<th>Mortality and Study</th>
<th>Hazard ratio (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Çöplak et al. 2019</td>
<td>1.48 (1.10, 1.97)</td>
<td>96.42</td>
</tr>
<tr>
<td>Wassim et al. 2023</td>
<td>3.13 (0.69, 14.20)</td>
<td>3.58</td>
</tr>
<tr>
<td>Subgroup, DL (I² = 0.0%, p = 0.340)</td>
<td>1.52 (1.14, 2.02)</td>
<td>100.00</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Çöplak et al. 2019</td>
<td>1.20 (1.13, 1.27)</td>
<td>89.05</td>
</tr>
<tr>
<td>Opina et al. 2019</td>
<td>1.30 (0.95, 1.79)</td>
<td>3.03</td>
</tr>
<tr>
<td>Lee et al. 2022</td>
<td>1.53 (1.05, 2.22)</td>
<td>2.17</td>
</tr>
<tr>
<td>Wassim et al. 2023</td>
<td>1.21 (0.96, 1.52)</td>
<td>5.75</td>
</tr>
<tr>
<td>Subgroup, DL (I² = 0.0%, p = 0.618)</td>
<td>1.21 (1.14, 1.28)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Heterogeneity between groups: p = 0.124
rates. Furthermore, dyspnoea often occurs due to underlying health conditions, such as respiratory and cardiovascular diseases, which can contribute to an increased mortality risk. Dyspnoea is often a manifestation of underlying diseases, such as COPD, heart failure, pulmonary hypertension, or interstitial lung disease. These conditions can significantly impact pulmonary function and overall health, leading to an increased mortality risk. Dyspnoea can also limit an individual’s ability to engage in physical activity and exercise, which is associated with various health benefits. Reduced physical activity can lead to deconditioning, muscle weakness, and an increased risk of other health complications. Additionally, decreased exercise tolerance can result in a sedentary lifestyle, which is associated with high mortality rates. Furthermore, dyspnoea often occurs due to inadequate oxygenation of the body, and impaired lung function leads to reduced oxygen uptake and increased carbon dioxide retention. Our research team recently found that ventilatory inefficiency was associated with small airway dysfunction, which is a key pathological feature in patients with COPD.

Strengths and limitations
One notable strength of this review is that the majority of the included studies exhibited a high quality of evidence and appropriately adjusted for confounding variables, which reduced the impact of these confounding variables on the association between non-obstructive dyspnoea and the observed health risk. Moreover, we used strict inclusion and exclusion criteria and pooled the data using the random-effects model to explain the variance between the studies.

This study also has some limitations. First, the number of available studies was small, and therefore we could not perform multiple subgroup analyses and funnel plot analyses to investigate the associations between non-obstructive dyspnoea and the risks of incident COPD and mortality. Future cohort studies are needed to analyse the associations of dyspnoea with COPD events and respiratory health outcomes in specific subgroups (male sex, female sex, never smokers, ever smokers, current smokers, female-age, and baseline age groups). Second, we could not access the data of individuals to exclude potential confounders. Third, the cause of the augmented risk observed in our investigation remains ambiguous. Whether the increased risk stemmed from non-obstructive dyspnoea or the progression from non-obstructive dyspnoea to COPD during the follow-up period remains uncertain. Finally, the majority of the included studies used prebronchodilator lung function as a diagnostic tool for COPD, whereas most studies now use the GOLD criterion of postbronchodilator FEV₁/FVC ratio to diagnose COPD. However, previous studies have shown that using prebronchodilator and postbronchodilator lung function is equally valuable in distinguishing long-term mortality risk. Therefore, the results of this study are unlikely to have been influenced by the use of prebronchodilator lung function to diagnose COPD.

CONCLUSIONS
This systematic review and meta-analysis comprehensively and rigorously summarised the data of eight studies involving 100,758 individuals to examine the association of non-obstructive dyspnoea with COPD incidence and all-cause/respiratory-related mortality risk. Individuals with non-obstructive dyspnoea were more likely to develop incident COPD and were at a higher risk of mortality than those without dyspnoea. Our research findings support the inclusion of non-obstructive dyspnoea in the pre-COPD population for enhanced follow-up, management, and intervention.
REFERENCES


Supplementary Material

Supplementary Material 1

Search strategies for all databases

1. PubMed
(dyspnea [All Fields] OR shortness of breath [All Fields]) AND (normal lung function [All Fields] OR normal pulmonary function [All Fields] OR normal spirometry [All Fields] OR without airflow obstruction [All Fields] OR without airflow limitation [All Fields] OR preserved lung function [All Fields] OR preserved pulmonary function [All Fields] OR preserved spirometry [All Fields])

2. Embase
('dyspnea' OR 'shortness of breath') AND ('normal lung function' OR 'normal pulmonary function' OR 'normal spirometry' OR 'without airflow obstruction' OR 'without airflow limitation' OR 'preserved lung function' OR 'preserved pulmonary function' OR 'preserved spirometry') AND [<1966-2023]/py

3. Web of Science
#1 ALL = (dyspnea)
#2 ALL = (shortness of breath)
#3 #1 or #2
#4 ALL = (normal lung function)
#5 ALL = (normal pulmonary function)
#6 ALL = (normal spirometry)

#7 ALL = (without airflow obstruction)

#8 ALL = (without airflow limitation)

#9 ALL = (preserved lung function)

#10 ALL = (preserved pulmonary function)

#11 ALL = (preserved spirometry)

#12 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

#13 #3 or #12
Supplementary Material 2

Seven additional studies from previous meta-analyses and systematic reviews.


