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Protocol for a systematic review of the associations between inflammatory markers and lung function, muscle force and exercise capacity in people with COPD

Nadhirah Mohd Noor,[1] Zawani Mustaffa,[1,2] Alia Nizam,[1,3] Mohd Arif Mohd Zim,[4] Li Whye Cindy Ng,[5,6] Fatim Tahirah Mirza [1]

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For numbered affiliations see end of article.

Correspondence to
Dr Fatim Tahirah Mirza; fatim_mirza@uitm.edu.my

ABSTRACT

Introduction The prevalence of chronic obstructive pulmonary disease (COPD) has been on the rise, with acute exacerbation of COPD associated with the highest burden and multiple pulmonary and systemic consequences. People with COPD have been found to have an abnormal response of systemic inflammation. To date, although limited, there are studies that suggest negative associations between inflammatory markers and important clinical outcomes such as exercise capacity and muscle force. This protocol aims to systematically review the evidence for (i) the associations between inflammatory markers and lung function, muscle force and exercise capacity and (ii) the influence of other factors (eg, hospitalisation, exercise programme) on the level of inflammatory markers in people with COPD.

Methods and analysis Scopus, PubMed, Cochrane, Web of Science and ProQuest will be searched from database inception to February 2023 using PEO search strategy (Population: adults with COPD; Exposure: inflammatory markers; Outcomes: lung function, muscle force and exercise capacity). Four reviewers working in pairs will independently screen articles for eligibility and extract data that fulfilled the inclusion criteria. Depending on the design of the included studies, either Cochrane risk-of-bias version 2 or the Newcastle-Ottawa Scale tools will be used to rate the methodological quality of the included studies. Effect sizes reported in each individual study will be standardised to Cohen's d and a random effects model will be used to calculate the pooled effect size for the association.

Ethics and dissemination Ethical approval is unnecessary as this study will only use publicly available data. The findings will be disseminated through publication in peer-reviewed journals and conferences.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review will provide synthesised evidence on the associations between inflammatory markers and lung function, muscle force and exercise capacity to help inform clinical decision making.
⇒ The review methods are in accordance with Cochrane methodology and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses publishing guidelines.
⇒ Studies in languages other than English will not be included because of language barriers, so language bias may exist.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable lung disease characterised by persistent airflow obstruction that is mostly progressive.[1] The global prevalence of COPD is high. In 2019, for example, the estimated global prevalence of COPD was 13.1%, which translated into over 1 billion cases of COPD in the 7.67 billion world population.[1 2] The clinical course of COPD includes periods of clinical stability punctuated by periods of acute worsening, known as an acute exacerbation of COPD (AECOPD). An AECOPD is an important event in the clinical course of patients with COPD. These events account for the largest direct cost associated with COPD treatment[3] and are associated with multiple pulmonary and systemic consequences.

COPD is associated not only with an abnormal inflammatory response in the lungs but also with evidence of systemic inflammation. When compared with healthy controls, people with COPD have increased levels of systemic oxidative stress,[4 5] enhanced chemotaxis in the circulating inflammatory cells (eg, neutrophils)[6] and increased plasma levels of inflammatory cytokines in their peripheral circulation. These abnormal systemic inflammatory responses have been shown to be further increased during an AECOPD.[5 7] The

origin of systemic inflammation in people with COPD is still unclear. However, it has been suggested in earlier studies that it could be due to the spill-over of inflammatory molecules from the inflamed pulmonary parenchyma to the pulmonary circulation.[8–10] Systemic inflammation has been demonstrated to be associated with several systemic consequences such as nutritional abnormalities, weight loss, skeletal muscle dysfunction, cardiovascular disease, glucose intolerance, osteoporosis and depression.[11]

Lung function, quadriceps muscle force (QMF) and exercise capacity were also shown to be reduced in people with COPD when compared with their healthy counterparts and further reduced during an AECOPD.[12–14] In fact, the decline in lung function in this population, specifically the forced expiratory volume in 1 s (FEV_1) was found to be associated with the rate of exacerbation.[12 15] Donaldson *et al*[12] found that the mean rate of decline in FEV_1 was 40.1 mL/year in patients with more than 2.92 exacerbations in a year compared with a decline of 32.1 mL/year in those who had less than 2.92 exacerbations in a year. With regard to muscle force, Spruit *et al*[13] found that the QMF was the lowest in people hospitalised for an AECOPD compared with those who were clinically stable and in healthy controls (66±22% vs 86±16% vs 103±20% predicted). The mean reduction in QMF was reported to be between 5%[13] and 8%[16] within only 5 days of hospitalisation. Exercise capacity has also been shown to be reduced in people with COPD and further reduced following an exacerbation.[17–19] For instance, Carr *et al*[17] found that the 6 min walk distance in 29 individuals with COPD was significantly lower two to 4 weeks following an AECOPD compared with measurements taken during the period of their clinical stability (299±99 m vs 359±85 m; p<0.001). There is also evidence suggesting that in some patients, the reduction in lung function, QMF and exercise capacity did not recover to the baseline values (ie, values during clinical stability) even 3 months after an exacerbation.[13 14 16 18]

Studies reporting the associations between inflammatory markers, lung function, QMF and exercise capacity in people with COPD are limited. However, there are preliminary findings that suggest a negative association between inflammatory markers such as interleukin 8 (IL-8), C-reactive protein (CRP) and IL-6 with lung function, muscle force and exercise capacity.[13 20 21] The increase in IL-8 in both COPD and during an AECOPD has been found to be associated with a decline in lung function and QMF.[13] Similarly, an increase in CRP and IL-6 has been found to be associated with a decline in exercise capacity.[13 20 21] Given the fact that the reduction in exercise capacity, QMF and lung function during an AECOPD appears to take a very long time to recover to its baseline values (ie, values during clinical stability),[13 20 22] we hypothesised that the rise in systemic inflammatory markers at the time of exacerbation also take a very long time to settle and are associated with the slow recovery in these outcomes (exercise capacity, QMF and lung function). Therefore, this review aims to conduct a systematic synthesis and a meta-analysis (if possible) of the evidence for the association between systemic inflammatory markers (ie, IL-6, IL-8 and CRP) and lung function, muscle force and exercise capacity in people with COPD.

A strong association between systemic inflammatory markers and lung function, muscle force and exercise capacity (if any) may suggest the presence of a biological link between the variables. Providing synthesised evidence on the association between inflammatory markers and the abovementioned clinical outcomes is expected to help inform clinical decision-making (eg, the expectation of rehabilitation during this phase should take the influence of raised inflammatory markers, which has a negative impact on lung function, muscle force and exercise capacity into consideration).

A preliminary search of PROSPERO, the Cochrane Database of Systematic Reviews, and *JBI Evidence Synthesis* was conducted, and no current or ongoing systematic reviews similar to this protocol were identified.

OBJECTIVES

In people with COPD, we will systematically review the evidence for:

i. The associations between inflammatory markers (IL-6, IL-8, CRP) and lung function, muscle force and exercise capacity (see table 1 for definition).
ii. The influence of other factors (eg, hospitalisation, exercise programme) on the levels of inflammatory markers.

METHODS AND ANALYSIS

This systematic review protocol was written following the Cochrane Methodology[23] and the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist[24] (refer to online supplemental appendix S1 for a completed checklist). The full systematic review will follow the process guidelines by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[25] This review is registered with PROSPERO. Any changes to the published record will be reported.

Search strategy

Electronic searches

A literature search strategy using medical subject headings (MeSH) and text words related to COPD, inflammatory markers, lung function, muscle force and exercise capacity will be developed. Comprehensive searches of electronic databases (Scopus, PubMed, Cochrane Library, Web of Science and ProQuest) will be conducted from database inception to February 2023. The reference lists of potentially relevant articles will be reviewed to identify studies not captured by the electronic searches. The search

Table 1 PEOs table for the search strategy

PEOs	Inclusion criteria	Exclusion criteria	Operational rule
Population	► Adults with a clinical diagnosis of COPD ► Age >18 years ► Best recorded FEV_1/forced vital capacity (FVC) ratio of <0.7	► Paediatric population ► Require mechanical ventilation ► Require non-invasive ventilation	We will include studies on participants diagnosed with COPD in both acute and stable phases. Postintensive care unit rehabilitation studies in this population will be excluded. We will also include studies that investigate the comparison between COPD and other chronic respiratory diseases
Exposure	► Increase in the level of inflammatory markers either in percentage or absolute values ► Studies reporting at least one of the following inflammatory markers: – IL-6 – IL-8 – CRP	► Any type of inflammatory markers other than IL-6, IL-8 and CRP	We will include studies that measure the level of inflammatory markers as the main interest of exposure
Outcome	The primary outcome will be any measures of exercise capacity and muscle force and secondary outcome will be the lung function	► Does not include any measurement of exercise capacity, muscle force or lung function as an outcome	We will consider any outcome that measures the following: ► Exercise capacity – Maximal oxygen uptake (VO_2 max) – 6MWD – Two-minute walk distance (2MWD) – Incremental shuttle walks test (ISWT) ► Muscle force – Upper limb strength (biceps or triceps muscle force) – Lower limb strength (QMF) ► Lung function – FEV_1 and FVC
Study design	Observational and interventional studies	► Review papers ► Survey ► Uncontrolled trial ► Intervention other than exercise programme	We will include studies with the following study design: ► Observational study – Case–control study – Cohort study – Cross-sectional study ► Interventional study – Randomised controlled trial – Quasi-randomised trial – Quasi-experimental trial
Setting	Any setting		
Language	No language restriction		

COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 s; IL, interleukin; 6MWD, 6 min walk distance; QMF, quadriceps muscle force.

strategies that will be used are presented in online supplemental appendix S2.

Selection process

Studies that assess the association between inflammatory markers (ie, IL-6, IL-8 and CRP) and lung function, muscle force and exercise capacity in people with COPD will be included (see details of PEOs in table 1). Four reviewers (NMN, AN, ZM and LWCN) working in pairs will independently examine the titles and abstracts of all articles identified from the search to determine eligibility for inclusion. Decisions will be recorded and any disagreement between each pair of review authors will be resolved through discussion. If agreement cannot be reached, a decision will be made by the third review author (FTM). After retrieval of the full text of potentially eligible studies, the same pairs of review authors will independently screen the studies using a standardised form. Disagreement will be resolved by discussion between each pair of review authors, or where necessary, by the inclusion of the third review author (FTM). All processes will be reported by using the PRISMA flow diagram.[25]

Additional information or uncertainties will be clarified by contacting the primary authors.

Outcome measurement

The primary outcome will be any measures of exercise capacity and muscle force and the secondary outcome will be the lung function. See table 1 for definition and details of primary and secondary outcomes.

Data management and extraction

Data regarding study characteristics (author, year, study design, study setting), populations (sample size, age, gender), exposures (ie, IL-6, IL-8 and CRP), outcomes (measurement tools used for measuring lung function, muscle force and exercise capacity) and measure(s) of the association will be extracted.

Risk of bias assessment

The methodological quality of all included studies will be assessed by all review authors independently (NMN, AN, ZM, LWCN, FTM) using the Cochrane risk-of-bias version 2[23] tool for randomised controlled trials and the Newcastle-Ottawa Scale (NOS)[26] for non-randomised studies and observational studies. Any disagreement will be resolved through discussion with the team. All studies will be included for data extraction and synthesis where possible regardless of their result of methodological quality. This protocol has slight deviation from the protocol published in PROSPERO in which the NOS will be used instead of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and the Jadad scale to assess the methodological quality of non-randomised trials. This deviation is made in order to minimise the number of tools used as NOS can be used to assess risk of bias for all non-randomised trials including observational study.

Heterogeneity and reporting bias

Heterogeneity across studies will be qualitatively assessed and will be quantified using the I^2 statistics (ie, high when I^2>50%).[27] Funnel plot will be used to assess any possible presence of publication bias (if we have more than 10 included studies).[28]

Strategy for data analysis

The standardised mean differences will be used as the summary statistics by calculating the effect size using the Cohen's d approach. For the first objective, studies reported Pearson correlation coefficient or Spearman correlation coefficient will be converted into Cohen's d using Cohen's conversion formula (1988): $d=\sqrt{4r^2/\left(1-r^2\right)}$.[29] Studies that reported data only on linear regression will be excluded due to the lack of ability to ascertain the relationship (r) between the variables from linear regression. For the second objective, all studies that reported mean±SD of the inflammatory markers of two groups (exercise group vs control group or acute vs stable) will also be converted to Cohen's d by using the formula $\frac{\mu_1-\mu_2}{\sigma}$.[29] A random-effects model will be used to calculate the pooled effect size for the association in both objectives. Statistical analysis will be conducted using Review Manager (RevMan) software V.5.3 (Copenhagen: The Nordic Cochrane Centre; The Cochrane Collaboration 2014). Graphical techniques (eg, Harvest plots)[30] will be used to illustrate their relationships. If quantitative synthesis is not appropriate, the information presented will be synthesised narratively to explain the characteristics and findings of the included studies, in line with the guidance from the Centre for Reviews and Dissemination.[31]

Interpretation of findings

We will use the Grading of Recommendation Assessment, Development and Evaluation (GRADE)[32] approach to assess the quality of the evidence and strength of the recommendation for both of the study objectives.

Patient and public involvement

There is no patient involvement in this protocol.

DISCUSSION

This systematic review will provide information on the existing evidence regarding the association between inflammatory markers (IL-6, IL-8 and CRP) and lung function, muscle force and exercise capacity in people with COPD. It will also determine which inflammatory markers are strongly/consistently associated with lung function, muscle force and exercise capacity and discuss their possible justification. Knowledge of the plausibility of a biological link between the inflammatory markers and lung function, muscle force and exercise capacity may facilitate healthcare professionals in setting a more realistic treatment goal by considering the influence of inflammatory markers on these important clinical outcomes.

ETHICS AND DISSEMINATION

This systematic review protocol will use data available to the public without any direct involvement of human participants. Therefore, approval from an ethics committee is not necessary. The review findings will be presented at national and international scientific meetings and conferences and published in a peer-reviewed journal.

Author affiliations
[1]Centre for Physiotherapy Studies, Faculty of Health Sciences, Universiti Teknologi MARA (UiTM), Bandar Puncak Alam, Malaysia
[2]Rehabilitation Department, KPJ Bandar Dato' Onn Specialist Hospital, Bandar Dato' Onn, Malaysia
[3]Department of Physiotherapy, Sunway Medical Centre, Bandar Sunway, Malaysia
[4]Respiratory Medicine, Internal Medicine, KPJ Damansara Specialist Hospital 2, Kuala Lumpur, Malaysia
[5]Department of Physiotherapy, Singapore General Hospital, Singapore
[6]Health and Social Sciences Cluster, Singapore Institute of Technology, Singapore

Twitter Fatim Tahirah Mirza @FatimMirza

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Contributors FTM led the team (NMN, ZM, AN, MAMZ and LWCN), who all contributed to the development of the protocol. NMN drafted the first version of the manuscript with support from ZM and AN. The manuscript was then revised by all the authors. All authors have critically reviewed and approved the final version of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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ORCID iD

Fatim Tahirah Mirza http://orcid.org/0000-0002-7515-3971

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