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*Review Article*

# Effects of pulmonary rehabilitation on systemic inflammation in chronic obstructive pulmonary disease: a meta-analysis

Xiaotian Alex Yue[2*], Yilan Sheng[1*], Jianhua Li[2]

[1]*Department of Rehabilitation, School of International Medical Technology, Shanghai Sanda University, Shanghai, China;* [2]*Department of Rehabilitation, Shanghai General Hospital, Shanghai Jiaotong University, Shanghai, China.* [*]*Equal contributors.*

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**Abstract:** Chronic obstructive pulmonary disease (COPD) is marked by both lung-related and systemic symptoms, notably chronic inflammation. Despite pulmonary rehabilitation (PR) being a critical treatment for COPD, its influence on systemic inflammation remains unclear. This meta-analysis was conducted to assess PR's effect on circulating inflammatory markers in COPD patients. We systematically reviewed databases like PubMed, EMBASE, and Web of Science to select randomized controlled trials and observational studies that investigated the impact of PR on systemic inflammation. We calculated the mean differences (MD) in inflammatory markers before and after PR using a random-effects model and assessed the risk of bias with established tools. Our study included six investigations (four RCTs, two observational) with 147 COPD patients. Our findings show notable increases in IL-6 (MD 0.44, 95% CI 0.17-0.70, P = 0.001), CRP (MD 0.56, 95% CI 0.31-0.81, P<0.00001), and TNF-alpha (MD 0.41, 95% CI 0.12-0.70, P = 0.005) following PR. However, sensitivity analysis pinpointed the study by El-Kader et al. as a key influence on these results. Excluding this study led to nonsignificant changes. Thus, our meta-analysis uncovers an unanticipated rise in inflammatory markers post-PR in COPD patients, questioning the assumed anti-inflammatory benefits of PR.

**Keywords:** Pulmonary rehabilitation (PR), inflammatory markers, COPD, meta-analysis, systemic inflammation, IL-6, CRP, TNF-α, exercise, protocol variability, clinical implications, future research directions

## Introduction

Chronic obstructive pulmonary disease (COPD), a progressive systemic disorder, affects approximately 300 million people worldwide [1]. Its hallmark symptoms, such as shortness of breath and chronic cough, often culminate in severe exacerbations frequently triggered by infections and environmental pollution [2, 3]. These recurring exacerbations accelerate the decline in lung function, significantly diminish quality of life, and increase mortality risk [4].

In addition to its lung-related effects, COPD is associated with systemic complications, including skeletal muscle dysfunction, osteoporosis, and mental health issues, notably depression and anxiety [5-8]. It affects approximately 10% of adults over the age of 40 and is responsible for over three million deaths annually, posing a substantial economic burden. Notably, the costs are largely driven by acute exacerbations [9-12]. With its prevalence increasing and its projected ranking as the third leading cause of death by 2030 [13], addressing the chronic inflammatory component of COPD is essential for enhancing management strategies [14, 15].

Chronic inflammation is a key element in the development of COPD and its systemic effects [15]. The inflammatory response in the lung parenchyma, primarily triggered by cigarette smoke, involves a persistent presence of inflammatory cells and mediators. This includes heightened levels of neutrophils and T lymphocytes causing tissue damage, accompanied by increased secretion of cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor

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necrosis factor-alpha (TNF-α) [16]. This inflammation, initially localized in the lungs, often extends systemically [17]. Evidence of this systemic spread is seen in the elevated levels of circulating cytokines and acute-phase reactants in COPD patients, suggesting a lung-originated low-grade systemic inflammation [18]. This concept of inflammation "spillover" is bolstered by studies, such as the one by Sinden et al. [19], showing strong positive correlations between sputum and plasma levels of cytokines like IL-6, C-reactive proteins (CRP), and TNF-α in COPD patients. Additionally, oxidative stress-induced reactive oxygen species contribute to the amplification of this inflammation [20]. Although the intensity of inflammation varies across different COPD subtypes, the systemic spread of lung inflammation impacts disease progression and associated conditions. Research into immunomodulatory therapies aims to address the critical role of inflammation in COPD [21]. Monitoring inflammatory biomarkers offers insights into disease activity and can aid in tailoring treatments specific to patient phenotypes. An essential aspect of managing COPD, including its pulmonary and systemic symptoms, is pulmonary rehabilitation (PR), a personalized treatment approach [22].

Pulmonary rehabilitation (PR) is a comprehensive intervention essential for managing stable COPD and post-acute exacerbation phases. It encompasses exercise training, education, nutritional advice, and personalized therapies [23]. PR aims to enhance physical and emotional functioning, foster sustainable healthy behaviors, and improve the overall well-being of those with COPD [23]. While numerous studies attest to PR's effectiveness in alleviating symptoms, boosting exercise tolerance, and improving life quality, its effects on systemic inflammation in COPD patients are not fully established [24]. Research presents conflicting findings: whereas acute exercise episodes might exacerbate inflammation [25], sustained regular training is suggested to have anti-inflammatory benefits by diminishing levels of cytokines like IL-6, CRP, and TNF-α [26]. This meta-analysis was conducted by our team to consolidate existing evidence on the influence of PR on inflammatory markers in COPD patients.

Our meta-analysis aimed to systematically compile and analyze data from various studies to assess the impact of pulmonary rehabilitation programs on inflammatory biomarkers, comparing levels before and after rehabilitation in patients with stable COPD or those recovering from COPD exacerbations.

## Material and method

This meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27].

### *Search strategies*

We conducted a detailed and systematic search to gather relevant studies. Our inclusion criteria were focused on randomized controlled trials (RCTs) and observational studies, providing a comprehensive perspective. We explored several electronic databases, including PubMed/MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science, Google Scholar, WanFang Data, and China National Knowledge Infrastructure. The search was completed by August 31st, 2023. We used key terms associated with "COPD", "Pulmonary Rehabilitation", "Exercise", "Physical Activity", and "Systemic Inflammation" or "Inflammatory Markers", employing Boolean operators like AND and OR for effective combination and search optimization. The search string for PubMed/MEDLINE was: ("COPD" OR "Chronic Obstructive Pulmonary Disease" OR "Chronic Obstructive Airway Disease" OR "Chronic Obstructive Lung Disease") AND ("Pulmonary Rehabilitation" OR "Exercise" OR "Physical Exercise") AND ("Systemic Inflammation" OR "Inflammation Status") AND ("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All Fields]). A similar, albeit simplified, approach was applied for databases like Google Scholar, WanFang Data, and China National Knowledge Infrastructure.

### *Inclusion and exclusion criteria*

Inclusion criteria were: 1) Longitudinal observational studies or RCTs published in English, Chinese, or other languages with accurate translations; 2) Original research involving COPD patients, including those with acute exacerbations; 3) Studies with a minimum of 8 weeks of pulmonary rehabilitation, primarily focused on exercise training, with detailed

descriptions of the training modality, intensity, and frequency; 4) Assessments of inflammatory markers, both serum and sputum, before and after the rehabilitation program; 5) Availability of adequate data for meta-analysis extraction.

Exclusion criteria included: 1) Animal studies; 2) Reviews, case reports, editorials, conference abstracts, or studies using secondary data; 3) RCTs lacking a control group; 4) Rehabilitation programs shorter than 7 weeks; 5) Studies without pre- and post-intervention inflammatory marker assessments; 6) Research involving patients with other respiratory diseases such as asthma, bronchiectasis, or cystic fibrosis.

*Screening process*

Our screening process involved two stages, meticulously designed to guarantee an objective and thorough evaluation of potential studies from the selected databases.

Stage 1: In the initial phase, two independent reviewers scrutinized the titles and abstracts of all articles retrieved. This step aimed to preliminarily assess the suitability of each study based on our predefined inclusion and exclusion criteria. Articles with titles and abstracts that did not provide enough information for a decisive eligibility determination were forwarded to the next stage for further assessment.

Stage 2: This phase involved a comprehensive review of the full-text articles. Any discrepancies in opinion between the reviewers were resolved through in-depth discussion and mutual agreement. If a consensus was not achievable, a third reviewer was brought in to facilitate a conclusive decision.

*Data extraction*

Upon completion of the screening, we extracted key data from each selected study. This included the study's title, first author's name, publication year, type of study, comprehensive details of the pulmonary rehabilitation program (encompassing frequency, intensity, duration, length, type, and setting), the inflammatory markers evaluated, and participant characteristics (like gender and average age). In instances where the original data appeared ambiguous or incomplete, we reached out directly to the corresponding author for clarification. Studies were subsequently excluded if we were unable to contact the authors or if the essential data remained unobtainable.

*Risk of bias assessment*

To evaluate the methodological quality and risk of bias in the included studies, we utilized established assessment tools. For the randomized controlled trials (RCTs), the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [28] was employed. This tool specifically examines bias related to the randomization process, adherence to intended interventions, missing outcome data, outcome measurement accuracy, and reporting of results.

For the observational studies, we applied the Cochrane Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool [29]. This tool assesses the risk of bias due to factors such as confounding, participant selection, intervention classification, deviations from planned interventions, missing data, outcome measurement, and result reporting. Two independent reviewers conducted the quality assessments, resolving any discrepancies through thorough discussion. For a study to be included, it needed to be deemed of fair to good quality and exhibit a low to moderate risk of bias. Studies assessed as poor quality or exhibiting a high risk of bias were excluded.

*Quality of evidence*

We assessed the quality of evidence using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework [30]. This system, applicable to both intervention and observational studies, categorizes the quality of evidence into four levels: high, moderate, low, or very low. This categorization considers factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias. In the case of RCTs, we initially considered the quality of evidence for each outcome as high. Conversely, for observational studies, the starting point was low quality due to their inherent bias potential. Two independent reviewers undertook the quality assessment, with any disagreements resolved through collaborative discussion. If a consensus was not achieved, a third reviewer was consulted for a definitive assessment.

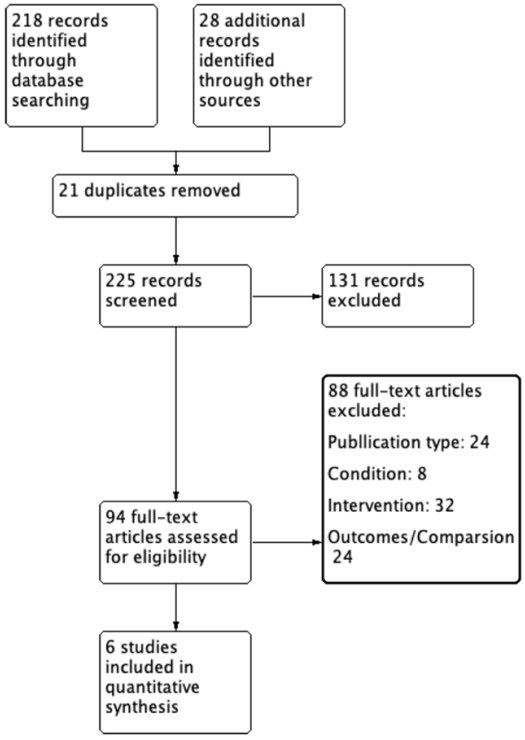


**Figure 1.** PRISMA flowchart illustrating the study selection process for the meta-analysis.

*Quantitative data synthesis*

For the synthesis of quantitative data, we utilized RevMan software (Review Manager Version 5.4, The Cochrane Collaboration, 2020). We calculated the mean difference (MD) for each inflammatory marker, comparing pre- and post-rehabilitation levels across studies. A pooled effect size was then derived using a random-effects model, allowing for the expected heterogeneity among studies. We extracted and descriptively summarized details about the pulmonary rehabilitation programs (including exercise modality, frequency, intensity, and duration) from each study. This summary was tabulated to provide clear insight into the rehabilitation specifics.

We assessed the statistical heterogeneity among the studies using the $I^2$ statistic. An $I^2$ value over 50% was indicative of significant heterogeneity. The chi-square test was used to ascertain statistical significance, with *p*-values less than 0.05 deemed significant. To further explore the results, subgroup analyses were conducted to compare different study designs (RCTs vs. Observational studies). Additionally, sensitivity analyses were performed by sequentially excluding studies to assess the robustness of our findings. To evaluate potential publication bias, characterized by a tendency to publish significant over nonsignificant findings, we visually inspected funnel plots. The threshold for the statistical significance of the overall effect sizes was established at $P<0.05$ [31].

## Result

*Study selection*

Our initial literature search identified 246 articles. Upon removal of 21 duplicates, we screened the titles and abstracts of 225 articles. This screening led to the exclusion of 131 studies due to irrelevance or ineligibility. We then conducted a thorough review of the full texts of the 94 remaining articles, assessing each against our pre-established inclusion and exclusion criteria. Throughout this process, any disagreements among the reviewers were resolved via discussion until consensus was reached. This detailed evaluation resulted in the exclusion of 88 additional articles. Ultimately, six studies [32-37] satisfied all eligibility requirements and were included in our quantitative synthesis. We summarized the study selection process and outcomes in a PRISMA flow diagram (**Figure 1**).

*Characteristics of included studies*

This meta-analysis incorporated six studies, consisting of four randomized controlled trials [32-35] and two longitudinal observational studies [36, 37], conducted between 2014 and 2022. These studies collectively enrolled 227 participants, with 147 of them being included in the analysis. The sample sizes of these studies ranged from 9 to 40 participants. The mean age of participants varied between 28 and 73 years. Although the original studies [32-37] examined a variety of inflammatory markers, our meta-analysis primarily focused on IL-6, CRP, and TNF-α due to their consistent measurement across the studies. It is important to note that not every study included all three markers; in some cases, only one or two were assessed, reflecting the diverse research goals and methodologies of the studies. The included COPD patients, both in treatment and control groups, were evaluated for these biomarkers before and after participating in pulmonary

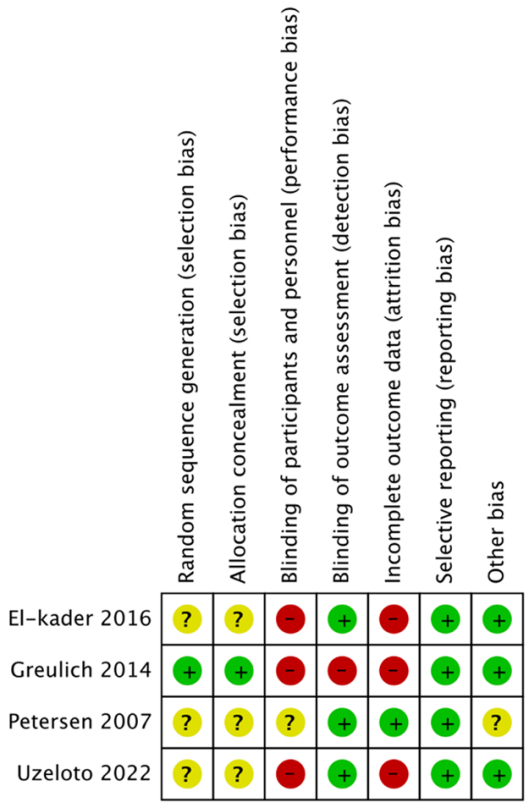


**Figure 2.** Risk of bias assessment for the included studies. Key: -: High risk of bias; +: Low risk of bias; ?: Unclear risk of bias.

rehabilitation programs. Comprehensive details on the study populations, specific components of the pulmonary rehabilitation programs, and the full range of inflammatory biomarkers analyzed in each original study, including those beyond the purview of this meta-analysis, are presented in **Table 1**.

*Quality assessment of included studies*

The quality assessment of the included studies is displayed in **Figure 2** for the 4 RCTs [32-35] and **Table 2** for the 2 observational studies [36, 37]. Overall, the RCTs exhibited some concerns regarding the risk of bias. Three RCTs [25, 32, 33] had unclear randomization and allocation concealment methods, and none blinded participants or personnel, raising the potential for selection and performance bias. One RCT [34] did not blinded outcome assessor. Three RCTs [32-34] had high dropout rates above 30%, increasing potential attrition bias. However, all 4 RCTs [32-35] scored well on reporting bias and assessed objective inflammatory biomarker outcomes. In summary, the RCTs [32-35] demonstrated a moderate to high risk of bias overall, primarily stemming from the lack of blinding. The 2 observational studies [36, 37] also showed some risk of bias. There was moderate risk from possible confounding factors, selection bias due to high dropout rates, and lack of blinding of outcome assessors. However, the observational studies [36, 37] clearly defined the intervention and had strengths in outcome reporting. Because of their design, observational studies have an inherent greater risk of bias versus RCTs. In total, the risk of bias of the included studies was moderate to high.

*Data synthesis of outcome measures*

Data synthesis demonstrated a significant increase in all three inflammatory markers following pulmonary rehabilitation (PR) versus control in COPD patients (**Figure 3**). This increase was unexpected and contrasts with previous studies that suggested PR might have anti-inflammatory effects. The finding raises new questions about the complex relationship between PR and systemic inflammation in COPD, which warrant further investigation.

*Interleukin-6 (IL-6):* Data from 5 studies [32-36] (n = 98) showed increased IL-6 with PR (standardized mean difference 0.44, 95% CI 0.17-0.70, P = 0.001), with substantial heterogeneity ($I^2$ = 88%).

*C-reactive protein (CRP):* Four studies [32, 34, 35, 37] (n = 118) revealed increased CRP after PR (SMD 0.56, 95% CI 0.31-0.81, P<0.00001), with substantial heterogeneity ($I^2$ = 93%).

*Tumor necrosis factor-alpha (TNF-α):* Four studies [32-35] (n = 84) demonstrated increased TNF-α with PR (SMD 0.41, 95% CI 0.12-0.70, P = 0.005), also with substantial heterogeneity ($I^2$ = 93%).

Additionally, sensitivity analyses were conducted to evaluate the impact of individual studies on the overall results. Notably, excluding the study by El-Kader (2016) markedly altered the outcomes, shifting the *p*-values for IL-6, CRP, and TNF-α to above 0.05, thus changing these results from significant to non-significant. This indicates that the observed increases in these biomarkers were predominantly influenced by

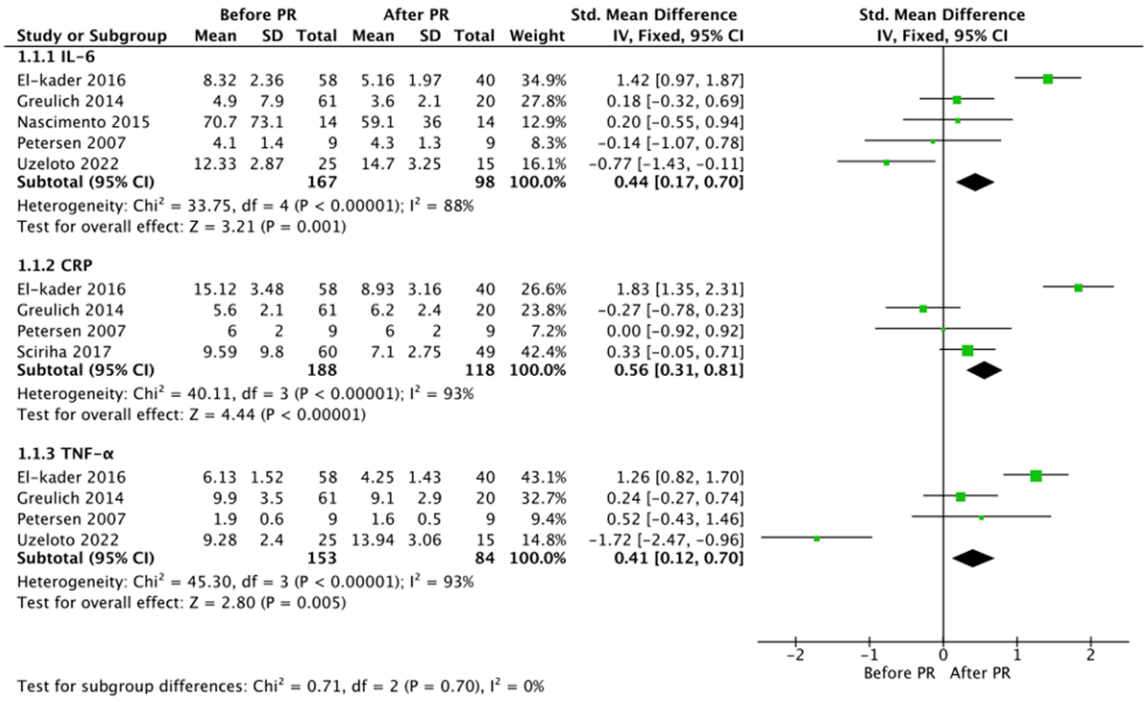


**Figure 3.** Forest plot of the standardized mean differences in inflammatory markers (IL-6, CRP, TNF-α) following pulmonary rehabilitation in COPD patients.

the El-Kader study. Without this study, the evidence suggesting a rise in inflammatory biomarkers following PR becomes considerably weaker.

*Grade evidence*

Our confidence in the estimated effects on the inflammatory biomarkers IL-6, CRP, and TNF-α is deemed moderate, primarily due to concerns regarding risk of bias and observed inconsistencies among the studies. These elements are crucial in determining the quality of evidence and, consequently, have a significant impact on the robustness of the conclusions drawn from the aggregated data. This assessment of evidence quality and its implications are detailed in **Table 3**.

## Discussion

This meta-analysis rigorously evaluated the impact of pulmonary rehabilitation (PR) on circulating inflammatory markers in patients with chronic obstructive pulmonary disease (COPD). Unexpectedly, we found that PR was associated with significant increases in IL-6, CRP, and TNF-α levels. This outcome starkly contrasts with an earlier systematic review that PR exerts anti-inflammatory effects [38]. Importantly, sensitivity analysis revealed that removing El-Kader et al. [32] from the dataset rendered these increases nonsignificant, highlighting the variability and heterogeneity within our findings.

The heterogeneity observed in our results is attributable to several factors. First, the included studies [32-37] in our meta-analysis demonstrated significant variations in the design of pulmonary rehabilitation (PR) programs, particularly in their duration, frequency, and modalities. Such diversity likely led to the varied inflammatory responses we observed. For example, one RCT [33] employing a high-intensity aerobic exercise program suggested a dose-response effect, indicating that more intensive aerobic PR might offer enhanced anti-inflammatory benefits. However, the moderate to high risk of bias in these studies [32-37], mainly due to issues like lack of blinding and high dropout rates, warrants a careful interpretation of these results.

Secondly, the variability among patient characteristics, including age, COPD severity, comorbidities, and baseline levels of inflammation,

**Table 1.** Characteristics of studies included in the meta-analysis of pulmonary rehabilitation effects on inflammatory markers

| Study | Study Design | Sample Size (Pre/Post-PR) | Age | PR Program Description | PR Program (Duration, Frequency, Length) | Inflammatory Biomarkers Measured | Outcome Measure |
|---|---|---|---|---|---|---|---|
| Nascimento et al., 2015 | Longitudinal observational study | 14/14 | 64.8 ± 5.1 | Warm up, aerobic walking, upper limb resistance exercises, stretching, relaxation | N/A, 3× a week, 8 weeks | IL-6, IL-8 | IL-6: no significant difference; CRP: not assessed; TNF-α: no significant difference |
| El-Kader et al., 2016 | RCT | 58/40 | 36.14 ± 4.79 | Treadmill aerobic exercise; and resistance exercises on gym machines | N/A, 3× a week, 12 weeks | TNF-α, IL-2, IL-4, IL-6, CRP | IL-6: significant difference; CRP: significant difference; TNF-α: significant decrease |
| Greulich et al., 2014 | RCT | 61/20 | 64.61 ± 9.02 | Gym-based individualized exercise training including endurance, strength, breathing exercises | 1 session per week for 12 weeks | CRP, WBC, IL-6, IL-8, TNF-alpha, PGC-1α, irisin | IL-6: no significant difference; CRP: no significant difference; TNF-α: no significant difference |
| Petersen et al., 2017 | RCT | 9/9 | 66 ± 2 | Endurance training (walking at 85% of maximum speed) twice weekly plus daily home-based endurance training. Ergometer cycling and conditioning exercises also performed during sessions | Endurance walking until exhaustion, cycling until exhaustion; 2× weekly + daily home training; 7 weeks | CRP, IL-6, IL-18, TNF-α, TNF receptor 1 | IL-6: no significant difference; CRP: no significant difference; TNF-α: no significant difference |
| Sciriha et al., 2017 | Longitudinal observational study | 60/49 | 66 ± 7.76 | Treadmill walking, step-climbing, arm ergometry, cycling, upper and lower limb strengthening exercises, and inspiratory muscle training | 2 hrs, 2× per week, 12 week program | CRP, ESR, SAA, NO, eosinophils, neutrophils, WBC | IL-6: not assessed; CRP: no significant difference; TNF-α: not assessed |
| Uzeloto et al., 2022 | RCT | 25/15 | 68 ± 5.96 | Aerobic training on treadmill at 80% of 6MWT, resistance training of upper and lower limbs at 60% of 1RM. Breathing exercises including inhalation therapy, pulmonary deflation techniques, diaphragmatic awareness, and inspiratory muscle exercises | 8 weeks, 3 times a week, 8 weeks | IL-8, IL-13, IL-17, IL-6, IL-2, IL-10, TNF-α in CD4+ T lymphocytes | IL-6: no significant difference; CRP: not assessed; TNF-α: significant difference |

PR = Pulmonary Rehabilitation; RCT = Randomized Controlled Trial; IL-6 = Interleukin-6; CRP = C-Reactive Protein; TNF-α = Tumor Necrosis Factor alpha; WBC = White Blood Cell Count; PGC-1α = Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ESR = Erythrocyte Sedimentation Rate; SAA = Serum Amyloid A; NO = Nitric Oxide; 6MWT = 6-Minute Walk Test; 1RM = One Repetition Maximum.

**Table 2.** Assessment of risk of bias in non-randomized studies using the cochrane risk of bias in non-randomized studies of interventions (ROBINS-I) tool

| Study | Bias due to Confounding | Bias in Selection of Participants | Bias in Classification of Interventions | Bias due to Deviations | Bias due to Missing Data | Bias in Measurement of Outcomes | Bias in Selection of Reported Result |
|---|---|---|---|---|---|---|---|
| Nascimento 2015 | Moderate risk | Serious risk | Low risk | Moderate risk | Serious risk | Moderate risk | Low risk |
| Sciriha 2017 | Moderate risk | Low risk | Low risk | Low risk | Low risk | Moderate risk | Low risk |

**Table 3.** Grade of recommendations assessment, development and evaluation (GRADE) evidence quality for each outcome

| Outcome | Number of Studies | Limitations | Inconsistency | Indirectness | Imprecision | Publication Bias | Quality of Evidence |
|---|---|---|---|---|---|---|---|
| IL-6 | 5 | Serious due to lack of blinding and heterogeneity | Serious $I^2$ = 86% | No serious concerns | No serious concerns | No serious concerns | Moderate⊕⊕⊕ |
| CRP | 4 | Serious due to lack of blinding and heterogeneity | Serious $I^2$ = 91% | No serious concerns | No serious concerns | No serious concerns | Moderate⊕⊕⊕ |
| TNF-α | 4 | Serious due to lack of blinding and heterogeneity | Serious $I^2$ = 91% | No serious concerns | No serious concerns | No serious concerns | Moderate⊕⊕⊕ |

Moderate Quality (⊕⊕⊕): The evidence is moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

significantly influenced the study outcomes. Furthermore, methodological differences in measuring inflammatory markers and the inclusion of observational studies introduced additional layers of variability. These observational studies might have incorporated uncontrolled confounding factors such as dietary habits, smoking status, and medication use, all of which could further contribute to the observed heterogeneity.

The results of our meta-analysis present a challenge to the widely accepted idea that exercise has a uniform anti-inflammatory effect in COPD cases. Although exercise is generally acknowledged for its anti-inflammatory properties, marked by an increased antioxidant capacity [26], it can also lead to a transient spike in inflammatory markers [39]. This temporary increase could mask the long-term adaptations that exercise induces. The substantial heterogeneity observed in our study underscores the need for more standardized research methodologies. This situation emphasizes the critical need for rigorously designed, standardized RCTs to more robustly establish the effects of PR on inflammation among COPD patients.

*Clinical implications*

The observed elevation in inflammatory markers post-pulmonary rehabilitation (PR) in COPD patients necessitates a nuanced interpretation. These results could prompt healthcare professionals to closely monitor inflammatory markers when initiating PR, acknowledging that while short-term increases are noted, their clinical relevance is yet to be fully understood. This variation in outcomes points to the possibility of customizing PR programs to individual needs, factoring in each patient's inflammatory profile, comorbidities, and lifestyle. This approach seeks to balance the short-term fluctuations in specific inflammatory markers with the broader, long-term health benefits PR offers in managing COPD. Moreover, clear communication about these potential short-term inflammatory responses, coupled with the anticipated long-term advantages of PR, is crucial. This should involve a collaborative effort among various healthcare providers, including physiotherapists and pulmonologists. Ultimately, our findings emphasize the ongoing need for research, the translation of evidence into practice, and the careful consideration of transient increases in inflammatory markers against the established long-term benefits of PR in COPD management.

*Future research directions*

For future endeavors, research should aim to validate or challenge our findings via meticulously planned randomized controlled trials (RCTs) that utilize standardized pulmonary rehabilitation (PR) protocols. A focus on comparative effectiveness research would be beneficial, particularly examining the impacts of varying PR durations, frequencies, and modalities. Additionally, a more extensive exploration into the long-term effects of PR, assessing a wider range of inflammatory markers, is crucial. Such studies would not only provide deeper insights but also help clarify the underlying biological mechanisms at play in PR's influence on systemic inflammation in COPD patients.

*Limitations*

This meta-analysis is subject to several limitations that warrant consideration. Firstly, focusing on only three inflammatory biomarkers may not fully capture the complexity of the inflammatory response in COPD. Including a wider range of markers from the original studies could have provided a more detailed understanding. Additionally, the observed increase in these biomarkers might have been influenced by methodological biases, such as the absence of blinding, high dropout rates, and variations in PR protocols, all contributing to the heterogeneity of the results and necessitating a cautious interpretation.

Furthermore, the exclusion of unpublished studies and research not published in English and Chinese could have introduced publication bias. The marked statistical heterogeneity observed in this analysis is likely due to differences in COPD patient populations and study designs. The presence of residual confounding factors in the observational studies could also have affected our findings. Lastly, the limited number of studies included restricted our ability to conduct extensive subgroup analyses and meta-regression to further investigate the sources of heterogeneity. These methodological constraints and the observed heterogeneity

are critical factors to consider, as they may have significantly influenced the noted increase in inflammatory markers, underscoring the need for a prudent interpretation of the results.

In summary, our meta-analysis has shed light on the complex and multifaceted relationship between inflammation and exercise in the context of COPD. The unexpected rise in inflammatory markers following pulmonary rehabilitation (PR) introduces new avenues for research and inquiry. However, it is crucial to consider the limitations of this analysis, including potential biases, the heterogeneity of the data, and methodological constraints, which might temper the widespread applicability of our findings. Despite these challenges, the study provides valuable insights and lays the groundwork for future research. It emphasizes the need for more detailed and rigorous investigations, particularly well-controlled trials, to fully understand PR's effects on systemic inflammation in COPD patients. Such research is essential for refining PR approaches to effectively manage both the pulmonary and systemic aspects of COPD. This meta-analysis, therefore, represents an important step towards a deeper understanding of these complex interactions and their implications for COPD treatment strategies.

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Jianhua Li, Department of Rehabilitation, School of International Medical Technology, Shanghai Sanda University, No. 2727, Jinhai Road, Shanghai 201209, China. Tel: +86-13651809012; E-mail: 805892636@qq.com

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