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The effects of aerobic exercise training on inflammatory markers in adult tobacco smokers: A systematic review and meta-analysis of randomized controlled trials

Morteza Ghojazadeh [a,1], Hadi Pourmanaf [b,1], Vahid Fekri [b], Saeid Nikoukheslat [b], Yasmin Nasoudi [c], Dean E. Mills [d,e,f,*]

[a] Road Traffic Injury Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Faculty of Physical Education and Sport Sciences, University of Tabriz, Tabriz, Iran
[c] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[d] School of Health and Medical Sciences, University of Southern Queensland, Ipswich, Queensland, Australia
[e] Respiratory and Exercise Physiology Research Group, School of Health and Medical Sciences, University of Southern Queensland, Ipswich, Queensland, Australia
[f] Centre for Health Research, Institute for Resilient Regions, University of Southern Queensland, Ipswich, Queensland, Australia

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ABSTRACT

Introduction: Aerobic exercise training may reduce systemic inflammation, but the effects of this on systemic inflammatory markers in adult tobacco smokers has not been systematically reviewed. Therefore, we evaluated the effects of aerobic exercise training on C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α) in adult tobacco smokers using a systematic review and meta-analysis of randomized controlled trials.
Methods: A comprehensive literature search was carried out using PubMed/Medline, Web of Science, EMBASE, Google Scholar, and hand search of bibliographies of the retrieved English or Persian articles up to August 2023. This review only included randomized controlled trials which investigated the effect of aerobic exercise training on CRP and TNF-α in adult smokers, based on a predefined inclusion and exclusion criteria.
Results: A total of 1641 articles were identified. Six studies were included in the review and four evaluated CRP and two evaluated TNF-α in only males. The meta-analysis demonstrated that aerobic exercise training significantly decreased TNF-α concentrations in males (MD = −6.68, 95 % CI = −13.90 to −0.54, $P = 0.05$). CRP concentrations did not decrease significantly when the data from the four studies were pooled (MD = −0.17, 95 % CI = −0.37 to 0.03, $P = 0.09$).
Conclusion: Aerobic exercise training may reduce the concentration of TNF-α in male smokers, but it does not have a significant effect on CRP concentrations. However, these findings are based upon a small number of studies, that enrolled either exclusively male or female participants, and further investigation is necessary to increase statistical inference.

1. Introduction

Tobacco smoking is one of the most important public health problems and while global smoking prevalence has fallen, it is still common in many countries and causes a significant health burden worldwide [1]. More than 8 million deaths per year were directly attributable to tobacco use or from exposure to tobacco smoke, and at least 1 billion people are expected to die from tobacco use in the 21st century [1,2]. Tobacco smoking causes chronic inflammation, fibrosis, and an imbalance between proteolytic and anti-proteolytic activity, oxidative stress, and apoptosis [3]. The pulmonary system is most affected by the toxic components of tobacco smoking, which causes altered mucosal permeability and pulmonary epithelial and cell membrane destruction [4,5]. These changes can lead to diseases including lung cancer and chronic obstructive pulmonary disease [5–7].

Inflammation is the body's protective response to prevent the effects of microorganisms or toxins on cells, to remove infarction and necrotic tissue resulting from injury, and to support organismal growth [3].

* Corresponding author. University of Southern Queensland, Room P214A, 11 Salisbury Road, Ipswich, Queensland, 4305, Australia.
E-mail address: dean.mills@unisq.edu.au (D.E. Mills).
[1] These authors have contributed equally.

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Inflammatory mediators, including tumor necrosis factor-α (TNF-α), interleukin (IL-) IL-6, C-reactive protein (CRP), and inflammatory cells including macrophages, neutrophils, and lymphocytes, are released from epithelial and smooth muscle cells by smoking and initiate the inflammatory process [5,8]. Additionally, harmful substances enter the bloodstream through capillaries and alveoli. These toxins are recognized by receptors in the immune system, which then trigger nuclear factor kappa B (NF-kB) in the bloodstream to start the inflammatory process [4]. By promoting the expression of genes for inflammatory markers including IL-6 and TNF-α, NF-kB play an important role in initiating inflammation [9].

Several pharmacological therapies have been proposed to combat inflammation in its early stage, but these may have undesirable side effects [10,11]. For instance, cyclooxygenase (COX)-2 inhibitors prevent the production of prostaglandin D2 and reduce inflammation. However, long-term use of these inhibitors is associated with a prolonged inflammatory response and cardiac side-effects [12,13]. Therefore, it has been suggested that non-pharmacological interventions, such as maintaining a healthy diet and engaging in exercise and physical activity may help to reduce inflammation [10,14,15]. Although smoking cessation is the primary method to reduce systemic inflammation in tobacco smokers, aerobic exercise training may reduce the concentration of various inflammatory markers in smokers, indicating an effect on systemic inflammation [5,16,17]. Aerobic exercise training regulates inflammation through the reduction of pro-inflammatory monocytes ($CD14^+$ and $CD16^+$) and the release of anti-inflammatory cytokines including IL-8 and IL-10 [18–20]. In spite of these findings, the evidence is contradictory, and some studies have failed to find a reduction in systemic inflammatory markers in tobacco smokers following aerobic exercise training [21,22]. To date, no systematic review has evaluated the response of systemic inflammatory markers to aerobic exercise training in tobacco smokers.

Therefore, we evaluated the effects of aerobic exercise training on the inflammatory markers CRP and TNF-α in adult tobacco smokers using a systematic review and meta-analysis of randomized controlled trials.

2. Methods

The study employed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines to assess the effects of aerobic exercise training on the systemic inflammatory markers CRP and TNF-α in adult tobacco smokers compared to a control group who did not undertake aerobic exercise training. The protocol of the study was registered in PROSPERO (ID: CRD42024520359).

2.1. Search strategy

A comprehensive literature search was carried out using PubMed/Medline, Web of Science, EMBASE, and Google Scholar, as well as hand search of bibliographies of the retrieved English or Persian articles up to March 2023. Medical subject headings (MeSH) were used to search for controlled vocabulary terms and text words. The main terms of the review were: smoker, water pipe, exercise, physical activity, physical exercise, aerobic exercise, exercise training, run, walk, inflammation, inflammatory factor, cytokine, myokine.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Study Type: This review included only randomized controlled trials that were published after peer review up to August 2023; (2) Population: The study population consisted of adult male or female tobacco smokers; (3) Intervention: The experimental group had to undertake any form of aerobic exercise training for at least 4 weeks, with 2 or more sessions per week; (4) Control: The control group consisted of adult male or female tobacco smokers who did not receive any intervention (exercise, supplement, etc.); and (5) Outcomes: This review included studies with available data on CRP or TNF-α concentrations. The final inclusion of studies was determined by two independent reviewers (HP and DM). In cases where studies were reported in multiple articles, data abstraction was performed using all available articles, but only one report was included in our systematic review. The articles meeting any of the following criteria were excluded: (1) review articles, case reports, and conference abstracts; (2) animal studies; (3) articles that were inaccessible after two attempts to request the paper from the corresponding author; (4) articles with unclear data descriptions; and (5) non-randomized trials.

2.3. Selection process

All searched citations were imported into an EndNote library, to remove duplicated records. Then, two reviewers (VF and YN) independently screened the titles, abstracts, and keywords, and determined the articles to be included according to the inclusion and exclusion criteria. The results of the screening were then discussed, and articles related were selected that were relevant to this topic. Differences of opinion between two reviewers were resolved by further reviewers (MG and HP). After reading the full text of the remaining studies, the final list of articles was included in the present review.

2.4. Literature quality assessment

Two authors independently (HP and SN) assessed the quality of each included study using the Cochrane risk of bias tool in Review Manager 5.4 [23]. The tool focused on seven items: (1) randomized sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other biases. In case of any discrepancies, there was a third-party referee (MG).

2.5. Data extraction

Data extraction commenced after the quality assessment was completed. Full text articles were used in order to extract the data. Two authors performed the data extraction from the text, figures, and tables, independently (SN and YN). The following data were extracted: first author; publication date; number of participants and sex; age of participants; duration of smoking; type of exercise; frequency of exercise; intensity of exercise; duration of exercise; and outcome findings. When essential data were missing in the text, the authors of the original studies were contacted.

2.6. Statistical analysis

A meta-analysis was performed to determine the change in CRP and TNF-α concentrations from baseline to post-intervention. The standardized mean difference (SMD) between the experimental and control groups was calculated, along with a 95 % confidence interval (CI). If two or more studies measured the same outcome and provided data in a format suitable for pooling, the data were pooled for the meta-analysis. The trial used the I^2 ($I^2 = 100\ \% \times (Q - df)/Q$) method to assess heterogeneity between studies. Heterogeneity was considered to be present if I^2 was greater than 50 %. The systematic meta-analysis was performed using Review Manager 5.4 software (version 5.4) and data analysis was carried out using the Random Effect Model. Statistical significance was set at $P \leq 0.05$.

3. Results

3.1. Description of studies

Fig. 1 shows the PRISMA flowchart of the review. A total of 1641

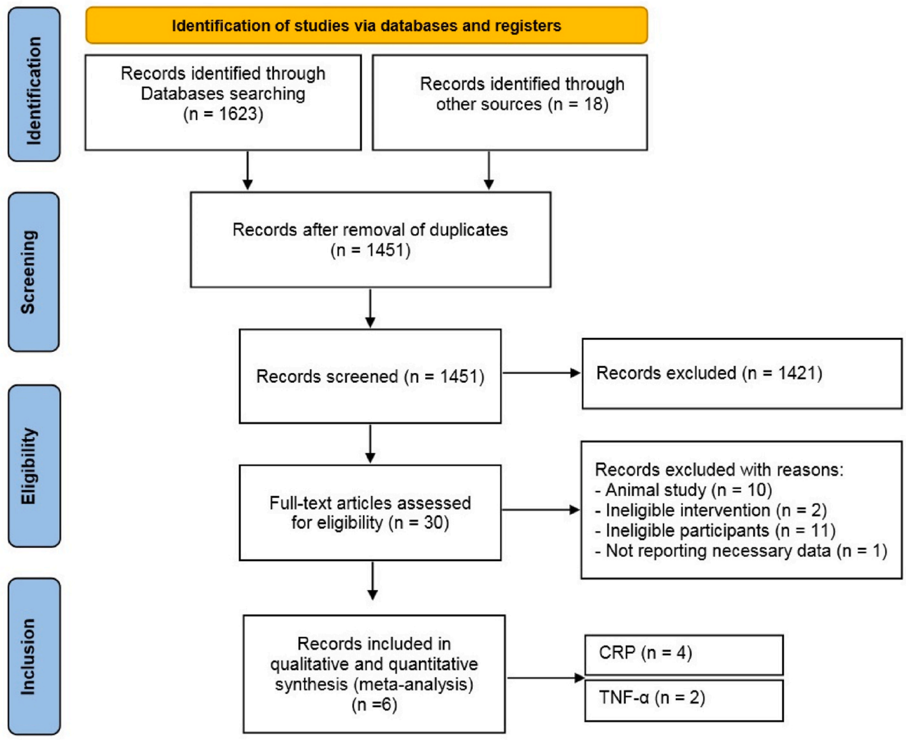

Fig. 1. PRISMA flow chart for search and selection of the included studies. CRP, C-reactive protein; IL-6, interleukin-6.

articles were identified through database searching and other sources and all searched citations were imported into an EndNote library. After excluding duplicate records (190 articles), 1451 articles remained for screening. At the first screening, 1421 articles were excluded due to irrelevant purposes, unclear indicators, review articles, case reports, and conference abstracts, as determined by their titles, abstracts, and keywords. Abstracts were obtained for the remainder of the 30 articles which were potentially relevant. Subsequently, the full text of the articles was carefully reviewed. 24 studies were excluded: 10 studies were conducted on animals [24–33], 11 studies used ineligible participants [34–44], two studies applied ineligible interventions [45,46], and one study did not report necessary data [47]. Finally, six studies were included in the systematic review and meta-analysis according to the inclusion and exclusion criteria [5,17,21,22,48,49].

Table 1
Characteristics of included studies.

Author (year)	Sample size		Age (years)	Smoking duration (years)	Aerobic exercise training				Results
	Total (Male/ Female)	Exe/ Con			Type	Frequency	Intensity	Duration (min)	
Barzegari, H. et al. (2018) [48]	20 (20/0)	Exe: 10 Con: 10	Exe: 25 ± 3 Con: 26 ± 3	NR	Running	3 sessions per week for 4 weeks	HRR: 55–65 %	20	↓ Serum CRP concentration
Laleh, B. et al. (2013) [17]	30 (30/0)	Exe: 15 Con: 15	Exe: 42 ± 5 Con: 41 ± 5	At least 3	Treadmill walking and stationary cycling	3 sessions per week for 12 weeks	HR_{max}: 60–80 %	50–65	↓ Serum TNF-α concentration
Eizadi, M. et al. (2016) [22]	36 (36/0)	Exe: 18 Con: 18	Exe: 42 ± 4.8 Con: 41 ± 3.9	At least 3	Running and group exercise	3 sessions per week for 12 weeks	HR_{max}: 60–80 %	45–60	↔ Serum CRP concentration
Hammett, CJK. et al. (2006) [21]	88 (0/88)	Exe: 48 Con: 40	Exe: 38 ± 12 Con: 39 ± 11	At least 2	Treadmill, cycle, or rowing ergometry	3 sessions per week for 6 weeks	HR_{max}: 60–70 %	45	↔ Serum CRP concentration
Nikniaz, L. et al. (2021) [5]	20 (20/0)	Exe: 10 Con: 10	Exe: 31 ± 4 Con: 32 ± 4	At least 1	Running	3 sessions per week for 4 weeks	HR_{max}: 50–70 %	30	↓ Serum TNF-α concentration
Saremi, A. et al. (2022) [49]	21 (0/21)	Exe: 11 Con: 10	Exe: 28 ± 3 Con: 27 ± 4	At least 2	Treadmill running	3 sessions per week for 8 weeks	HR_{max}: 30–65 %	35–50	↓ Serum CRP concentration

NR, not reported; Exe, exercise; Con, Control; HR_{max}, maximum heart rate; HRR, heart rate reserve; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α.

3.2. Characteristics of included studies

Table 1 reports the characteristics of the studies included. A total of 215 sedentary smokers (male = 106 and female = 109) aged 18–65 years participated in these six studies. Of the six studies, four evaluated CRP [21,22,48,49] and two evaluated TNF-α [5,17]. The four studies that evaluated CRP concentrations consisted exclusively of either male [22,48] of female [21,49] participants. The two studies that evaluated TNF-α concentrations consisted of only male [5,17] participants. The publication date of the studies was between 2006 and 2022. Participants in five of the studies [5,17,21,22,48] were cigarette smokers and participants in one study were hookah (pipe) smokers [49]. The participants had smoked for at least 1 year. The intervention groups used different types of aerobic exercise training, including outdoor running [5,22,48], treadmill running [17,21,49], cycle ergometry [21], and rowing ergometry [21]. The duration of the exercise was between 20 and 65 min and the intensity was between 30 and 80 % of maximum heart rate. The duration of the interventions varied between four and twelve weeks.

3.3. Risk of bias of the included studies

The risk of bias in the included studies is shown in Fig. 2. The majority of studies had a low risk of bias in random sequence generation, blinding of outcomes assessment, incomplete outcome data, and selective reporting. However, most of the studies included had a high risk of bias in allocation concealment and blinding of participants and personnel.

3.4. Meta-analysis

3.4.1. Heterogeneity

There was no significant between-study heterogeneity for CRP (Tau^2 = 0.01, Chi^2 = 4.37, df = 3, P = 0.22, I^2 = 31 %) and TNF-α (Tau^2 = 0.00, Chi^2 = 0.05, df = 1, P = 0.82, I^2 = 0 %).

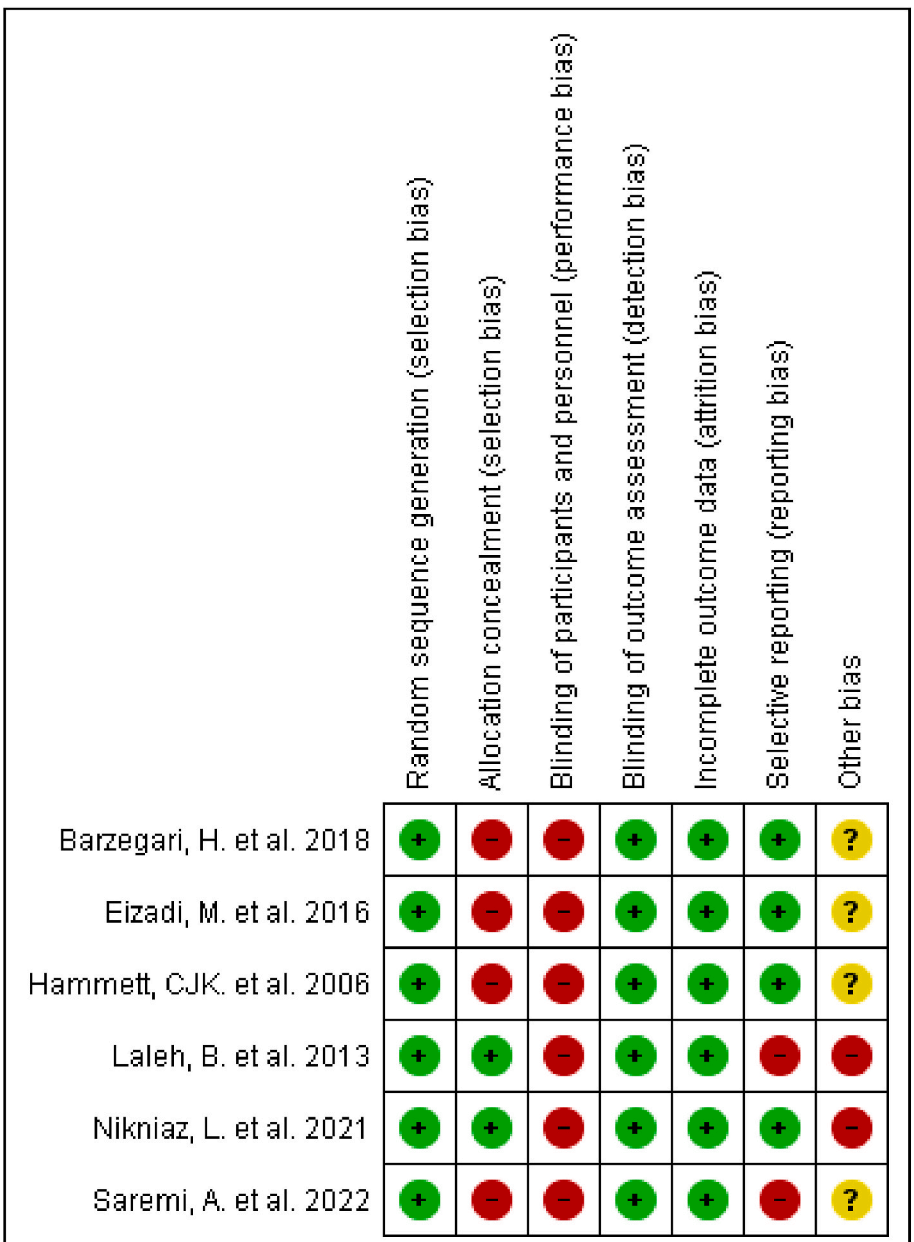

Fig. 2. Risk of bias in the included studies.

3.4.2. C-reactive protein

Mean and standard deviation (SD) was used to report pre- and post-aerobic exercise training data in three studies [22,48,49], and median (range) was used in one [21]. Two [48,49] of the four studies [21,22] showed a significant decrease in the concentration of CRP after aerobic exercise training compared with the control group, while the other two studies did not report a significant change in CRP. The meta-analysis also showed that aerobic exercise training did not significantly reduce CRP concentrations (MD = −0.17, 95 % CI = −0.37 to 0.03, $P = 0.09$) (Fig. 3).

Post-hoc subgroup analysis by sex revealed no significant difference in CRP concentrations ($P = 0.32$) after aerobic exercise training between females (Female: MD = −0.07, 95 % CI = −0.34 to −0.18, $P = 0.04$) and males (male: MD = −0.55, 95 % CI = −1.40 to 0.30, $P = 0.20$), but females experienced a significant reduction in CRP after aerobic exercise training (Fig. 4).

Post-hoc subgroup analysis also revealed no difference in the concentration of CRP ($P = 0.53$) after aerobic exercise training between the shorter (<8 weeks: MD = −0.41, 95 % CI = −1.22 to 0.40, $P = 0.32$) and the longer (≥8 weeks: MD = −0.15, 95 % CI = −0.30 to −0.01, $P = 0.04$) duration of the intervention, but aerobic exercise training for 8 weeks or longer significantly decreased CRP concentrations in tobacco smokers (Fig. 5).

3.4.3. Tumor necrosis factor-α

Mean and SD was used to report pre- and post-aerobic exercise training data in the two studies [5,17]. Compared with a control group, both studies reported a significant decrease in TNF-α concentrations after aerobic exercise training. The differences between aerobic exercise training and control groups in male smokers were also significant (MD = −6.68, 95 % CI = −13.81 to −0.08, $P = 0.05$) when the data from these two studies were pooled (Fig. 6).

4. Discussion

4.1. Main findings

The aim of this systematic review and meta-analysis was to evaluate the effects of aerobic exercise training on the systemic inflammatory markers CRP and TNF-α in adult tobacco smokers. Out of 1641 articles, six studies, with a total of 215 (male: 106 and female: 109) adult tobacco smokers, had necessary information to be included in this systematic review and meta-analysis. This is the first systematic review and meta-analysis to report that aerobic exercise training may reduce the concentration of TNF-α in male smokers, but it does not have a significant effect on CRP concentrations.

4.2. Tumor necrosis factor-α

Out of the six studies included, two evaluated serum TNF-α concentrations between the aerobic exercise training group and the control group in adult male tobacco smokers. Both studies found a significant reduction in TNF-α concentrations after aerobic exercise training compared with the control group. Further, the meta-analysis showed a significant decrease in TNF-α concentrations when the data from these two studies were pooled. However, it should be noted that this finding is based upon only two studies that consisted exclusively of male participants. Previous systematic reviews and meta-analyses have reported that regular aerobic exercise training can reduce inflammation in overweight and obese individuals [18] and in healthy middle-aged and older adults [50]. There is also a reduction in inflammatory markers after aerobic exercise training in mice exposed to chronic smoking [25,27,31]. Aerobic exercise may reduce inflammation through anti-inflammatory myokines including IL-10, which are released during muscle contraction [31]. These myokines reduce tissue damage due to inflammation and may limit the effects of pro-inflammatory cytokines CRP, TNF-α, and IL-6 [51] that have been linked to systemic inflammation [18].

4.3. C-reactive protein

Out of the six studies included in this systematic review, four compared serum CRP concentrations between the aerobic exercise training group and the control group in adult smokers. Two studies reported a significant reduction in CRP after aerobic exercise training, but the two others found no significant changes. The results of our meta-analysis demonstrated that aerobic exercise training does not reduce CRP concentrations in adult smokers. However, the post-hoc subgroup analysis revealed that studies with an aerobic exercise training duration of 8 weeks or more had a significant reduction in CRP concentrations. Possibly, a longer duration of aerobic exercise training (8 weeks or more) is required to reduce CRP concentrations in adult smokers, but to confirm this, studies comparing longer and shorter intervention periods are needed. In the post-hoc subgroup analyses, females experienced a significant decrease in serum CRP concentrations after the aerobic exercise training compared with the control group and it has been suggested that the sex differences should be studied because sex hormones can affect CRP [52]. However, it should be noted that these findings are based upon only four studies that consisted exclusively of either male [22,48] of female [21,49] participants.

4.4. Limitations

The limitations of this systematic review and meta-analysis should be considered when interpreting the results. First, the frequency, type, intensity and duration of aerobic exercise training varied between the included studies. Second, other inflammatory markers including IL-6, IL-8 and IL-10 were not included in the meta-analysis because there were not enough studies evaluating them. Third, with regard to the specificity of the intervention, performance bias may be unavoidable in aerobic exercise interventions because it may not be possible to blind participants and exercise trainers. Fourth, a search of the literature revealed only two studies that examined serum TNF-α concentrations after aerobic exercise in adult male smokers only. Consequently, further studies are required to conclude definitively whether TNF-α concentrations are reduced after aerobic exercise training. Fifth, we performed post-hoc subgroup analysis by sex and exercise duration with limited studies. These results should be therefore considered exploratory. In particular,

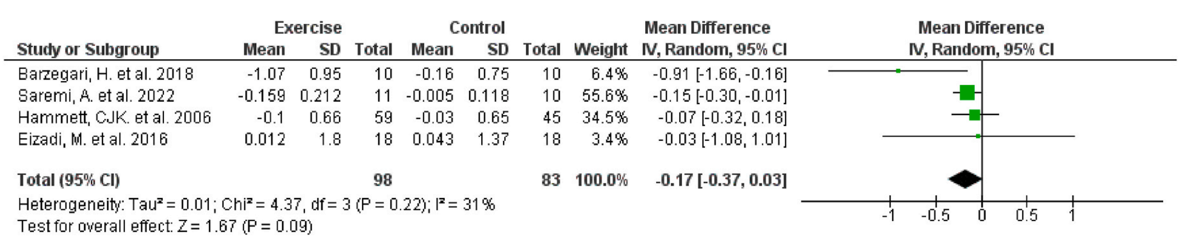

Fig. 3. Forest plots of the effect of aerobic exercise training on C-reactive protein in adult smokers compared with the control group.

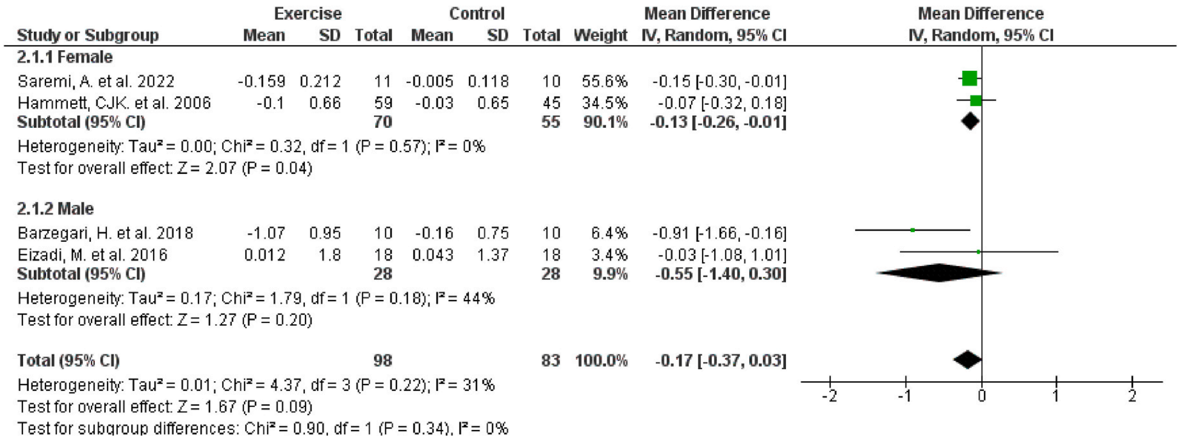

Fig. 4. Post-hoc subgroup analysis of the effect of sex on C-reactive protein in adult smokers.

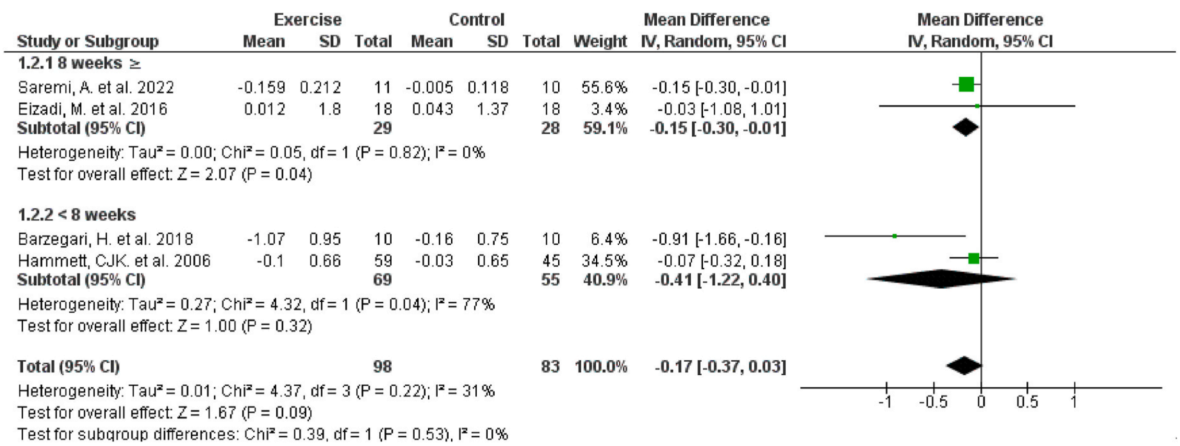

Fig. 5. Post-hoc subgroup analysis of the effect of the duration of the intervention on C-reactive protein in adult smokers.

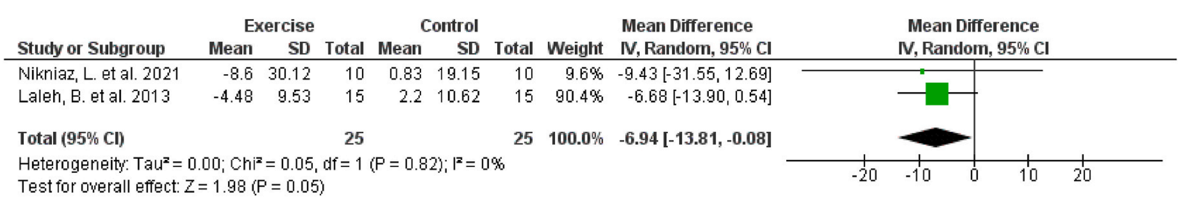

Fig. 6. Forest plots of the effect of aerobic exercise training on tumor necrosis factor-α in adult male smokers compared with the control group.

subgroup differences by sex could actually be due to study differences, since the studies enrolled exclusively males or female participants. It is recommended that further clinical studies be conducted in order to make definitive statements about the observed results. Finally, only published articles in English or Persian were included in this review.

5. Conclusion

The aim of this systematic review and meta-analysis was to evaluate the effects of aerobic exercise training on the systemic inflammatory markers CRP and TNF-α in adult tobacco smokers. Out of 1641 articles, six studies, with a total of 215 (male: 106 and female: 109) adult smokers, had necessary information to be included in this systematic review and meta-analysis. We found that aerobic exercise training may reduce the concentration of TNF-α in male smokers, but it does not have a significant effect on CRP concentrations. However, these findings are based upon a small number of studies, that enrolled either exclusively male or female participants, and further investigation is necessary to increase statistical inference.

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Data availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Morteza Ghojazadeh: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hadi Pourmanaf:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Vahid Fekri:** Writing – review & editing, Data curation. **Saeid Nikoukheslat:** Writing – review & editing, Data curation. **Yasmin Nasoudi:** Writing – review & editing, Data curation. **Dean E. Mills:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflict of interests.

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