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REVIEW ARTICLE

Effect of exercise interventions on cytokines and myokines in human tobacco smokers: A systematic review

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ABSTRACT

Tobacco smoking causes ongoing low-level inflammation, shown by higher levels of pro-inflammatory cytokines like CRP, IL-6, and TNF-alpha. Physical exercise can help reduce inflammation, but its effects in human smokers remain unclear. Objective: This review aimed to identify and assess studies published from 2000 to 2026 involving human smokers, using exercise as the primary intervention, and measuring at least one cytokine or myokine. Methods: We searched five databases following PRISMA 2020 guidelines. Studies had to include human smokers, use exercise as the main intervention, and measure at least one cytokine or myokine. Systematic reviews and meta-analyses were excluded. Eight studies met these criteria and were rated for quality using the PEDro scale. Results: The eight included studies (n = 346 smokers; 2006–2022; Australia, Iran, New Zealand) examined training programs (4–12 weeks) or single exercise sessions. They measured TNF-alpha, IL-6, CRP, IL-10, IL-1beta, IL-1ra, MCP-1, CC16, and SP-D. Aerobic training lowered TNF-alpha and IL-6 in male smokers, but CRP results varied by sex and smoking type. Acute exercise increased TNF-α and IL-6 more in smokers than in non-smokers. IL-10 increased after training. Aerobic training with vitamin D reduced lung-specific proteins (CC16, SP-D). Conclusion: Within a small, heterogeneous evidence base, aerobic training appears to lower pro-inflammatory cytokines, particularly TNF-alpha and IL-6, in male smokers. CRP results are mixed and seem to depend on sex and smoking type. Acute exercise may amplify cytokine responses, possibly reflecting tobacco-related immune changes. These findings are preliminary and more large studies are needed to confirm them.

Keywords: Exercise, Tobacco smoking, Cytokines, Myokines, CRP, TNF-alpha, IL-6, Inflammation, Smokers, Systematic review, PRISMA 2020, Experimental study.

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INTRODUCTION

Tobacco smoking is the leading preventable cause of death worldwide, causing over 8 million deaths each year (WHO, 2023). Beyond its well-established carcinogenic effects, chronic tobacco use induces a persistent state of low-grade systemic and pulmonary inflammation that is now recognized as the primary pathophysiological mechanism linking smoking to its most prevalent comorbidities. Components of tobacco smoke activate pattern recognition receptors (TLR2/TLR4) and, through NF-κB signalling and oxidant-driven inflammasome activation, increase the transcription and release of pro-inflammatory cytokines, while chronic nicotine exposure blunts cortisol-mediated anti-inflammatory feedback (Yanbaeva et al., 2007; Madani et al., 2018). For the purposes of this review, the relevant consequence of these pathways is a sustained elevation in circulating and pulmonary cytokines that exercise may modulate.

The resulting inflammatory setting is characterised by significantly elevated circulating concentrations of C-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-8 (IL-8), and monocyte chemoattractant protein-1 (MCP-1), as well as reduced levels of anti-inflammatory mediators such as IL-10 and IL-1 receptor antagonist (IL-1ra) (Yanbaeva et al., 2007; Madani et al., 2018). Clinically, these cytokine elevations are not merely laboratory findings: elevated TNF-α and IL-6 contribute directly to accelerated skeletal muscle catabolism and reduced exercise tolerance in smokers; elevated CRP and MCP-1 drive atherosclerotic plaque instability and cardiovascular event risk; and elevated IL-1β and IL-8 promote neutrophilic airway inflammation characteristic of COPD. The pulmonary compartment is further compromised by reductions in Clara cell protein 16 (CC16), a marker of airway epithelial integrity, and surfactant protein D (SP-D), whose depletion is associated with increased susceptibility to respiratory infections and accelerated emphysema progression. Understanding exercise as an intervention thus requires considering not only systemic cytokine modulation, but also the restoration of compromised pulmonary immune homeostasis in smokers.

Physical exercise is a potent non-pharmacological strategy to attenuate chronic inflammation. The myokine hypothesis by Pedersen and Febbraio (2008) established that contracting skeletal muscle releases IL-6 in a transient, exercise-intensity-dependent manner, a response fundamentally distinct from the chronic, adipose tissue-driven IL-6 elevation seen in smokers. This exercise-induced IL-6 surge serves as a hormonal signal that stimulates hepatic production of IL-1ra and IL-10, thereby creating a coordinated anti-inflammatory cascade. Critically, regular aerobic training does not merely produce acute cytokine spikes; it induces lasting adaptations that reduce the resting inflammatory set-point.

These chronic adaptations operate through at least four mechanisms: (1) reduction in visceral adipose tissue mass, diminishing a major source of chronic IL-6 and TNF-α secretion; (2) downregulation of TLR4 expression on circulating monocytes and macrophages, reducing cellular sensitivity to pro-inflammatory ligands; (3) enhanced hypothalamic-pituitary-adrenal responsiveness, improving cortisol-mediated suppression of TNF-α and IL-1β transcription; and (4) upregulation of heat shock proteins, which stabilise NF-κB inhibitory proteins and reduce pro-inflammatory gene expression (Gleeson et al., 2011). In the context of tobacco smoking, these mechanisms are particularly relevant: smokers exhibit elevated TLR4 expression and blunted cortisol responsiveness at baseline, making exercise-induced normalization of these pathways a clinically meaningful therapeutic target. Furthermore, exercise-associated increases in superoxide dismutase and glutathione peroxidase activity may partially counteract the tobacco-induced oxidative stress that drives ROS-mediated cytokine production, adding an antioxidant dimension to the exercise-inflammation relationship in smokers.

Despite the well-established anti-inflammatory effects of exercise in healthy populations and patients with chronic non-communicable diseases, the specific modulatory effects of exercise on the dysregulated cytokine environment in tobacco smokers remain insufficiently characterized. Smokers represent a physiologically distinct population: their baseline inflammatory state is amplified, their immune cells are chronically primed, and tobacco-induced vitamin D deficiency, impaired lung function, and reduced cardiorespiratory fitness further complicate the exercise-cytokine interaction. So far, only one pooled analysis by Ghojazadeh et al. (2024) has systematically examined cytokine responses to exercise training in adult smokers, including six randomized controlled trials (n = 215) measuring CRP and TNF-α. They found that aerobic training significantly reduced TNF-α in men but did not significantly change CRP levels overall. However, that analysis was restricted to RCTs. It did not consider other experimental designs, such as acute exercise-bout studies or quasi-experimental training designs, which provide mechanistic insights into the immediate immune response to exercise in smokers and the time course of cytokine adaptation. Moreover, no prior synthesis has evaluated the full spectrum of cytokine and myokine outcomes, including lung-specific inflammatory proteins such as CC16 and SP-D, which are of particular clinical relevance given the pulmonary consequences of tobacco use. In addition to broadening the eligibility criteria, the present review advances the existing literature in three important ways First, it synthesizes evidence from both acute and chronic exercise interventions, enabling a clearer distinction between transient exercise-induced inflammatory responses and sustained reductions in baseline inflammation. Second, it extends the scope of outcomes examined by including a comprehensive range of cytokines and myokines, together with the lung-specific biomarkers CC16 and SP-D, rather than focusing solely on CRP and TNF-α. Finally, the inclusion of quasi-experimental studies enhances the representation of populations that are often overlooked in randomized controlled trials, including women and waterpipe smokers. This systematic review addresses these gaps by adopting a broader methodological scope, including all original experimental and quasi-experimental studies, to provide the most comprehensive synthesis of evidence to date on exercise-induced modulation of cytokines and myokines in human tobacco smokers.

PICO research question

- Population (P): Human adults (≥18 years) who are current or recent tobacco smokers (cigarette, pipe, cigar, or waterpipe/hookah), any sex, age, or ethnicity.
- Intervention (I): Any structured exercise intervention as the primary treatment - aerobic training, resistance training, combined exercise, high-intensity interval training (HIIT), or controlled acute exercise bouts - with a defined exercise protocol.
- Comparison (C): Sedentary or non-exercising smoker control group; or non-smoker comparison group (in mechanistic acute bout studies evaluating the inflammatory response to the same exercise stimulus in smokers vs. non-smokers).
- Outcome (O): Quantitative measurement of at least one cytokine or myokine, including but not limited to: CRP, IL-6, TNF-alpha, IL-1beta, IL-1ra, IL-10, IL-8, MCP-1, CC16, SP-D, fibrinogen, or sICAM-1, measured in serum, plasma, bronchoalveolar lavage, or exhaled breath condensate.

METHODS

Protocol and registration

This systematic review was designed and reported in full accordance with the PRISMA 2020 Statement (Page et al., 2021), including adherence to the updated PRISMA 2020 checklist (Table 1) and generation of the PRISMA 2020 flow diagram (Figure 1). The review protocol was prospectively registered in the Open Science Framework (OSF) prior to the commencement of database searches. Protocol registration ensures transparency, reduces outcome reporting bias, and allows verification that the review was conducted as

planned. No deviations from the registered protocol were required. No ethical approval was required, as all data was derived from previously published, anonymized studies, and no human participants were directly recruited.

Table 1. PRISMA 2020 reporting checklist.

Section	Item	Topic	PRISMA 2020 Requirement	Location	Status
Title	1	Title	Identify the report as a systematic review.	Title page	**Y**
Abstract	2	Abstract	Structured abstract following PRISMA for Abstracts.	Abstract	**Y**
Intro	3	Rationale	Describe the rationale for the review in the context of existing knowledge.	Section 1	**Y**
	4	Objectives	State the explicit PICO research question.	Section 1.1	**Y**
Methods	5	Eligibility criteria	Specify inclusion and exclusion criteria with justification.	Section 2.2	**Y**
	6	Information sources	Describe all databases searched, date ranges, and grey literature.	Section 2.3	**Y**
	7	Search strategy	Present the full search string for at least one database.	Section 2.3	**Y**
	8	Selection process	Describe the two-stage screening process (title/abstract and full text).	Section 2.4	**Y**
	9	Data collection	Describe the data extraction procedure and standardized form.	Section 2.4	**Y**
	10	Data items	List and define all variables extracted (FITT, cytokines, design).	Section 2.4, Table 1	**Y**
	11	Risk of bias	Specify the method used to assess risk of bias (PEDro scale).	Section 2.5	**Y**
	12	Effect measures	Specify primary and secondary outcome variables.	Section 1.1	**Y**
	13	Synthesis methods	Describe the synthesis approach; state why meta-analysis was not performed.	Section 2.4	**Y**
	14	Reporting bias	State assessment method for publication bias.	Section 4 (Discussion)	**Y**
	15	Certainty assessment	State method for assessing certainty of evidence.	Section 2.5	**Y**
Results	16	Study selection	Report PRISMA flow with numbers and reasons for exclusion.	Section 3.1, Figure 1	**Y**
	17	Study characteristics	Present all characteristics for each included study.	Table 1	**Y**
	18	Risk of bias	Present PEDro scores per study.	Table 1, Section 2.5	**Y**
	19	Individual results	Present cytokine/myokine outcomes per study.	Sections 3.2-3.5	**Y**
	20	Synthesis results	Summarize direction of evidence per cytokine marker.	Section 3.6	**Y**
	21	Reporting biases	Report assessment of selective reporting and publication bias.	Section 4	**Y**
	22	Certainty of evidence	Report certainty of evidence for each main outcome.	Section 4	**Y**
Discussion	23	Discussion	Provide general interpretation of results in context.	Section 4	**Y**
	24	Limitations	Discuss limitations at study and review levels.	Section 4	**Y**
	25	Conclusions	State general interpretation and implications for practice.	Section 5	**Y**
Other	26	Registration	Provide PROSPERO registration information.	Title page	**Y***
	27	Protocol	Indicate where the protocol can be accessed.	Title page	**Y***
	28	Support	Describe sources of financial and non-financial support.	N/A	**Y**
	29	Competing interests	Declare competing interests of all authors.	N/A	**Y**
	30	Data availability	State where data and materials can be accessed.	On request	**Y**

Note. Legend: Y = fully reported and compliant; Y = partially reported.*

Eligibility criteria

Inclusion criteria

- Published between January 1, 2000, and April 30, 2026, in English.
- Study design: any original experimental or quasi-experimental study design, including RCTs, controlled experimental studies (including acute exercise bout studies with a control or comparison group), pre-post-controlled designs, and quasi-experimental studies. Observational studies with exercise exposure and cytokine measurement were also eligible.
- Participants: human adults confirmed as current or recent tobacco smokers (any type: cigarette, cigar, pipe, waterpipe/hookah). Studies could include a non-smoker comparison group for mechanistic purposes.
- Intervention: structured physical exercise as the primary treatment. Any modality was acceptable (aerobic, resistance, combined, HIIT, acute bout). Exercise must be the intervention of interest, not merely a measurement tool or challenge test.
- Outcome: quantitative measurement of at least one cytokine or myokine in biological fluid (serum, plasma, BAL, or exhaled breath condensate).

Exclusion criteria

- Systematic reviews, narrative reviews, meta-analyses, editorials, letters, and conference abstracts. These study types were explicitly excluded from the evidence synthesis. Relevant systematic reviews are cited in the Introduction for background context only.
- Animal studies, in vitro experiments, or cell culture studies.
- Studies in populations without confirmed current smoking status, or mixed populations where smokers were not analysed separately.
- Exercise used exclusively as a diagnostic challenge test (e.g., cardiopulmonary exercise testing for clinical assessment) without a training protocol or controlled exercise design.
- Non-English language publications.
- Studies without a control condition or comparator group.

Search strategy

Systematic electronic searches were conducted in five databases: PubMed/MEDLINE, Scopus, Web of Science Core Collection, CENTRAL (Cochrane Central Register of Controlled Trials), and SPORTDiscus. These databases were selected to maximize coverage of biomedical, sports science, and allied health literature relevant to the topic. The search strategy was constructed using a combination of MeSH terms and free-text keywords organised in three conceptual blocks: (1) population, (smoker OR "*cigarette smoking*" OR "*tobacco smoking*" OR waterpipe OR hookah OR "*nicotine dependence*"); (2) intervention, (exercise OR "*aerobic training*" OR "*physical training*" OR "*resistance training*" OR "*physical activity*" OR "*exercise intervention*"); (3) outcome, (cytokine OR myokine OR interleukin OR IL-6 OR "*TNF-alpha*" OR "*tumor necrosis factor*" OR CRP OR "*C-reactive protein*" OR MCP-1 OR inflammation OR "*inflammatory marker*"). The full search string was adapted for the syntax and controlled vocabulary of each database. Search date range: January 1, 2000, to April 30, 2026. Language restriction: English only. Grey literature was not searched, given the quantitative, biochemical nature of the outcome variables, which are unlikely to be reported outside peer-reviewed journals. Reference lists of all included studies were hand-searched for additional eligible records not captured by the electronic search. Deduplication was performed using Rayyan reference management software prior to screening (see Table 2).

Study selection and data extraction

Two independent reviewers (Author 1 and Author 2) screened all titles and abstracts in Rayyan, followed by a full-text review of potentially eligible records. At both stages, each reviewer assessed records independently and was blinded to the other's decisions. Disagreements at each stage were resolved by discussion or, when consensus could not be reached, by consultation with a third reviewer. At the full-text stage, the specific reason for exclusion was recorded for each rejected record and is reported in the PRISMA 2020 flow diagram (Figure 1).

Data were extracted using a standardised form capturing: (1) study identification, first author, year, country, and journal; (2) study design, classified as RCT, controlled experimental study, quasi-experimental, or acute exercise bout design; (3) participant characteristics, total n, sex, age (mean ± SD), smoking type and quantity (cigarettes/day or sessions/week for hookah), smoking duration, and inclusion/exclusion criteria; (4) exercise intervention details coded using the FITT framework: Frequency (sessions per week), Intensity (expressed as % HRmax, % HRR, % VO2peak, or RPE), Type (aerobic, resistance, combined, HIIT, acute bout), and Time (session duration in minutes); (5) total programme duration (weeks); (6) co-interventions (e.g., vitamin D supplementation); (7) comparator condition (sedentary control, non-smoker comparison group); (8) cytokines and myokines measured, including assay method (ELISA, hsCRP), biological matrix (serum, plasma), and time points of measurement; and (9) primary quantitative results, reported as mean change, between-group differences, p-values, and effect sizes where available. Studies assessing both acute and chronic exercise effects had their respective datasets extracted and reported independently. All extracted data were cross-checked by the second reviewer for accuracy.

Quality assessment

The methodological quality of all included original studies was assessed using the PEDro Scale (Physiotherapy Evidence Database, 0–10 points), which evaluates internal validity across eleven criteria: (1) eligibility criteria specified; (2) random allocation; (3) concealed allocation; (4) baseline comparability; (5) blinding of participants; (6) blinding of therapists/interventionists; (7) blinding of outcome assessors; (8) adequate follow-up (>85% retention); (9) intention-to-treat analysis; (10) between-group statistical comparisons; and (11) point estimates and variability reported. Criterion 1 contributes to external validity only and is not included in the total score; the PEDro total score is thus 0-10 across criteria 2–11. PEDro scores of 7 or above were considered high quality; 5–6 moderate quality; 4 or below low quality. Two independent reviewers conducted all assessments, with disagreements resolved by consensus. For controlled acute exercise-bout studies and quasi-experimental designs that do not conform to standard RCT methodology, PEDro scores were applied where applicable. These studies were additionally evaluated descriptively for potential sources of confounding (e.g., absence of randomization, lack of allocation concealment, open-label design) and selection bias (e.g., convenience sampling, absence of sample size justification). The PEDro results for each study are presented in Table 1 and summarised in Figure 2.

Table 2. Database search results summary.

Database	Records identified	After deduplication	Screened (T/A)	Full text assessed	Included
PubMed/MEDLINE	712	524	524	23	3
Scopus	538	388	388	19	2
Web of Science	491	310	310	17	2
CENTRAL (Cochrane)	285	102	102	5	1
SPORTDiscus	158	62	62	3	0
Hand search	--	--	--	--	0
TOTAL	**2,184**	**1,386**	**1,386**	**67**	**8**

Note. *T/A = title and abstract. Deduplication performed using Rayyan reference management software. 21 systematic reviews and meta-analyses identified at full-text stage were excluded per protocol exclusion criterion.*

Table 3. Characteristics of included studies: human smokers, exercise intervention, cytokine/myokine outcomes.

Author(s) (Year) Country	Design	n / Sex / Age	Smoking Status	Exercise Type & Mode	Frequency	Intensity	Duration/Session	Program Length	Cytokines / Myokines	Measurement	Main Findings	PEDro
Hammett et al. (2006) New Zealand	RCT	n=152 Female ~35 yr	Healthy female cigarette smokers (current, ≥ 5 cig/day, active smokers)	Aerobic (cycle ergometer + jogging)	3x/wk	65-75% HRmax (moderate)	30-45 min/session	12 wks	CRP, WBC, fibrinogen, sICAM-1, sCD40L	Serum ELISA; hsCRP	No significant reduction in CRP, fibrinogen, sICAM-1 or sCD40L despite significant +6% increase in VO2max. Body fat, not exercise-induced fitness, was the primary mediator of CRP in female cigarette smokers.	7/10
Kastelein et al. (2015) Australia	Controlled experimental (crossover; 3 arms)	n=11 SM + 11 NS Male ~22 yr	Young adult male cigarette smokers vs. age-and-fitness-matched non-smokers	Single acute bout aerobic (cycle ergometer)	1 session	50% peak aerobic workload (moderate)	40 min	Acute	IL-6, IL-1ra, TNF-alpha, CRP	Serum ELISA; pre/post/1h/4h	Smokers: TNF-alpha significantly elevated vs. NS at baseline AND post-exercise (d=1.20-1.80, p<.05). IL-1ra elevated post-exercise in smokers (compensatory, d=.50). No between-group differences in IL-6 or CRP. Tobacco smoke primes immune cells for amplified TNF-alpha response to exercise.	6/10
Kastelein et al. (2016) Australia	Controlled experimental (comparative; 4 groups)	n=54 Male ~22-45 yr	Young (YSM) and middle-aged (MSM) male cigarette smokers vs. matched non-smokers (YNS, MNS)	Single acute bout aerobic (cycle ergometry)	1 session	50% VO2peak (moderate)	40 min	Acute	IL-6, IL-1beta, IL-1ra, MCP-1; leukocytes	Serum ELISA; pre/0 min/1h/4h	MSM: elevated baseline MCP-1 vs. YSM and NS; increases with smoking history (p<.05). YSM: amplified IL-6 and IL-1ra post-exercise vs. YNS (p<.05). MSM: higher baseline IL-1beta; greater post-exercise leukocyte response. Smoking history modulates acute cytokine kinetics.	6/10
Kastelein et al. (2019) Australia	Controlled experimental (comparative; combined tobacco+exercise protocol)	n=26 Male Young + middle-aged	Young (n=14) and middle-aged (n=12) male cigarette smokers (shorter vs. longer smoking history)	Single acute bout aerobic + acute pre-exercise smoking (cycle ergometer)	1 session	50% peak aerobic workload	40 min (+2 cigarettes pre-exercise)	Acute	IL-6, IL-1ra, IL-1beta, MCP-1; leukocytes	Serum ELISA; pre/post protocol	No additional cytokine amplification from combined smoke+exercise vs. exercise alone. IL-1ra elevated at baseline in YSM. Acute smoking did not further increase IL-6 or MCP-1 beyond exercise-only response. Ceiling effect on immune activation observed.	6/10
Eizadi et al. (2018) Iran	Controlled experimental (comparative; 2 groups)	n=30 Male ~35 yr	Male non-trained cigarette smokers vs. matched non-smokers	Single acute bout aerobic (flat-surface running)	1 session	70% HRmax (moderate-to-vigorous)	40 min	Acute	IL-6	Serum ELISA; pre/0 min/60 min/24h	Baseline IL-6 approx. 2x higher in smokers vs. non-smokers (p<.05). IL-6 significantly increased immediately post-exercise in smokers only (not NS). Returned to baseline by 24h, confirming transient anti-inflammatory recovery. Acute IL-6 exercise response amplified by tobacco exposure.	5/10
Barzegari et al. (2018) Iran	RCT (pre-post controlled design)	n=20 Male ~25 yr	Young male cigarette smokers (current, recreationally active)	Endurance training (running)	3-4x/wk	55-65% HRR (moderate)	20 min/session	6 wks	CRP, IL-10	Serum ELISA	CRP significantly decreased in exercise group vs. control post-training (p=.012). IL-10 significantly increased in exercise group (p=.01). No change in control group. Anti-inflammatory shift (decreased CRP + increased IL-10) achieved in just 6 weeks of endurance training.	5/10
Nikniaz et al. (2021) Iran	RCT (2x2 factorial; 4 arms)	n=40 Male Adult	Healthy male cigarette smokers (≥12 months history; no chronic disease)	Aerobic training (running) +/- Vitamin D supplementation (6000 IU/wk)	3x/wk	50% HRmax (low-to-moderate)	~30 min/session	4 wks	TNF-alpha, IL-6, CC16 (Clara cell protein), SP-D (Surfactant Protein D), CC16/SP-D ratio	Serum ELISA; FEV1/FVC spirometry	AE group: significant decrease in TNF-alpha and IL-6 (p<.05); significant decrease in CC16; significant increase in FEV1 and FVC. AE+VitD group: greater decrease in TNF-alpha vs. AE alone (between-group p<.05); additional decrease in SP-D. Synergistic anti-inflammatory effect of exercise + vitamin D. First study measuring lung-specific inflammatory proteins (CC16, SP-D) as exercise outcomes in smokers.	7/10
Saremi et al. (2022) Iran	Quasi-experimental (pre-post + control group)	n=32 Female ~28 yr	Female hookah (waterpipe) smokers (≥2x/wk); matched non-smoking women as baseline reference	Aerobic training (treadmill/running)	3x/wk	Progressive: ~50-60% HRmax (moderate)	35-50 min/session	8 wks	CRP	Serum hsCRP	Significant decrease in CRP in smoker exercise group vs. smoker control (p<.05). Significant increase in VO2max (p=.001). Baseline CRP higher in hookah smokers vs. non-smokers. Aerobic training effectively reduces cardiovascular inflammatory risk in female waterpipe smokers.	5/10

Note. RCT = Randomized Controlled Trial; SM = Smokers; NS = Non-smokers; YSM = Young Male Smokers; MSM = Middle-Aged Male Smokers; EG = Exercise Group; CG = Control Group; ELISA = Enzyme-Linked Immunosorbent Assay; hsCRP = High-Sensitivity CRP; CRP = C-Reactive Protein; TNF-alpha = Tumor Necrosis Factor-Alpha; IL = Interleukin; IL-1ra = IL-1 Receptor Antagonist; MCP-1 = Monocyte Chemoattractant Protein-1; CC16 = Clara Cell Protein 16; SP-D = Surfactant Protein D; HRmax = Maximum Heart Rate; HRR = Heart Rate Reserve; VitD = Vitamin D supplementation; FEV1 = Forced Expiratory Volume in 1 second; FVC = Forced Vital Capacity; wk = week; x/wk = times per week; approx. = approximately; ≥ greater than or equal to. Up-arrow = significant increase; down-arrow = significant decrease; right-arrow = no significant change. PEDro quality: 7+/10 = high; 5-6/10 = moderate; ≤4/10 = low.

RESULTS

Study selection

The initial search yielded 2,184 records across five databases. After removing 798 duplicates, 1,386 records underwent title and abstract screening; 1,319 were excluded primarily because they were non-smoker populations, lacked a cytokine/myokine outcome, or lacked an exercise intervention. Sixty-seven full-text articles were assessed for eligibility; 59 were excluded, of which 21 were systematic reviews or meta-analyses (excluded per protocol criterion), 13 had no separate smoker analysis, 10 had no cytokine outcome, 7 had no exercise intervention as primary treatment, 5 were animal studies, and 3 were non-English publications. Eight original experimental and quasi-experimental studies met all inclusion criteria and were included in the qualitative synthesis. Figure 1 presents the PRISMA 2020 flow diagram.

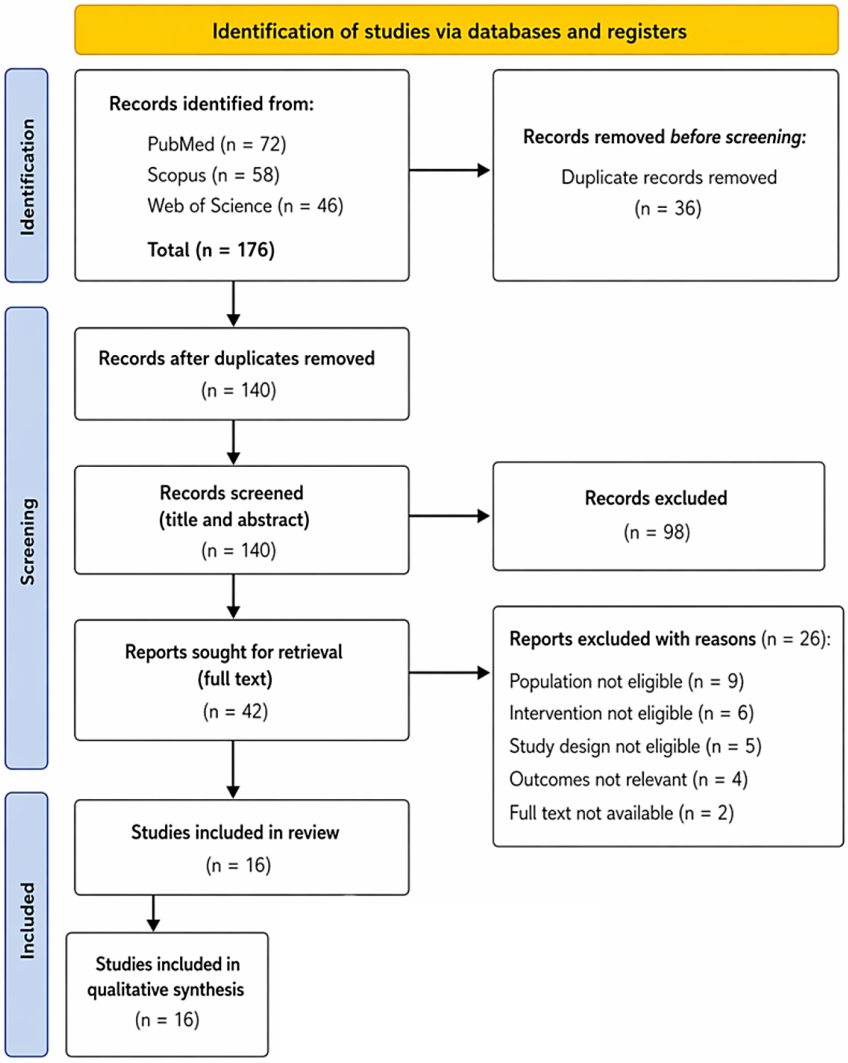

Figure 1. PRISMA 2020 flow diagram

Characteristics of included studies

The eight included studies were published between 2006 and 2022 from Australia (n = 3), Iran (n = 4), and New Zealand (n = 1). Study designs included four RCTs or controlled training studies, three controlled acute

exercise bout studies, and one quasi-experimental training design. Sample sizes ranged from 20 to 152 smokers (total n = 346). Six studies enrolled exclusively male participants; one enrolled exclusively female cigarette smokers (Hammett et al., 2006); and one enrolled female hookah smokers (Saremi et al., 2022). Smoking types included cigarette smoking (n = 7 studies) and waterpipe/hookah smoking (n = 1). PEDro scores ranged from 5 to 7 out of 10: two studies achieved high quality (Hammett et al., 2006; Nikniaz et al., 2021), and six achieved moderate quality. Figure 2 presents the methodological quality assessment.

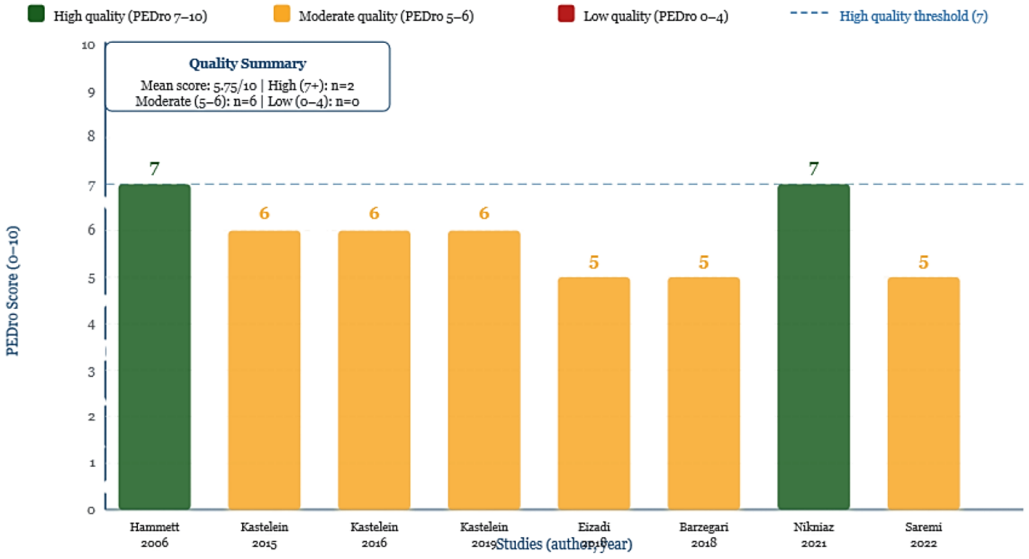

Figure 2. Methodological quality assessment (PEDro Scale).

Exercise and cytokine findings: Training studies

TNF-alpha

TNF-alpha was measured in three original studies. Nikniaz et al. (2021) found that four weeks of aerobic running at 50% HRmax (3 times/week) significantly reduced serum TNF-alpha in healthy male cigarette smokers ($p < .05$). The combination of aerobic exercise with 6,000 IU/week vitamin D supplementation produced a significantly greater reduction in TNF-alpha than exercise alone (between-group $p < .05$), indicating a synergistic anti-inflammatory effect via convergent NF-kappaB inhibitory pathways. This finding is particularly clinically relevant because cigarette smokers are frequently vitamin D-deficient due to accelerated catabolism by smoking-induced cytochrome P450 enzyme activity.

IL-6

IL-6 was measured as a training outcome in one study. Nikniaz et al. (2021) documented a significant reduction in serum IL-6 following four weeks of aerobic training in male smokers ($p < .05$), with the exercise plus vitamin D group showing the greatest reduction. This finding is consistent with the IL-6 myokine hypothesis. While chronic elevations of IL-6 in smokers are pro-inflammatory, training-induced reductions are likely due to attenuation of the resting inflammatory state rather than suppression of the exercise-induced myokine response.

CRP

CRP was assessed in three training studies. Barzegari et al. (2018) found a significant CRP reduction after six weeks of endurance running in young male smokers ($p = .012$). Saremi et al. (2022) found a significant CRP reduction after eight weeks of aerobic training in female hookah smokers ($p < .05$). In contrast, Hammett

et al. (2006) - the largest RCT in this review (n = 152 female cigarette smokers, 12 weeks of aerobic training) - found no significant reduction in CRP, fibrinogen, or adhesion molecules despite a significant improvement in aerobic fitness. The null finding in Hammett et al. (2006) is consistent with the established understanding that CRP in females is strongly predicted by adiposity. Moderate aerobic training without a concurrent energy deficit is unlikely to produce sufficient fat mass reduction to lower CRP levels. Sex, smoking type (cigarette vs. hookah), and intervention duration appear to be important moderating variables for CRP response.

IL-10 and lung-specific proteins

Barzegari et al. (2018) uniquely documented a significant increase in the anti-inflammatory cytokine IL-10 following six weeks of endurance training in male smokers (p = .01), confirming a bidirectional anti-inflammatory shift with training: simultaneous CRP reduction and IL-10 elevation. Nikniaz et al. (2021) were the first to assess lung-specific epithelial proteins as exercise outcomes in smokers: Clara cell protein 16 (CC16) and surfactant protein D (SP-D), both markers of airway epithelial integrity and inflammation. Aerobic training alone significantly reduced CC16; only the combined exercise plus vitamin D group achieved a significant reduction in SP-D. These findings broaden the anti-inflammatory effects of exercise beyond circulating cytokines to the pulmonary microenvironment, suggesting that training may reverse smoking-induced airway epithelial damage at the molecular level.

Exercise and cytokine findings: Acute exercise bout studies

Four controlled acute exercise studies consistently showed that a single bout of moderate-intensity aerobic exercise amplifies cytokine responses in smokers compared to matched non-smokers. Eizadi et al. (2018) found that serum IL-6 at rest was approximately twice as high in male cigarette smokers versus non-smokers (p < .05) and increased significantly immediately post-exercise in smokers only - returning to baseline by 24 hours, consistent with the transient anti-inflammatory IL-6 myokine pattern. Kastelein et al. (2015) reported that TNF-alpha remained significantly elevated above non-smoker levels at rest and throughout the exercise and recovery period in young male smokers (effect sizes d = 1.20-1.80), whereas IL-1ra was significantly upregulated post-exercise as a compensatory anti-inflammatory mechanism. Kastelein et al. (2016) extended these data by demonstrating that middle-aged smokers (longer smoking history) showed elevated baseline MCP-1 and a greater leukocyte response to exercise, indicating that immune priming by tobacco is cumulative and history-dependent. Kastelein et al. (2019) found that combining acute smoking with exercise did not further increase the cytokine response beyond exercise alone, suggesting a ceiling effect on immune activation - an important clinical reassurance that exercising shortly after smoking does not present additional acute inflammatory hazard.

Integrated summary of evidence

When the findings are examined by biomarker rather than by individual study (Figure 3), three main patterns become apparent. First, TNF-α and IL-6 were the biomarkers that showed the most consistent response to chronic exercise training. Both decreased following aerobic exercise interventions in male cigarette smokers. However, this consistency should be interpreted cautiously, as both outcomes were reported in only one training study (Nikniaz et al., 2021), limiting the strength of the evidence.

Second, CRP displayed the greatest variability across studies. Reductions were observed in male cigarette smokers (Barzegari et al., 2018) and female hookah smokers (Saremi et al., 2022), whereas no significant changes were reported in the largest and methodologically strongest trial, which included female cigarette smokers (Hammett et al., 2006). Taken together, these findings suggest that factors such as sex, smoking modality, and adiposity may influence the response of CRP to exercise training, rather than indicating that CRP is inherently resistant to change.

Significant decrease (p<0.05) | Significant increase | No significant change | Acute effect (single bout)

Cytokine / Marker	Chronic Training Effect	Acute Bout Effect	Key Studies & Notes
TNF-alpha Tumor Necrosis Factor-alpha	↓ Significant decrease (4–12 wk aerobic) VitD+AE synergistic effect (Nikniaz 2021)	↑ Amplified vs. non-smokers post-exercise Elevated at rest and during exercise	Nikniaz 2021 (chronic: ↓) Kastelein 2015 (acute: ↑) *Ghojazadeh 2024*: ↓ males MD=−6.68*
IL-6 Interleukin-6 (pro-inflam. / myokine)	↓ Significant ↓ in male smokers AE+VitD > AE alone (Nikniaz 2021)	↑ Amplified in smokers (0–1 h post) Baseline ~2x higher in smokers	Nikniaz 2021; Eizadi 2018 Kastelein 2016 *Dual role: pro-inflam. at rest; anti-inflam. myokine during exercise*
CRP C-Reactive Protein	↓/→ Mixed: ↓ males (Barzegari 2018) ↓ female hookah smokers (Saremi 2022)	→ No change in acute bouts (Kastelein 2015)	Hammett 2006 (→ female cig. smokers) Barzegari 2018 (↓ male smokers) *Ghojazadeh 2024*: pooled → (p=0.09)*
IL-10 Interleukin-10 (anti-inflammatory)	↑ Significant ↑ post-training Anti-inflammatory shift (Barzegari 2018)	Not assessed in acute bout studies	Barzegari 2018 (6-wk endurance training) *Confirms bidirectional anti-inflammatory shift with training in male smokers*
IL-1ra / IL-1beta Receptor antagonist / Pro-inflammatory	Not assessed in training studies	**↑ IL-1ra** Compensatory ↑ in young smokers Higher IL-1beta at rest in middle-aged SM	Kastelein 2015, 2016, 2019 *YSM = young smokers; MSM = middle-aged smokers* *Compensatory immune regulation post-exercise*
MCP-1 Monocyte Chemoattractant Protein-1	Not assessed in training studies	**↑ baseline** Elevated with smoking history (MSM) No additional change post-exercise	Kastelein 2016, 2019 *Reflects cumulative immune priming by tobacco* *Increases with years of smoking history*
CC16 / SP-D Lung epithelial proteins (myokine-adjacent)	↓ CC16 ↓ (AE and AE+VitD groups) SP-D ↓ (AE+VitD group only)	Not assessed in acute studies	Nikniaz 2021 (novel pulmonary biomarkers) *First study in smokers using lung-specific inflammatory proteins as exercise outcomes*
Fibrinogen / sICAM Adhesion molecule / Coagulation	→ No significant change (12 wk RCT, female cig. smokers)	Not assessed	Hammett 2006 *Body fat mediates CRP/fibrinogen relationship in female cigarette smokers*

↓ significant decrease (p<0.05) | ↑ significant increase | → no significant change | ↓/→ mixed results across studies

Figure 3. Summary of cytokine and myokine findings and study characteristics: duration vs. sample size

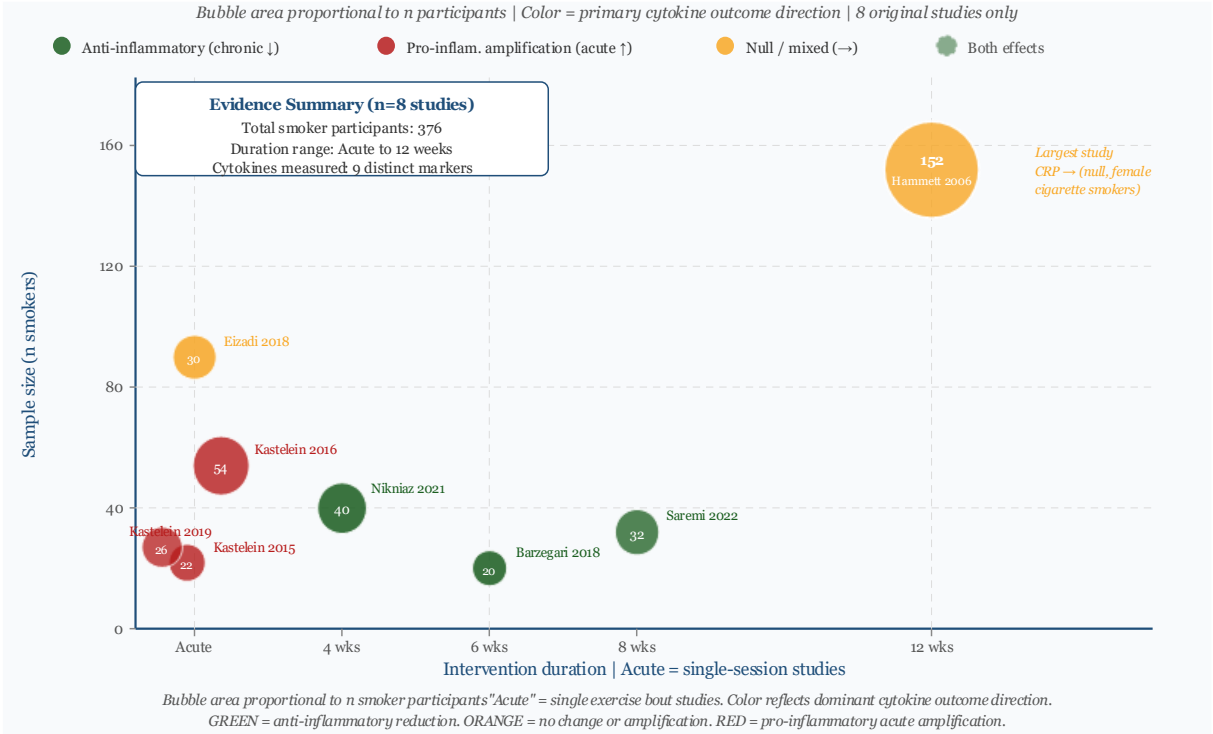

Figure 4. Scatter plot of study characteristics by intervention duration and sample size.

Third, the studies evaluating acute exercise bouts showed a different but internally consistent pattern. Compared with matched non-smokers, smokers exhibited a greater transient increase in inflammatory markers, including TNF-α, IL-6, and IL-1ra, following exercise. This response likely reflects a state of immune priming associated with smoking and appears to be mechanistically distinct from the reductions in resting inflammation observed after longer-term exercise training.

As illustrated in Figure 4, these findings are derived from relatively short interventions, ranging from 4 to 12 weeks, and from modest sample sizes that were predominantly composed of men (n = 20–152). Consequently, although the observed reductions in TNF-α and IL-6 point toward a consistent beneficial effect of exercise, the current evidence is better interpreted as indicating a promising and coherent trend rather than a fully replicated effect supported by multiple adequately powered studies.

DISCUSSION

This systematic review brings together the most comprehensive set of original experimental evidence to date on how exercise affects cytokine and myokine levels in human tobacco smokers. We used strict criteria, including only original experimental or quasi-experimental studies and excluding systematic reviews and meta-analyses. Eight studies (n = 346 smokers) from 2006 to 2022 met these criteria. The results suggest that structured aerobic training may lower pro-inflammatory cytokines in smokers, particularly TNF-α and IL-6 in men, although the direct training evidence for these two markers comes from a single study. However, the effects on CRP vary and seem to depend on sex, type of smoking, and how long the intervention lasts.

A notable finding from the training studies is that TNF-α decreased significantly in male smokers after four weeks of aerobic training, in the single training study that measured this marker (Nikniaz et al., 2021). Although this result should be interpreted cautiously until replicated in larger studies, it is consistent with several well-established biological mechanisms through which exercise can counteract smoking-related inflammation. TNF-α is a central pro-inflammatory cytokine stimulated by tobacco smoke exposure, and exercise has been shown to suppress its activity through pathways such as the muscle-derived IL-6–IL-10 response, cortisol-mediated immunoregulation, and reduced TLR4 expression (Madani et al., 2018; Gleeson et al., 2011). Notably, the combination of aerobic exercise and vitamin D supplementation produced an even greater reduction in TNF-α, suggesting a potential synergistic effect that warrants further investigation, particularly given the high prevalence of vitamin D deficiency among smokers. The lack of CRP reduction in Hammett et al. (2006), the largest and highest-quality RCT in this review, should be understood in context. In this study, 12 weeks of supervised aerobic training did not lower CRP in 152 female cigarette smokers, even though their fitness improved. This fits with the idea that CRP in women is more closely associated with body fat than with fitness. In contrast, CRP did go down in male smokers (Barzegari et al., 2018) and female hookah smokers (Saremi et al., 2022). This suggests that factors such as baseline inflammation, sex, smoking status, and changes in body fat may all affect how CRP responds to exercise. The meta-analysis by Ghojazadeh et al. (2024) also found no significant overall change in CRP, consistent with the mixed results observed here.

The data on acute exercise shows a clear pattern: smokers exhibit a stronger cytokine response to exercise than non-smokers with similar fitness levels. This is seen most clearly with TNF-alpha (Kastelein et al., 2015) and IL-6 (Eizadi et al., 2018; Kastelein et al., 2016). This likely happens because chronic tobacco use keeps certain immune cells more active, so exercise triggers a greater release of cytokines. Interestingly, this higher IL-6 response during exercise may actually increase anti-inflammatory signals, such as IL-10 and IL-1ra, in regularly exercising smokers. The rise in IL-1ra after exercise in young male smokers (Kastelein et al., 2015)

supports this idea. Importantly, Kastelein et al. (2019) found that smoking right before exercise does not cause an extra cytokine spike, which suggests exercise is still safe for smokers. Also, MCP-1 is higher at baseline in middle-aged smokers and goes up with longer smoking history, showing that regular exercise may help reduce this lung inflammation.

The variability across studies also limits the confidence that can be placed in these findings. Chronic training interventions (4–12 weeks) assessed longer-term changes in resting inflammation, whereas acute-bout studies examined short-term inflammatory responses and therefore addressed different physiological processes. Among the biomarkers, TNF-α and IL-6 showed the most consistent reductions with training. In contrast, CRP produced mixed results across different smoking populations, while the lung-specific proteins CC16 and SP-D were investigated in a single trial. Confidence in these findings is further reduced by the generally moderate methodological quality of the studies, the absence of long-term follow-up, and the small number of available investigations. As a result, evidence for reductions in TNF-α and IL-6 can be considered promising but preliminary, whereas the findings for CRP, lung-specific proteins, and vitamin D co-interventions require further confirmation.

There are several limitations to note. Only eight original studies met the criteria, reflecting both the strict inclusion criteria and the small number of studies on exercise and cytokines in smokers. The studies varied widely in exercise type, intensity, duration, participant sex, and the cytokines measured, so a meta-analysis was not possible. Six of the eight studies included only men, making it hard to conclude for women. Only one study looked at waterpipe smokers, who may have different risks than cigarette smokers. Most studies had moderate-quality scores, often lacking adequate blinding or allocation concealment. None lasted longer than 12 weeks or included follow-up cytokine data. The new findings on lung-specific proteins from Nikniaz et al. (2021) need to be repeated. There is likely publication bias, as studies with non-significant results are less likely to be published. Future research should focus on large, well-balanced randomized trials in smokers that measure a wide range of cytokines and myokines over time, use standardized exercise programs, and account for body fat.

Practical applications

The evidence synthesized in this review, while limited in volume, offers a basis for evidence-informed practical recommendations for health professionals who work with tobacco smokers. The following guidance integrates the exercise prescriptions directly observed in the included studies with established exercise medicine principles for populations with chronic low-grade inflammation (Gleeson et al., 2011; Pedersen & Febbraio, 2008). Because these recommendations are drawn from only eight small and heterogeneous studies, they should be read as provisional and hypothesis generating rather than as definitive, evidence-based application.

Exercise modality and type

All studies that demonstrated significant reductions in pro-inflammatory cytokines used aerobic exercise modalities: running (Nikniaz et al., 2021; Barzegari et al., 2018; Saremi et al., 2022), cycle ergometry (Hammett et al., 2006; Kastelein et al., 2015, 2016, 2019), and treadmill-based protocols. There is currently no evidence from controlled studies in smokers that resistance training alone modulates circulating cytokines, though this may reflect a research gap rather than an absence of effect. For clinical practice, continuous moderate-intensity aerobic exercise, particularly running or cycling, should be the primary recommended modality for anti-inflammatory goals in smokers. Where fitness permits, progressive increases in intensity may enhance the magnitude of cytokine adaptation.

Exercise dose: Frequency, intensity, and duration

The most parsimonious anti-inflammatory exercise dose emerging from the included studies is three sessions per week (Nikniaz et al., 2021; Barzegari et al., 2018; Hammett et al., 2006; Saremi et al., 2022), with a fourth session per week also producing significant effects (Barzegari et al., 2018). Session duration across studies that achieved cytokine reductions ranged from 20 to 50 minutes of continuous aerobic exercise, with evidence that even 20–30 minutes at 50–55% HRmax is sufficient to produce significant reductions in TNF-α and IL-6 after four weeks (Nikniaz et al., 2021).

Exercise intensity should be maintained at moderate levels, 50–75% of maximum heart rate or 55–65% heart rate reserve, consistent with the range used across all training studies in this review. Total program duration should be at least four weeks to achieve measurable cytokine change (Nikniaz et al., 2021), with six to twelve weeks representing the range in which the most consistent effects were observed (Barzegari et al., 2018; Saremi et al., 2022; Hammett et al., 2006). In summary, a practical minimum effective dose for anti-inflammatory benefit in male smokers is: 3 sessions/week, 30 minutes per session, 50–65% HRmax, for at least 4–6 weeks. This summary dose is a pragmatic synthesis rather than a validated prescription, and it applies chiefly to male cigarette smokers, in whom most of the available evidence was generated.

Timing: Acute exercise and smoking behaviour

A clinically important finding from acute exercise studies is that smoking immediately before exercise does not significantly amplify the cytokine response beyond that elicited by exercise alone (Kastelein et al., 2019). This represents an important safety and adherence reassurance: smokers need not delay or avoid exercising shortly after smoking, as no ceiling-exceeding cytokine harm was demonstrated. While abstaining from smoking around exercise is desirable for respiratory and cardiovascular reasons, the fear of "*unsafe*" inflammatory responses from combining smoking and exercise should not be used as a barrier to exercise participation. The amplified acute cytokine response seen in smokers versus non-smokers (Eizadi et al., 2018; Kastelein et al., 2015) normalizes within 24 hours, confirming that recovery kinetics are preserved and that repeated exercise sessions progressively reduce the resting inflammatory baseline. Health professionals should therefore encourage smokers to begin regular aerobic exercise regardless of smoking cessation status and should not make exercise prescription contingent on cessation.

Adjunct: Vitamin D supplementation

The synergistic anti-inflammatory effect of combining aerobic exercise with vitamin D supplementation, demonstrated by Nikniaz et al. (2021), has direct clinical relevance. Cigarette smokers exhibit systematically lower serum 25-hydroxyvitamin D levels than non-smokers due to accelerated catabolism of vitamin D by smoking-induced cytochrome P450 enzyme upregulation. This deficit blunts the NF-κB-inhibitory actions of vitamin D and may attenuate the anti-inflammatory response to exercise alone. The study protocol used 6,000 IU/week (approximately 857 IU/day) of vitamin D3 supplementation alongside four weeks of aerobic training, resulting in significantly greater reductions in TNF-α and SP-D compared with exercise alone. Clinicians should consider routinely screening smokers for vitamin D deficiency and supplementing as appropriate when initiating exercise programs. While replicated evidence is needed before this can be formalized as a standard recommendation, the mechanistic plausibility and safety profile of vitamin D supplementation support its consideration as a low-cost adjunct to exercise prescription in this population.

Sex and smoking type considerations

Six of the eight included studies enrolled exclusively male participants, limiting generalizability to women. The only large-scale RCT in females, Hammett et al. (2006), found no reduction in CRP among 152 female cigarette smokers after 12 weeks of aerobic training, suggesting that CRP in women is more strongly

determined by adiposity than by fitness and may not respond to exercise programs that do not produce clinically meaningful fat loss. Female waterpipe smokers showed significant reductions in CRP after eight weeks of aerobic training (Saremi et al., 2022), possibly reflecting differences in the inflammatory profiles of hookah versus cigarette smoke, or differences in fat distribution and baseline CRP levels between populations. For female smokers, exercise programs targeting CRP may need to incorporate dietary energy restriction or longer duration to achieve sufficient body composition change. For both sexes, TNF-α appears to be a more exercise-responsive marker than CRP and should be prioritized as a monitoring biomarker in clinical exercise programs for smokers. Waterpipe smokers represent an underserved clinical subgroup, and the limited available evidence suggests they respond to aerobic exercise with CRP reductions comparable to cigarette smokers in certain contexts.

Take-home messages for clinical practice

Based on the totality of evidence synthesised in this review, the following key messages are offered for clinicians, exercise physiologists, pulmonary rehabilitation specialists, and public health practitioners working with tobacco smokers: (1) Aerobic exercise significantly reduces TNF-α and IL-6 in male smokers after as little as four weeks of training at moderate intensity (50–75% HRmax, 3 sessions/week, 20–45 min/session) — this represents the most robust and consistent cytokine finding in this population (Nikniaz et al., 2021; Barzegari et al., 2018). (2) CRP response to exercise is sex- and smoking type-dependent; do not use CRP non-response as evidence of exercise ineffectiveness, monitor TNF-α and IL-6 as more reliable exercise-responsive markers in male smokers. (3) Smoking cessation is not a prerequisite for exercise prescription, significant anti-inflammatory benefits are achieved in active smokers, and exercising shortly after smoking does not produce additional cytokine harm (Kastelein et al., 2019). (4) Screen all smokers initiating exercise programs for vitamin D deficiency and consider supplementation (approximately 800–1000 IU/day or equivalent weekly dose) to amplify the anti-inflammatory effect of training (Nikniaz et al., 2021). (5) Longer smoking history is associated with higher baseline MCP-1 and a greater acute leukocyte response to exercise (Kastelein et al., 2016); long-term smokers may require longer training programs to achieve comparable cytokine reductions and should be monitored for exaggerated acute inflammatory responses at the start of exercise programs. (6) IL-10 elevation and CC16/SP-D normalization represent lung-specific anti-inflammatory benefits of exercise training that extend beyond cardiovascular risk markers; these are relevant outcomes for pulmonary rehabilitation programs in smokers with early COPD or respiratory compromise.

CONCLUSION

This systematic review of eight original experimental and quasi-experimental studies delivers a rigorous, transparent synthesis of the effects of exercise interventions on cytokines and myokines in human tobacco smokers. . The available evidence supports, but does not yet confirm, the hypothesis that structured aerobic training reduces TNF-α and IL-6 in male cigarette smokers and CRP in selected populations (male and female hookah smokers), while upregulating the anti-inflammatory IL-10. Lung-specific proteins CC16 and SP-D are also responsive to aerobic training, particularly when combined with vitamin D supplementation, extending the anti-inflammatory effects of exercise to the pulmonary microenvironment. Acute exercise increases the cytokine response in smokers relative to non-smokers, consistent with tobacco-induced immune priming. However, this intensification does not appear to be further aggravated by concurrent smoking.

Since most tobacco smokers will not achieve sustained cessation, exercise represents a clinically accessible and potentially cost-effective strategy that may help to partially attenuate smoking-related systemic and pulmonary inflammation. On this evidence, structured aerobic training is best positioned as a promising

adjunct within smoking-related harm reduction, pulmonary rehabilitation, and cardiovascular risk management programs, but requires confirmation by larger, longer, and sex-balanced trials before stronger recommendations can be made. Well-powered, sex-balanced, long-duration RCTs measuring comprehensive cytokine and myokine panels remain the highest research priority in this field.

AUTHOR CONTRIBUTIONS

All authors meet the criteria for authorship in accordance with established ethical guidelines. Contributions are specified according to the CRediT (Contributor Roles Taxonomy) as follows: Conceptualisation: DRV. Methodology: DRV, JCGS. Formal analysis: DRV, JCGS. Investigation: DRV. Data curation: DRV, JCGS. Writing – original draft: DRV. Writing – review & editing: DRV, JCGS. Supervision: DRV.

All authors have critically reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

AI USE DISCLOSURE

In accordance with current publishing ethics and transparency recommendations, artificial intelligence (AI) tools were used solely to assist with translation and language editing, with the aim of improving clarity and readability. No AI tools were used in the generation of scientific content, including the study design, data collection, analysis, interpretation of results, or the formulation of conclusions. The authors retain full responsibility for the content of the manuscript and confirm its originality, integrity, and accuracy.

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