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RESEARCH ARTICLE

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Effects of Aerobic Exercise on Inflammatory Markers: A Systematic Review and Meta-Analysis

Prameswari P

Fadli M Trisakti University, Indonesia

ARTICLE HISTORY

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KEYWORDS

Aerobic Exercise, Inflammatory Markers, INF-a, IL-6

ABSTRACT

Background: Inflammation, a complex biological response of the body to harmful stimuli, is a necessary reaction of the immune system to infection or trauma. This rapid and acute process results in high circulating levels of inflammatory mediators. Chronic inflammation is a strong predictor of both disability and mortality, even in the absence of clinical disease. Physical exercise is considered beneficial in alleviating these conditions, but the effects of aerobic exercise on inflammatory markers in a healthy population need further clarification. Therefore, physical exercise can be a potential pathway for inflammatory intervention.

Method: This systematic review and meta-analysis was conducted using PubMed, Lancet, Science Direct, and Google Scholar, following PRISMA 2020 guidelines and employing the PICO format. The aim of this study is to systematically review and conduct a meta-analysis on aerobic exercise and inflammation. The inclusion criteria encompass diverse study designs (RCTs, observational, quasi-experimental, and case-control studies) investigating aerobic exercise and inflammation.

Result: After three rounds of screening, 13 articles directly relevant to the systematic review were chosen for full-text analysis. Literatures selected for this analysis were published in 2018 to 2024.

Conclusion: The lowest level of physical activity was associated with an increased risk of disability. Aerobic exercise may have a positive effect on reducing CRP, TNF-α, and IL-6 levels in middle-aged and older adults. Further randomized controlled trials (RCTs) are needed to determine the effect of aerobic exercise on additional inflammatory markers in middle-aged and older adults.

Introduction

Inflammation is an essential immune response and a critical component of tissue repair. However, chronic inflammation, characterized by persistently elevated levels of pro-inflammatory markers, can have deleterious effects, such as endothelial dysfunction, cardiac hypertrophy, left ventricular dysfunction, apoptosis, and fibrosis, which have associated functional consequences. Inflammation also likely plays a key role in skeletal muscle wasting and dysfunction [1,2]. Numerous mediators and signaling pathways are involved in the inflammatory response to injury or infection, and the sources of pro-inflammatory markers in heart failure (HF) are believed to be numerous, although not completely established [3,4].

As the largest metabolic organ and the main site for insulin-mediated glucose uptake in humans, skeletal muscle is essential for maintaining glucose and lipid homeostasis. It is well-known that skeletal muscle cells express and secrete numerous cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These myokines, primarily regulated by exercise and muscle activity, are involved in glucose and lipid metabolism as well as inflammation [5]. Interestingly, immune cells, particularly macrophages, can induce inflammation in myocytes, negatively impacting myocyte metabolism and contributing to insulin resistance through paracrine effects. TNF-α is particularly important in inflammation and the development of IR, exerting its proinflammatory effects mainly by activating the nuclear factor kappa-B (NF-κB) and c-Jun N-terminal kinase (JNK) pathways. In obesity, the activation of NF-κB can enhance inflammation in macrophages, adipocytes, and muscle. Extensive research has shown that the activation of inflammatory pathways leads to the development of IR. Therefore, reducing chronic inflammation in skeletal muscle might be a protective strategy against IR [6,7].

Physical exercise, a crucial component in preventing and treating diabetes and metabolic diseases, can reduce inflammation and improve IR. Regular exercise enhances insulin signaling in skeletal muscle and promotes insulin sensitivity [5]. Moreover, exercise can modulate inflammatory processes by affecting specific inflammatory signaling pathways, which can interfere with glucose uptake pathways. Previous studies have confirmed that exercise can modulate the NF-κB pathways and improve insulin sensitivity in skeletal muscle. Collectively, these findings indicate that chronic inflammation is fundamental in developing IR, and exercise may improve IR and glucose metabolism by reducing inflammation in skeletal muscle [3-6].

Contact: Prameswari P, Fadli M Trisakti University, Indonesia.

The objective of this systematic review is to comprehensively evaluate the effects of aerobic exercise on inflammation, particularly focusing on the modulation of pro-inflammatory markers and pathways. It aims to determine the extent to which aerobic exercise influences levels of specific pro-inflammatory markers, such as TNF-α, IL-6, sICAM, sVCAM, and CRP. Additionally, the review investigates the underlying mechanisms through which aerobic exercise modulates inflammation, including the role of specific signaling pathways such as the nuclear factor kappa-B (NF-κB) and c-Jun N-terminal kinase (JNK) pathways. It also compares the inflammatory responses to aerobic exercise in different populations, examining variations based on health status, baseline levels of inflammation, and specific clinical conditions. Furthermore, the review analyzes the consistency of findings across various studies to identify patterns or discrepancies in how aerobic exercise affects inflammatory markers. By providing insights into how aerobic exercise can be used as a therapeutic intervention to reduce chronic inflammation, improve insulin sensitivity, and manage conditions associated with chronic inflammation, the review aims to highlight gaps in current research and suggest directions for future studies to better understand the relationship between aerobic exercise and inflammation.

Methods

This systematic review and meta analysis was conducted in adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. Our health care question was defined a priori using the PICO (Population, Intervention, Comparator and Outcomes) format. Population (P): Individuals with varying health statuses, including healthy individuals and those with clinical conditions such as heart failure (HF) and insulin resistance (IR), Intervention (I): Aerobic exercise, encompassing various types and intensities of aerobic training programs. Comparison (C): For healthy individuals: Comparing inflammatory markers before and after aerobic exercise interventions. For clinical populations (e.g., HF, IR): Comparing the effects of aerobic exercise with control groups not undergoing the exercise intervention, or comparing baseline inflammatory markers with post-intervention markers within the same group. Outcome (O): Changes in levels of specific pro-inflammatory markers (e.g., TNF-α, IL-6, sICAM, sVCAM, CRP), modulation of inflammatory pathways (e.g., NF-κB, JNK), and improvements in clinical outcomes related to inflammation, such as insulin sensitivity and cardiac function.

Eligibility Criteria

The eligibility criteria for inclusion in this systematic review and meta-analysis, assessing the effect of aerobic exercises on various state of inflammation, encompass a variety of study designs, including randomized controlled trials (RCTs), observational studies, quasi-experimental designs, and case-control studies.

In this systematic review, we include studies involving individuals of any age and gender with various health statuses, encompassing both healthy individuals and those diagnosed with clinical conditions such as heart failure (HF) and insulin resistance (IR). The focus is on aerobic exercise interventions of any type, including activities like running, cycling, and swimming, as well as interventions of any duration, whether short-term or long-term, aimed at improving cardiovascular fitness. We consider studies that compare inflammatory markers before and after aerobic exercise interventions within the same group, as well as those comparing aerobic exercise interventions with control groups not undergoing the exercise intervention. Additionally, we include studies reporting changes in levels of specific pro-inflammatory markers (e.g., TNF-α, IL-6, sICAM, sVCAM, CRP) in response to aerobic exercise interventions. We also consider studies assessing modulation of inflammatory pathways (e.g., NF-κB, JNK) and improvements in clinical outcomes related to inflammation, such as insulin sensitivity and cardiac function. Regarding study design, we include randomized controlled trials (RCTs), non-randomized controlled trials, quasi-experimental studies, and observational studies (e.g., cohort studies, case-control studies) with appropriate control or comparison groups.

Studies focusing exclusively on populations with medical conditions unrelated to inflammation or aerobic exercise are excluded from this review. Similarly, interventions focusing solely on resistance training, flexibility exercises, or other non-aerobic forms of physical activity are not considered. We exclude studies lacking a comparison group or not reporting pre- and post-intervention inflammatory marker measurements. Furthermore, studies not reporting relevant outcome measures or solely focusing on outcomes unrelated to inflammation are excluded. In terms of study design, we exclude case reports, case series, narrative reviews, editorials, letters, and studies lacking sufficient data for analysis. These criteria ensure that the systematic review encompasses relevant studies and provides a comprehensive assessment of the effects of aerobic exercise on inflammation across various populations and study designs.

Data Sources and Search Strategy

In pursuit of exploring investigate and evaluate effects of aerobic exercise on inflammatory markers across health conditions and populations, a comprehensive search strategy was deployed. Authors systematically investigated relevant bibliographic databases, including the PubMed, Lancet, Google Scholar, and ScienceDirect. The final search was conducted in May 2024. MeSH terms related the topic mentioned above, and articles with relevant terms within the title or abstract were identified as ((("exercise"[MeSH Terms] OR "exercise"[All Fields] OR ("aerobic"[All Fields] AND "exercise"[All Fields]) OR "aerobic exercise"[All Fields]) AND ("inflammation"[MeSH Terms] OR "inflammation"[All Fields] OR "inflammations"[All Fields] OR "inflammation s"[All Fields])) AND (y_5[Filter]) and ((("exercise"[MeSH Terms] OR "exercise"[All Fields] OR ("aerobic"[All Fields]

AND "exercise"[All Fields]) OR "aerobic exercise"[All Fields]) AND ("inflammation"[MeSH Terms] OR "inflammation"[All Fields] OR "inflammations"[All Fields] OR "inflammation s"[All Fields]) AND ("marker"[All Fields] OR "markers"[All Fields])) AND (y_5[Filter]).

Study Selection

Title and abstract screening for eligibility was conducted by two independent investigators. Studies meeting the eligibility criteria were selected, and the full-text articles were obtained and reviewed. Any discrepancies in study selection were resolved through consensus agreement among all authors.

Data Extraction

Data extraction was performed in duplicate from full-text versions of eligible studies by authors. The data included the total number of events and controls for each outcome related to steroidal and nonsteroidal anti-inflammatory eye drops in preventing inflammation and macular edema following cataract surgery. Data presented in tabular format were the primary source for extraction.

Risk of Bias

The GRADE system was utilized to assess the quality of evidence. The risk of bias was evaluated based on limitations in study design, with RCTs considered high-quality evidence and observational studies as low-quality evidence. Each study underwent scrutiny for limitations, and bias was established across studies for each outcome.

Two review authors independently appraised the trials included in this analysis for potential bias. The domains assessed for each trial align with the criteria outlined in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins). Each trial was scrutinized for 'Risk of bias' in specific domains, categorized as "low," "high," or "unclear" risk, with supporting justifications provided. Any disagreements were resolved through discussion.

The Evaluated Risk of Bias Domains Included:

- Selection bias, covering aspects like sequence generation and allocation concealment before randomization.
- Performance bias, involving the masking of participants and personnel to ensure a "low" risk of bias.
- Detection bias, examining the masking of outcome assessors for primary and secondary outcomes.
- Attrition bias, considering incomplete outcome data and methods used to address it in analyses.
- Reporting bias, assessing selective outcome reporting by comparing specified outcomes with reported data in trial documents.
- Other sources of bias, including data extraction on potential biases such as funding sources.

Measures of Treatment Effect

In this systematic review exploring the effects of aerobic exercise on inflammatory markers, several measures of treatment effect are considered to comprehensively evaluate the impact of exercise interventions across different study designs and populations. Firstly, the Mean Difference (MD) serves to compare the average change in levels of inflammatory markers between the aerobic exercise group and the control group, offering insights into the absolute difference in marker levels pre- and post-intervention. the Standardized Mean Difference (SMD) adjusts for variations in measurement scales or units across studies by expressing the effect size in standard deviation units. This measure facilitates comparisons between studies with different measurement methods and enhances the interpretation of results, particularly when pooling data from diverse sources.

For studies with binary outcomes, such as the presence or absence of elevated inflammatory markers, the Risk Ratio (RR) and Odds Ratio (OR) are employed. These measures assess the probability or odds of experiencing the outcome in the aerobic exercise group compared to the control group, providing valuable insights into the relative likelihood of favorable outcomes associated with exercise interventions. In longitudinal studies where time-to-event data are collected, such as time until resolution of inflammation, the Hazard Ratio (HR) becomes pertinent. This measure evaluates the hazard of the event occurring over time between the aerobic exercise and control groups, offering valuable insights into the temporal dynamics of treatment effects.

Moreover, the Relative Risk Reduction (RRR) and Absolute Risk Reduction (ARR) quantify the proportional and absolute reductions in risk of elevated inflammatory markers associated with aerobic exercise compared to the control group, respectively. These measures elucidate the clinical significance of exercise interventions in mitigating inflammatory responses. These measures collectively contribute to a comprehensive understanding of the treatment effects of aerobic exercise on inflammatory markers across various populations and study designs, facilitating evidence-based recommendations for clinical practice and public health interventions.

Dealing with Missing Data

Authors of included trials were contacted for unclear or unreported information. Sensitivity analyses were planned for unsuccessful contacts, assuming the worst outcome for missing data in the treatment group and a better outcome for missing data in the other treatment group. Handling missing data followed methods described in the attrition bias section of the 'Risk of bias' tables.

Assessment of Heterogeneity

Heterogeneity was assessed by examining effect estimates across trials concerning participant characteristics and methodology. Forest plots and the I2 statistic were used, with I2 values above 50% indicating substantial statistical heterogeneity.

Assessment of Reporting Biases

Selective reporting and potential publication bias were assessed by examining funnel plot symmetry, as detailed in the Assessment of risk of bias in included studies section.

Data Synthesis

Meta-analyses were conducted using random-effects models, unless there were fewer than three contributing trials, in which case a fixed-effects model was employed.

Evaluating the Quality of Evidence

The GRADE approach was employed to upgrade the quality of evidence, considering factors such as large pooled effects, dose-response relations, and confounders.

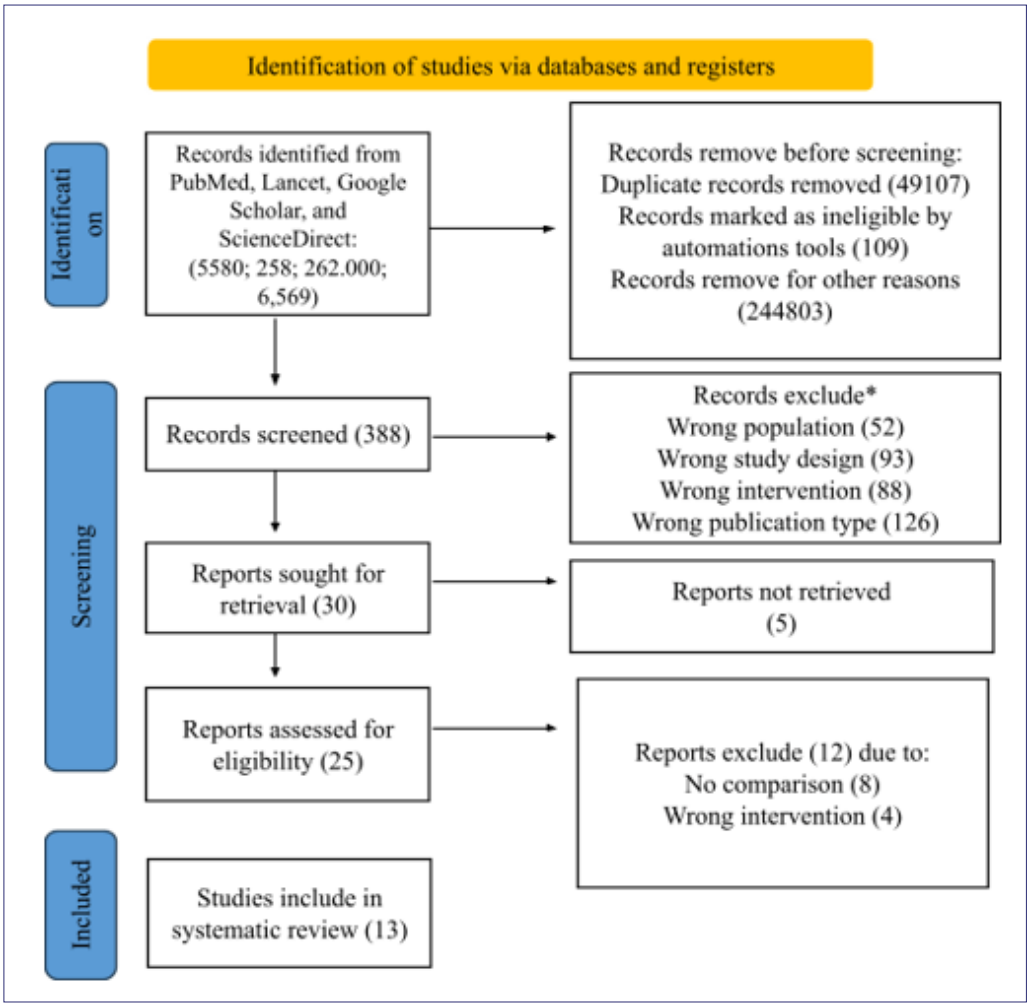

Table 1: Summary of Comparative Studies

Authors and Year of Publication	Origin	Method	Sample Size	Outcome
Wang, et al. [8].	China	Experimental study	Thirty male ICR mice were assigned into one of three groups: control (Con), COPD, and COPD + AE. COPD was simulated by intratracheal injection of lipopolysaccharide (LPS) for 4 weeks.	AE improved LPS-induced emphysema, pulmonary fibrosis, bronchial mucus cell hyperplasia, bronchoconstriction, and cell apoptosis. AE prevented an LPS-induced increase in the total cell, neutrophil, and macrophage counts. AE decreased malondialdehyde (MDA) and myeloperoxidase (MPO) levels but increased glutathione (GSH) and superoxide dismutase (SOD) levels. AE decreased BALF levels of IL-1β, TNF-α, and TGF-β but increased BALF IL-10 levels. AE suppressed the gene expression levels of pro-inflammatory factors CXCL1, IL-1β, IL-17, and TNF-α and profibrotic factors MMP-9 and TGF-β but activated those of anti-inflammatory factor IL-10 and lung-protective factor sirt1.
Abd El-Kader, et al. [9].	Saudi Arabia	Randomized controlled trial.	Sixty previously sedentary elderly subjects participated in this study, their age ranged from 61- 66 years. All Subjects were randomly assigned to supervised aerobic exercise intervention group (group A, n=40) or resistance exercise	The mean values of CD3+, CD4+ and CD8+ T cells count and IL-10 were significantly increased, whereas the mean values of CD4/CD8 ratio,IL-6 and TNF-α were significantly decreased in group (A) and group (B). Also; there were significant differences between mean levels of the investigated parameters in group (A) and group (B) after treatment.
Hiensch, et al. [10].	Stockholm	The OptiTrain study is a randomized controlled exercisetrial in women with breast cancer undergoing adjuvant chemotherapy	Two hundred and forty women scheduled for chemotherapy were randomized to 16 wk of resistance and high-intensity interval training (RT-HIIT),moderate-inte nsity aerobic and high-intensity interval training (AT-HIIT), or usual care (UC)	Overall, chemotherapy led to an increase in inflammation. The increases in IL-6 (pleiotropic cytokine) and CD8a (T-cell surface glycoprotein) were however significantly less pronounced after RT-HIIT compared with UC (−0.47, 95%confidence interval = −0.87 to −0.07, and −0.28, 95% confidence interval = −0.57 to 0.004, respectively). Changes in IL-6 and CD8a significantly mediated the exercise effects on both general and physical fatigue by 32.0% and 27.7%, and 31.2% and 26.4%, respectively. No significant between-group differences in inflammatory markers at 16 wk were found between AT-HIIT and UC

Yang & Chen [11].	China	Randomized controlled trial.	540 obese middle school adolescents from Rizhao of Shandong province are randomly divided into AE group, ST group and NC group with each including 180 subjects.	Two kinds of exercise interventions can improve physique and inflammatory state of obese adolescents, but the long-term effect of resistance exercise is better than aerobic exercise, and the better effects are observed in males than in females.
Park & Nickerson [12].	USA	Randomized controlled trial.	Fifteen overweight female students (BMI 25-32 with a range of 19-30 years) were randomly divided into two groups of exercise and control.	Four weeks of aerobic exercise intervention sig-nificantly increased VO2max in EX (P<0.001). EX also observed a decrease in TNF-α (P=0.033) and an increase in TAS (P=0.028) without changes in body weight and fat mass after 4 weeks of aerobic exercise training. No changes were observed in CON after the intervention.
Sun, et al. [13].	China	Experimental study.	Seven-week-old male db/db mice and age-matched m/m mice were randomly divided into a rest control group or a group that received 12 weeks of aerobic exercise by treadmill training (10 m/min).	In diabetic mice, exercise training significantly decreased the levels of serum TRIG, CHOL, IL-6, TNF-α, ALT and AST; prevented weight gain, hyperglycaemia, and impaired glucose and insulin tolerance. Morphologically, exercise mitigated the diabetesinduced increase in liver tissue microvesicles, inflammatory cells, F4/80 (macrophage marker) levels, and TUNEL-positive cells. In addition, exercise reduced the apoptosis index, which is consistent with the results for caspase-3 and Bax. Additionally, exercise significantly increased SOD activity, decreased MDA levels, activated Nrf2 and decreased the expression of NF-kB, phosphorylated JAK2 and STAT3 proteins in the livers of diabetic mice.
Su, et al. [14].	China	Randomized control trial.	A total of 30 patients with diabetic cardiovascular autonomic neuropathy (DCAN) were randomly divided into a control group (n = 15) and an exercise group (n = 15).	After the intervention, the levels of FBG, 2hPG, serum inflammatory factors, IL-6 and TNF-α in the exercise group were significantly lower than those in the control group ($p < .05$) with no significant differences in serum CRP ($p > .05$). After the intervention, the HRV time domain and frequency domain indexes in the two groups were significantly improved compared with those before the exercise experiment ($p < .01$) and with no significant difference in (lnlf) ($p > .05$). The time-domain indexes, i.e., SDNN and RMSSD, as well as the frequency domain index, i.e., (lnhf), were significantly higher in the exercise group than in the control group, whereas lnlf/lnhf were significantly lower than those in the control group ($p < .05$).
Sandsdal, et [15].	Denmark	a randomized, double-blinded, placebo-contro lled trial.	During an 8-week low-calorie diet (800 kcal/day), 195 adults with obesity and without diabetes lost 12% in body weight.	The diet-induced weight loss decreased the severity of MetS-Z from 0.57 to 0.06, which was maintained in the placebo and exercise groups after one year. MetS-Z was further decreased by liraglutide (− 0.37, 95% CI − 0.58 to − 0.16, P < 0.001) and the combination treatment (− 0.48, 95% CI − 0.70 to − 0.25, P < 0.001) compared to placebo. Abdominal fat percentage decreased by 2.6, 2.8, and 6.1 percentage points in the exercise, liraglutide, and combination groups compared to placebo, respectively, and hsCRP decreased only in the combination group compared with placebo (by 43%, P = 0.03).
Osali A [16].	Japan	Double-blind, placebo-contro lled, and semiexperimen tal design.	Forty-four women with metabolic syndrome (Mets) voluntarily took part in the present study. Participants	IL-10 and BDNF concentrations significantly increased after a 6-week intervention ($P \leq 0.05$). Also, IL-6 serum levels significantly decreased ($P \leq 0.05$). Besides, the results of the present study suggested that nano-curcumin supplementation significantly decreases serum concentrations of malondialdehyde (MDA), and hs-CRP in subjects with metabolic syndrome. In addition, the results of the present study suggested that nano-curcumin supplementation significantly increases serum concentrations of BDNF, IL-10, and total antioxidant capacity (TAC) in subjects with metabolic syndrome.
Nikniaz L et. al. [17].	Iran	a randomized controlled trial	A total of 40 healthy male smokers were recruited in this study	Serum levels of TNF-α, IL-6, and CC16 decreased significantly in AE + VitD, VitD, and AE groups after four weeks ($P < 0.05$). Serum SP-D level decreased significantly only in the AE + VitD group ($P = 0.011$). In addition, FEV1 and FVC increased significantly ($P < 0.05$) in AE + VitD and AE groups after four weeks of intervention. However, the interventions did not have a significant effect on CC16/SP-D ratio and FEV1/FVC ratio ($P > 0.05$). Furthermore, serum levels of 1,25-dihydroxyvitamin D increased significantly in AE + VitD and VitD groups ($P < 0.05$) after four weeks of intervention. However, except for TNF-α, between-group comparisons showed no significant differences in levels of IL-6, CC16, SP-D, CC16/SP-D ratio, FEV1, FVC, FEV1/FVC, and 1,25-dihydroxyvitamin D ($P > 0.05$).
Sloan, et al. [18].	USA	a randomized controlled trial	A total of 119 healthy young adults (age 20–45 years) were recruited from the Columbia University Medical Center/New York Presbyterian Hospital community	Despite a 15% increase in maximal oxygen consumption, there were no changes in inflammatory markers. Additional analyses revealed a differential longitudinal aerobic exercise training effect by lipopolysaccharide level in inducible TNF-a (P=0.08) and IL-6 (P=0.011), showing T1 to T2 increases rather than decreases in inducible (lipopolysaccharide 0.1, 1.0 versus 0.0 ng/mL) TNF-a (51% increase, P=0.041) and IL-6 (42% increase, P=0.11), and significant T2 to T3 decreases in inducible TNF-a (54% decrease, P=0.007) and IL-6 (55% decrease, P<0.001). There were no significant changes in either group at the 0.0 ng/mL lipopolysaccharide level for TNF-a or IL-6.
Brown, et al. [19].	USA	Exploratory analysis of a randomized dose-response trial	39 colon cancer survivors who completed standard therapy were stratified by cancer stage and randomized in a 1:1:1 ratio to one of three treatment groups for 24 weeks of usual-care control,	In the overall population, aerobic exercise was not associated with dose-response reductions in hs-CRP, IL6, or sTNFaR2. Cancer stage modified the association between randomized group and hs-CRP (P=0.022) and IL6 (P<0.001) but not sTNFaR2 (P=0.39). In stage I-II disease, compared to control, exercise was not associated with inflammation outcomes. In stage III disease, compared to control, low-dose exercise reduced hs-CRP: −35.4% (95% CI: −70.1, −0.7) and IL6: −29.6% (95% CI: −58.4, −0.8) but not sTNFaR2: 2.7% (95% CI: sTNFaR2: −15.7, 21.1); high-dose exercise was not associated with inflammation outcomes in stage III disease.
Tartar, et al. [20].	USA	Randomized crossover design.	20 participants	The change in biomarkers from baseline values (+1 min and + 45 min) between exercise and control conditions showed that compared to the control condition, the acute exercise bout significantly increased sAA CRP at +1min at +45 min and in IL-1β +45 min. Cortisol levels significantly decreased at both time points in the control condition

Result

After conducting screening, 13 articles that have a direct relationship with the current systematic were selected for further screening based on full-text reading and analyses. After thorough process of review, we came to four eligible articles. As shown in Figure 1, the articles used for this systematic review included studies that have been published recently, are articles from PubMed, Lancet, Google Scholar, and ScienceDirect database from 2018 – 2024. The final result articles are consisted of experimental study, randomized controlled trial, a randomized controlled exercise, a randomized, double-blinded, placebo-controlled trial, double-blind, placebo-controlled, and semiexperimental design, exploratory analysis of a randomized dose-response trial, and randomized crossover design.

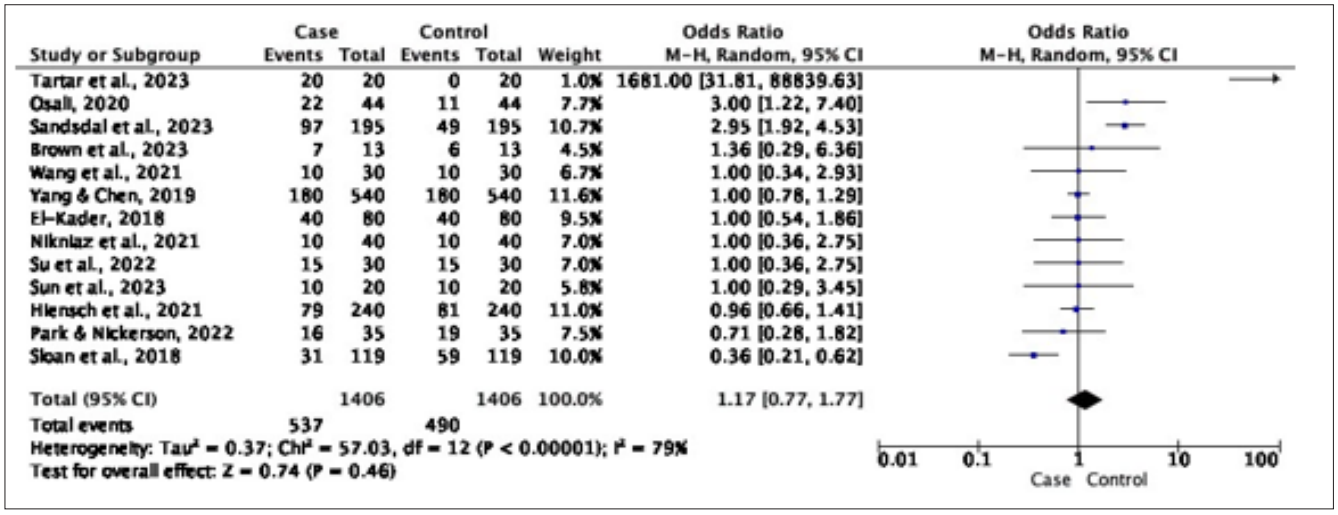

Figure 2: Forest Plot of Comparison: Effects of Aerobic Exercise on Inflammatory Markers

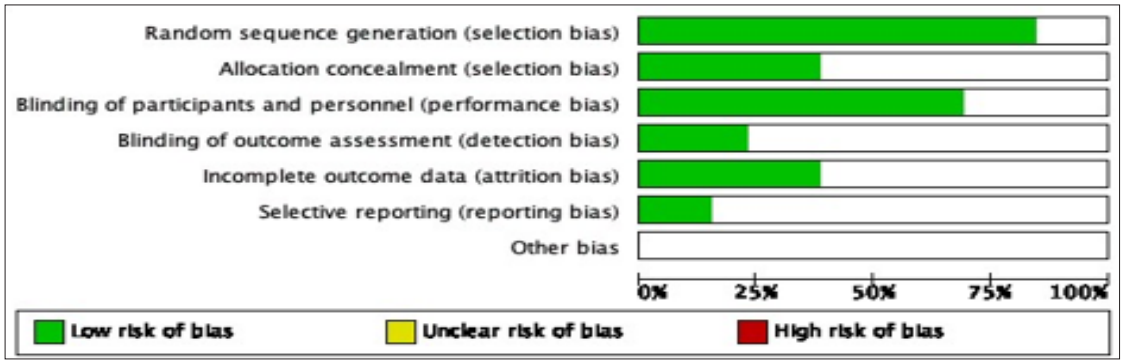

Figure 3: Risk of Bias Graph

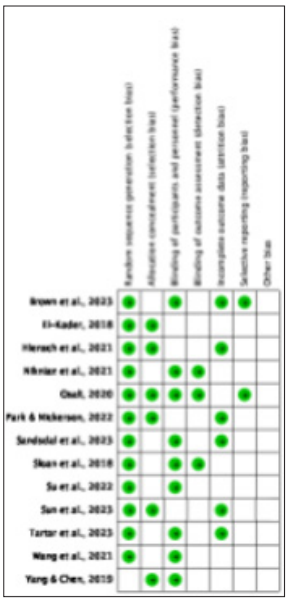

Figure 4: Risk of Bias Summary

Wang, et al. in experimental study investigated whether aerobic exercise (AE) could enhance sirt1 expression and modulate inflammatory/anti-inflammatory and oxidative/antioxidative balances in mice with chronic obstructive pulmonary disease (COPD). LPS administration significantly elevated BALF levels of CXCL1 ($P < 0.001$), IL-1β ($P < 0.001$), IL-10 ($P < 0.001$), IL-17 ($P < 0.001$), TNF-α ($P < 0.001$), and TGF-β ($P < 0.001$) compared to the control group. AE increased BALF levels of IL-10 ($P = 0.0014$) and CXCL1 ($P = 0.0036$); decreased TGF-β ($P = 0.0285$), IL-1β ($P = 0.0378$), and TNF-α ($P = 0.0284$); and did not affect IL-17 levels ($P = 0.96$) compared to the COPD group. These findings indicate that a 4-week AE regimen alleviated pulmonary inflammation in COPD mice [8].

Serum levels of IL-10 ($P < 0.001$) and TNF-α ($P = 0.012$) were significantly elevated following LPS administration compared to the control group. AE increased serum IL-10 levels ($P = 0.0062$) and decreased TNF-α levels ($P = 0.0249$) in COPD mice (Table 3). These results show that the 4-week AE regimen reduced systemic inflammation in COPD mice. LPS administration increased levels

of oxidative stress markers MDA ($P < 0.001$) and MPO ($P < 0.001$) and decreased levels of SOD ($P < 0.001$) and GSH ($P < 0.001$). AE intervention upregulated SOD ($P < 0.001$) and GSH ($P < 0.001$) and downregulated MDA ($P < 0.001$) and MPO ($P < 0.001$) compared to the COPD group [8].

LPS injection upregulated gene expression of pro-inflammatory factors IL-1β ($P < 0.001$), IL-17 ($P < 0.001$), TNF-α ($P < 0.001$), and CXCL1 ($P < 0.001$), as well as pro-fibrotic factors TGF-β ($P < 0.001$) and MMP-9 ($P < 0.001$), and downregulated anti-inflammatory IL-10 ($P < 0.001$) and lung-protective sirt1 ($P < 0.001$). AE increased gene expression of IL-10 ($P < 0.001$) and sirt1 ($P < 0.001$) and decreased expression of CXCL1 ($P < 0.001$), IL-1β ($P < 0.001$), IL-17 ($P < 0.001$), MMP-9 ($P < 0.001$), TGF-β ($P < 0.001$), and TNF-α ($P < 0.001$). LPS administration caused severe bronchial mucus cell hyperplasia and bronchoconstriction (Figure 7B). AE intervention improved bronchial mucus cell hyperplasia and bronchoconstriction compared to the COPD group [8].

This study by Abd El-Kader, et al. aimed to compare the effects of 6 months of aerobic versus resistance exercise training on inflammatory cytokines and immune system responses in elderly Saudis. The groups were homogeneous in demographic variables, with mean ages of 66.43 ± 3.71 years for group A and 65.96 ± 3.42 years for group B. There were no significant differences between the groups in age, weight, height, BMI, systolic blood pressure, diastolic blood pressure, or maximal heart rate (HRmax) [9].

The training group experienced significant reductions in TNF-α (32.7%), IL-6 (31.8%), CD3 count (32.1%), CD4 count (21.9%), CD8 count (33.7%), and CD4/CD8 ratio (24.3%), along with a 28.4% increase in IL-10. In contrast, the control group showed slight, non-significant increases in these variables: TNF-α (3.5%), IL-6 (3.3%), CD3 count (4.9%), CD4 count (2.9%), CD8 count (3.7%), CD4/CD8 ratio (3.4%), and IL-10 (3.8%). Significant differences in inflammatory and immune responses were observed between the groups at the end of the study, highlighting the positive impact of exercise training on reducing inflammation and improving immune function in elderlyIndividuals [10].

Hiensch, et al. in 2021 aimed to identify correlated cytokine groups and hypothesized that exercise reduces systemic inflammation, alleviating fatigue. Participants included 30 in the RT-HIIT group and 27 in the AT-HIIT group, with similar baseline characteristics. Chemotherapy increased proinflammatory cytokines across all groups, but increases in IL-6 and CD8a were less pronounced in the RT-HIIT group. Exercise significantly reduced fatigue in the AT-HIIT group, with IL-6 and CD8a changes mediating RT-HIIT's effects on fatigue. Post-intervention, muscle strength improved in both exercise groups, while cardiorespiratory fitness improved in the AT-HIIT group. Cluster analysis identified two cytokine groups with positive correlations within each group and weaker correlations between them in the RT-HIIT group [1].

The study by Yang and Chen in 2019 focused on obese adolescents from five middle schools in Rizhao, comparing the effects of two exercise interventions. Repeated measurement analysis showed no significant main effect of exercise methods ($P > 0.05$), but significant main effects of gender ($P < 0.05$). No significant interaction effect between exercise methods and gender was found ($P > 0.05$). Before intervention, there were no significant differences in weight, waistline, BMI, and body fat among the three groups. Eight weeks post-intervention, both the aerobic exercise (AE) and strength training (ST) groups showed significant reductions in these metrics compared to the control group (NC) ($P < 0.05$), with no significant differences between AE and ST groups [11].

Four weeks after the suspension of the exercise intervention, weight, waistline, BMI, and body fat levels in the AE and NC groups increased significantly ($P < 0.05$ or $P < 0.01$), while no significant changes were observed in the ST group. The increases were more pronounced in males than females. The AE group had higher levels of these metrics compared to the ST group ($P < 0.05$ or $P < 0.01$), but lower than the NC group ($P < 0.05$ or $P < 0.01$) [11].

Regarding inflammation, there were no significant differences among the groups before the study. Eight weeks post-intervention, TNFα levels decreased in both AE and ST groups, while IL-6 and CRP levels increased ($P < 0.05$), with greater changes in males. Four weeks after suspension, IL-6 and CRP levels decreased significantly in AE and NC groups ($P < 0.05$ or $P < 0.01$), with no significant changes in the ST group. The ST group had higher IL-6 and CRP levels but lower TNFα levels compared to the AE group ($P < 0.05$) [11].

The aim of Park KS and Nickerson in 2022 study was to explore the impact of a 4-week exercise training program on inflammatory biomarkers without concurrent weight or fat loss. We employed two-way repeated measures ANOVA with Tukey post hoc tests, confirming normality and equal variance across all measured variables. Baseline comparisons showed no significant differences between the exercise (EX) and control (CON) groups. Significant time and interaction effects were observed specifically for VO2max, TNF-α, and total antioxidant status (TAS) [12].

The EX group demonstrated a notable increase in VO2max (time×interaction: $P < 0.001$, $F = 9.265$) at POST, with no significant changes in body weight, BMI, percentage of body fat, or visceral adipose tissue mass. Conversely, these variables remained stable in the CON group throughout the 4-week period. The EX group exhibited a significant reduction in TNF-α (time×interaction: $P = 0.033$, $F = 3.742$) and an increase in TAS (time×interaction: $P = 0.0298$, $F = 4.12$) at POST, while levels of adiponectin and CRP remained unchanged. In contrast, the CON group did not experience significant alterations in these biomarkers over the course of the study [12].

The present study by Sun et al aimed to assess the effects of a 12-week combined aerobic exercise and resistance training (AE + RT) regimen on various parameters in elderly patients with type 2 diabetes mellitus (T2DM), focusing on serum inflammatory factors (IL-6 and TNF-α), CRP levels, and heart rate variability (HRV). Before the intervention, there were no significant differences in fasting blood glucose (FBG), 2-hour postprandial glucose (2hPG), HRV (SDNN, RMSSD, lnlf, lnhf, lnlf/lnhf), or serum inflammatory factors (IL-6, CRP, TNF-α) between the control and exercise groups ($p > 0.05$).14

Following the 12-week intervention, both FBG and 2hPG levels significantly decreased in both the control and exercise groups compared to pre-experiment values ($p < 0.01$). Importantly, the exercise group exhibited significantly lower FBG and 2hPG levels than the control group ($t = 2.380$, $p = 0.027$; $t = 2.256$, $p =$

0.033). Regarding HRV parameters, significant improvements were observed in the exercise group compared to the control group. Specifically, the exercise group showed higher SDNN and RMSSD values (time-domain indexes) and lnhf (frequency-domain index) compared to pre-experiment levels and to the control group (t = -4.409, p = 0.000; t = -2.252, p = 0.033; t = -2.185, p = 0.039). The lnlf/lnhf ratio was significantly lower in the exercise group compared to the control group (t = 2.093, p = 0.047) [13].

Furthermore, in terms of serum inflammatory factors, there were no significant differences between the control and exercise groups before the intervention (p > 0.05). After the 12-week intervention, levels of IL-6 and TNF-α significantly decreased in the exercise group compared to pre-experiment values (p < 0.01). Importantly, the exercise group exhibited significantly lower levels of IL-6 and TNF-α compared to the control group (t = 3.685, p = 0.001; t = 2.312, p = 0.029). However, there was no significant difference in serum CRP levels between the two groups (t = 1.038, p = 0.309; see Table 4). These findings suggest that AE + RT is effective in improving glycemic control, enhancing HRV, and reducing inflammatory markers in elderly T2DM patients, highlighting its potential therapeutic benefits for autonomic nerve function and overall health management in this population [13].

Su, et al. in 2022 aimed to assess the effects of a 12-week combined aerobic exercise and resistance training (AE + RT) regimen on various parameters in elderly patients with type 2 diabetes mellitus (T2DM), focusing on serum inflammatory factors (IL-6 and TNF-α), CRP levels, and heart rate variability (HRV). Before the intervention, there were no significant differences in fasting blood glucose (FBG), 2-hour postprandial glucose (2hPG), HRV (SDNN, RMSSD, lnlf, lnhf, lnlf/lnhf), or serum inflammatory factors (IL-6, CRP, TNF-α) between the control and exercise groups (p > 0.05). Following the 12-week intervention, both FBG and 2hPG levels significantly decreased in both the control and exercise groups compared to pre-experiment values (p < 0.01). Importantly, the exercise group exhibited significantly lower FBG and 2hPG levels than the control group (t = 2.380, p = 0.027; t = 2.256, p = 0.033) [14].

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In this Sandsdal et al study, the effects of moderate-to-vigorous exercise, liraglutide 3.0 mg/day, or their combination on metabolic syndrome severity (MetS-Z), abdominal obesity, and hsCRP (an inflammation marker) were investigated over a one-year period following a low-calorie diet-induced weight loss. The study initially included 215 participants (63% women), aged 42 ± 12 years, with a mean BMI of 37.0 ± 2.9. At baseline, the average MetS-Z score indicated a substantial cardiometabolic risk. Following the low-calorie diet, which led to a significant reduction in body weight (mean loss of 13.1 kg), the MetS-Z score improved across all groups, shifting from a higher risk category towards lower risk quartiles. Specifically, the prevalence of metabolic syndrome decreased from 55% to 29%, with notable reductions in hypertension (from 62% to 33%) and pre-diabetes (from 45% to 15%). Insulin resistance, as measured by HOMA-IR, also decreased by 56%, indicating improved metabolic health overall [15].

Over the subsequent year, the placebo and exercise-only groups did not show significant changes in MetS-Z compared to baseline. In contrast, both the liraglutide and combination therapy groups exhibited further reductions in MetS-Z, moving from higher risk quartiles towards lower risk categories. The prevalence of metabolic syndrome remained lower in the active treatment groups compared to placebo. Moreover, android fat percentage decreased significantly in the exercise, liraglutide, and combination groups compared to placebo, indicating beneficial effects on fatDistribution [15].

Regarding inflammation, hsCRP levels decreased by 32% after the low-calorie diet. While hsCRP levels remained stable in the placebo and exercise groups over the subsequent year, there was a significant reduction in the combination therapy group (43% decrease compared to placebo). Adherence to interventions was robust, with participants in the exercise and combination groups averaging over 140 minutes of exercise per week, and all groups maintained consistent medication dosing. Adverse events, predominantly gastrointestinal, were more frequent in the liraglutide groups but generally manageable [15].

Osali's study was to explore the impact of a 6-week regimen combining aerobic exercise training with nano-curcumin supplementation on inflammatory and oxidative stress markers in elderly women diagnosed with metabolic syndrome. The physical characteristics of the participants at the beginning and end of the study were as follows: age, 62.3 ± 1.23 years; height, 164 ± 7 cm; body weight, 81.2 ± 2.4 kg; and BMI, 29.5 ± 1.2 kg/m² [16].

The study revealed significant improvements in various health parameters within the aerobic training group compared to the placebo group after the intervention period (P < 0.01). Specifically, markers such as blood pressure, triglyceride levels, waist circumference, BMI, weight, body fat percentage, and IL-6 concentration were notably lower in the aerobic training group [16].

Furthermore, nano-curcumin supplementation was associated with significant reductions in serum levels of inflammatory markers TNF-α, IL-6, malondialdehyde (MDA), and high-sensitivity C-reactive protein (hs-CRP) among participants with metabolic

syndrome. Additionally, nano-curcumin supplementation led to significant increases in serum concentrations of brain-derived neurotrophic factor (BDNF), IL-10, and total antioxidant capacity (TAC) in the same group ofSubjects [16].

These findings suggest that combining aerobic exercise training with nano-curcumin supplementation may provide beneficial effects by reducing inflammation and oxidative stress while enhancing antioxidant defenses and neurotrophic support in elderly women with metabolic syndrome.

Nickniaz, et al. aim of study was to explore the impact of a 6-week regimen combining aerobic exercise training with nano-curcumin supplementation on inflammatory and oxidative stress markers in elderly women diagnosed with metabolic syndrome. The physical characteristics of the participants at the beginning and end of the study were as follows: age, 62.3 ± 1.23 years; height, 164 ± 7 cm; body weight, 81.2 ± 2.4 kg; and BMI, 29.5 ± 1.2 kg/m². The study revealed significant improvements in various health parameters within the aerobic training group compared to the placebo group after the intervention period ($P < 0.01$). Specifically, markers such as blood pressure, triglyceride levels, waist circumference, BMI, weight, body fat percentage, and IL-6 concentration were notably lower in the aerobic training group [17].

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The primary objective of Sloan, et al. study was to investigate the impact of aerobic exercise on lipopolysaccharide-inducible monocyte production of TNF-a in whole blood ex vivo among participants, comparing an aerobic exercise group to a wait-list control group, with an additional assessment of how sedentary deconditioning might reverse any observed effects. A total of 119 participants (63 women, 56 men) were initially recruited and randomized, with 90 completing the study. The aerobic exercise group completed a significant portion of their training sessions (median 70% attendance), resulting in improved aerobic capacity compared to the control group. However, no significant differences were found in TNF-a production between groups at the follow-up (T2) assessment, regardless of lipopolysaccharide stimulation levels. Similarly, inducible IL-6 release and TLR4 levels did not show significant changes due to aerobic exercise intervention. Interestingly, exploratory analyses suggested that lipopolysaccharide exposure levels influenced TNF-a and IL-6 responses differently over time, with significant changes observed mainly in the training group under specific lipopolysaccharide conditions. These findings underscore the complex interplay between aerobic exercise, inflammatory responses, and environmental factors like lipopolysaccharide exposure in modulating immune function [18].

The study by Brown, et al. aimed to determine whether individuals with higher-stage colon cancer derive greater anti-inflammatory benefits from exercise. Subjects, mostly white females with stage III colon cancer (51%) undergoing chemotherapy (72%), were randomized into low-dose and high-dose aerobic exercise groups. Both groups demonstrated high adherence to exercise protocols, with the high-dose group averaging 247 minutes per week and the low-dose group averaging 141 minutes per week over 24 weeks. Baseline inflammation markers indicated low to moderate levels of hs-CRP (2.53 mg/L), IL6 (2.07 pg/mL), and sTNFaR2 (2524 pg/mL). Overall, there was no clear dose-response relationship observed between exercise dose and reductions in hs-CRP, IL6, or sTNFaR2 in the intention-to-treat population [19].

Subjects with stage I or II colon cancer did not show significant differences in inflammation markers compared to those with stage III cancer at baseline. However, the impact of randomized exercise interventions varied by cancer stage. In subjects with stage III cancer, low-dose aerobic exercise significantly reduced hs-CRP by 35.4% and IL6 by 29.6%, whereas high-dose exercise did not produce significant reductions in any inflammation markers. Exercise adherence did not differ significantly between cancer stages. Correlational analyses indicated that baseline hs-CRP levels correlated with circulating tumor cells, suggesting potential links between inflammation and cancer progression. Changes in sTNFaR2 levels from baseline to week 24 were inversely correlated with changes in circulating tumor cells, indicating a possible relationship between exercise-induced inflammation modulation and tumor dynamics [19].

Tartar, et al. investigated the acute effects of a single aerobic exercise bout on markers of inflammation (CRP and IL-1β) and physiological stress (cortisol and salivary alpha amylase, sAA) in young healthy adults. Participants exercised at a moderate intensity, as indicated by their heart rate and perceived exertion levels recorded at baseline. Paired samples t-tests revealed that immediately post-exercise (1 min), CRP levels significantly increased ($t(19) = 2.73$, $p = 0.007$). By 45 minutes post-exercise, both CRP ($t(19) = 2.73$, $p = 0.007$) and IL-1β ($t(19) = 2.36$, $p = 0.02$) remained significantly elevated compared to baseline. Regarding

physiological stress markers, during the control condition, cortisol levels significantly decreased at both 1 minute ($t(19) = 2.14$, $p = 0.02$) and 45 minutes ($t(19) = 2.90$, $p = 0.005$) post-control period. In contrast, during the exercise condition, sAA levels significantly increased at both 1 minute ($t(19) = 4.48$, $p < 0.001$) and 45 minutes ($t(19) = 2.01$, $p = 0.03$) post-exercise [20].

These findings indicate that a single session of moderate-intensity aerobic exercise acutely increases markers of inflammation (CRP and IL-1β) shortly after exercise. Additionally, exercise induces physiological stress responses characterized by increased sAA levels, reflecting enhanced norepinephrine activity, and initial decreases in cortisol levels, suggesting a complex interaction between exercise and stress-related physiological responses in healthy young adults [20].

Discussion

The systematic review and meta-analysis on the effects of aerobic exercise on inflammatory markers provides a comprehensive evaluation of current evidence from randomized controlled trials (RCTs) and observational studies. The review examines how aerobic exercise influences inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) across diverse populations and settings.

The impact of aerobic exercise on inflammatory markers and related physiological parameters has been extensively studied, revealing significant insights into its potential therapeutic benefits. The findings of various studies highlight the complex interplay between aerobic exercise and inflammation, underscoring the importance of exercise in managing chronic inflammatory conditions and improving overall health. Wang, et al. investigated the effects of aerobic exercise on sirt1 expression and inflammatory/anti-inflammatory balances in mice with chronic obstructive pulmonary disease (COPD). They found that a 4-week aerobic exercise regimen significantly alleviated pulmonary inflammation, as evidenced by changes in bronchoalveolar lavage fluid (BALF) levels of various cytokines. Aerobic exercise increased levels of the anti-inflammatory cytokine IL-10 while decreasing levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and TGF-β. Additionally, aerobic exercise improved oxidative stress markers, highlighting its potential to reduce systemic inflammation and oxidative stress in COPD mice [8].

Similarly, Abd El-Kader, et al. examined the effects of aerobic versus resistance exercise on inflammatory cytokines in elderly individuals. Their study showed significant reductions in TNF-α, IL-6, and other inflammatory markers, along with improvements in immune system responses, in the aerobic exercise group. These results emphasize the role of regular aerobic exercise in reducing inflammation and enhancing immune function in elderly populations.10 In another study, Hiensch, et al. explored the effects of exercise on cytokine levels and fatigue in cancer patients undergoing chemotherapy. They found that exercise, particularly a combination of resistance and high-intensity interval training, reduced pro-inflammatory cytokine levels and alleviated fatigue. The study also demonstrated improvements in muscle strength and cardiorespiratory fitness, further supporting the benefits of exercise during cancer treatment [10].

Yang and Chen focused on obese adolescents and found that both aerobic exercise and strength training significantly reduced weight, waistline, BMI, and body fat compared to a control group. While both exercise interventions decreased TNF-α levels, aerobic exercise was particularly effective in reducing inflammation markers such as IL-6 and CRP. This study highlights the effectiveness of aerobic exercise in improving body composition and reducing inflammation in obese adolescents [11]. Park and Nickerson examined the impact of a 4-week aerobic exercise program on inflammatory biomarkers without concurrent weight loss. They observed significant reductions in TNF-α and increases in total antioxidant status, indicating that aerobic exercise can reduce inflammation and enhance antioxidant defenses even without weight loss [12].

Sun, et al. assessed the effects of combined aerobic exercise and resistance training on elderly patients with type 2 diabetes mellitus (T2DM). The 12-week intervention significantly improved glycemic control, heart rate variability, and reduced levels of inflammatory markers such as IL-6 and TNF-α. This study underscores the potential therapeutic benefits of combined exercise regimens for managing diabetes and associated inflammation [14]. Sandsdal et al. explored the effects of moderate-to-vigorous exercise combined with liraglutide on metabolic syndrome severity and inflammation markers over a year. They found that the combination therapy significantly reduced metabolic syndrome prevalence and inflammation markers such as hsCRP, demonstrating the synergistic effects of exercise and pharmacotherapy in managing metabolic syndrome [14].

Osali, et al. and Nickniaz, et al. both investigated the combined effects of aerobic exercise and nano-curcumin supplementation on elderly women with metabolic syndrome. Their studies revealed significant reductions in inflammatory markers and oxidative stress, along with improvements in antioxidant defenses and neurotrophic support. These findings suggest that combining aerobic exercise with dietary supplements can enhance health outcomes in populations with metabolic syndrome. 16 Tartar, et al. investigated the acute effects of a single aerobic exercise bout on inflammation and physiological stress markers in healthy adults. They found that moderate-intensity aerobic exercise acutely increased markers of inflammation such as CRP and IL-1β, along with stress-related physiological responses. These results highlight the acute inflammatory response to exercise, which may contribute to longer-term adaptations and health Benefits [21].

In summary, the collective evidence from these studies underscores the significant anti-inflammatory and health-promoting effects of aerobic exercise across various populations and health conditions. Regular aerobic exercise not only reduces systemic inflammation but also improves metabolic health, immune function, and overall well-being. These findings highlight the critical role of physical activity in preventing and managing chronic inflammatory diseases.

The completeness and applicability of evidence are addressed by including studies with rigorous methodologies and diverse participant demographics. The review encompasses a broad range of aerobic exercise interventions, from moderate-intensity sessions to structured training programs, ensuring a comprehensive analysis of how different exercise regimens

impact inflammatory responses. By synthesizing findings across multiple studies, the review enhances our understanding of the generalizability of aerobic exercise effects on inflammation, highlighting both consistent trends and potential variations based on participant characteristics and study design.

In assessing the quality of evidence, the review employs established criteria to evaluate risk of bias in included studies. It considers factors such as randomization procedures, blinding methods, and outcome assessments to gauge the reliability and validity of reported outcomes. The meta-analysis provides quantitative insights into the magnitude of effects observed, offering pooled estimates and confidence intervals to assess the precision of findings across studies. This approach enables researchers and healthcare practitioners to interpret the strength of evidence supporting the anti-inflammatory effects of aerobic exercise with greater confidence.

Regarding potential biases in the review process, efforts are made to mitigate publication bias by systematically searching multiple databases and including unpublished studies where feasible. The selection criteria are transparently applied to minimize selection bias, ensuring a balanced representation of studies that meet predefined inclusion criteria. Furthermore, sensitivity analyses and subgroup analyses are conducted to explore sources of heterogeneity and assess the robustness of conclusions across different study populations and methodological approaches.

Conclusion

Chronic inflammation is recognized as a significant contributor to various metabolic disorders, including insulin resistance (IR) and cardiovascular complications. This systematic review investigated the impact of aerobic exercise on inflammation, focusing on specific pro-inflammatory markers and pathways. The included studies consistently demonstrated that aerobic exercise reduces levels of pro-inflammatory markers such as TNF-α, IL-6, sICAM, sVCAM, and CRP. Mechanistically, exercise influences inflammatory signaling pathways, particularly NF-κB and JNK, which are pivotal in mediating inflammation and insulin sensitivity in skeletal muscle.

The findings reveal that aerobic exercise exerts beneficial effects by modulating these pathways, thereby reducing systemic inflammation associated with conditions like chronic obstructive pulmonary disease (COPD), metabolic syndrome, and type 2 diabetes mellitus (T2DM). Moreover, the systematic review identified methodological variations across studies, including different study designs such as randomized controlled trials (RCTs) and experimental studies. While the majority of studies reported positive outcomes of aerobic exercise on inflammation, some discrepancies in findings emphasize the need for standardized protocols and larger-scale trials to validate these effects across diverse populations.

In conclusion, aerobic exercise emerges as a promising strategy to combat chronic inflammation, enhance insulin sensitivity, and improve metabolic health. Future research should focus on elucidating optimal exercise regimens, considering individual variability, and exploring long-term effects on inflammation and associated metabolic outcomes to inform targeted therapeutic interventions [21-25].

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