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SYSTEMATIC REVIEW

Physiology and Biochemistry

Effects of various exercise types on inflammatory response in individuals with overweight and obesity: a systematic review and network meta-analysis of randomized controlled trials

Chaofan Chen[1,4], Dong Zhang[2,4], Mingyi Ye[3], Yanwei You[1], Yiling Song[1] and Xiaoke Chen[1]✉

OBJECTIVE: To explore effective exercise types for reducing chronic inflammation in individuals with overweight and obesity (IOO) while accounting for confounders.
METHODS: A systematic search for RCTs in English between January 2000 and August 2023 was conducted to evaluating exercise effects on inflammatory biomarkers in IOO. A network meta-analysis conducted.
RESULTS: A total of 123 RCTs were analyzed. Different exercise type yielded distinct effects on various inflammatory biomarkers. Specifically, aerobic exercise combined with resistance training (COM) and aerobic exercise (AE) were the most effective for improving leptin levels. AE exhibited the greatest effectiveness in reducing CRP and increasing adiponectin. High-intensity interval training (HIIT) was identified as the most effective exercise modality for ameliorating IL-6, TNF-α, and IL-10. Resistance training (RT) had the least effect compared to other exercise types. Meta regression and subgroup analyses revealed that high-intensity AE demonstrated a greater effect size compared to moderate-intensity AE. The impact of AE on IL-10 was positively associated with both the training period and the age of participants. Positive correlations were observed between reductions in body fat and the effect sizes of CRP, TNF-α, and IL-10. Gender influenced AE effects on IL-6 and TNF-α, with females responding better.
CONCLUSION: This study highlights the potential of exercise in alleviating the inflammatory status in IOO, with different exercise types showing various effects on specific inflammatory biomarkers. The intensity and duration of exercise had a dose-response relationship with intervention effectiveness. Changes in body composition correlated with the effectiveness of the intervention. COM, AE, and HIIT are recommended exercise approaches.

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INTRODUCTION

Over the past 50 years, the incidence of obesity worldwide has increased drastically to pandemic levels [1]. Obesity is associated with a range of additional heath-problems including hypertension, type II diabetes, cardiovascular disease, osteoarthritis, kidney failure, liver disease and several types of cancer [2, 3], it has brought a serious economic and social burden to society. Obesity is frequently accompanied by a low-grade chronic inflammatory state marked out by an increase in systemic markers of inflammation [4–6]. This state contributes to the pathogenesis of many metabolic disorders [7], which can lead to several diseases, such as cardiovascular disease, non-alcoholic fatty liver disease and neurodegenerative disorders.

A low-grade chronic inflammatory state is evident from elevated plasma concentrations of pro-inflammatory biomarkers such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), leptin [8, 9], which can be produced by adipose tissue [10, 11]. The ongoing disorder of these inflammatory markers may cause or exacerbate inflammatory response and induce a series of inflammation-related complications in individuals with overweight and obesity (IOO). Many key inflammatory biomarkers have been consistently associated with both obesity and risk of adverse outcomes in obesity associated disease. A meta-analysis of 51 independent cross-sectional studies provides evidence supporting a positive association between body composition and C-reactive protein (CRP), a biomarker of systemic inflammation [12]; TNF-α, as an important pro-inflammatory biomarker [13], is involved in inflammation and immune response in the body. The accumulated adipose tissue secretes a large amount of TNF-α. The concentration of TNF-α in serum of IOO is higher than that of ordinary people, thus forming a vicious cycle. Adipose-derived IL-6 is an inflammatory biomarker that is upregulated in IOO, playing a

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catalytic role in the development of obesity-related diseases and chronic inflammation. Elevated levels of circulating IL-6 are associated with obesity-related insulin resistance and may potentially predict the development of type II diabetes in various populations [8, 14]. Clinically, plasma IL-6 levels are positively correlated with the presence of obesity [6, 15]. Leptin regulates energy balance [16] and elevated levels promote the development of chronic inflammatory states [6, 17]. Interestingly, common forms of obesity are characterized by an elevated, rather than reduced, concentration of leptin in plasma [18].

Anti-inflammatory markers such as adiponectin and interleukin-10 (IL-10), which play an important role in regulating the inflammatory response, are known to be associated with improved endothelial function [19–21], insulin sensitivity [22–24] and the inhibition of pro-inflammatory mediators. However, these anti-inflammatory markers are suppressed in populations with obesity and insulin resistance, and are coordinated with increased pro-inflammatory markers. In contrast to leptin, circulating levels of anti-inflammatory biomarkers, such as adiponectin and IL-10, are usually reduced in IOO [5, 6, 25, 26]. The unbalanced expression of pro- and anti-inflammatory biomarkers may result in a subclinical inflammatory state and potential development of metabolic and cardiovascular abnormalities [27, 28]. Therefore, it is crucial to study how to effectively intervene in the inflammatory response process and reduce these inflammatory biomarkers in IOO.

The academic community has conducted numerous of studies on the influence of exercise on inflammatory biomarkers in IOO. Many studies have demonstrated that exercise has the potential to ameliorate chronic low-grade inflammation in IOO by facilitating the upregulation of anti-inflammatory biomarkers and suppressing the expression of pro-inflammatory biomarkers [29, 30]. However, the conclusions drawn from previous studies regarding the effects of various types of exercise on inflammatory biomarkers remain highly controversial [31–34]. It is crucial to acknowledge the varying impacts that different forms of exercise have on inflammatory biomarkers. To comprehensively evaluates and understand these findings, conducting a systematic review that effectively compiles and examines relevant studies on the subject matter is imperative. However, the number of studies included in previous meta-studies on the exploration and analysis of inflammatory biomarkers in IOO is insufficient [35–37], resulting in controversy between the conclusions of various studies, and the differences between exercise types and the most effective exercise method remain clear [38]. Previous meta-analysis only explored limited inflammatory biomarkers, while present study expanded the exploration to include interleukin-10.

Based on the above views, this study used a network meta-analysis (NMA) method to summarize the randomized controlled trials (RCTs) regarding the effects of long-term exercise on inflammatory biomarkers in IOO. The study aimed to clarifies the effects of different types of exercise on the inflammatory response in IOO, and to explore appropriate and effective exercise methods for alleviating chronic inflammation in IOO.

METHODS

Registration

This systematic review and NMA were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement Guidelines for Network Meta-Analyses (PRISMA-NMA). The study protocol was registered and approved on the international prospective register of systematic reviews PROSPERO (ID: CRD42023438965).

Search strategy

Articles were retrieved from Cochrane, Embase, PubMed, Web of Science and EBSCO. For searches in Cochrane, Embase and PubMed, combination of MeSH and Emtree terms and keywords were used. All RCTs published in English between January 2000 and August 2023 were included. The search strategy was developed based on key phrases related to the components of the PICOS tool: (P) Population: individuals with overweight and/or obesity; (I) Intervention: aerobic exercise (AE), resistance training (RT), aerobic exercise combined with resistance training (COM), and high-intensity interval training (HIIT); (C) Comparator: no exercise intervention; (O) Outcomes: IL-10, TNF-α, IL-6, CRP, leptin and adiponectin; (S) Study type: RCTs. In addition to the database, a search of the references list of relevant articles and reviews was retrieved to avoid any potentially relevant studies that electronic searches might have missed. The complete strategy search for each database is available in Supplementary 2.

Inclusion and exclusion criteria

The article review and selection process were strictly followed the updated guidelines of PRISMA, as previously described [39]. According to the inclusion and exclusion criteria provided below, two reviewers conducted a thorough screening of database search results by reviewing titles and abstracts to identify all studies that could potentially be relevant. Subsequently, the full-text articles of studies that met the inclusion criteria were identified and independently evaluated by the same two reviewers. In the event of any discrepancies or disagreements between the reviewers regarding the inclusion or exclusion of articles, a consensus was reached through discussions or by seeking the opinion of a third investigator.

Eligible studies met the following criteria: (1) they were RCTs published in English; (2) they included at least one experimental group that underwent a structured exercise training program lasting a minimum of 8 weeks, without concurrent supplementation or dietary restrictions. The classification of exercise training is provided in Supplementary 3. The control group followed a non-exercise routine and maintained their previous lifestyle. Studies that involved two or more exercise interventions without a control group were also included, allowing for direct data comparison between exercise modes. (3) The participant criteria included IOO, with a body mass index (BMI) > 25 kg/m^2 (for European individuals with overweight) and/or BMI ≥ 30 kg/m^2 (for European individuals with obesity), BMI ≥ 24 kg/m2 (for Asian individuals with overweight) and/or BMI ≥ 28 kg/m^2 (for Asian individuals with obesity). In cases where BMI data were not provided, body fat percentage (%BF) was used as a criterion (%BF ≥ 30 for females and %BF ≥ 25 for males). The age of participants in the included studies was not restricted. (4) The studies assessed circulating (plasma or serum) inflammatory biomarkers (IL-6, TNF-α, IL-10, CRP, leptin, or adiponectin) as outcomes before and after the exercise intervention.

If a study met any of the following criteria, it was excluded from the analysis. The exclusion criteria were as follows: (1) duplicate publications, letters to the editor, dissertations, acute effects of a single exercise session, or animal model studies; (2) non-original research articles, such as literature review papers, abstracts published in conference proceedings, or case reports; (3) exercise interventions combined with other interventions or lifestyle changes; (4) articles with insufficient information regarding participant characteristics or intervention details; (5) inability to obtain the full article or relevant data despite contacting the author.

Data extraction

For each record, two reviewers independently extracted the following information: (1) lead author; (2) year of publication; (3) country; (4) subject characteristics (sample size in the experimental and control groups, gender, mean age, BMI, %BF, and complications); (5) detailed information about the exercise intervention (type of exercise, frequency, duration, period, supervision status, and intensity); and (6) outcomes.

Quality assessment

According to the Cochrane Risk of Bias Tool, two reviewers independently assessed the risk of bias (ROB) in the included studies. Any discrepancies were resolved through discussion to reach a consensus or by consulting a third party for a final decision. The Cochrane ROB assessment tool consists of seven domains: (1) randomized sequence generation, (2) concealment of allocation, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) addressing of incomplete outcome data, (6) selective reporting bias, and (7) sources of other bias. Given the inherent difficulty of blinding participants in exercise interventions, this particular component was excluded from the overall ROB score. For each bias domain, the studies were evaluated and categorized as having low, high, or unclear risk based on the available information (insufficient reporting hindered the assessment of certain domains). We utilized the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to evaluate the certainty of evidence for the network estimates of the outcomes.

Data synthesis and statistical analyses

To account for the baseline differences, this study conducted effect size pooling using the change in mean and standard deviation (SD) before and after intervention. The calculation for SD change was done according to the formula provided in the Cochrane Systematic Review Guidelines (version 6.3) [40]. Following the PRISMA network meta-analysis guidelines [39], a random-effects model was employed within the framework of frequency statistics to perform effect size pooling and calculate the 95% confidence interval using STATA 16.0 software (StataCorp, College Station, TX, USA) [41]. As the measurement units of outcome variables were inconsistent, the standardized mean difference (SMD) was used for effect size pooling. Then we conducted the meta-regression analysis by using STATA 16.0 software.

The relationship between different measures of exercise intervention was described through a network diagram, with lines connecting the nodes represent direct comparisons between the intervention measures. The thickness of the lines being proportional to the number of studies. The size of the nodes is proportional to the sample size.

The consistency of each closed loop was evaluated by calculating the inconsistency factor and its 95% confidence interval (95% CI) [42]. The inconsistency was tested using an inconsistency model. When the inconsistency is non-significant ($p > 0.05$), a consistency model analysis was conducted [43]. Consistency of both direct and indirect comparisons was examined using node-splitting method, with $p > 0.05$ indicating non-significant inconsistency.

The intervention effects of different types of exercise were ranked and compared using the Surface Under the Cumulative Ranking (SUCRA) based on the cumulative probability plot [44]. The SUCRA value ranges from 0 to 100, where a value of 100 indicates the best intervention effect and 0 represents the worst intervention effect [45]. The symmetry of the funnel plot was examined to determine the presence of publication bias or small sample effects in the Network Meta-Analysis (NMA).

RESULTS

Literature selection

A total of 5979 potentially eligible articles were initially identified, 5975 of which were from database searches and 4 from reference lists. After 2317 duplicates were removed, 3662 articles remained for screening. By screening the titles and abstracts, 3439 articles were deleted, and 100 articles were deleted after obtaining and reading the full text, The remaining 123 studies were included in this review for quantitative synthesis. The flow diagram reporting trial selection is shown in Fig. 1.

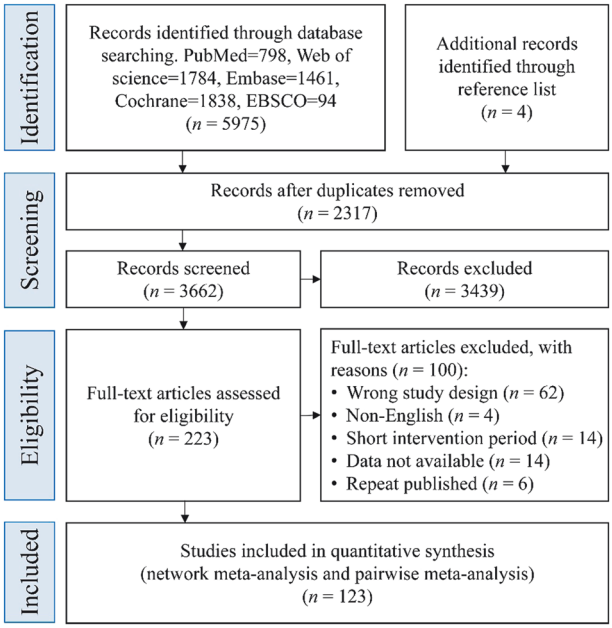

Fig. 1 PRISMA flow diagram depicting the study selection process. The PRISMA flow diagram indicating the number of studies retained and excluded at each stage of the review process.

Characteristics of the included studies

The details characteristics of the included studies were presented in Supplementary 4. A list of included studies is shown in Supplementary 5. All RCTs published in English between January 2000 until August 2023 were included. Overall, most of included studies were conducted in Iran ($n = 33$), America ($n = 20$), Brazil ($n = 12$), Korea ($n = 10$) and Australia ($n = 8$). In terms of participants, 39 studies involved females only, 28 were males only, 27 included both males and females, and the remaining 29 did not report gender or gender ratios. Reported baseline demographics included BMI and %BF. A total of 29 studies involved participants with symptoms of diabetic, non-alcoholic fatty liver disease, knee osteoarthritis, metabolic syndrome, intellectual disability, polycystic ovary syndrome, coronary heart disease, dyslipidemia, chronic insomnia syndrome, and non-alcoholic steatohepatitis.

In terms of exercise characteristics, four types of exercise, AE, RT, COM and HIIT were included. Regarding exercise intervention groups, the distribution of the adopted interventions was as follows: 77 studies applied AE, 30 studies RT, 38 studies applied COM, 30 studies applied HIIT and 113 studies applied CON. The control groups did not engage in exercises or only did light stretching or health education. The exercise interventions ranging from 8 to 52 weeks with most of the studies primarily 8 and 12 weeks in duration. The following outcome measures were reported: over a half study reported CRP (studies = 74, participants in intervention group = 2080, control group = 1373); IL-6 (studies = 47, intervention group = 1300, control group = 814); TNF-α (studies = 45, intervention group = 1162, control group = 770); IL-10 (studies = 17, intervention group = 338, control group = 233). In terms of adipokines outcomes, the leptin was reported in 43 studies (intervention group = 1323, control group = 751) and 50 studies were reported the adiponectin (intervention group = 1358, control group = 819). Different studies have employed various units of measurement to assess identical outcomes.

Results of ROB assessment

We presented full details about the risk of bias of all included studies is reported graphically in the Supplementary 6. Overall, a

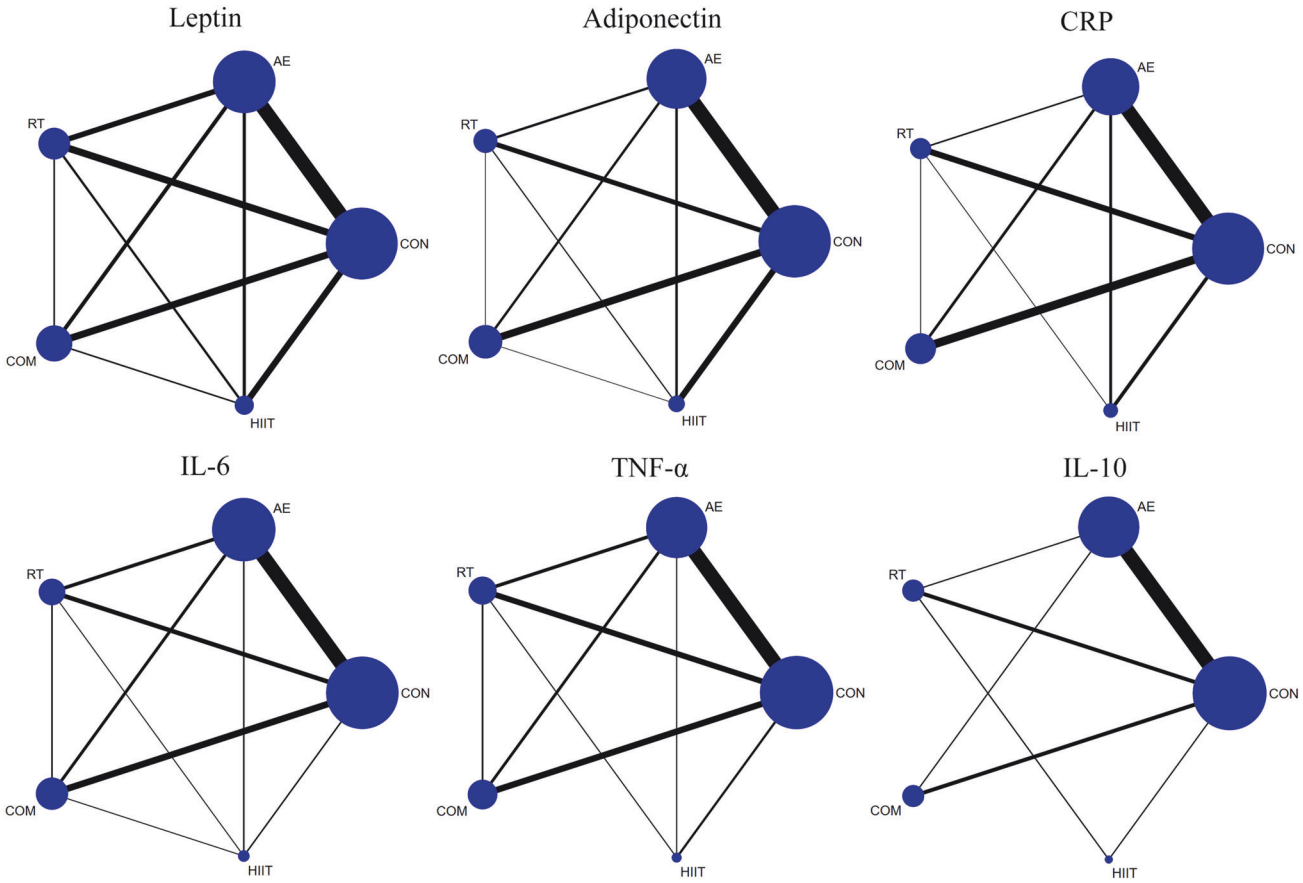

Fig. 2 Network plot presenting the effects of different exercise type on inflammatory biomarkers in IOO. Network diagrams depicting the direct and indirect comparisons for the network meta-analyses. The size of the nodes represents the number of participants in each intervention. The connections between the nodes represent a direct comparison of different exercise interventions, and their thickness indicates the amount of direct evidence.

total of 58 articles clearly stated the method of group allocation, 43 stated allocation concealment, and 28 reported blinding of outcome assessment. Furthermore, a total of 79 studies reported dropout rates. A dropout rate of more than 20% was considered high risk (unless an intention-to-treat analysis was performed). Twelve included studies had a drop rate of more than 20%. In other bias, 25 studies were evaluated as high risk due to small sample size (any arm in the study is less than 10 participants), lack of supervision, and have conflict of interest. In summary, 71 articles were rated to be of low, 28 as moderate, and the remaining 24 rated as high risk of bias.

Network meta-analysis

The supporting materials for inflammatory biomarkers are shown below.

Figure 2 demonstrates NMA plots of eligible studies illustrating the impact of exercise categories on inflammatory biomarkers. The size of the nodes corresponds to the sample size within each exercise category, while the thickness of the lines connecting exercise modes represents the number of studies addressing that specific comparison. Among the interventions, AE appeared to be the most frequently studied type, whereas HIIT was the least commonly investigated.

Supplementary 7 presents the contributions of direct and indirect comparisons to the NMA and the number of studies for each direct comparison.

In order to assess the inconsistency of inflammatory biomarkers, loop-specific heterogeneity estimates, inconsistency models, and node splitting analysis were conducted (Supplementary 8). The inconsistency model indicated no inconsistency in any of the outcomes.

Supplementary 9 displays the forest plots for eligible comparisons of inflammatory biomarkers, which include the 95% confidence intervals and 95% prediction intervals.

Supplementary 10 presents the funnel plot graphics of inflammatory biomarkers to examine the presence of potential publication bias in the NMA. The funnel plots for all outcomes exhibit a generally symmetric shape, indicating a low likelihood of publication bias or a minimal sample effect in the NMA.

Leptin. AE (SMD = −0.89, 95% CI [−1.28, −0.49], $p < 0.001$), COM (SMD = −0.90, 95% CI [−1.42, −0.39], $p < 0.001$), HIIT (SMD = −0.62, 95% CI [−1.17, −0.08], $p = 0.025$), but not RT (SMD = −0.36, 95% CI [−0.89, 0.17], $p = 0.186$) are likely to decrease leptin when compared with CON (Table 1). The SUCRA probability sorting result showed that COM (SUCRA = 81.4) and AE (SUCRA = 81.3) had the highest probability of being the best exercise intervention for leptin, whereas RT (SUCRA = 30.5) is most likely the least effective exercise intervention (Table 2 and Fig. 3).

Adiponectin. AE (SMD = 0.75, 95% CI [0.36, 1.14], $p < 0.0001$), COM (SMD = 0.62, 95% CI [0.12,1.11], $p = 0.015$), and HIIT (SMD = 0.54, 95% CI [0.00, 1.09], $p = 0.05$), but not RT (SMD = 0.47, 95% CI [−0.14, 1.08], $p = 0.13$), show a greater increase in adiponectin when compared with CON (Table 1). The SUCRA probability sorting result showed that AE (SUCRA = 80.4) had the highest probability of being the best exercise intervention for Adiponectin, whereas RT (SUCRA = 48.2) is most likely the least effective exercise intervention (Table 2 and Fig. 3).

Table 1. Network meta-analysis matrix results of leptin and adiponectin, CRP, IL-6, TNF-α, and IL-10.

Leptin	AE	0.28 (−0.38, 0.94)	0.13 (−0.44, 0.70)	0.21 (−0.40, 0.82)	**0.75 (0.36, 1.14)**	Adiponectin
	−0.53 (−1.09, 0.03)	RT	−0.14 (−0.90, 0.61)	−0.07 (−0.83, 0.69)	0.47 (−0.14, 1.08)	
	0.02 (−0.55, 0.58)	0.54 (−0.14, 1.23)	COM	0.07 (−0.63, 0.77)	**0.62 (0.12, 1.11)**	
	−0.26 (−0.86, 0.34)	0.27 (−0.42, 0.95)	−0.28 (−0.96, 0.41)	HIIT	**0.54 (−0.00, 1.09)**	
	−0.89 (−1.28, −0.49)	−0.36 (−0.89, 0.17)	**−0.90 (−1.42, −0.39)**	**−0.62 (−1.17, −0.08)**	CON	
CRP	AE	**−1.06 (−1.72, −0.39)**	**−0.64 (−1.27, −0.02)**	0.32 (−0.59, 1.24)	**−0.83 (−1.24, −0.42)**	IL-6
	−0.24 (−0.66, 0.18)	RT	0.41 (−0.37, 1.20)	**1.38 (0.38, 2.39)**	0.23 (−0.41, 0.87)	
	−0.32 (−0.67, 0.03)	−0.08 (−0.55, 0.38)	COM	**0.97 (−0.00, 1.94)**	−0.18 (−0.75, 0.38)	
	−0.14 (−0.57, 0.29)	0.10 (−0.43, 0.64)	0.19 (−0.32, 0.69)	HIIT	**−1.15 (−2.06, −0.24)**	
	−0.69 (−0.92, −0.45)	**−0.45 (−0.82, −0.07)**	**−0.36 (−0.66, −0.06)**	**−0.55 (−0.97, −0.13)**	CON	
TNF-α	AE	0.43 (−0.89, 1.75)	0.30 (−1.11, 1.71)	−0.29 (−2.56, 1.99)	**0.77 (0.07, 1.47)**	IL-10
	−0.97 (−1.64, −0.29)	RT	−0.13 (−1.91, 1.65)	−0.72 (−2.90, 1.47)	0.34 (−0.89, 1.57)	
	−0.70 (−1.39, −0.01)	0.27 (−0.55, 1.09)	COM	−0.58 (−3.13, 1.97)	0.48 (−0.83, 1.78)	
	0.40 (−0.56, 1.36)	**1.37 (0.34, 2.39)**	**1.10 (0.01, 2.19)**	HIIT	1.06 (−1.14, 3.26)	
	−1.27 (−1.71, −0.84)	−0.31 (−0.94, 0.32)	−0.58 (−1.20, 0.05)	**−1.68 (−2.60, −0.75)**	CON	

Bold indicates significant differences between the two intervention groups. And each cell shows the SMD, along with the 95% CI.
AE aerobic exercise, *RT* resistance exercise, *COM* combined aerobic and resistance training, *HIIT* high-intensity interval training, *CON* control, *CRP* C-reactive protein, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor-alpha, *IL-10* interleukin-10.

CRP. In contrast to CON, AE (SMD = −0.69, 95% CI [−0.92, −0.45], $p < 0.0001$), RT (SMD = −0.45, 95% CI [−0.82, −0.07], $p = 0.02$), COM (SMD = −0.36, 95% CI [−0.66, −0.06], $p = 0.017$) and HIIT (SMD = −0.55, 95% CI [−0.97, −0.13], $p = 0.011$) show a greater decrease in CRP (Table 1). The SUCRA probability sorting result showed that AE (SUCRA = 89.2) had the highest probability of being the best exercise intervention for CRP, whereas RT (SUCRA = 40.8) is most likely the least effective exercise intervention (Table 2 and Fig. 3).

IL-6. AE (SMD = −0.83, 95% CI [−1.24, −0.42], $p < 0.0001$) and HIIT (SMD = −1.15, 95% CI [−2.06, −0.24], $p = 0.013$), but not RT (SMD = 0.23, 95% CI [−0.41, 0.87], $p = 0.485$) and COM (SMD = −0.18, 95% CI [−0.75, 0.38], $p = 0.525$), are likely to decrease IL-6 when compared with CON (Table 1). The intervention effect of AE was significantly better than RT (SMD = −1.06, 95% CI [−1.72, −0.39]) and COM (SMD = −0.64, 95% CI [−1.27, −0.02]), and HIIT was significantly better than RT (SMD = −1.38, 95% CI [−2.39, −0.38]) and COM (SMD = −0.97, 95% CI [−1.94, −0.00]). The SUCRA probability sorting result showed that HIIT (SUCRA = 93.1) had the highest probability of being the best exercise intervention for IL-6, whereas RT (SUCRA = 9.9) is most likely the least effective exercise intervention (Table 2 and Fig. 3).

TNF-α. In contrast to CON, AE (SMD = −1.27, 95% CI [−1.71, −0.84], $p < 0.0001$), and HIIT (SMD = −1.68, 95% CI [−2.60, −0.75], $p < 0.0001$) but not RT (SMD = −0.31, 95% CI [−0.94, 0.32], $p = 0.336$) and COM (SMD = −0.58, 95% CI [−1.20, 0.05], $p = 0.07$) show a greater decrease in TNF-α (Table 1). The intervention effect of AE was significantly better than RT (SMD = −0.97, 95% CI [−1.64, −0.29]) and COM (SMD = −0.70, 95% CI [−1.39, −0.01]). HIIT was significantly better than RT (SMD = −1.37, 95% CI [−2.39, −0.34]) and COM (SMD = −1.10, 95% CI [−2.19, −0.01]). The SUCRA probability sorting result showed that HIIT (SUCRA = 94.2) had the highest probability of being the best exercise intervention for TNF-α, whereas RT (SUCRA = 27.6) is most likely the least effective exercise intervention (Table 2 and Fig. 3).

IL-10. In contrast to CON, AE (SMD = 0.77, 95% CI [0.07, 1.47], $p = 0.03$), but not RT (SMD = 0.34, 95% CI [−0.89, 1.57], $p = 0.587$), COM (SMD = 0.48, 95% CI [−0.83, 1.78], $p = 0.475$), and HIIT (SMD = 1.06, 95% CI [−1.14, 3.26], $p = 0.345$) show a greater increase in IL-10 (Table 1). The SUCRA probability sorting result showed that HIIT (SUCRA = 71.2) had the highest probability of being the best exercise intervention for IL-10, whereas RT (SUCRA = 41.8) is most likely the least effective exercise intervention (Table 2 and Fig. 3).

GRADE assessment

Supplementary 11 shows the GRADE assessment of each comparison and the SUCRA ranking of treatments for the inflammatory biomarkers. Overall, it was high to moderate for most of the comparisons in leptin, CRP and TNF-α, and moderate to low for most of the comparisons in IL-6 and IL-10. The GRADE of the SUCRA ranking was high in leptin and moderate in other outcomes.

Meta-regression

Due to the significant heterogeneity in the analysis results of inflammatory biomarkers in response to different exercise types, further meta-regression is necessary to explore the sources of heterogeneity and investigate the potential dose-response relationship between various regressors and the magnitude of intervention effects. The regressors to be explored include training duration, total intervention sessions, age, gender, %BF change rate, and BMI change rate. Among the four exercise interventions included in this study, there are fewer original studies on RT, COM, and HIIT, which may lead to unstable results in meta-regression analysis. Therefore, meta-regression analysis will not be conducted for these intervention modes. AE shows significant intervention effects on all included outcomes and has a relatively larger number of original studies, thus only the AE intervention group

Table 2. Ranking of exercise interventions in order of effectiveness.

Leptin (43 studies, $N = 2074$)		Adiponectin (50 studies, $N = 2177$)		CRP (74 studies, $N = 3453$)		IL-6 (47 studies, $N = 2114$)		TNF-a (45 studies, $N = 1932$)		IL-10 (17 studies, $N = 571$)	
Treatment	**SUCRA**	**Treatment**	**SUCRA**	**Treatment**	**SUCRA**	**Treatment**	**SUCRA**	**Treatment**	**SUCRA**	**Treatment**	**SUCRA**
COM	81.4	AE	80.4	AE	89.2	HIIT	93.1	HIIT	94.2	HIIT	71.2
AE	81.3	COM	63.6	HIIT	66.9	AE	80.5	AE	79.3	AE	69.8
HIIT	54.2	HIIT	55.4	RT	52.6	COM	40.7	COM	43.8	COM	49.2
RT	30.5	RT	48.2	COM	40.8	CON	25.9	RT	27.6	RT	41.8
CON	2.7	CON	2.4	CON	0.6	RT	9.9	CON	5.1	CON	18

AE aerobic exercise, *RT* resistance exercise, *COM* combined aerobic and resistance training, *HIIT* high-intensity interval training, *CON* control, *CRP* C-reactive protein, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor-alpha, *IL-10* interleukin-10.

will undergo meta-regression analysis. The results show that the % BF change rate ($\beta = 0.069$, $p = 0.02$, $R^2 = 32.57$) is a significant regression factor for CRP. When BMI change rate is used as the regressor, it significantly affects the intervention effect size of AE on TNF-α ($\beta = 0.180$, $p = 0.006$, $R^2 = 38.49$). The magnitude of intervention effect of AE on IL-10 is influenced by training period ($\beta = 0.127$, $p < 0.0001$, $R^2 = 71.49$), age ($\beta = 0.048$, $p < 0.0001$, $R^2 = 80.97$), %BF change rate ($\beta = -0.271$, $p = 0.029$, $R^2 = 60.72$), and BMI change rate ($\beta = -0.533$, $p = 0.05$, $R^2 = 25.19$) (Fig. 4). The intervention effect size of AE on IL-6 ($\beta = 0.916$, $p = 0.066$, $R^2 = 20.60$) and TNF-α ($\beta = 1.841$, $p = 0.011$, $R^2 = 38.33$) was influenced by gender regressor. The effect size of AE on IL-6 and TNF-α in females was larger than that in males (Supplementary 13). No statistically significant regression models were identified in the other outcomes (Supplementary 12).

Dose-response analysis of aerobic exercise intervention

Dose-response analysis of different intensity aerobic exercise intervention. Subgroup analyses were undertaken to investigate the role of various intensity influencing the effect size of AE on inflammatory biomarkers and accounting for the heterogeneity of the models. AE was divided into high intensity, moderate intensity and progressive intensity (the intensity of the exercise is gradually increased over time) according to the characteristics of aerobic exercise intervention intensity in the original study, and the division was based on the study of O'Donoghue et al. [46]. Further subgroup analysis of the intervention effect of different AE intensity was performed. The results demonstrated that for leptin, adiponectin, CRP, IL-6, and TNF-α, the high-intensity AE yielded a larger effect size compared to the moderate-intensity AE (Fig. 5).

To mitigate potential confounding effects caused by different intervention periods, this study examines the intervention effects of varying intensities of AE within the same period. The findings demonstrate that, under the consistent intervention period, all the included outcomes exhibit a higher intervention effect size for high-intensity AE compared to moderate-intensity AE (Fig. 6). Additionally, a meta-regression analysis was conducted, revealing a significant positive correlation between different exercise intensities and the intervention effects size on leptin ($\beta = 1.368$, $p = 0.023$, $R^2 = 100$) and TNF-α ($\beta = 1.723$, $p = 0.003$, $R^2 = 91.77$) after 8 weeks (Supplementary 14).

DISCUSSION

This present NMA revealed that the exercise interventions have a positive effect on several inflammatory biomarkers involved in the systemic inflammatory response process. It is noteworthy that when each training type was analyzed separately, difference between the effect size of interventions were observed. COM and AE yielded the most favorable results in leptin. In terms of adiponectin and CRP, AE demonstrated a significant and optimal effect. Furthermore, for IL-6, TNF-α, and IL-10, HIIT proved to be the most effective intervention with the largest effect size. Meta-regression and subgroup analyses of the intervention effect of AE revealed that the amount of intervention effect of high-intensity AE was greater than that of moderate-intensity AE within the same control period, the intervention effect of AE on IL-10 was positively correlated with the intervention period and the age of the participants, and the degree of improvement in %BF and BMI was positively correlated with the intervention effect of CRP, TNF-α, and IL-10. The gender factor correlated with the intervention effect of AE on IL-6 and TNF-α, with the magnitude of intervention effect being greater for both females than males.

Effects of different types of exercise on inflammatory response in IOO

Leptin and adiponectin are adipokines primarily secreted by white adipose tissue and are closely associated with obesity-related

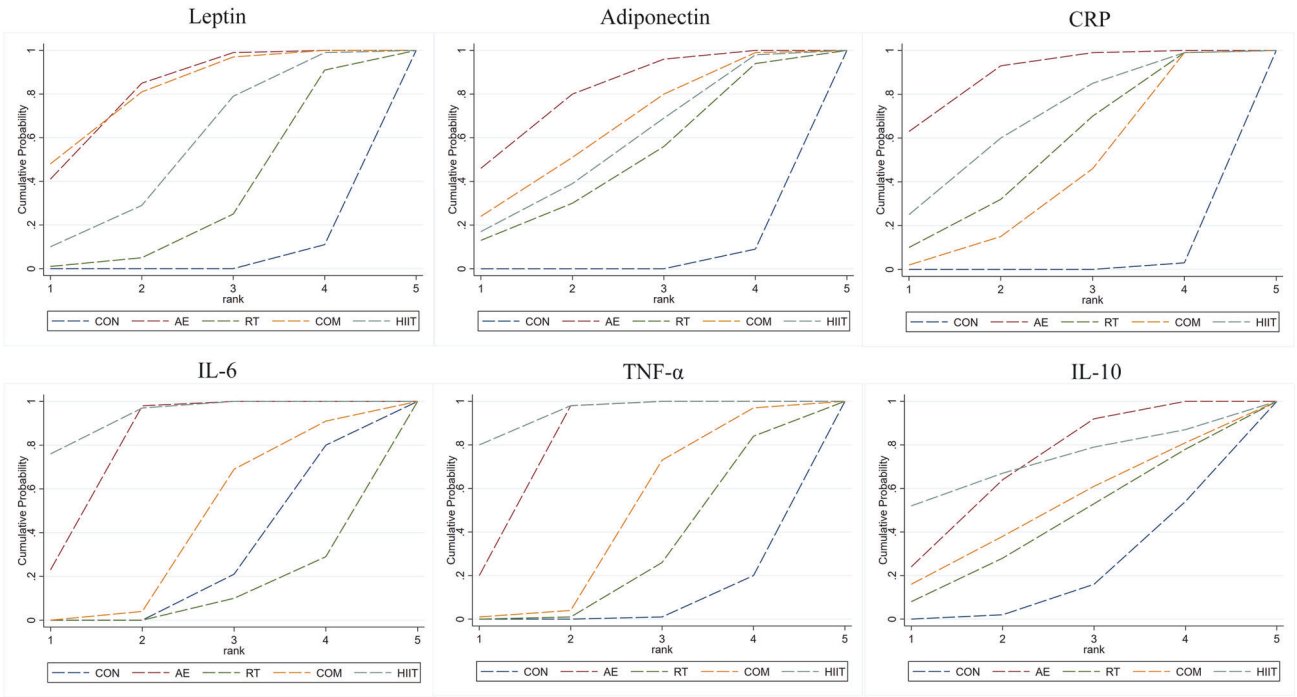

Fig. 3 Area under the curve for cumulative ranking probability of each intervention. Cumulative probability means the probability that a particular exercise modality ranks in efficacy. Surface under the cumulative ranking curve (SUCRA) values were used to assess the relative effect between different exercise interventions. Higher SUCRA values and cumulative ranking curves nearer the top left indicate better performance. CON control group, AE aerobic exercise, RT resistance training, COM combined aerobic and resistance exercise, HIIT high-intensity interval training, CRP C-Reaction protein, IL-6 interleukin-6, TNF-α tumor necrosis factor-α, IL-10 interleukin-10.

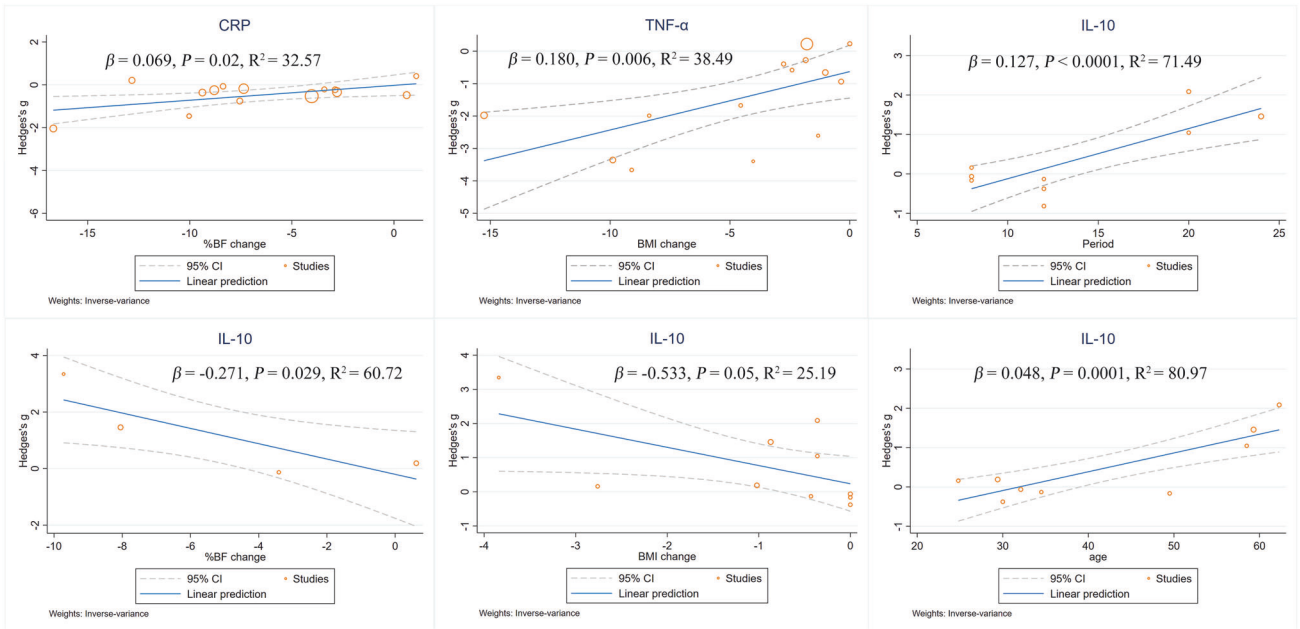

Fig. 4 Meta-regression of the influence of various regressors in the AE groups on the effect size. CRP C-Reaction protein, TNF-α tumor necrosis factor-α, IL-10 interleukin-10.

complications such as insulin resistance, impaired glucose tolerance, and diabetes [16, 47, 48]. Leptin regulates energy balance [16], and its elevated levels promote the development of chronic inflammatory states [6]. Adiponectin improves insulin sensitivity and inhibits inflammation [49]. It is well-documented that IOO typically exhibit elevated levels of leptin and reduced levels of adiponectin [10, 35, 36, 47]. Previous reports have shown that exercise improves serum leptin and adiponectin abnormalities in IOO; however, the current results obtained are still controversial [50]. The study found that AE, COM and HIIT significantly reduced leptin and adiponectin levels, and RT did not show a statistically difference compared to the control group. In the study of Del Rosso et al. [51], it was found that AE, COM and RT can significantly reduce leptin, while for adiponectin, only AE can

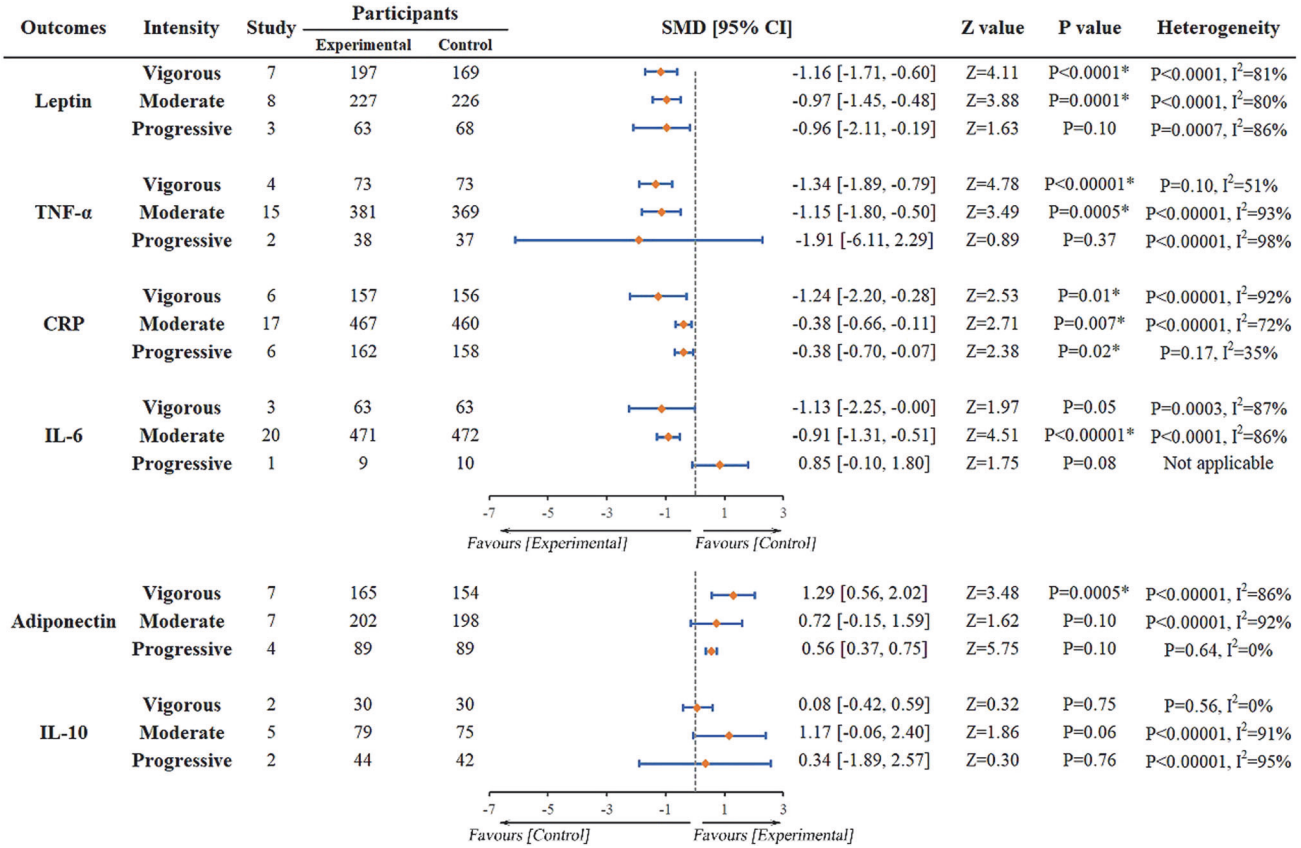

Fig. 5 The difference of intervention effect of aerobic exercise with different intensity. CRP C-Reaction protein, IL-6 interleukin-6, TNF-α tumor necrosis factor-α, IL-10 interleukin-10. * Indicates that the difference in intervention effect size between the exercise group and the control group is statistically significant. Vigorous: >65% VO_2 max or >65% HRR or >75% HRmax; Moderate: 45–65% VO_2 max or 50–65% HRR or 65–75% HRmax; Progressive: the intensity increases from moderate to vigorous week by week.

significantly improve it. Wang et al. [36] found that AE, COM, RT and HIIT showed no statistical difference in the improvement of adiponectin compared with the control group, which may be due to insufficient inclusion in the original study. The SUCRA results demonstrated that COM (SUCRA = 81.4) and AE (SUCRA = 81.3) were the best intervention for adiponectin and AE (SUCRA = 80.4) was most effective for leptin. However, Yu et al. [50] found that only AE was effective for these two adipokines, but not RT and COM. The reason behind the disparity may lie in the fact that, Yu et al. incorporated a smaller number of original studies on COM intervention. Furthermore, they opted for a fixed-effect model during data processing, resulting in a notably dominant contribution from a single article. As far as we know, the potential mechanism of the improvement effect of exercise on these two adipokines may be due to the fact that the levels of serum leptin and adiponectin may be closely related to a range of anthropometric changes, including body composition, weight loss, BMI and body fat distribution [48].

The pathophysiological mechanism linking obesity with elevated CRP levels is well established [52–55]. It was found that CRP levels were positively associated with body composition [12, 14]. Adipose tissue functions as an endocrine organ, that releases a variety of cytokines and hormones, promoting an increase in CRP levels [12]. Elevated CRP is associated with an increased risk of obesity-related diseases, such as cardiovascular disease, diabetes, and hepatic fat accumulation. CRP, through its interaction with vascular endothelial cells, can induce an inflammatory response and endothelial injury. Additionally, it can activate the vascular smooth muscle cells, increase cholesterol uptake and lipid deposition, and further promote the development of atherosclerosis [56]. Therefore, decreasing CRP levels is important for reducing the risk of obesity-related diseases. All exercise types included in this study demonstrated significant improvements in CRP when compared to the control group. Furthermore, the SUCRA results revealed that AE (SUCRA = 89.2) showed the most promising results as an intervention for CRP. In the NMA results of Del Rosso et al. [51], it was found that AE and RT had a significant effect on improving CRP compared with the control group, and the pairwise direct comparison showed that the intervention effect of COM was superior to AE, which contradicted our SUCRA results. We observed that the potential reason for this bias towards COM in the pairwise comparison results might be the greater sensitivity of one of the articles included. Assessing the effects of exercise training on CRP levels raises a controversial question: Do improvements in CRP occur independently from changes in body weight or %BF? Previous studies have revealed a positive association between higher %BF and elevated CRP levels, suggesting that changes in these factors might be necessary for witnessing an improvement in CRP [12, 57]. The meta-regression results presented in this manuscript indicate that the changes in %BF correlate with the improvement in CRP, although they account for only a small portion of the variation in CRP changes resulting from AE interventions. Fedewa et al. [58] have reported similar findings. These results suggest that exercise not only ameliorates CRP by reducing % BF but may also influence CRP changes by regulating other factors.

IL-6, primarily secreted by adipose tissue, muscle, and liver [6], is recognized as a pro-inflammatory cytokine and a key stimulator of CRP production in the liver [59], contributing significantly to the development of chronic inflammation. Clinical evidence indicates a positive correlation between plasma IL-6 levels and obesity [6, 15]. Elevated plasma IL-6 levels are linked to obesity-related

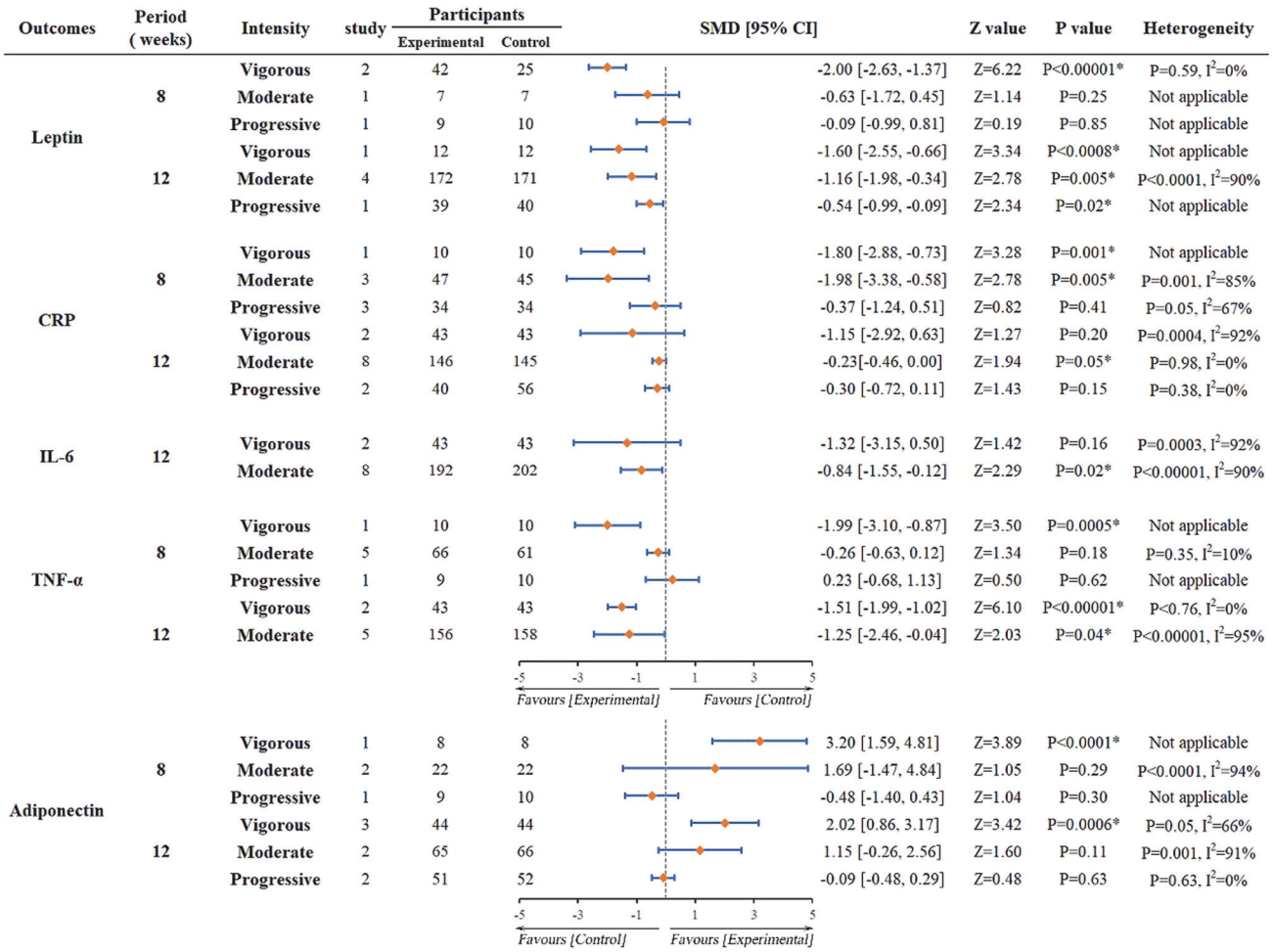

Fig. 6 The difference of intervention effect of aerobic exercise with different intensity within the same period. CRP C-Reaction protein, IL-6 interleukin-6, TNF-α tumor necrosis factor-α, IL-10 interleukin-10. * Indicates that the difference in intervention effect size between the exercise group and the control group is statistically significant. Vigorous: >65% VO_2 max or >65% HRR or >75% HRmax; Moderate: 45–65% VO_2 max or 50–65% HRR or 65–75% HRmax; Progressive: the intensity increases from moderate to vigorous week by week.

insulin resistance and serve as a predictor for the development of type II diabetes [8, 14]. While exercise is an effective strategy to address abnormalities in IL-6 levels, the impact varies across different exercise modalities. Notably, this study revealed that both HIIT and AE led to a significant reduction in IL-6 levels compared to the control group. Conversely, the study by Wang et al. [36] reported no significant impact of HIIT and AE on IL-6. Additionally, a separate study highlighted the positive effect of RT on IL-6, contrasting with the limited impact of COM [51]. The upsurge in pro-inflammatory IL-6 production predominantly results from adipose tissue expansion. Exercise interventions can mitigate adipose tissue size and macrophage infiltration, ultimately down-regulating IL-6. The superior weight loss effects observed with HIIT and AE could explain the substantial differences from the control group. The SUCRA probability ranking results favor HIIT (SUCRA = 93.1) as the most effective exercise intervention for lowering IL-6 levels, which could be attributed to the pronounced impact of HIIT on improving body composition and reducing monocyte production, a significant source of IL-6 secretion in the circulation. Notably, Tenorio et al. [60] noted a significant reduction in monocyte count among adolescents with obesity following HIIT compared to low-intensity training, underscoring the potential suitability of higher-intensity exercises like HIIT for IL-6 modulation in research and clinical practice.

TNF-α, an important pro-inflammatory biomarker, is involved in the inflammatory response and immune response in the body, and its elevated level will reduce insulin sensitivity and promote fat accumulation [61]. The accumulated adipose tissue will secrete large amounts of TNF-α, resulting in the serum TNF-α level of IOO is higher than in the general population. TNF-α is involved in the regulation of insulin resistance and dyslipidemia and is one of the risk factors for inducing type II diabetes [62]. Inhibition of TNF-α may improve hyperinsulinemia caused by obesity and reduce the impact of oxidative stress [63]. Therefore, reducing the level of TNF-α in IOO is particularly important for their health management. This study found that AE and HIIT can significantly reduce TNF-α compared with non-exercise group, with HIIT (SUCRA = 94.2) being the most effective intervention. The possible mechanism by which long-term exercise improves TNF-α is due to the several factors. Long-term exercise may improve the inflammatory state by decreases the amount of pro-inflammatory monocytes [64], which, although they make up only 10% of the whole monocyte family, are major producers of pro-inflammatory biomarkers, such as TNF-a [65]. Long-term exercise may reduce the inflammatory state by improving the damaged endothelial cells in individuals with obesity. Damaged endothelial cells express and release adhesion molecules, leading to the enrichment of circulating white blood cells [66]. Exercise can repair endothelial cells by increasing the number of endothelial progenitor cells [67], improving hemodynamics [68], and reduce the infiltration of macrophages into adipose tissue. Exercise can reduce adipose tissue inflammation in IOO, accelerate the

transformation of macrophages from M1 to M2 [65], and reduce the content of TNA-α produced by macrophages [69].

The circulating level of IL-10 in IOO is lower than that in individuals with normal weight [6]. The reduction of IL-10 leads to the activation of immune cells and excessive release of inflammatory biomarkers, which further aggravates the development of obesity-related diseases [21]. The main functions of IL-10 are to down-regulate the adaptive immune response [21] and to minimize inflammation-induced tissue damage. IL-10 down-regulates or completely inhibits the expression of several pro-inflammatory biomarkers, thereby affecting the ability of effector T cells to maintain an inflammatory response [21, 70], proving that IL-10 is a potent promoter of the anti-inflammatory state [71]. Increasing IL-10 in IOO plays an important role in improving their chronic inflammatory state and preventing obesity-related complications. The present results show a significant increase in IL-10 in IOO with an AE intervention compared to controls. No significant effects were observed for the other three exercise modalities, but it is noteworthy that the effect size of HIIT appeared to be larger than that of AE, and it ranked first in the HIIT SUCRA ranking, suggesting that HIIT (SUCRA = 71.2) may be the best intervention for IL-10. The mechanism by which exercise improves IL-10 may be that exercise can reduce adipose tissue mass and macrophage infiltration, increase the number of endothelial progenitor cells, blood flow, laminar shear stress, and reduce the release of adhesion molecules to alleviate endothelial cell inflammation, and promote the conversion of macrophages from pro-inflammatory M1-type to anti-inflammatory M2 type [65]. Exercise training can increase the number of circulating regulatory T cells, which mainly release anti-inflammatory biomarkers such as IL-10 [65]. Exercise training also increases muscle-derived IL-6 levels [72], which create an anti-inflammatory environment by inducing anti-inflammatory biomarkers such as IL-10 and IL-1Ra, inhibiting TNF-a production in adipose tissue and infiltrating macrophages [73].

Meta-regression

Meta-regression was employed to further investigate the impact of potential factors on the intervention effect of AE. The findings revealed that the training period and age influenced the intervention effect of AE on IL-10. The total number of intervention sessions exhibited a marginally significant effect on the intervention effect of AE on IL-6. Moreover, a significant gender difference was observed in the intervention effect of AE on TNF-a and IL-6. Specifically, the intervention effect was found to be significantly higher in women compared to men.

IOO are usually accompanied by an increase of inflammatory biomarkers. Excessive accumulation of adipose tissue is considered a crucial factor contributing to the upregulation of these inflammatory biomarkers. Therefore, this study aimed to investigate the predictive effect of changes in body composition, specifically the rate of change in %BF and BMI, on the impact of exercise on inflammatory biomarkers. Our findings revealed significant correlations between the rate of change in body composition and the intervention effect of exercise on CRP, TNF-α, and IL-10. Reductions in %BF were positively associated with improvements in CRP, while reductions in BMI were positively associated with improvements in TNF-α. Additionally, improvement in IL-10 was positively correlated with improvements in %BF and BMI. Prior studies have confirmed that excessive adipose tissue accumulation is a primary cause of increased CRP and TNF-α levels [12, 74], whereas a reduction in adipose tissue can downregulate CRP and TNF-α while simultaneously upregulating the anti-inflammatory biomarker, IL-10.

Dose-response of aerobic exercise at different intensities

Based on the characteristics of aerobic intensity interventions in the original research, this study categorized intensity into three levels: high, moderate, and progressive, in order to explore whether intensity covariates were related to the intervention effect size. It was found that the intensity regressor had a significant predictive effect on the meta-regression results of leptin and TNF-α. Further subgroup analysis was conducted and revealed that higher intensity was associated with a larger intervention effect size. As the meta-regression also indicated that the intervention period was one of the factors influencing the effect size, a consistent intervention period was maintained to control this variable, allowing the effects of different intensities within the same period to be observed. The subgroup results showed that 8 weeks of moderate-intensity of AE intervention did not show statistically significant differences in leptin, adiponectin, and TNF-a, indicating that short duration and low-intensity exercise interventions had poorer effects. Moderate intensity only showed significant differences after a 12-week intervention, suggesting that an adequate intervention period can compensate for the lack of exercise intensity. In contrast, high-intensity aerobic exercise, whether at 8 weeks or 12 weeks, showed significant effects on the aforementioned three indicators, indicating that intensity was a crucial factor in generating differences in intervention effects.

Strength and limitations

To the best of our knowledge, this is the first systematic review and meta-analysis to encompass a significant number of original studies focusing on the inflammatory response to exercise in IOO. Additionally, the inclusion of a substantial number of original studies investigating the optimal intervention approach for IL-10 adds to the scientific significance of this research. Furthermore, meta-regression analyses and subgroup analyses were performed to explore and elucidate the dose-response relationship between exercise characteristics and the intervention effect size in the AE group; to clarify the association between changes in body composition and the effects of the intervention.

Our study had a few limitations that should be acknowledged. In the NMA analysis results, we did not investigate the impact of gender and age on the outcomes. The majority of the studies we reviewed did not provide explicit information on the gender distribution, and some of them included participants of both genders. Moreover, the age range of the included studies was wide. Consequently, our analysis did not account for potential differences or interactions related to gender and age. It is important to note that, if we had examined these factors separately, the sample size within each subgroup may have been insufficient to draw robust conclusions. Hence, future studies should consider incorporating a more balanced representation of different gender and age groups, allowing for a more comprehensive analysis. Diets were not considered in this study. Some original studies have reported that diet combined with exercise has a better effect on the improvement of inflammatory state in people with obesity than exercise alone [75, 76]. Future research should delve deeper into examining the effect of exercise combined with diet and explore appropriate exercise prescriptions for people with obesity. Considering the quality of the methodology, only original studies published after the year 2000 were included.

CONCLUSION

The findings from this study highlight the potential of exercise in alleviating the inflammatory biomarkers in IOO, while distinct exercise types exhibiting varied impacts on specific inflammatory biomarkers. A dose-response relationship was observed between the intensity and duration of exercise and the effect size of intervention. Furthermore, a significant correlation was found between changes in body composition and the efficacy of the intervention. Our results suggest that COM, AE, and HIIT emerge as

viable exercise approaches to alleviate the inflammatory status in IOO, whereas RT is not recommended. Reducing the level of inflammation in IOO is of clinical significance for preventing obesity-related and inflammation-related complications such as type II diabetes, metabolic syndrome, and hypertension. Future research should delve deeper into examining the impact of a combined exercise and diet regimes on the inflammatory state of IOO, while also exploring suitable exercise prescriptions in order to enhance their overall well-being.

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AUTHOR CONTRIBUTIONS

This systematic review and network meta-analysis was designed by CFC and XKC. CFC and DZ conducted literature searches and selected articles for inclusion. YLS extracted data checked the extracted data. YWY contributed to data curation and analysis. CFC and DZ wrote the manuscript. XKC revised the manuscript, and YE polished the language. All author read and approved the final version. XKC responsible for supervision, review and editing, project administration, funding acquisition.

COMPETING INTERESTS

The authors declare no competing interests.

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