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Effect of resistance exercise on peripheral inflammatory biomarkers in healthy adults: a meta-analysis of randomized controlled trials

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Abstract. – OBJECTIVE: This study aimed to evaluate the effect of resistance exercise on peripheral inflammatory biomarkers in healthy adults.

MATERIALS AND METHODS: Four databases, including PubMed, Web of Science, Cochrane Library, and SPORTDiscus, were searched from inception until April 1st, 2022. A meta-analysis was conducted using a random-effects model, followed by sensitivity analysis, subgroup analysis, meta-regression analysis, and publication bias analysis.

RESULTS: 15 randomized controlled trials were included in the meta-analysis. The pooled results showed that resistance exercise significantly decreased TNF-α levels (SMD = -0.81, 95% CI: -1.42 to -0.20, *p* = 0.009) but did not affect IL-6 and CRP levels. Individuals with BMI 18.5-24.9 exhibited significantly decreased IL-6 levels, while moderate strength resistance exercise could significantly decrease TNF-α levels. Finally, age might be a confounding factor influencing the effect of resistance exercise on IL-6.

CONCLUSIONS: Resistance exercise could reduce TNF-α levels in healthy adults, and resistance exercise with moderate intensity could reduce TNF-α levels more effectively.

Key Words:
Resistance exercise, Inflammatory biomarkers, Meta-analysis.

Introduction

Systemic chronic low-grade inflammation is not uniformly defined or measured as a disease. Over the years, plasma biomarkers and cell biomarkers have gained significant momentum as reliable disease indicators[1]. Systemic chronic low-grade inflammation is a significant risk factor for developing several chronic diseases and a key factor in the pathogenesis of many chronic diseases, including cancer[2], diabetes mellitus type 2[3], cardiovascular disease[4] and Alzheimer's disease[5], accounting for more than 50% of all deaths worldwide[6]. Systemic chronic low-grade inflammation is reportedly an independent risk factor for death in healthy adults. Current evidence suggests that decreased levels of inflammatory factors secondary to lifestyle changes are related to decreased risk of disease and death[7]. It is widely thought that the novel coronavirus-2019 (COVID-2019) infection is caused by an increased inflammatory response in the body that damages the immune system. Moreover, novel coronavirus infection in elderly subjects with chronic inflammation is often fatal[8].

It has been reported that adults lose 3-8% of their muscle mass every decade due to a lack of physical activity, conducive to a decrease in resting metabolic rate and fat accumulation, resulting in an increased risk of obesity[9]{Westcott, 2012 #29;Rose, 2021 #40}, and the prevalence rate of chronic disease[10] and dementia[11]. Resistance exercise can reduce visceral fat and increase resting metabolic rate[12]. Moreover, it can enhance cardiovascular health by lowering resting blood pressure, low-density lipoprotein cholesterol and triglycerides, and increasing high-density lipopro-

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tein cholesterol[13]. Due to its minimal side effects, resistance exercise has been extensively studied to prevent and treat numerous chronic diseases[14]. Theoretically, resistance exercise may play an anti-inflammatory role by producing cytokines to reduce visceral fat and enhance skeletal muscle contraction[15]. In practice, randomized controlled trials have yielded inconsistent results, attributable to the heterogeneity of research samples (age, gender, baseline inflammatory factor level) and the complexity of the resistance exercise intervention program (exercise duration, intensity, frequency).

Based on these grounds, we conducted a meta-analysis of randomized controlled trials that assessed the effect of resistance exercise on biomarkers of peripheral inflammation in healthy adults to identify the resistance exercise program with the best anti-inflammatory effect. We sought to explore the effect of resistance exercise on the level of inflammatory biomarkers in healthy adults and differences in demographic characteristics and duration and intensity of resistance exercise.

Materials and Methods

Literature Search

This meta-analysis was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[16]. Four databases, including PubMed, Web of Science, Cochrane Library, and SPORTDiscus, were searched from inception until April 1st, 2022. The following search strategy was used: "resistance exercise" OR "Anaerobic exercise" OR "Exercise resistance" AND "Inflammation" OR "Interleukins" OR "Tumor Necrosis Factors" OR "Cytokines" AND "randomized controlled trial".

Study Selection

All documents retrieved from various databases were imported into Endnote reference management software to remove duplicates. The screening of the literature was performed by two researchers independently. The titles and abstracts of the relevant literature were screened. The full texts were then retrieved, further screened and read independently. Disagreements were resolved by a discussion with a third author. Research articles were included in the study based on the following inclusion criteria: (1) parallel or crossover randomized controlled trials; (2) the study participants were healthy individuals; (3) the experimental group was subjected to resistance exercise of any intensity, duration, and frequency, while the control group received no treatment; (4) the outcomes of interest were plasma or serum inflammatory biomarkers. The exclusion criteria included: (1) subjects with comorbid diseases or obesity; (2) the description of the experimental data was not clear, and the difference before and after the experiment could not be calculated; (3) the intervention was aerobic exercise or mixed exercise; (4) conference and review articles.

Data Extraction and Quality Assessment

The researchers used a pre-designed form to extract the information included in the literature. The extracted information includes (1) basic information of the study: first author, year of publication, and research country; (2) participant information: number of participants, age and gender of participants, baseline body mass index (BMI) of participants; (3) resistance exercise intervention information: duration, intensity, and frequency of resistance exercise intervention; (4) outcome indicators: plasma or serum levels of inflammatory biomarkers (IL-6, CRP, TNF-α).

The methodological quality and risk of bias of each included study were assessed by the Physiotherapy Evidence Database (PEDro) scale[17]. According to the total PEDro scores, the methodological quality can be divided into four grades (9 to 10 points = high quality, 6 to 8 points = good quality, 4 to 5 points = medium quality, and lower than 4 points = very poor quality). The dimensions of the scale include: "description of subject inclusion conditions", "random allocation", "hidden allocation", "no significant difference at baseline", "blinding of subjects and evaluators", "blinding of results", "withdrawal rate of subjects before and after the experiment ≤ 15%", "intention to treat analysis", "statistical comparison between groups", "point estimation and difference measurement". The Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) system was used to evaluate the evidence level of each result[18]. The study design determined the baseline quality of evidence according to the specific provisions of the GRADE guidelines (randomized controlled trials were initially defined as high quality). However, other factors could reduce (unexplainable heterogeneity) or increase the quality level (significant impact).

Statistical Analysis

Considering the heterogeneity of the population, resistance exercise regimen, and biomarker measurement, the combined effect quantity was calculated using a random-effects model for the net change of inflammatory biomarker concentration (the change in the intervention group minus the change in the control group), which was expressed by the standardized mean difference (SMD) and its 95% confidence interval (95% CI).

First, a preliminary meta-analysis was performed to determine the overall effect of resistance exercise on each inflammatory biomarker. Then sensitivity analysis was used to evaluate the robustness of the results of the primary meta-analysis, subgroup analysis was used to investigate the potential sources of heterogeneity, and meta-regression analysis was used to test the differences between groups and further explore the sources of heterogeneity. To improve the sensitivity of finding sources of heterogeneity, the results of the meta-regression analysis were considered statistically significant when $p < 0.1$.

The heterogeneity between studies was tested by the Cochrane Q test and quantified by I^2 statistics[19]. I^2 < 25%, 25 to 50% and > 50% indicated insignificant, moderate, and high heterogeneity, respectively. As for the Cochrane Q test, a p-value < 0.1 was statistically significant. Evaluation of publication bias was conducted by Begg's test and Egger's test[20]. A p-value < 0.05 indicated the existence of publication bias. If publication bias was present, pruning and filling methods were used to remove minimal studies and iteratively recalculate the set effect until the funnel was symmetrical[21]. All analyses were performed by STATA version 11.0 (StataCorp LLC, College Station, TX, USA). Unless otherwise mentioned, a p-value < 0.05 was statistically significant.

Results

The Flow of Study Selection

A total of 2784 documents were retrieved from four databases, and 864 duplicates were removed using the Endnote reference manager. After screening the title and abstract, 1274 studies were excluded, and 646 potentially eligible studies were obtained. After reading the full text, studies were excluded due to non-healthy subjects (n=187), non-RCT trials (n=214), inconsistent intervention methods (n=135), and inconsistent outcome indicators (n=95). Finally, 15 studies[22-36] were included in the meta-analysis (Figure 1).

Basic Information of Included Studies

15 articles were included with a total number of 646 participants, published between 2009 and 2019. The average age of participants ranged from 21 to 86 years old. Among them, the average age was less than 45 years old in one study[22], 45-60 years old in two studies[28,29], and more than 60 years old in 11 studies[23,24,26,27,30-36]. One study did not describe the age[25]. The control group in the 15 studies were mostly treated by maintaining the same lifestyle, and the duration of resistance exercise intervention lasted for 8[22] (n=1), 12[23,24,26,33,36] (n=5), 10[25,28,31,32] (n=4), 16[29,30] (n=2), 18[35] (n=1) and 24[27,34](n=2) weeks (Table I).

Quality Evaluation of Included Studies

Among the 15 included studies, the score of the PEDro scale was 7-9, with an average score of 8. The overall research quality was good (Table II). All 15 studies reported "condition description", "random assignment", "baseline level", "statistical difference between groups", and "point estimation and difference detection". However, none of the 15 studies scored in "blinding subjects and evaluators" and "blinding results". The "withdrawal rate of the number of participants" was ≤ 15% in 13 studies, 4 studies did not report "allocation concealment", and 3 studies did not report "intention to treat analysis" (Table II).

Evaluation of the Quality of Evidence

As shown in Table III, according to the GRADE criteria, since the preliminary meta-analysis results had no significant effect and there was significant heterogeneity, the evidence level for IL-6 and CRP was low, indicating that the credibility of our results was not high, and the actual effect might be very different from the estimated value. Despite the heterogeneity of the results of TNF-α, the level of evidence was moderate, indicating that the results were highly reliable, and the effect observed in our study was close to the real effect.

Meta-Analysis of the Effect of Resistance Exercise on IL-6 in Healthy Adults

12 studies[22,23,25-29,31-35] (15 intervention groups) that reported the effect of resistance exercise on IL-6 levels in healthy adults were analyzed using a random-effects model. The pooled results (Table IV) showed that resistance exercise had no significant effect on IL-6 (SMD = -0.09, 95% CI: -0.48 to 0.29, p = 0.638), and there was high heterogeneity (I^2 = 77.5%, p < 0.001) (Figure 2). To explore the source of heterogeneity, subgroup analysis was conducted on the research characteristics that may cause heterogeneity. A subgroup analysis was conducted

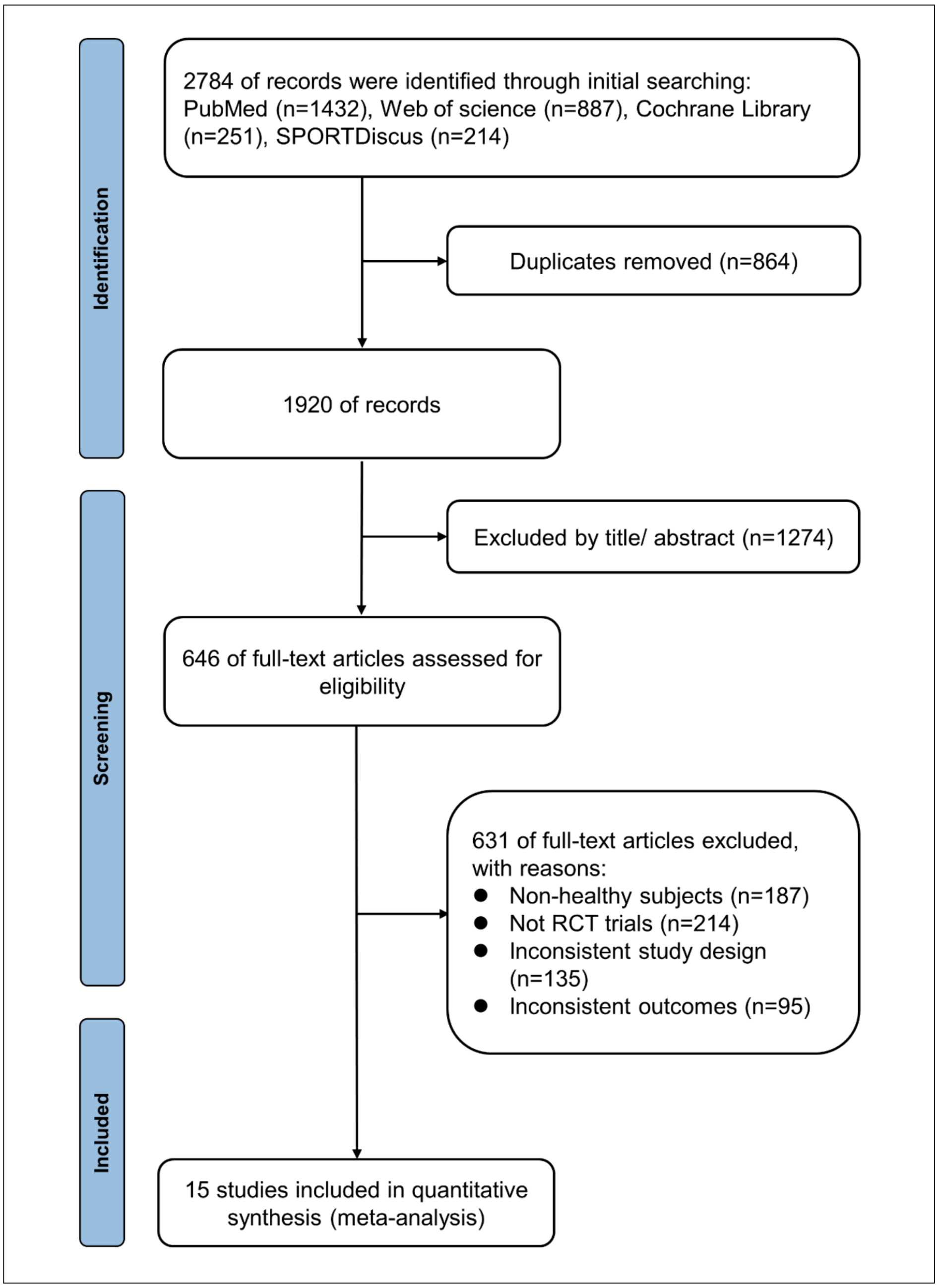

Figure 1. Flowchart of the literature retrieval process.

based on the region, gender, age, BMI, exercise intensity, and resistance exercise intervention cycle. The results showed that studies conducted in America (SMD = -0.66, 95% CI: -1.29 to -0.04, p = 0.037) showed a significant reduction in IL-6 levels (Table IV). Studies with subjects with a BMI of 18.5 to 25 showed that resistance exercise could significantly reduce IL-6 levels (SMD = -0.54, 95% CI: -0.96 to -0.12, p = 0.012) (Table IV).

Univariate meta-regression analysis based on age found that there was a significant difference (p= 0.068) in studies with participants aged < 45 years old (Figure 3). Therefore, region, BMI, and age may account for the heterogeneity of the effect of resistance exercise on IL-6 levels.

Table I. Characteristics of included studies in this meta-analysis (15 studies).

Author	Year	Age	Country	No (Intervention/ control)	Comparators	Intervention	Duration	Outcomes
Azizbeigi et al[22]	2015	21.1	Iran	20/10	/	Intensity: 65-70%1RM or 85-90%1RM Frequency: 3 times/week	8 weeks	IL-6, TNF-α
Donges et al[25]	2010	/	Australia	76/26	Maintain a sedentary lifestyle	Intensity: 70-75%10RM Frequency: 2-3 times/week	10 weeks	IL-6, CRP
Forti et al[27]	2014	67.1	Belgium	20/20	Maintain daily activity level	Intensity: 50-80%1RM Frequency: 3 times/week	12 weeks	IL-6
Ihalainen et al[28]	2019	70	Finland	78/18	Maintain daily activities	Intensity: 70-90% 1RM Frequency: 1 times/week or 2 times/week or 3 times/week	24 weeks	IL-6, CRP
Levinger et al[28]	2009	49.3	Australia	12/13	No physical exercise	Intensity: Gradually increase from 40-50% 1RM to 75-85% 1RM Frequency: 3 times/week	10 weeks	IL-6, CRP, TNF-α
Libardi et al[29]	2012	49.2	Brazil	34/13	Maintain previous nutrition	Intensity: 8-10RM Frequency: /	16 weeks	IL-6, CRP, TNF-α
Phillips et al[31]	2010	71.5	USA	28/7	Rest quietly during the experiment	Intensity: 70-80% 1RM Frequency: 3 times/week	10 weeks	IL-6, TNF-α
Rodriguez-Miguelez et al[32]	2014	69.4	Finland	16/10	Maintain daily activities	Intensity: 60-80% 1RM Frequency: 2 times/week	10 weeks	IL-6, CRP
Martins et al[30]	2010	78.5	Portugal	14/13	Maintain healthy living habits	Intensity: moderate Frequency: 3 times/week	16 weeks	CRP
Tomeleri et al[35]	2017	70.4	Brazil	22/23	No physical exercise	Intensity: / Frequency: 3 times/week	18 weeks	IL-6, CRP, TNF-α
Beltran Valls et al[23]	2014	72	Italy	13/10	Maintain normal living habits	Intensity: 70%1RM Frequency: /	12 weeks	IL-6, TNF-α
So et al[33]	2013	69.8	Korea	18/22	No physical exercise	Intensity: moderate Frequency: 3 times/week	12 weeks	IL-6, CRP, TNF-α
Strandberg et al[34]	2015	68	Sweden	21/21	maintain their normal activities of daily living.	Intensity: increasing gradually Frequency: 2 times/week	24 weeks	CRP, TNF-α
Urzi et al[36]	2019	86.4	Slovenia	11/9	No physical exercise	Intensity: moderate Frequency: 3 times/week	12 weeks	CRP
Cunha et al[24]	2019	70.3	Brazil	25/23	Maintain daily activities	Intensity: moderate Frequency: 3 times/week	12 weeks	CRP

CRP, C-reactive protein; IL-6, interleukin 6; TNF-α, tumor necrosis factor α; RM: maximum number of repetition.

Meta-Analysis of the Effect of Resistance Exercise on CRP in Healthy Adults

Eleven studies[24,25,27-30,32-36] (13 intervention groups) reported the effect of resistance exercise on CRP levels in healthy adults. The pooled analysis (Figure 4) showed that resistance exercise had no significant effect on CRP level (SMD = -0.30, 95% CI: -0.72 to 0.13, $p = 0.168$), and there was high heterogeneity ($I^2 = 80.8\%$, $p < 0.001$) (Figure 3). To explore the source of heterogeneity, subgroup analyses were conducted based on the region characteristics, gender, age, BMI, exercise intensity, and resistance exercise intervention

Table II. Quality evaluation of included studies.

Study	Condition	Random assignment	Hide assignments	Baseline	Blinding of subjects and evaluators	Blinding results	Exit rate ≤ 15%	Intention to treat analysis	Statistical comparison between groups	Point estimation and difference measuremen	Score
Azizbeigi et al[22]	1	1	0	1	0	0	1	1	1	1	7
Cunha et al[24]	1	1	1	1	0	0	1	1	1	1	8
Donges et al[25]	1	1	0	1	0	0	1	1	1	1	7
Forti et al[26]	1	1	1	1	0	0	1	0	1	1	7
Ihalainen et al[27]	1	1	1	1	0	0	0	1	1	1	7
Levinger et al[28]	1	1	0	1	0	0	1	1	1	1	7
Libardi et al[29]	1	1	1	1	0	0	1	0	1	1	7
Phillips et al[31]	1	1	1	1	0	0	1	0	1	1	7
Rodriguez-Miguelez et al[32]	1	1	0	1	0	0	1	1	1	1	7
So et al[33]	1	1	1	1	0	0	1	1	1	1	8
Strandbeg et al[34]	1	1	1	1	1	0	1	1	1	1	9
Martins et al[30]	1	1	1	1	0	0	0	1	1	1	7
Tomeleri et al[35]	1	1	1	1	0	0	1	1	1	1	8
Urzi et al[36]	1	1	1		0	0	1	1	1	1	8
Beltran Valls et al[23]	1	1	1	1	0	0	1	1	1	1	8

Scoring criteria of PEDro scale: 9-10: excellent; 6-8: good; 4-5: average; < 4: poor.

Table III. Grades of Recommendation, Assessment, Development and Evaluation (GRADE) quality of evidence.

Outcomes	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect size	Plausible residual confounding	Dose-response gradient	Grade rating
IL-6	0	-1†	0	-1‡	0	0	0	0	Low
CRP	0	-1†	0	-1‡	0	0	0	0	Low
TNF-α	0	-1†	0	0	0	0	0	0	Moderate

†There is significant and unexplainable heterogeneity in the preliminary meta-analysis; ‡95% confidence interval of effect quantity in preliminary meta-analysis.

Table IV. Results of sensitivity analysis, subgroup analysis and publication bias stratified by study characteristics.

Outcomes	Interventions	SMD (95% CI)	p^1	Heterogeneity test		p^3	p^4	
				I^2 (%)	p^2		Begg's test	Egger's test
IL-6								
Overall	15	-0.09 (-0.48, 0.29)	0.638	77.5	**<0.001**		0.843	0.763
Location						**0.018**		
Asia	3	1.01 (0.46, 1.56)	**<0.001**	22.8	0.274	-	-	-
Europe	7	-0.32 (-0.88, 0.23)	0.255	78.2	**<0.001**	-	-	-
America	3	**-0.66 (-1.29, -0.04)**	**0.037**	51.0	0.130	-	-	-
Oceania	2	0.00 (-0.62, 0.63)	0.994	46.1	0.173	-	-	-
Gender						0.477		
male	3	0.44 (-0.96, 1.84)	0.537	85.6	**0.001**	-	-	-
female	3	-0.40 (-1.01, 0.22)	0.211	77.5	**<0.001**	-	-	-
mix	9	-0.13 (-0.63, 0.38)	0.624	80.0	**<0.001**	-	-	-
Age						**0.068**		
<45	3	1.01 (0.46, 1.56)	**<0.001**	22.8	0.274	-	-	-
45-60	2	-0.20 (-1.40, 1.00)	0.743	76.8	0.038	-	-	-
>60	9	-0.38 (-0.85, 0.08)	0.103	75.2	**<0.001**	-	-	-
BMI						0.868		
<18.5	4	0.63 (-0.05, 1.30)	0.069	62.4	**0.046**	-	-	-
18.5-25	9	**-0.54 (-0.96, -0.12)**	**0.012**	71.1	**0.001**	-	-	-
25-30	1	**0.97 (0.31, 1.63)**	**0.004**	-	-	-	-	-
Duration of exercise						0.357		
< 1 day	1	0.40 (-0.39, 1.20)	0.319	-	-	-	-	-
1-12 weeks	8	-0.05 (-0.81, 0.70)	0.888	87.1	**<0.001**	-	-	-
>12 weeks	6	-0.20 (-0.47, 0.07)	0.147	7.4	0.369	-	-	-
Intensity of exercise						0.979		
moderate	11	-0.14 (-0.66, 0.39)	0.614	82.6	**<0.001**	-	-	-
high	4	-0.03 (-0.46, 0.39)	0.879	38.9	0.178	-	-	-

CRP	Interventions	Net change (95% CI)	p^1	I^2 (%)	p^2	p^3	p^4	
							Begg's test	Egger's test
Overall	**13**	-0.30 (-0.72, 0.13)	0.168	80.8	**<0.001**		0.669	0.648
Location						0.846		
Asia	1	0.13 (-0.49, 0.76)	0.679	-	-	-	-	-
Europe	7	-0.30 (-0.71, 0.10)	0.144	57.6	**0.028**	-	-	-
America	3	-0.50 (-2.05, 1.05)	0.528	93.8	**<0.001**	-	-	-
Oceania	2	0.01 (-1.38, 1.39)	0.994	87.8	**0.004**	-	-	-
Gender						0.908		
male	1	**1.03 (0.17, 1.89)**	**0.019**	-	-	-	-	-
female	4	-0.78 (-1.69, 0.14)	0.098	87.2	**<0.001**	-	-	-
mix	8	-0.20 (-0.61, 0.21)	0.330	67.0	**0.003**		-	-
Age						**0.041**		
45-60	2	**0.88 (0.29, 1.47)**	**0.003**	0.0	0.642	-	-	-
>60	10	**-0.47 (-0.94, -0.01)**	**0.046**	79.4	**<0.001**		-	-
Duration of exercise						0.901		-
1-12 weeks	6	-0.41 (-0.95, 0.13)	0.141	72.4	**0.003**	-	-	-
>12 weeks	7	-0.20 (-0.87, 0.47)	0.559	86.3	**<0.001**	-	-	-
Intensity of exercise						0.691		
moderate	10	-0.37 (-0.92, 0.18)	0.185	84.1	**<0.001**	-	-	-
high	3	-0.06 (-0.49, 0.67)	0.768	32.6	0.227	-	-	-

Continued

Table IV. Results of sensitivity analysis, subgroup analysis and publication bias stratified by study characteristics.

TNF-α	Interventions	Net change (95% CI)	p^1	I^2 (%)	p^2	p^3	p^4	
							Begg's test	Egger'stest
Overall	8	**-0.81 (-1.42, -0.20)**	**0.009**	77.7	**<0.001**	-	1.000	0.494
Location						0.780		
Asia	2	**-0.72 (-1.36, -0.07)**	**0.028**	0.0	0.490	-	-	-
Europe	2	-0.35 (-1.51, 0.81)	0.554	79.4	**0.028**	-	-	-
America	3	-1.37 (-2.99, 0.25)	0.097	91.2	**0.000**	-	-	-
Oceania	1	-0.51 (-1.30, 0.29)	0.215	-	-		-	-
Gender						0.850		
male	3	-0.41 (-1.03, 0.21)	0.197	34.0	0.220	-	-	-
female	3	**-1.66 (-2.80, -0.53)**	**0.004**	84.5	**0.002**	-	-	-
mix	2	-0.13 (-0.89, 0.63)	0.746	42.8	0.186	-	-	-
Age						0.685		
<45	2	**-0.72 (-1.36, -0.07)**	**0.029**	0.0	0.490	-	-	-
45-60	2	-0.19 (-0.81, 0.42)	0.251	15.2	0.227	-	-	-
>60	4	**-1.20 (-2.31, -0.09)**	**0.035**	87.7	**<0.001**	-	-	-
BMI						0.463		
<18.5	3	-0.37 (-1.08, 0.34)	0.308	48.5	**0.143**	-	-	-
18.5-25	3	-1.37 (-2.99, 0.25)	0.097	91.2	**<0.001**	-	-	-
25-30	1	**-0.92 (-1.57, -0.26)**	**0.016**	-	-			
Duration of exercise						0.914		
< 1 day	1	-0.51 (-1.30, 0.29)	0.215	-	-	-	-	-
1-12 weeks	5	**-1.02 (-1.99, -0.05)**	**0.039**	83.9	**<0.001**	-	-	-
>12 weeks	2	-0.53 (-1.75, 0.70)	0.397	82.6	**0.016**	-	-	-
Intensity of exercise						0.717		
moderate	7	**-0.79 (-1.48, -0.11)**	**0.023**	80.8	**<0.001**	-	-	-
high	1	**-0.95 (-1.88, -0.02)**	**0.044**	-	-	-	-	-

p^1 value for net change; p^2 value for heterogeneity in the subgroup; p^3 value for heterogeneity between groups with meta-regression, analyzed as categorical variables; p^4 value for publication bias; significant *p*-values are highlighted in bold prints. BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin 6; TNF-α, tumour necrosis factor alpha.

cise. The potential mechanism underlying this phenomenon remains unclear, warranting further study. Univariate meta-regression was conducted based on the age of the study participants. The results showed a negative correlation between age and the effect of resistance exercise on IL-6 levels. Indeed, age may account for the heterogeneity in findings among studies. A longitudinal review reported that most people develop a chronic low-grade proinflammatory state as they age, representing a significant risk factor for various diseases, physical and cognitive impairment, weakness, and death[42]. Even in the elderly without chronic diseases, serum pro-inflammatory factors such as IL-6 could increase by 2 to 4 times. Even in the elderly without chronic diseases, serum proinflammatory factors such as IL-6 exhibit a 2 to 4-fold increase. In general, the concentration of peripheral inflammatory factors is lower in younger individuals than in older individuals, and the effect of improving inflammatory levels through resistance exercise may be weaker in younger individuals than in older individuals, which partially explains the negative correlation between age and the effect of resistance exercise on IL-6 concentration.

As an acute phase reactant, CRP is released upon stimulation by cytokines in the inflammatory cascade[43]. Our findings revealed that resistance training yielded no substantial effect on CRP levels. Although a stratified analysis revealed that significantly increased CRP levels were observed in males, only a single study enrolled exclusively male participants. Accordingly, additional RCTs are necessary to confirm our findings.

TNF-α is a proinflammatory cytokine and one of the most common biomarkers released in response to inflammation[44]. Our results showed that moderate- and high-intensity resistance exercises could significantly reduce TNF-α

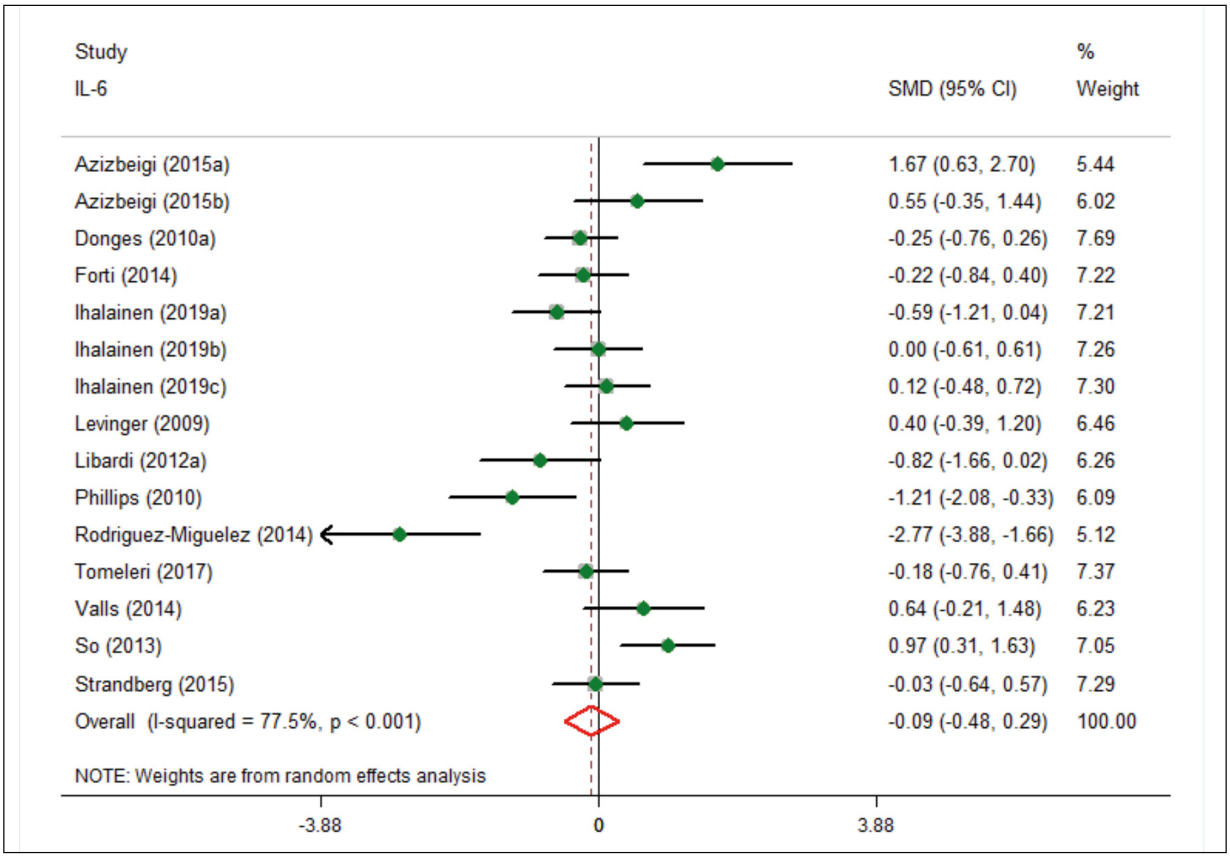

Figure 2. Forest plot of the effect of resistance exercise on IL-6 level.

cycle. The results showed significantly increased levels of CRP in males (SMD = 1.03, 95% CI: 0.17 to 1.89, $p = 0.019$) (Table IV). Participants with age <45 years old (SMD = 0.88, 95% CI: 0.29 to 1.47, $p = 0.003$) exhibited significantly increased CRP levels, and participants aged >60 years old (SMD = -0.47, 95% CI: -0.94 to -0.01, $p = 0.046$) exhibited significantly reduced CRP levels. Therefore, sex and age may account for the heterogeneity in the effect of resistance exercise on CRP levels.

Meta-Analysis of the Effect of Resistance Exercise on TNF-α in Healthy Adults

7 studies[22,23,28,29,31,33,35] (8 intervention groups) reported the effect of resistance exercise on TNF-α levels in healthy adults. The meta-analysis showed that resistance exercise could significantly reduce TNF-α levels in healthy adults (SMD = -0.81, 95% CI: -1.42 to -0.20, $p = 0.009$), but there was a large heterogeneity among studies ($I^2 = 77.7\%$, $p < 0.001$) (Figure 5).

To explore the sources of heterogeneity, a subgroup analysis was conducted based on the region, gender, age, BMI, exercise duration and exercise intensity (Table IV). The results showed that significantly reduced TNF-α levels were observed in studies in Asia (SMD = -0.72, 95% CI: -1.36 to -0.07, $p = 0.028$), women (SMD = -1.66, 95% CI: -2.80 to -0.53, $p = 0.004$), age < 45 years old (SMD = -0.72, 95% CI: -1.36 to -0.07, $p = 0.029$), and age >60 years old (SMD = -1.20, 95% CI: -2.31 to -0.09, $p = 0.035$). Resistance exercise with a duration of 12 weeks (SMD = -1.02, 95% CI: - 1.99 to -0.05, $p = 0.039$), moderate exercise intensity (SMD = - 0.79, 95% CI: - 1.48 to -0.11, $p = 0.023$) and high intensity (SMD = -0.95, 95% CI: - 1.88 to -0.02, $p = 0.044$) significantly reduced the level of TNF-α in healthy adults. Although only one study reported the results of high-intensity exercise, it was suggested that region, gender, age, duration of resistance exercise and intensity of resistance exercise may be sources of heterogeneity among studies.

Publication Bias

Begg's test and Egger's test were used to assess whether there is publication bias. The test

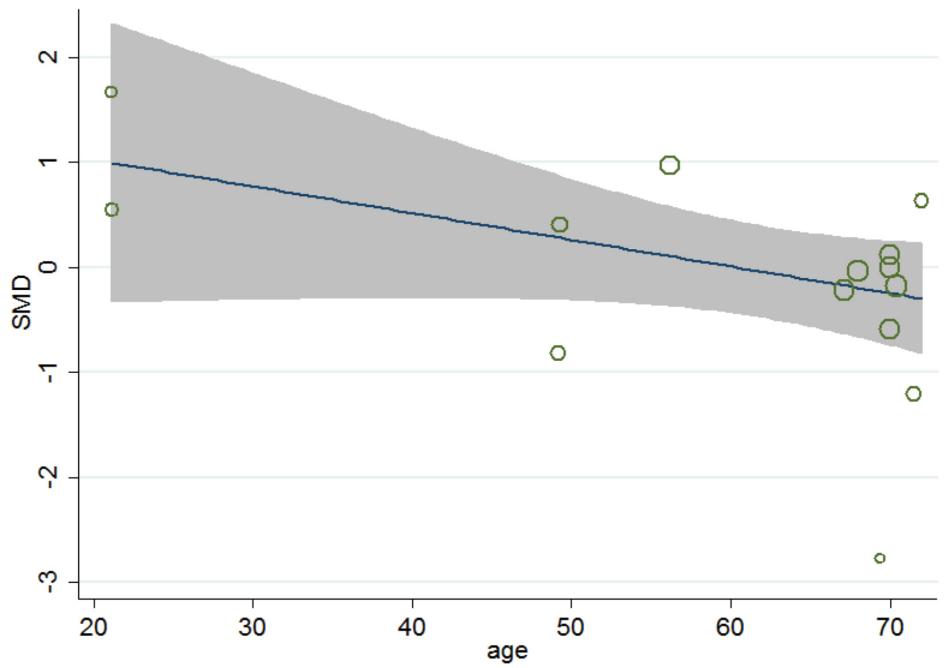

Figure 3. Meta-regression analysis of the effect of resistance exercise on IL-6 level (adjusted by age).

results (Table IV) yielded p-values > 0.05, indicating no publication bias.

Discussion

The effect of resistance exercise on biomarkers of peripheral inflammation in healthy adults was evaluated in this meta-analysis based on 15 randomized controlled trials. Our pooled results substantiated that resistance exercise significantly reduced TNF-α levels in healthy adults but did not affect IL-6 and CRP levels. Interestingly, this study discovered that resistance exercise could significantly reduce IL-6 levels in America and participants with a BMI ranging from 18.5 to 25. Moreover, studies in Asia and male populations showed that resistance exercise could significantly increase CRP levels. Moreover, subgroup analysis showed that studies in Asia, women, people aged > 60 years old, medium intensity, and intervention duration within 12 weeks indicated significantly reduced TNF-α levels with resistance exercise.

Our findings differed from those of a previous meta-analysis on the effect of exercise on inflammatory biomarkers in the elderly, which demonstrated that exercise could significantly reduce CRP and IL-6 but did not affect TNF-α levels[37]. Taking into account the methodological differences between the two meta-studies, the differences in the study samples, and the inclusion of different types of exercise in that meta-analysis, the study results might vary. IL-6 is a functional pleiotropic cytokine that regulates metabolic and neural processes as well as inflammation and infection. It is widely acknowledged that IL-6 is produced rapidly during infection or tissue damage and promotes host defense by stimulating acute phase response, hematopoiesis, and immune response[38]. Although IL-6 has long been thought of as a proinflammatory cytokine, it exerts a very important anti-inflammatory effect on muscle when it is produced and released by skeletal muscle cells during exercise[37]. In healthy adults with a BMI between 18.5 and 25, subgroup analysis revealed that resistance exercise could significantly reduce IL-6 levels. A recent meta-analysis showed that IL-6 pathway inhibitors were associated with increased body weight and BMI[39]. An increasing body of evidence suggested that IL-6 might inhibit appetite, resulting in weight loss by interacting with leptin and influencing hypothalamic neuropeptides[40,41]. It was widely thought that there might be an interaction between BMI and IL-6 levels in the human body, which might influence the effectiveness of resistance exer-

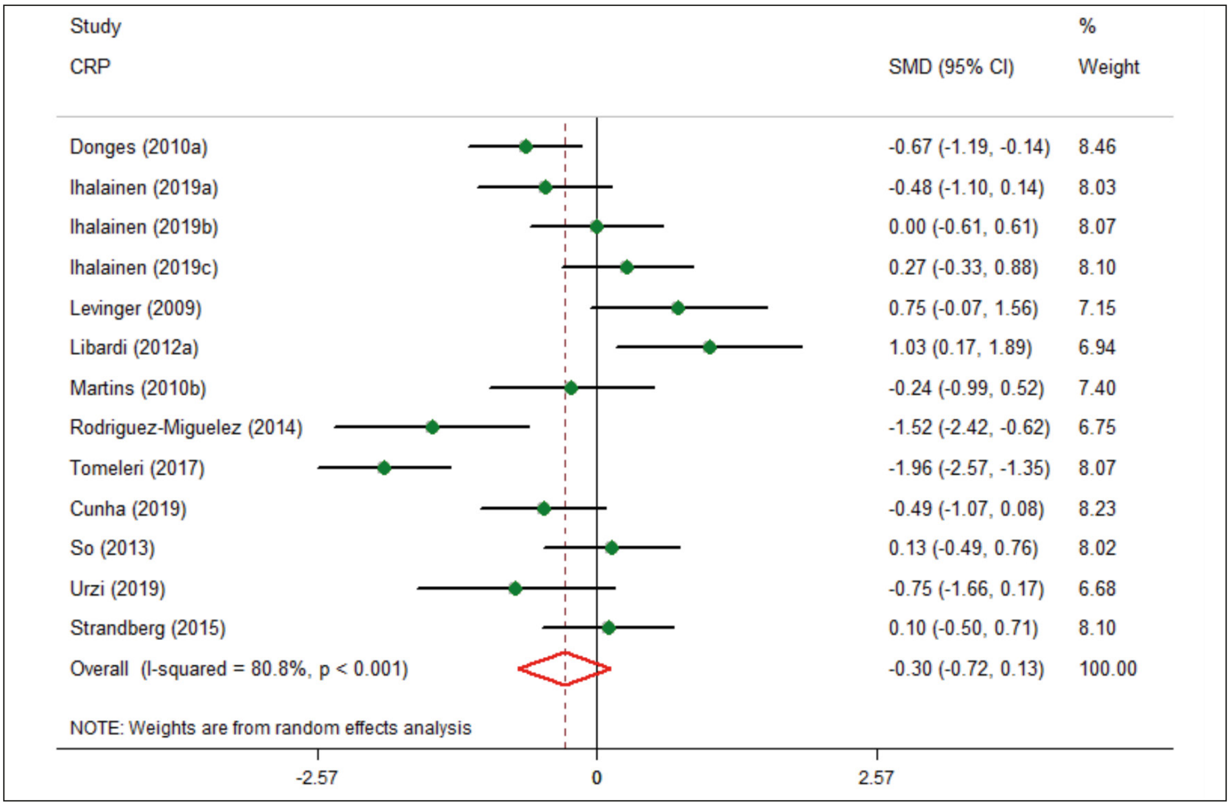

Figure 4. Forest plot of the effect of resistance exercise on CRP level.

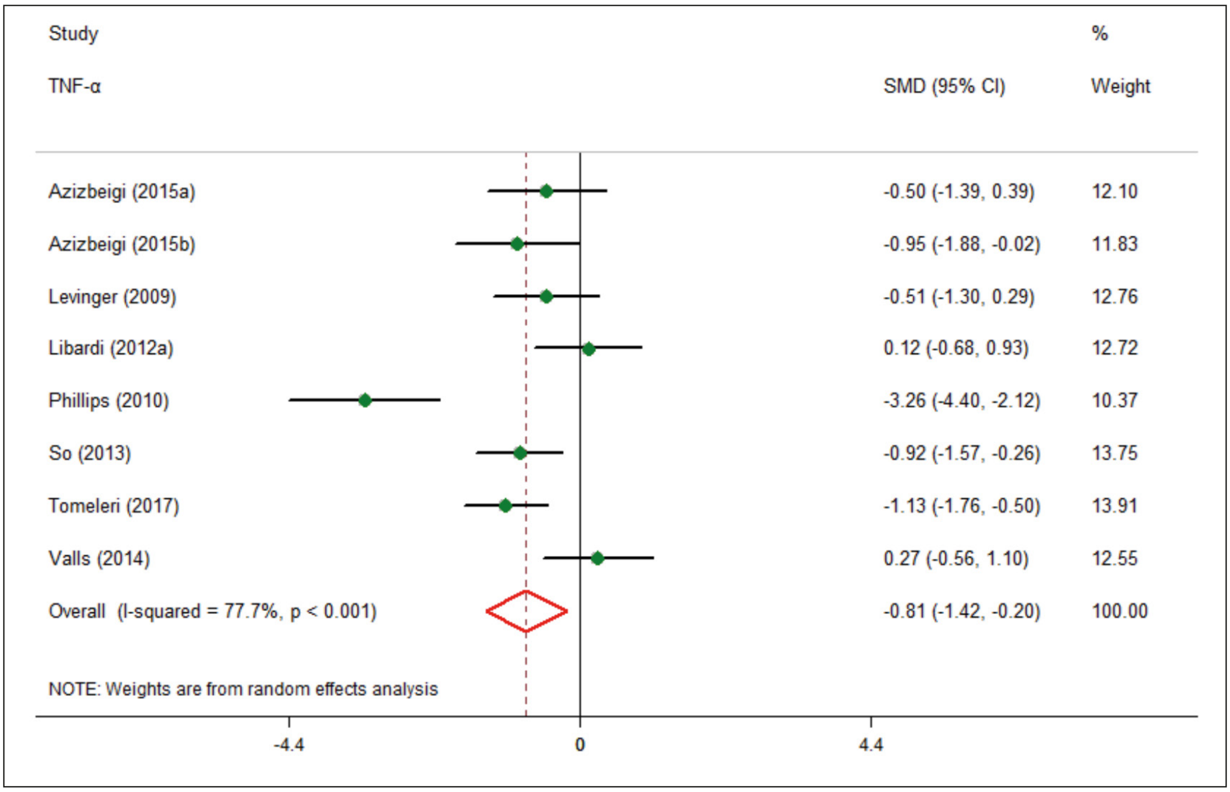

Figure 5. Forest plot of the effect of resistance exercise on TNF-α level.

expression. However, our study only included one study on high-intensity resistance exercise, and the reliability and stability of the results are poor. It is currently impossible to draw a definitive conclusion regarding the effect of high-intensity resistance exercise on TNF-α levels in healthy adults. It is widely acknowledged that high-intensity exercise can induce the most significant release of muscle cytokines. In the future, high-quality RCTs are still needed to determine the impact of high-intensity resistance exercise on the level of TNF-α. A previous meta-analysis of the effect of exercise intensity on inflammatory biomarkers in adults found that moderate-intensity exercise was more likely to induce an anti-inflammatory environment and reduce TNF-α levels in the body[45]. The underlying mechanism might be that moderate-intensity exercise first reduces neopterin levels, which activate the transcription factor Nrf2. Indeed, Nrf2 is a key regulator of the cellular antioxidant response, which can further enhance cellular antioxidant defense, mitochondrial activity, and an anti-inflammatory environment[46].

Studies conducted in America showed that resistance exercise could significantly reduce IL-6 levels in healthy adults, while studies in Asia showed that resistance exercise could significantly reduce CRP and TNF-α. And the heterogeneity of studies within the group was smaller than that without stratification, indicating that regional factors might be the source of heterogeneity among studies. This might be related to differences in economic power, climate conditions, medical level, eating habits, and lifestyles in different regions.

Several limitations were found in this study. Only a few studies employed a blinding method, leading to substantial heterogeneity. Although the sources of heterogeneity were assessed via sensitivity analysis, subgroup analysis, and meta-regression analysis, the interpretation of some results was also limited by the small sample size in subgroups.

Conclusions

In summary, resistance exercise could reduce TNF-α levels in healthy adults, and resistance exercise with moderate intensity could reduce TNF-α levels more effectively. In healthy adults, resistance exercise did not affect the levels of IL-6 and CRP, but the older the subjects were, the greater the effect of resistance exercise on IL-6 reduction. For the prevention of inflammation-related diseases, moderate-intensity resistance exercise has a positive guiding significance, particularly for fitness enthusiasts and sub-health individuals.

Conflict of Interests

The authors declare that they have no competing interest.

Ethics Approval and Informed Consent

All analyses were based on previously published studies; thus, no ethical approval and patient consent are required.

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Authors' contributions

Study concept and design: Yahai Wang, Haichao Jiang and Donglin Luo. Data extraction and analysis: Yahai Wang and Haichao Jiang. Manuscript drafting: Donglin Luo, Yahai Wang, Haichao Jiang, Binggang Jiang and Yanjin Shen. All authors were involved in data analysis, drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

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Availability of Data

All data used in the study can be obtained from the original articles and this published article.

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