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The Impact of Resistance Training on IL-6, TNF-a, and CRP Levels in the Elderly: A Systematic Review and Meta-Analysis Study

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Abstract

Background: Inflammatory markers have been linked to an increased risk of cardiovascular diseases including atherosclerosis, coronary artery disease, and heart failure in the elderly individuals. Resistance exercises are one effective method to manage inflammation in this population. **Objectives:** This meta-analysis aimed to explore the impact of resistance training on inflammatory markers in the elderly. **Methods:** All randomized controlled clinical trials (from 2004 to 2023) that examined the effect of resistance training on tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), and C-reactive protein (CRP) in individuals over 50 years old were selected through a systematic search of PubMed, Google Scholar, Web of Science and SID databases, that out of 600 studies identified, 31 met the inclusion criteria for our analysis. Random and fixed effects models, along with the I2 heterogeneity test, Egger test, and funnel plot, were used to determine publication bias using CMA2 software. The effect size (ES) was reported in terms of the standard mean difference (SMD) and a 95% confidence interval (CI). **Results:** The meta-analysis results indicated that resistance training significantly reduced CRP (ES = -0.49, 95% CI = -0.34 to -0.64, P = 0.001) and IL-6 (ES = -0.27, 95% CI = -0.41 to -0.13, P = 0.001) levels. However, it did not have a significant effect on TNF-α levels (ES = -0.22, 95% CI = 0.02 to -0.47, P = 0.075). Subgroup analyses revealed that resistance training for more than 16 weeks and a training frequency of three times a week led to a greater decrease in CRP and IL-6 levels in the elderly. **Conclusions:** The findings of this meta-analysis suggest a significant decrease in CRP and IL-6 levels in the elderly due to resistance training. Furthermore, the subgroup analysis indicated that higher training volumes (training duration and frequency) result in a greater reduction in these markers' levels. Based on these findings, it is advisable for elderly individuals to consider incorporating resistance training into their regular exercise routines.

Keywords: Exercise, Aging, Inflammation, Geriatrics, Randomized Controlled Trials

1. Background

Aging is a natural and intricate process that is becoming more prevalent in various societies. The global proportion of elderly individuals is increasing, and projections indicate that by 2030, 1 in 6 people worldwide will be aged 60 years or older. Additionally, the population of individuals aged 60 years and above is expected to grow from 1 billion in 2020 to 1.4 billion (1). As individuals age, significant structural and functional changes occur in most physiological systems, even in the absence of detectable diseases (2). These age-related physiological changes impact various tissues and systems, ultimately affecting daily activities and physical independence in older adults. Additionally, there is a decline in maximum aerobic capacity (VO2 max) and skeletal muscle function with age, known as physiological aging (3). Franceschi et al. (2000) have highlighted that aging disrupts body homeostasis and contributes to low-grade chronic inflammation in old age (4). This chronic inflammation is a significant risk factor for the development of chronic diseases, including cardiovascular diseases (5).

Chronic heart failure is a significant global issue and the leading cause of death. This complex clinical syndrome, with various underlying causes, is characterized by heightened inflammation and increased levels of inflammatory markers (6-8). Cytokines, a group of soluble secreted proteins, play a crucial role in immune cell proliferation, differentiation, lifespan, and function (9), as well as in the inflammatory response during infections and other conditions (10). These proteins also contribute to the development and progression of chronic diseases like cardiovascular disorders and type 2 diabetes (11).

Studies suggest that chronic low-grade inflammation, marked by an increased production of cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in the bloodstream, results in sarcopenia and a decline in muscle function (12). Heightened levels of inflammatory indicators such as C-reactive protein (CRP) amplify the grisk of cardiovascular diseases by a factor of 2 to 5 (13). Research has demonstrated that physical activities, especially resistance exercises, are effective in combating sarcopenia in the elderly. These exercises can also lower the baseline levels of inflammatory cytokines linked with low-grade inflammatory conditions like atherosclerosis, obesity, and insulin resistance (14-16).

Engaging in regular physical activity is crucial for maintaining a healthy lifestyle and preventing chronic diseases (17, 18). However, as people age, their level of physical activity tends to decrease. As such, physical training becomes essential to enhance or sustain the physical health of older adults (19, 20). Given the significance of health maintenance in the elderly and the need to focus on physical activities like resistance exercises to prevent diseases caused by systemic inflammation, comprehensive research in this area is necessary. The financial and psychological burdens resulting from illness in this demographic necessitate societal policies that prioritize their health.

Existing research presents mixed findings on the impact of exercise, specifically resistance to inflammatory cytokines, in the elderly. Some studies found no effect of resistance training on inflammatory cytokines (21-27). Conversely, other studies observed a reduction in inflammatory markers (IL-6, TNF-α, and CRP) in older adults post-resistance training (28-33).

2. Objectives

Given the importance of this issue, the conflicting findings on the impact of resistance training on inflammatory cytokine levels in the elderly, and the lack of comprehensive research summarizing and investigating the effect of resistance training on the inflammatory markers IL-6, TNF-α, and CRP in older adults, this meta-analysis aims to examine and summarize the effects of resistance training on these inflammatory indices in the elderly.

3. Methods

3.1. Eligibility Criteria

In this meta-analysis, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to investigate the impact of resistance training on the levels of circulating proteins IL-6, TNF-a, and CRP in the elderly. For this review and meta-analysis, we selected the inclusion criteria based on the PICO (Participant-Intervention-Comparator-Outcomes) framework. The criteria include (a) population: human subjects over 50 years of age, irrespective of gender and health status, (b) intervention: studies demonstrating the effect of resistance training with an exercise intervention duration of at least 4 weeks, (c) comparison: randomized controlled trials (RCTs) with a control group, (d) variable: studies where the levels of IL-6, TNF-a, and CRP were measured in circulation, and (e) studies with either a single group or two groups. The exclusion criteria were as follows: (1) Studies conducted on animals, (2) studies concentrating on the acute impacts of resistance exercises on the specified variables, and (3) conference papers. Characteristics of the intervention studies in the meta-analysis are presented in Table 1.

3.2. Search Strategy

In this meta-analysis, we utilized the Boolean Logic method to select suitable articles, specifically using the connectors "AND," "OR," and "NOT," for a systematic search in PubMed, Google Scholar, Web of Science and SID databases from 2004 until June 2023. We did not impose any language restrictions for the search, and articles in any language were considered eligible for inclusion in this meta-analysis. The search included keywords related to the main topic, such as "inflammatory factors", "resistance training", "biological markers", "cytokines", "interleukin", "tumor necrosis factor alpha", "C-reactive protein", "interleukin-6", "strength training", "weight training", "aging", "elderly", and "heart failure".

3.3. Study Selection

After conducting the database search, all retrieved articles were imported into EndNote software version 20. In the first stage, duplicate articles were removed by the authors. The next screening was performed using the title, abstract, and keywords. Subsequently, a secondary screening was conducted on the remaining articles by reviewing the full text to determine if they met the inclusion criteria for this study. All study selection steps were independently performed by two authors (Z.M.; M.R.R.), and any disagreements were resolved through consultation with another author. The systematic and comprehensive process of study search, along with the inclusion or exclusion criteria of studies, is outlined in the PRISMA 2020 flow chart (Figure 1).

Table 1. Characteristics of the Intervention Studies in the Meta-Analysis

Number	Study, Year	Study design	Subjects/Gender	Sample Size (Training/Control)	Age (Mean: Years)	Training Intensity	Type of Exercise Training	Sessions Per Week/Total Training Duration	Training Effects on Outcomes	Supplement or Drug Use
1	Bruunsgaard, 2004 (34)	RCT	Both	T:11 - C:12	86 - 95	50 - 80% 1RM	RT	3 sessions/12 weeks	IL-6, TNF-a (↔)	No
2	Bautmans, 2004 (35)	RCT	Both	T:31 - C:31	63 - 73	50 - 80% 1RM	RT	3 sessions/6 weeks	IL-6 (↓)	No
3	Brooks, 2006 (21)	RCT	Both	T:31 - C:31	65 - 85	60 - 80% 1RM	RT	3 sessions/16 weeks	CRP (↓)	No
4	Reynolds, 2004 (36)	RCT	Both	T:11 - C:11	65 - 69	50% 1RM	RT	3 sessions/16 weeks	TNF-a (↓)	No
5	Martins, 2010 (37)	RCT	Both	T:32 - C:13	66 - 89	Not reported	RT/AT	3 sessions/ 16 weeks	CRP (↓)	No
6	Soheyli,2010 (38)	RCT	Male	T:10 - C:10	60 - 70	50 - 65% 1RM	RT	3 sessions/8 weeks	CRP (↓)	No
7	Deibert, 2011, (22)	RCT	Male	T:13 - C:9	50 - 65	60% 1RM	RT	2 sessions/12 weeks	CRP, IL-6 (↓)	No
8	Libardi,2012 (39)	RCT	Male	T:34 - C:13	60 - 63	50 % 1RM	RT/ET/AT	3 sessions/16 weeks	CRP, IL-6, TNF-a (↔)	No
9	Stensvold, 2012 (40)	RCT	Both	T:21 - C:10	50 - 51	40 - 50 % 1RM	RT/AT	3 sessions/12 weeks	CRP, IL-6 (↔); TNF-a (↓)	No
10	Feiereisen, 2013 (41)	RCT	Both	T:30 - C:15	52 - 64	60 - 75% 1RM	RT/ET	3 sessions/13 weeks	IL-6, TNF-a (↓)	No
11	Karabulut, 2013 (24)	RCT	Male	T:26 - C:10	55 - 59	80% 1RM	RT	3 sessions/6 weeks	IL-6 (↔)	No
12	Wanderley, 2013 (42)	RCT	Both	T:31 - C:19	57 - 65	80% 1RM	RT/AT	3 sessions/32 weeks	CRP, IL-6, TNF-a (↔)	No
13	Mavros, 2014 (25)	RCT	Both	T:41 - C:47	60 - 70	80% 1RM	RT	3 sessions/52 weeks	CRP (↓)	No
14	Mir, 2014 (31)	RCT	Male	T:12 - C:12	60 - 70	60 - 70% 1RM	RT	3 sessions/8 weeks	CRP, IL-6 (↓)	No
15	Rodriguez-Miguelez, 2014 (43)	RCT		T:16 - C:10	65 - 78	60% of 1RM	RT	2 sessions/8 weeks	CRP, TNF-a (↔)	NO
16	Ribeiro, 2015 (44)	RCT	Female	T:35 - C:30	63 - 75	50 % 1RM	RT	3 sessions/24 weeks	CRP (↓)	No
17	Strandberg, 2015 (45)	RCT	Female	T:17 - C:18	66 - 70	75 - 85% 1RM	RT	3 sessions/24 weeks	CRP, IL-6 (↔)	No
18	Hagstrom, 2016 (23)	RCT	Female	T:20 - C:19	50-61	80% 1RM	RT	3 sessions/32 weeks	CRP, IL-6, TNF-a (↔)	No
19	Hsieh, 2018 (46)	RCT	Both	T:30 - C:32	67-75	75 % 1RM	RT	3 sessions/12 weeks	CRP (↔)	No
20	Mehrabani,2016 (47)	RCT	Female	T:15 - C:14	52-60	60 - 75% 1RM	RT	3 sessions/ 8 weeks	CRP (↓)	No
21	Nunes, 2016 (48)	RCT	Female	T:11 - C:11	57 - 65	70% 1RM	RT	3 sessions/16 weeks	IL-6 (↓)	No
22	Theodorou,2016 (49)	RCT	Male	T:11 - C:15	54 - 70	75% 1RM	RT	3 sessions/32 weeks	CRP (↓)	No
23	Chupel, 2017 (29)	RCT	Female	T:16 - C:17	77 - 88	50-70% 1RM	RT	3 sessions/28 weeks	CRP, TNF-a (↓)	No
24	Kabir, 2018 (50)	RCT	Male	T:10 - C:10	65 - 80	60 - 80% 1RM	RT	3 sessions/12 weeks	CRP (↓)	No
25	Tolouei Azar, 2018 (51)	RCT	Male	T:10 - C:10	64 - 77	70% 1RM	RT	3 sessions/8 weeks	IL-6, TNF-a (↔)	No
26	Tomeleri, 2018 (52)	RCT	Female	T:19 - C:19	64 - 72	50% 1RM	RT	3 sessions/32 weeks	CRP, TNF-a (↓)	No
27	Macedo Santiago, 2018 (30)	RCT	Female	T:19 - C:10	60 - 70	Not reported	RT	3 sessions/8 weeks	CRP, IL-6, TNF-a (↓)	No
28	Nabuco, 2019 (53)	RCT	Female	T:13 - C:13	64 - 74	50% 1RM	RT	3 sessions/12 weeks	CRP, IL-6, TNF-a (↓)	Whey protein
29	Abd El-Kader, 2019 (28)	RCT	Both	T:40 - C:40	61 - 66	60-80% 1RM	RT/AT	3 sessions/24 weeks	IL-6, TNF-a (↓)	No
30	Ogawa,2010 (26)	RCT	Female	T:10 - C:0	80 - 90	50-80% 1RM	RT	3 sessions/12 weeks	CRP (↓), IL-6, TNF-a (↔)	No

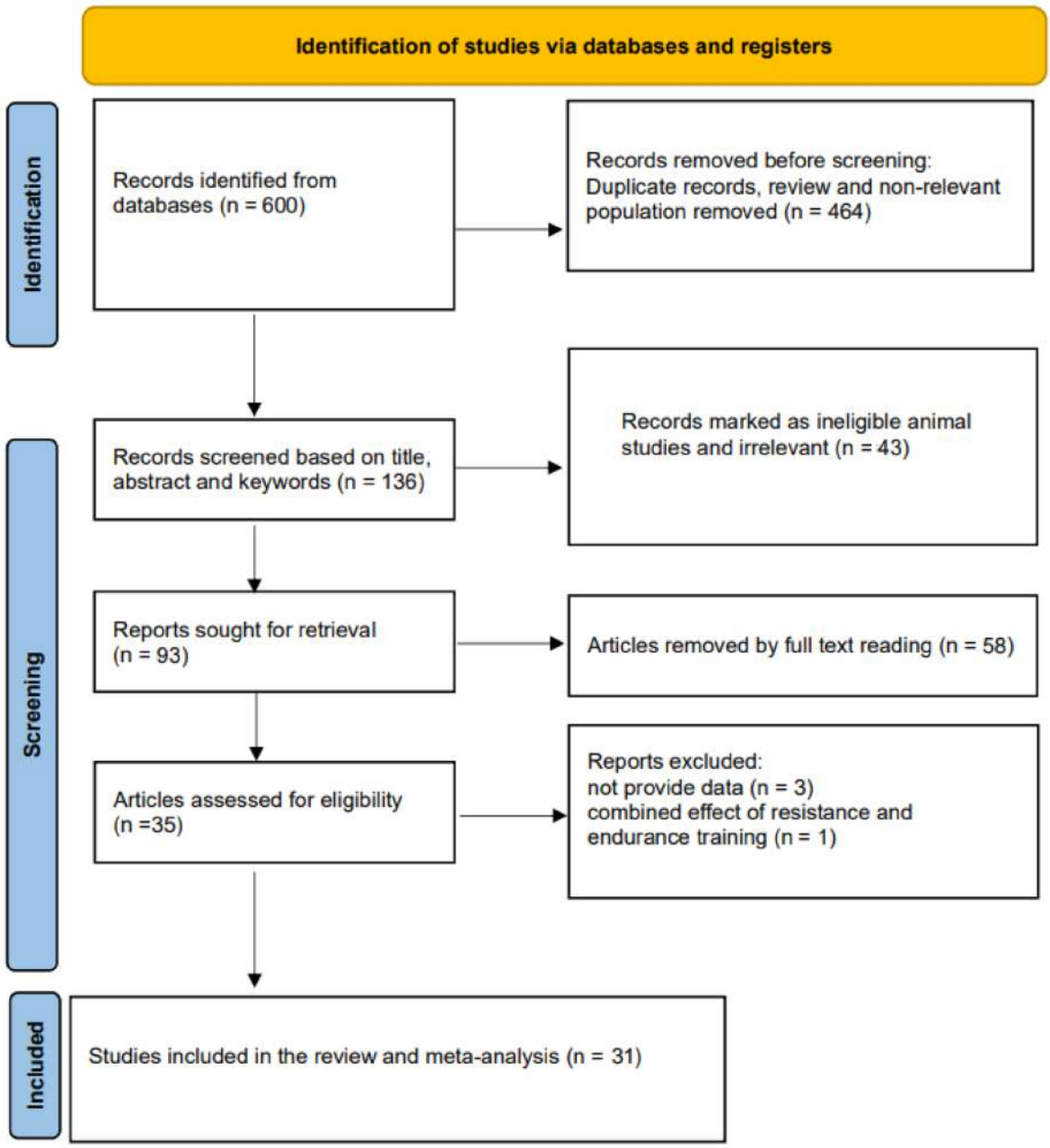

Figure 1. Flow chart of study selection according to PRISMA guidelines.

3.4. Data Extraction

The full text of the eligible articles was reviewed to extract data related to TNF-α, IL-6, and CRP concentrations before and after the exercise intervention. This was done independently by two researchers (Z.M.; M.R.R.). Any disagreements were resolved with the help of a third, impartial researcher. Information related to the research method and other study characteristics was also extracted.

3.5. Study Quality

The quality of the studies was assessed using Pedro's eleven-point scale, which includes specific criteria such as eligibility, randomization, and pre-test characteristic similarity. However, due to the nature of the research,

two criteria related to single-blinding of subjects and therapists were excluded. The quality of the articles was scored on a scale of 0 to 9, with a higher score indicating higher quality (Table 2).

3.6. Statistical Method

In this meta-analysis, data related to the effect of resistance training on TNF-α, IL-6, and CRP concentrations in the elderly were analyzed using CMA version 2 software. The effect size was calculated using the standardized mean difference (SMD) based on the standard deviation and mean between the training and control groups. Heterogeneity of the studies was determined using I square (I^2) tests. If heterogeneity was observed ($P < 0.05$ and $I^2 > 50\%$), a random effects model was used. If no heterogeneity was observed, a fixed effects model was used. Publication bias was evaluated using a funnel plot, and if bias was detected, the trim and fill method and Egger's test were used. In the subgroup analysis, studies were categorized based on their subgroups, and the significance level of each subgroup and the comparison between subgroups were also calculated.

4. Results

4.1. Impact of Resistance Training on CRP

The data from 21 studies examining the impact of resistance training on CRP were analyzed using CMA software. However, due to the presence of a few studies with extremely high effect sizes, which led to heterogeneity in the meta-analysis, the results from two studies (Rodriguez-Miguels et al. (43), Macedo Santiago et al. (30)) were omitted using a case-by-case approach. Consequently, a total of 19 articles were included in the final review (Figure 2).

In this meta-analysis, the standardized mean difference (SMD) was utilized to compute the overall effect size. The preliminary analysis of data from 19 studies showed moderate heterogeneity ($I^2 = 53.04\%$), hence a random effects model was employed. The results indicated a significant reduction in CRP due to resistance training in the elderly (ES = -0.57, 95% CI = -0.80 to -0.34; P = 0.0001). A funnel plot was used to assess publication bias (Figure 3). The plot's asymmetry suggested publication bias, which was further confirmed by Egger's test. After manually removing the 2017 Kabir study from the analysis (50), the remaining 18 studies showed a significant decrease in CRP by 0.50 mg/liter in the elderly due to resistance training (ES = -0.50, 95% CI = -0.69 to -0.30; P = 0.0001) (Figures 4 and 5).

4.2. Impact of Resistance Training on IL-6

The overall effect size (SMD) was calculated to examine the impact of resistance training on IL-6 concentration in the elderly. Data from 18 studies were included in the meta-analysis, showing low heterogeneity ($I^2 = 46.97\%$), thus a fixed effects model was used. The results showed a significant decrease in IL-6 concentration by -0.27 pg due to resistance training in the elderly (ES = -0.27, 95% CI = -0.41 to -0.13; P = 0.0001). A funnel plot used to check publication bias related to IL-6 indicated no such bias. Egger's linear regression test also confirmed this (B0 = 0.83, 95% CI = -2.8 to 0.94; one-tailed P = 0.20, two-tailed P = 0.41) (Figures 6 and 7).

4.3. Impact of Resistance Training on TNFα

Regarding the impact of resistance training on TNF-α levels in the elderly, data from 19 studies were included in the meta-analysis (Figures 8 and 9). The results showed high heterogeneity ($I^2 = 68.44\%$, P = 0.0001), hence a random effects model was used. The findings indicated a non-significant decrease in TNF-α concentration by -0.227 pg/mL due to resistance training in the elderly (ES = -0.227, 95%CI = -0.47 to -0.02; P = 0.075). A funnel plot used to investigate publication bias related to TNF-α indicated such bias. Therefore, using the trim and fill method, 5 studies were moved to the left side of the chart, and the average effect size was corrected to 0.47 pg/mL (P = 0.075, 95%CI = -0.67 to -0.17).

4.4. Subgroup Meta-Analyses of the Impact of Resistance Training on IL-6, TNFα, and CRP Levels

The results of the subgroup meta-analysis of the impact of resistance training on CRP, IL-6, and TNFα levels are presented in Tables 3 - 5. This meta-analysis examined studies based on age, gender, health status, baseline CRP level, intensity, duration, and frequency of exercise training per week. The average effect size, 95% confidence interval, heterogeneity test results, and P-value of intra-subgroup and inter-subgroup comparisons are reported. A P-value > 0.05 in the heterogeneity test results indicates publication bias. The significance level of intra-subgroup and inter-subgroup comparisons is calculated as $P < 0.05$, and values at or below this level are considered significant.

5. Discussion

This meta-analysis explored the beneficial impacts of various resistance training programs, differing in intensity and duration, on the concentrations of CRP, TNF-a, and IL-6 in the elderly. The results of the

Table 2. Studies Method Quality Assessment by PEDro Scale

Study	Eligibility	Random Allocation	Allocation Cocealed	Groups Similar at Baseline	Assessors Blinded	Outcome Measures Assessed in 85% of Participant	Ntention to Treat Analysis	Statistical Comparison Between Groups	Measurement at Steps and Intervals	Total Score
Kabir, 2018 (50)	1	1	0	1	1	1	0	1	1	7
Mir, 2014 (31)	1	1	0	1	0	1	0	1	1	6
Soheyli, 2010 (38)	1	1	0	1	0	1	1	1	1	7
Mehrabani, 2016 (47)	1	1	0	1	0	1	0	0	1	5
Libardi, 2012 (39)	1	1	0	1	0	0	1	1	1	6
Ribeiro, 2015 (44)	1	1	0	1	0	1	0	1	1	6
Cordova,2011 (54)	1	1	0	1	0	0	0	0	1	4
MacedoSantiago, 2018 (30)	1	1	0	1	1	1	0	1	1	7
Mavros, 2014 (25)	1	1	1	1	0	0	0	1	1	6
Ogawa, 2010 (26)	1	1	0	1	0	1	0	0	1	5
Chupel, 2017 (29)	1	1	0	1	0	0	0	1	1	5
Karabulut, 2013 (24)	1	0	0	1	0	1	0	1	1	5
Hsieh, 2018 (46)	1	1	1	1	1	1	0	1	1	8
Theodorou, 2016 (49)	1	1	0	1	0	1	0	1	1	6
Deibert, 2011 (22)	0	1	0	1	0	1	0	0	1	4
Nunes, 2016 (48)	1	1	0	1	0	1	0	1	1	6
Hagstrom, 2016 (23)	1	1	1	1	1	0	1	0	1	7
Wanderley, 2013 (42)	1	1	1	1	0	0	0	1	1	6
Tomeleri, 2018 (52)	1	1	0	1	0	1	1	1	1	7
Strandberg, 2015 (45)	1	1	0	1	0	1	0	0	1	5
Feiereisen, 2013 (41)	1	1	0	1	0	1	1	0	1	6
Abd El-Kader, 2019 (28)	1	1	0	1	0	0	1	1	1	6
Bautmans, 2004 (35)	1	1	0	1	0	1	0	0	1	5
Martins, 2010 (37)	1	1	0	1	0	0	0	1	1	5
Brooks, 2006 (21)	1	1	0	1	1	0	1	0	1	6
Tolouei Azar, 2018 (51)	1	1	0	1	1	1	0	1	1	7
Nabuco, 2019 (53)	1	1	0	1	1	0	1	0	1	6
Reynolds, 2004 (36)	1	1	0	1	1	0	0	1	1	6
Stensvold, 2012 (40)	1	1	0	1	1	1	1	0	1	7
Bruunsgaard, 2004 (34)	1	1	0	1	1	1	0	1	1	7

Abbreviations: Q, question; NAPP, not applicable.

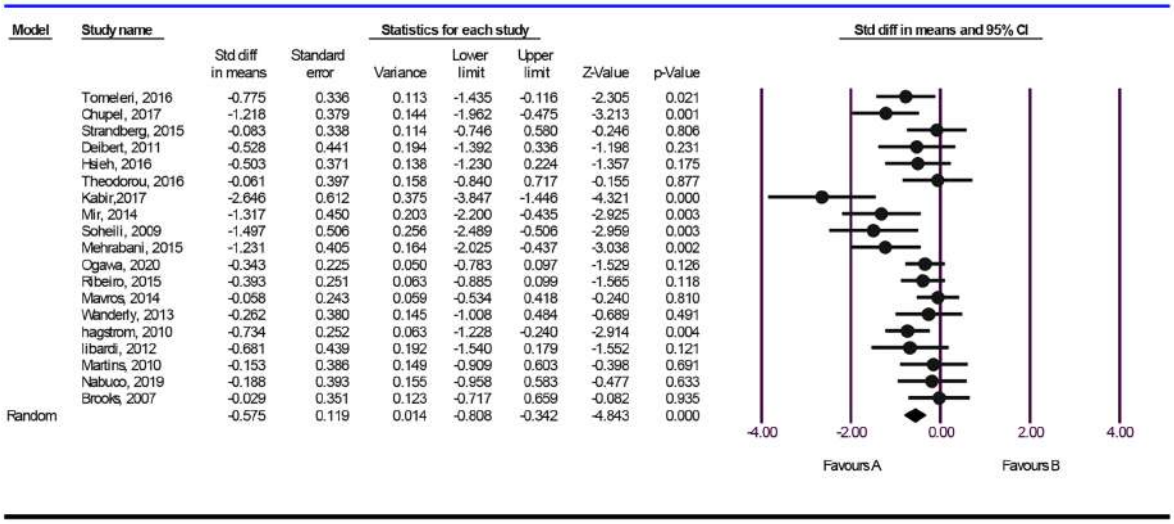

Figure 2. Forest diagram of mean effect size of resistance training on CRP.

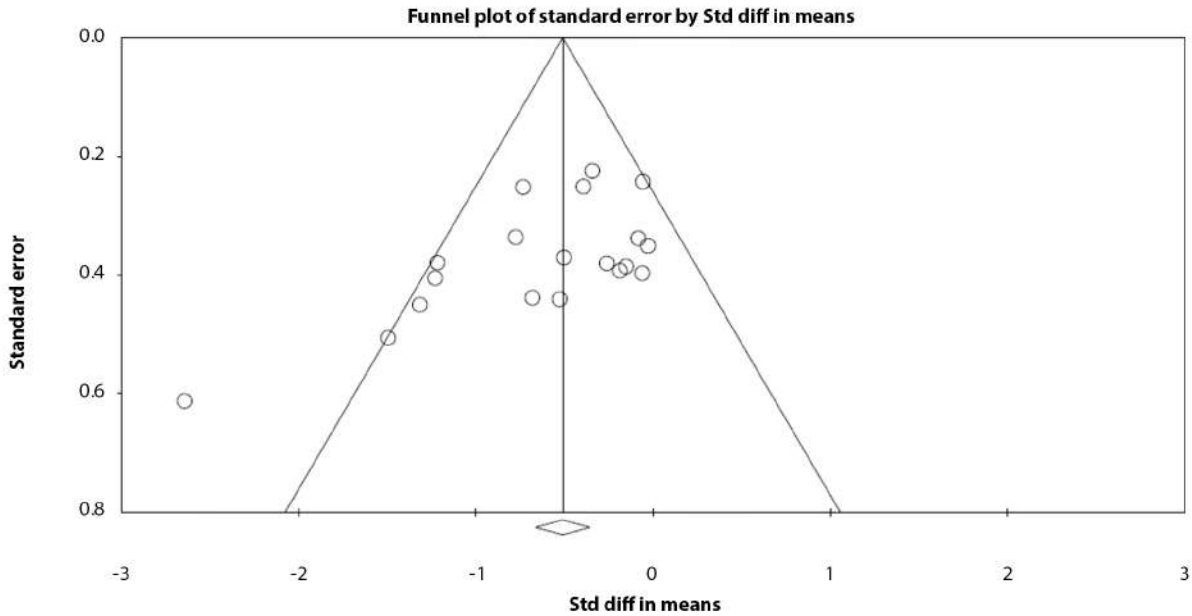

Figure 3. Funnel diagram related to the effect of resistance training on CRP levels in biased conditions.

meta-analysis were derived by calculating the effect size of each study and combining them to determine the overall effect size. Generally, the findings of this meta-analysis regarding CRP concentration show a significant decrease in CRP in the elderly due to resistance training, with an effect size (ES) of -0.618 and a 95% confidence interval of -0.368 to -0.868.

The meta-analysis results on the impact of resistance training on CRP levels suggest that resistance training reduces the amount of C-reactive protein, regardless of the characteristics of the subjects or the specifics of the training, with an average effect size of 0.618 mg/liter and a 95% confidence interval between -0.368 and -0.868. Only seven articles showed a significant effect size when

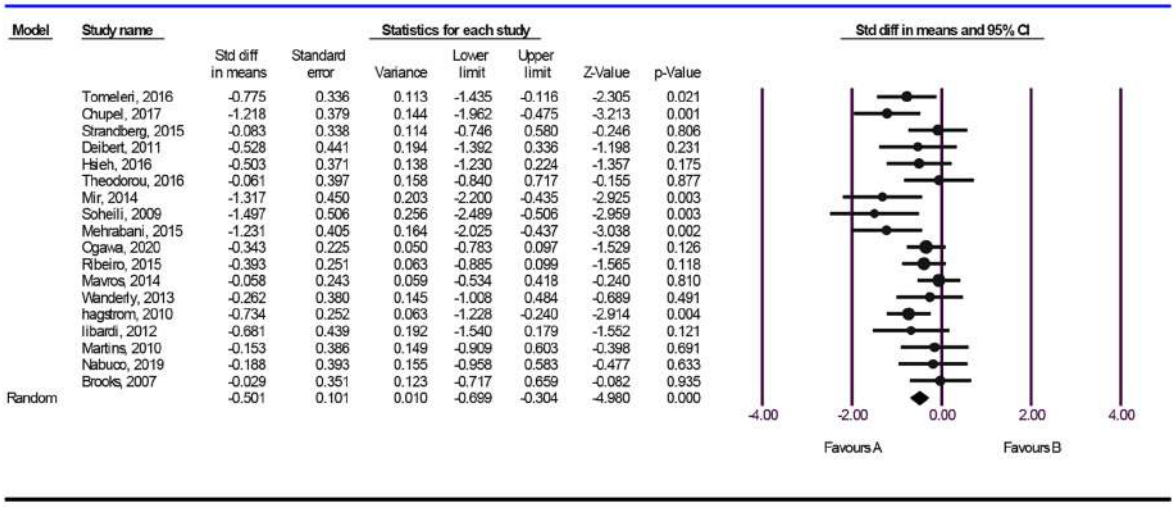

Figure 4. Forest diagram of the average effect size of resistance training on CRP after removing bias.

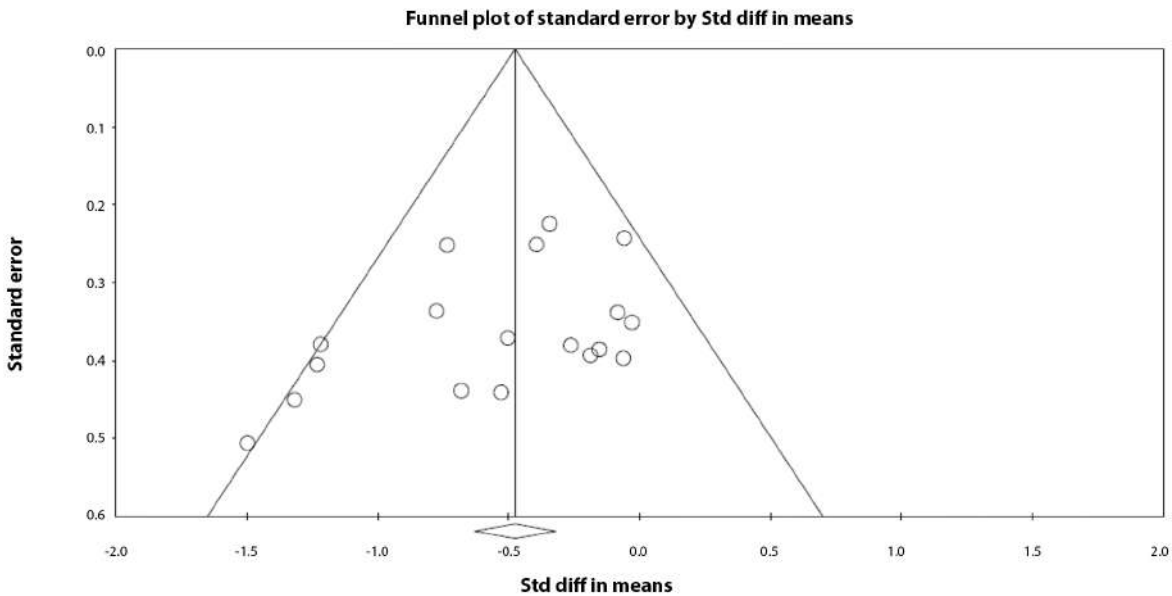

Figure 5. Funnel diagram related to the effect of resistance training on CRP levels in biased conditions.

calculating the effect size of individual studies (Figure 2).

Subgroup analysis results showed that resistance training led to a greater decrease in this protein's levels (ES = -0.899) in individuals with a baseline CRP greater than 3 mg/liter. Similar studies have been conducted on the effect of resistance training on CRP levels in the elderly, aligning with the findings of this research. For instance, Mirseyyedi et al. (2014) observed a significant 19.14% decrease in CRP after eight weeks of resistance training (31). Also, Sardeli et al. (2018) found that resistance training decreased the level of CRP in individuals over 50 years old with an average effect size of -0.61 - 3 mg/liter and a 95% confidence interval between -0.395 and -0.832 (55).

Soheyli et al.'s study (2018) reported a significant decrease in CRP following eight weeks of resistance training, which aligns with the results of this study (38).

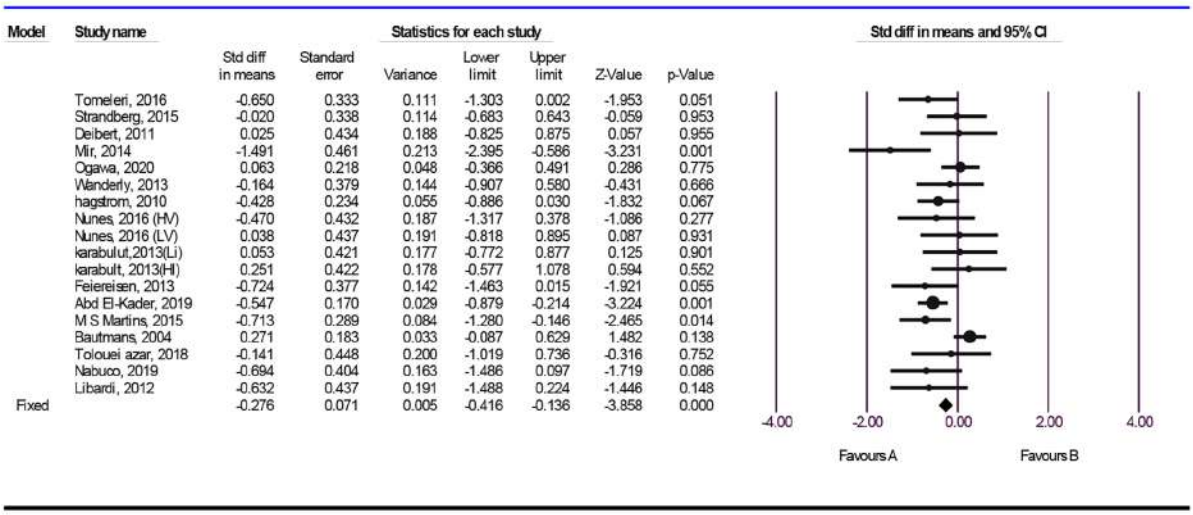

Figure 6. Forest diagram of the effect of resistance training on the level of IL-6.

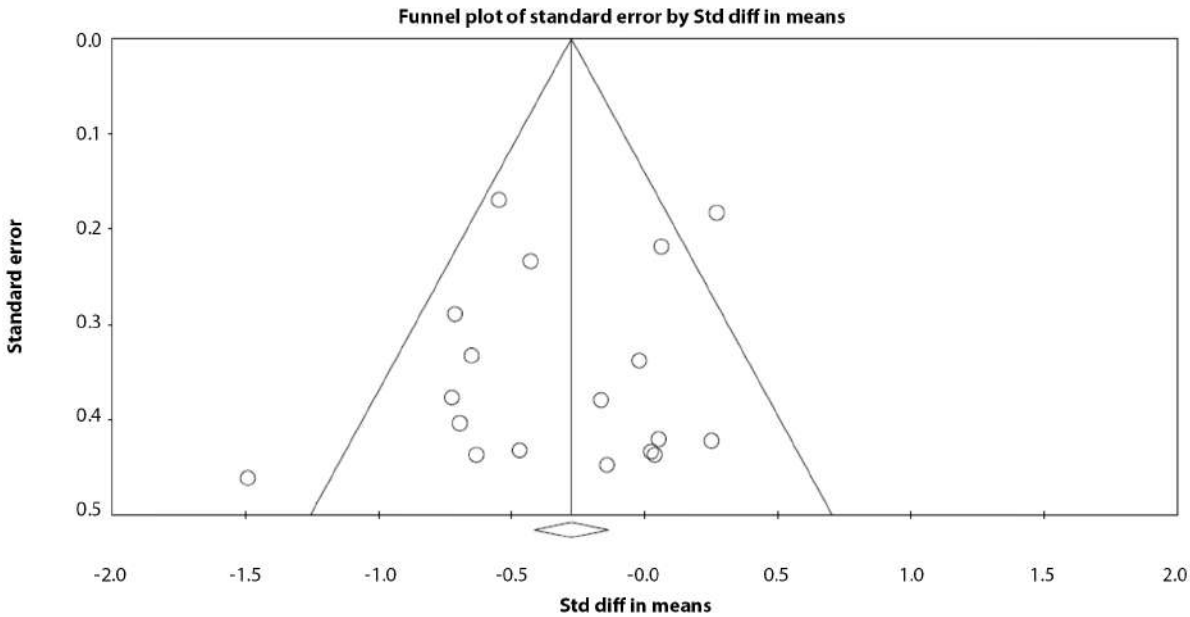

Figure 7. Funnel diagram related to the effect of resistance training on the amount of IL-6.

However, Peake et al. found no significant change in blood serum CRP level in the resistance training group compared to the control group (56). Similarly, Libardi et al. (2012) found no significant difference in CRP levels between any of the experimental groups and the control group, which could be attributed to the underlying disease (type 2 diabetes) of the resistance training group (39). Mavros et al. (2014) also reported that resistance training reduced the protein amount by 0.58 mg/liter with a 95% confidence interval between -0.534 and 0.418, but this reduction was not significant, which could be attributed to the underlying disease (type 2 diabetes) of the resistance training group (25).

The results of the subgroup meta-analysis align with

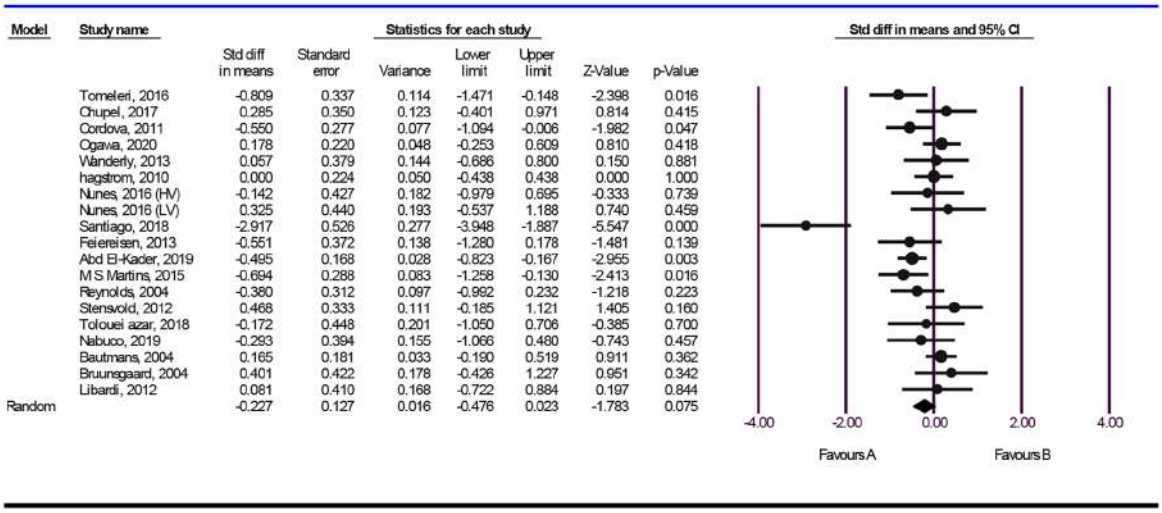

Figure 8. Forest diagram of the effect of resistance training on TNFα in elderly people.

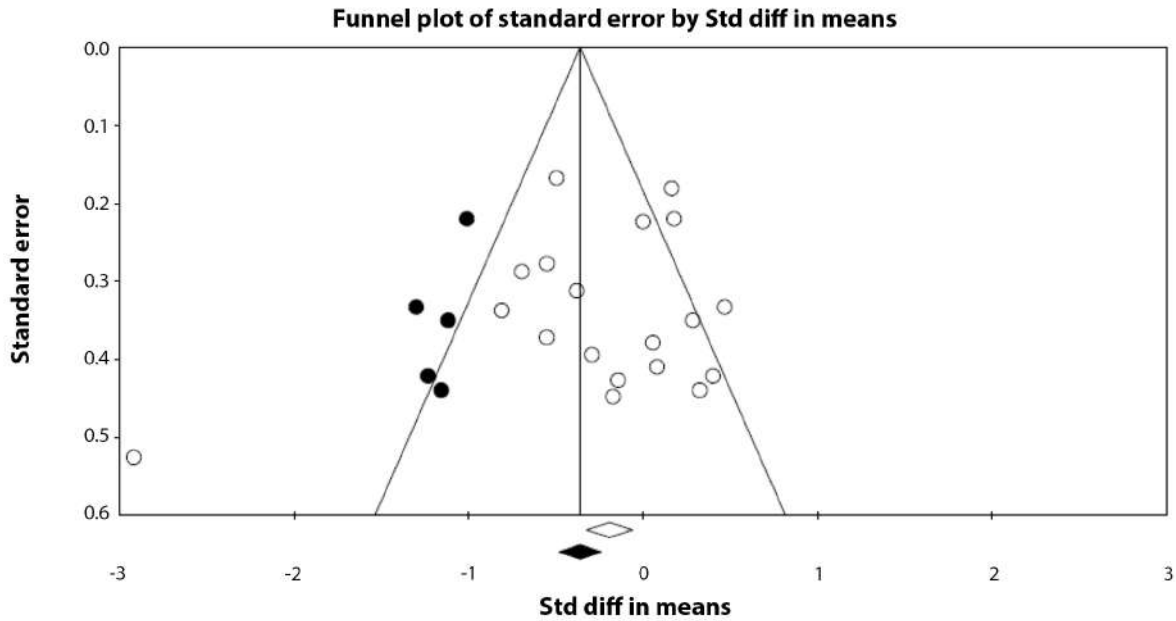

Figure 9. Funnel diagram related to the effect of resistance training on TNFα level in elderly people.

the study by Tomeleri et al. (2016), which demonstrated that performing resistance exercises three times per week for 32 weeks led to a significant decrease in CRP levels by 1.422 mg/liter, with a 95% confidence interval between -2.134 and -0.710 (33). Similarly, Chupel et al. (2017) found that performing resistance exercises twice a week for 28 weeks resulted in a significant decrease in CRP (P = 0.001) by 1.218 mg/L, with a 95% confidence interval between -0.962 and -1.0 (29). In this meta-analysis, the most significant effect was observed in exercise periods longer than 16 weeks and baseline CRP higher than 3 mg/liter of blood.

Furthermore, this meta-analysis found that a training frequency of three times a week and a healthy status had a

Table 3. The Results of Subgroup Analysis of the Effect of Resistance Training on CRP Levels in the Elderly

Characteristics and Subgroups	Number of Studies	Effect Size with 95% Confidence	Heterogeneity Test	P-Value	P-Value Between Groups
Age (y)					0.889
$\geq$ 60	15	-0.620	I^2 = 63.90; P $\leq$ 0.001	$\leq$ 0.001	
< 60	4	-0.665	I^2 = 32.326; P = 0.218	$\leq$ 0.001	
Health status					0.277
Healthy	10	-0.777	I^2 = 62.97; P = 0.004	$\leq$ 0.001	
Unhealthy	9	-0.491	I^2 = 56.08; P = 0.02	0.002	
Gender					0.015
Female	8	-0.662	I^2 = 55.96; P = 0.026	$\leq$ 0.001	
Male	6	-1.048	I^2 = 68.33; P = 0.007	0.002	
Both	5	-0.168	I^2 = 0; P = 0.871	0.255	
Baseline CRP, mg/L					0.236
Moderate risk (< 3)	12	-0.469	I^2 = 35.94; P = 0.103	$\leq$ 0.001	
High risk (> 3)	7	-0.899	I^2 = 75.33; P < 0.001	0.005	
Training intensity					0.425
Moderate (< 70% 1RM)	12	-0.706	I^2 = 50.10; P = 0.024	$\leq$ 0.001	
High (> 70% 1RM)	7	-0.486	I^2 = 69.05; P = 0.004	0.035	
Training durations, week					0.019
8	3	-1.329	I^2 = 0.; P = 0.919	$\leq$ 0.001	
8 - 16	8	-0.508	I^2 = 55.86; P = 0.026	0.012	
Over 16	8	-0.512	I^2 = 59.96; P = 0.015	0.004	
Training frequency, sessions per week					0.943
2	3	-0.598	I^2 = 60.01; P = 0.0.082	0.088	
3	16	-0.625	I^2 = 61.39; P = 0.01	$\leq$ 0.001	

greater impact on CRP than twice a week. This is consistent with the findings of Macedo Santiago et al. (2018), who demonstrated that resistance training for eight weeks significantly reduced CRP levels in 19 elderly women (30).

In the subgroup meta-analyses, the results indicate that the effect of resistance training on CRP levels was significant in all subgroups, except for the "twice a week" frequency and the "both sexes" subgroup. However, only the gender of the subjects (female, male, both) and the exercise duration subgroup showed a significant difference between subgroups in terms of CRP reduction, with the largest decrease observed in the female subgroup and the long-term training subgroup (more than 16 weeks). This reduction in CRP following resistance training is thought to be influenced by several factors. Firstly, resistance training can lead to a decrease in body fat percentage and an increase in lean muscle mass, which in turn may contribute to a reduction in systemic inflammation, including CRP levels. Additionally, resistance training has been shown to improve insulin sensitivity and glucose metabolism, thereby potentially impacting CRP levels. Furthermore, the release of myokines during and after resistance exercise, such as IL-6 from skeletal muscle, may have anti-inflammatory effects, influencing CRP levels. Lastly, resistance training's impact on reducing visceral adiposity and improving cardiovascular health could also play a role in lowering CRP. These combined effects showcase the multifaceted influence of resistance training on CRP reduction, emphasizing its potential as a valuable intervention in managing inflammation-related conditions.

The meta-analysis results on the effect of resistance training on blood interleukin-6 levels suggest that resistance training significantly reduces interleukin-6, with an average effect size of -0.276 pg/mL and a 95% confidence interval between -0.136 and -0.416. This finding aligns with the research of Sardeli et al. (2018), who found that resistance training tends to decrease interleukin-6

Table 4. Results of Subgroup Analysis of the Effect of Resistance Training on IL-6 Levels in Elderly People

Characteristics and Subgroups	Number of Studies	Effect Size with 95% Confidence	Heterogeneity Test	P-Value	P-Value Between Groups
Age (y)					0.445
≥ 60	12	-0.311	$I^2 = 56.22$; P = 0.09	0.025	
< 60	6	-0.364	$I^2 = 21.22$; P = 0.274	0.008	
Health status					0.172
Healthy	11	-0.215	$I^2 = 55.27$; P = 0.013	0.160	
Unhealthy	7	-0.395	$I^2 = 23.43$; P = 0.250	< 0.001	
Gender					0.596
Female	7	-0.260	I2 = 6.71; P = 0.377	0.026	
Male	7	-0.407	$I^2 = 49.42$; P = 0.065	0.007	
Both	4	-0.263	$I^2 = 76.43$; P = 0.005	0.309	
Training intensity					0.587
Moderate (< 70% 1RM)	10	-0.410	$I^2 = 64.57$; P = 0.003	0.02	
High (> 70% 1RM)	8	-0.317	$I^2 = 0.0$; P = 0.499	0.003	
Training durations, week					0.026
8	5	-0.155	$I^2 = 69.26$; P = 0.011	0.601	
8 - 16	8	-0.328	$I^2 = 20.89$; P = 0.264	0.519	
Over 16	5	-0.437	$I^2 = 0.0$; P = 0.580	0.022	
Training frequency, sessions per week					0.289
2	2	-0.03	$I^2 = 0.0$; P = 0.935	0.991	
3	16	-0.242	$I^2 = 51.50$; P = 0.009	0.009	

levels (P = 0.07) with an average effect size of -0.19 pg/mL and a 95% confidence interval between 0.02 and -0.42 (55).

Macedo Santiago et al. (2018) reported that performing resistance training for eight weeks in 19 elderly women led to a significant decrease in interleukin-6 from 38.43 ± 9.48 pg/mL to 11.76 ± 5.19 pg/mL (P < 0.001) (30). Tomeleri et al. (2016) found that 32 weeks of resistance training with 50% intensity of one maximum repetition significantly decreased interleukin-6 (P = 0.05) with an average effect size of -0.650 pg/mL and a 95% confidence interval between 0.002 and -1.303 pg/mL, which is consistent with the results of this meta-analysis (33).

Hagstrom et al. (2016) examined the impact of 32 weeks of resistance training, at an intensity of 80% of one maximum repetition, on 19 elderly women with breast cancer. The study found that resistance training reduced IL-6 levels with an average effect size of 0.428 pg/mL of blood. Although this reduction was not significant, the current meta-analysis's subgroup findings indicated a greater effect of resistance exercises longer than 16 weeks on IL-6 levels (23).

Reiss et al. (2017) discussed the dual nature of IL-6, which can have both anti-inflammatory and pro-inflammatory properties depending on the target cell type. Increased IL-6 levels can lead to endothelial cell activation, prothrombic effects on platelets, smooth muscle proliferation enhancement, macrophage fat accumulation, and plaque formation in the vessel wall, resulting in atherosclerosis and arteriosclerosis. IL-6 is also a primary producer of acute phase proteins, which can increase the risk of atherosclerosis. Therefore, resistance training is recommended to reduce IL-6 levels and prevent atherosclerosis in the elderly (57).

The subgroup meta-analysis results, based on health status, age, gender, and exercise protocols, indicate that resistance exercise significantly reduces IL-6 in subgroups of elderly people over and under 60 years old, people with specific conditions, both genders, moderate and intense training intensity, training duration longer than 16 weeks, and training frequency of three times a week. However, in subgroup comparisons, a significant difference was observed only during the training period.

Studies have shown that TNF-α, produced by CD4+ T cells, can increase inflammation and exacerbate many

Table 5. Results of Subgroup Analysis of the Effect of Resistance Training on TNFα Levels in Elderly People

Characteristics and Subgroups	Number of Studies	Effect Size with 95% Confidence	Heterogeneity Test	P-Value	P-Value Between Groups
Age (y)					0.854
$\geq$ 60	15	-0.241	$I^2 = 71.06$; P < 0.001	0.113	
< 60	4	-0.187	$I^2 = 65.18$; P = 0.035	0.459	
Health status					0.672
Healthy	9	-0.291	$I^2 = 79.86$; P < 0.001	0.210	
Unhealthy	10	-0.148	$I^2 = 46.73$; P = 0.05	0.125	
Gender					0.508
Female	9	-0.369	$I^2 = 79.32$; P < 0.001	0.125	
Male	3	-0.381	$I^2 = 25.16$; P = 0.263	0.068	
Both	7	-0.080	$I^2 = 58.27$; P = 0.026	0.631	
Training intensity					0.574
Moderate (< 70% 1RM)	14	-0.289	$I^2 = 74.59$; P < 0.001	0.092	
High (> 70% 1RM)	5	-0.223	$I^2 = 30.67$; P = 0.317	0.056	
Training durations, week					0.418
8	3	-0.923	I2=93.48; P < 0.001	0.278	
8 - 16	10	-0.075	$I^2 = 34.71$; P = 0.130	0.480	
Over 16	6	-0.315	$I^2 = 49.51$; P = 0.078	0.002	
Training frequency, sessions per week					0.149
2	1	0.285	$I^2 = 0$; P = 1	0.415	
3	18	-0.225	$I^2 = 69.15$; P < 0.001	0.053	

autoimmune disease symptoms by secreting several immune system molecules, including interleukin-1 and 6. This highlights the importance of containment and prevention methods for this inflammatory index (58).

In this meta-analysis, resistance training in the elderly resulted in a decrease in tumor necrosis factor alpha by -0.227 pg/mL of blood with a 95% confidence interval between 0.023 and -0.476, but this decrease was not significant (P = 0.075). Previous studies have shown that resistance training did not significantly affect the amount of TNF-alpha in the blood in some cases (26, 29).

The subgroup meta-analysis results show no significant difference between pre-test and post-test values in any of the subgroups, except for the training period longer than 16 weeks. Also, in some subgroups, the average effect size related to TNF-a tended to decrease, but this decrease was not significant (P > 0.05). Furthermore, no significant difference was observed between the subgroups in each of the groups (classes). The statistical analysis shows that the extent and manner of the effect of resistance training on TNFα levels are unclear, and the increase or decrease of this index is not affected by resistance training. Other effective treatment methods to reduce TNFα levels, such as the use of TNFα inhibitors, chimeric antibodies, blood-soluble TNFα receptors, drugs that block the mRNA translation of the factor, and other treatment methods, can be a way to prevent the increase of TNFα levels (59). Examining the impact of resistance training on IL-6, TNF-a, and CRP levels in the elderly are crucial from a clinical perspective for several reasons. Firstly, they shed light on the potential of resistance training as a non-pharmacological intervention for managing inflammatory markers in the elderly population. As inflammation is associated with various age-related diseases, including cardiovascular conditions and musculoskeletal disorders, understanding the effects of resistance training on these specific markers provides valuable insights into potential preventive and therapeutic strategies.

Furthermore, such studies contribute to our understanding of exercise as a modifiable factor affecting inflammatory processes in aging individuals. This knowledge is essential for developing evidence-based exercise regimens tailored to the unique needs of elderly

individuals, potentially offering a non-invasive approach to mitigating age-related inflammation and its associated health risks.

Additionally, a systematic review and meta-analysis help consolidate and synthesize existing evidence, providing a comprehensive overview of the effects of resistance training on specific inflammatory markers. This is particularly valuable for clinicians and healthcare professionals, as it aids in making informed decisions regarding exercise prescriptions and interventions for elderly patients, ultimately contributing to improved health outcomes and quality of life in this demographic.

5.1. Conclusions

This meta-analysis revealed that resistance training significantly decreases CRP and IL-6 levels in individuals over 50 years old, particularly with a regimen exceeding 16 weeks and a frequency of three times a week. The reduction was more pronounced in the female subgroup. However, resistance training did not significantly affect the blood levels of tumor necrosis factor alpha in this age group.

While this study focused on the effects of resistance training on inflammatory markers, other factors like diet and genetic predispositions also need further exploration. Addressing these factors necessitates public education about improving physical health, environmental support, suitable sports facilities, motivation enhancement, proper media training, and the involvement of other stakeholders to maintain public health.

The study had limitations such as limited access to subjects, uncertainty about the subjects' sports knowledge and familiarity with resistance exercises, the sampling method, the degree of control, and the influence of other nutritional and genetic factors.

Footnotes

Authors' Contribution: M.R.R. was responsible for the conceptualization, methodology, statistical analysis using CMA 3.0, investigation, visualization, and supervision of the study. Z.M. was involved in developing the methodology for the systematic review and meta-analysis, curating the data, statistical analysis using CMA 3.0, and writing the initial draft of the manuscript. All authors have reviewed the manuscript and consent to its content.

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