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Effect of resistance training on inflammatory markers in middle-aged and older adults: A meta-analysis

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HIGHLIGHTS

- Meta-analysis on resistance training of middle-aged and elderly people is conducted.
- Physical Therapy Evidence Database was used to evaluate the research quality.
- Resistance training reduced CRP levels and IL 6 concentrations.
- It explores resistance training program to reduce inflammatory markers.

ARTICLE INFO

Keywords:
Resistance training
Middle-aged and elderly people
Inflammatory markers
Meta-analysis

ABSTRACT

Background and Objective: A meta-analysis was conducted to evaluate the impact of resistance training on pro-inflammatory cytokines c-reactive protein (CRP), interleukin 6 (IL 6), and tumor necrosis factor- α (TNF- α) in middle-aged and elderly individuals.

Methods: The retrieval period for the Web of Science and other large electronic databases is set by default to March 2022. Both included and excluded researchers are independent examination literature on the impact of resistance exercise on markers of inflammation in the elderly. The physical medical care Evidence Database scale (Physical Therapy Evidence Database, PEDro) was used to evaluate the research quality, and Revmen 5.3 was used to end the index analysis.

Results: After a total of four rounds of elimination, 12 items were eventually included. The total sample size for the research was 388 persons. Resistance training substantially reduced CRP levels in middle-aged and older individuals, with SMD = -0.56 and 95 % confidence interval ([-0.78, -0.34], $P < 0.00001$, correspondingly. Resistance training can successfully lower IL6 concentrations in middle-aged and older adults, although the combined impact is not substantial. SMD = -0.25, 95 % CI [-0.54, 0.04]; $P = 0.09$. TNF- concentrations did not alter significantly following resistance exercise in middle-aged and older adults. The overall effect was SMD = -0.07, with a 95 % confidence interval [-0.37, 0.23], while $P = 0.64$.

Conclusion: Resistance training reduces CRP, IL6, and TNF-α levels among middle-aged and elderly people. However, it has no significant anti-inflammatory effects on TNF-α. Resistance exercise at a moderate level for 3 times / week with a duration of 6–12 weeks or 16–32 weeks, significantly reduced CRP levels. This work contributing to exploring the resistance training program for the elderly to reduce inflammatory markers, and further, providing suggestions for the elderly to participate in resistance training and reduce the concentration of inflammatory markers.

1. Introduction

With increasing age, higher inflammatory marker levels are often present in the circulating system of middle-aged and elderly people (Guarner & Rubio-Ruiz, 2015). Getting old has been confirmed to raise inflammatory signs in the blood, indirectly damage the immune system of middle- and elderly-aged people, and induce chronic low-rate inflammation that is harmful to health (Michaud et al., 2013; Poland

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et al., 2014). Clinical studies have found that the elevation of c-reactive protein (CRP), interleukin 6 (IL 6), and tumor necrosis factor- α (TNF- α) pro-inflammatory cytokines in inflammatory markers can cause higher cardiovascular mortality and morbidity in middle-aged and elderly people (Chodzko-Zajko et al., 2009; Woods et al., 2014). Furthermore, high levels of inflammatory biomarkers are associated with decreased physical function (Newman et al., 2003). The increased level of inflammatory markers can aggravate the deterioration of sarcopenia and other related diseases, seriously affecting the mental and physical health of middle-aged and elderly people (Argiles et al., 2015; Arnold et al., 2018). A study revealed the relationship between skeletal muscle mass and chronic pro-inflammatory cytokines. The research found that CRP and IL-6 are positively correlated with total fat mass and negatively correlated with skeletal muscle mass (Mikkelsen et al., 2013). Additionally, other studies have shown that high levels of IL-6, CRP, and TNF-α are associated with low muscle mass and can lead to a decline in muscle strength (Alemán et al., 2011; Schaap et al., 2006).

Resistance exercise, as a type of training that maintains muscle resistance at a constant speed, for the elderly holds significant research value in regulating pro-inflammatory cytokines such as CRP, IL-6, and TNF. This type of exercise can effectively reduce the levels of these cytokines, thereby decreasing the risk of chronic inflammation (Schaap et al., 2006; Bavaresco Gambassi et al., 2019). Chronic inflammation is a key factor in various age-related diseases, including cardiovascular disease, diabetes, and arthritis. Therefore, studying the impact of resistance exercise on pro-inflammatory cytokines in the elderly not only enhances our understanding of the physiological mechanisms through which exercise benefits aging individuals but also has important clinical applications (Kohut et al., 2006; Campos et al., 2018). These research findings can provide scientific evidence for developing exercise intervention strategies for the elderly, ultimately helping to improve their overall health and quality of life. Furthermore, this knowledge also helps strength training professionals educate clients on the broader health benefits of resistance training, boosting motivation and adherence to exercise programs.

Previous studies have revealed that resistance training has been confirmed to have constructive effects on muscle strength and muscle hypertrophy, helping to maintain physical mobility and reduce the risk of falls, but the effects on inflammatory biomarkers in middle-aged and elderly people remain controversial (C M Tomeleri et al., 2018; Rech et al., 2019). Studies have shown that resistance training can produce anti-inflammatory impacts on inflammatory signs in the human body (Lera et al., 2014; Nunes et al., 2016; Tomeleri et al., 2016). However, some scholars did not find that resistance training can effectively reduce inflammatory markers (Tomeleri et al., 2016; Azizbeigi et al., 2015; Calle & Fernandez, 2010; Franceschi & Campisi, 2014). These different findings may be due to different populations (e.g., age, gender, disease, etc.) and resistance training programs (intervention intensity, frequency, and exercise cycle, etc.). Based on this, this study conducts a meta-analysis of randomized controlled trials on resistance training interventions targeting inflammatory markers in the elderly. The aim is to understand the impact of resistance training on inflammatory markers in the elderly and to explore suitable resistance training programs through subgroup analysis to reduce inflammatory markers. This provides recommendations for elderly individuals to participate in resistance training and reduce the concentration of inflammatory markers.

2. Methods

The study followed the criteria of the meta-analysis (PRISMA) guidelines (Moher et al., 2010).

2.1. Literature search strategy

The two researchers performed independent systematic searches in electronic databases like PubMed, Web of Science, EBSCOhost, and CNKI, with a March 2022 search deadline. Chinese keywords include “inflammatory markers”, “inflammation”, “inflammatory response”, “immune response”, “cytokines”, “interleukin 6”, “C reactive protein”, “tumor necrosis factor”, “resistance training”, “strength training”, “middle-aged”, “elderly”, “randomized control trial”, and English keywords include “biological signs”, “inflammation”, “inflammatory”, “immune response”, “interleukin”, “cytokines”, “myokines”, “C-reactive protein”, “weight training”, “tumor necrosis factor alpha”, “weight lifting”, “strength training”, “resistance exercise”, “strength exercise”, “age”, “elderly”, “older adults”, and “randomized control trial”.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria

① Randomized controlled trial; ② Participants were middle-aged and senior persons aged 50 years; ③ Experimental group received resistance training for 4 weeks, with one control group; ④ Experimental group consisted of the entire body; ⑤ Outcome indicators included C-reactive protein, interleukin-6, and tumor necrosis factor-α concentration indicators; ⑥ The literature has several sets of data that may be used for numerous investigations.

2.2.2. Exclusion criteria

① Non-RCT literature; ② Non-Chinese or English literature; ③ Animal experiments; ④ Non-elderly subjects; ⑤ Single acute intervention in the experimental group; ⑥ Non-resistance training literature in the experimental group, such as resistance training combined with aerobic training or pressurized resistance; ⑦ No control group; ⑧ Low-quality literature; and ⑨ Literature in which the outcome measures were not in the form of MD $\pm$ SD.

2.3. Data extraction

After reading the abstracts and titles, two researchers independently sorted through the obtained literature using the inclusion and exclusion criteria. They then eliminated any extraneous material. To determine if a piece of literature may be included in this meta-analysis, the whole text of any potential qualifying works is read. The group will debate the solution or contact the third researcher if the two researchers cannot agree.

Basic information extracted from the included literature includes the author, year of publication, sample size, age, health status, and baseline data; information about the intervention program includes the number of movements, cycle, frequency, and amount of exercise as well as the amount and intensity of the exercise; information about the outcome data index includes the CRP protein level, IL-6 protein level, TNF-α protein level, muscle strength, and body composition.

2.4. Evaluation of literature quality

Two evaluators evaluated the included literature using the Physical Therapy Evidence Database Scale (The Physiotherapy Evidence Database, PEDro). Eleven criteria make up the PEDro scale, which became used to assess the literature’s excellence. All requirements include ① Report on compliance standards; ② Apply the method of random distribution; ③ allocation hiding; ④ As a way as the most substantial prognostic elements have been worried, the agencies have been comparable at baseline; ⑤ Blinding the assessors who measure crucial variables; ⑥ Blinding the topics; ⑦ Blinding the experimental interventions; ⑧ At least one critical outcome for almost eighty five % of the patients who to begin with took element; ⑨ Every situation were given the allocated intervention or manipulate; ⑩ Present the findings of the statistical comparisons among the organizations; ⑪ For at the least one primary final results, the look at offers point and variability measures. Two raters assessed the first-rate of the blanketed literature, the scale scored the randomized controlled test from 0 to 10 points (low to high quality), for each blanketed take a look at there was 1 factor, 0 factors for no compliance, and a reduce-off factor for high nice become 6 points. When there was any disagreement between the two raters, a meeting was held, and if no agreement was reached, the third rater gave an additional score to reach a consensus.

2.5. Data analysis

The three meta-analyses used data analysis of the included outcome measures by the Revman 5.3 software, and evaluated the degree of heterogeneity between studies by I^2 statistics according to Cochrane Handbook evaluation criteria, using 25 %, 50 % and 75 % as the cut-off points of low heterogeneity, intermediate heterogeneity and high heterogeneity, respectively. When $I^2 \geq 50$ %, the random-effect model is selected, and the intermediate variables of the heterogeneity diploma among the studies are explored via subgroup evaluation; in any other case, for meta-analysis, the fixed-effect version should be carried out. Standardized mean difference (Standardized Mean Difference, SMD) turned into the impact size utilized in all protected guides. It changed into computed with a 95 % confidence c programming language, and a P-cost of much less than 0.05 indicated that the distinction turned into significant. Funnel plots were used to analyze e-book bias, and post-check outcomes for the experimental and control groups were used to conduct a meta-evaluation.

3. Results

3.1. Literature search information

Two retrieval persons from EBSCOhost, PubMed, Web of Science, China's electronic database to 413 relevant literatures. The study included 12 articles after eliminating 84 articles that did not meet the inclusion criteria, 96 articles with no inflammatory markers, acute intervention, or control group (75), and 21 articles with invalid data literature (9) Fig. 1.

3.2. Basic characteristics of the included literature

The researchers assessed the collected literature using inclusion and exclusion criteria, and a total of 12 publications were included in the meta-analysis. The included literature was published between 2010 and 2019, and the subjects were middle-aged and elderly persons aged 50 to 88. Some of the subjects had sarcopenia, cognitive impairment, coronary heart disease and type 2 diabetes. The number of subjects in the 12 studies ranged between 21 and 48, with a total sample size of 388 subjects, including 191 in the resistance training group and 197 in the control group. The intervention program of the experimental group included in the literature was resistance training, and the control group was the daily activity group. The basic information in the included literature also includes health status, exercise cycle, number of movements, frequency, intensity, amount of exercise, muscle strength, body composition, and outcome measures (Tables 1 and 2).

3.3. Included in the literature quality analysis

The average PEDro score for the included articles was 6.25, ranging from 5 to 8, and 7 of them were rated as high quality and had high overall scores. All 12 studies reported "meeting eligibility criteria", "similar baseline in each group" and "point and measured and variation measurements", but neither reported "blind to subjects" and "blind to experimental interventionists". Eleven of the 12 articles reported randomly assigning subjects into groups, and five adopted allocation concealment. Only Hsieh et al. and Tomeleri et al. were blinded to assessors, and nine articles reported key outcome data measurements for

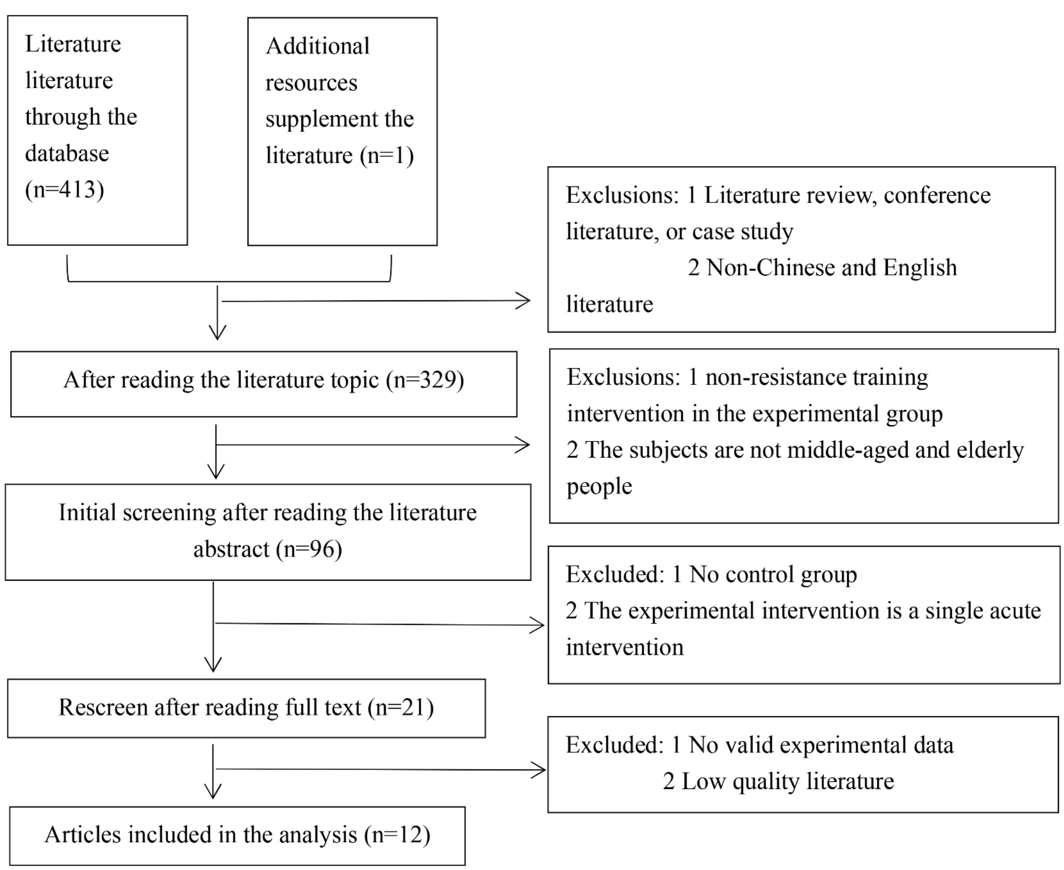

Fig. 1. Included the literature screening process.

Table 1
Basic Information of Included Studies.

literature reference	country	sample capacity Experimental group / control group	health condition	Age / year	Exercise cycle / week
Chen et al., (2018)	China	17/16	Muscular sarcopenia	65–75	8
Chupel et al., (2017)	Portuguesa	16/17	cognitive disorder	82.7 ± 5.7	28
Cunha et al., (2019)	Baxi	25/23	health	>60	12
Deiber et al., (2011)	Germany	13/9	health	50–65	12
Hsieh et al. (2016) (Calle & Fernandez, 2010)	China	15/15	Type 2 diabetes	71.2 ± 4.3	12
Karabulut et al., (2013)	America	11/10	health	56.6 ± 0.6	6
Martins et al., (2010)	Portuguesa	14/13	health	73.2 ± 6.5	16
Strandberg et al., (2015)	Sweden	17/18	health	68±2	24
Theodorou et al., (2016)	Cyprus	11/15	coronary disease	62±8	32
Tomeleri et al., (2016)	Baxi	19/19	health	68.2 ± 4.2	8
C M Tomeleri et al., (2018)	Baxi	22/23	health	70.4 ± 5.7	12
Wanderley et al., (2013)	Portuguesa	11/19	health	>60	32

Table 2
Experimental Design and Outcome Index of Included Studies.

literature reference	Motor intervention characteristics					Outcome indicators
	Exercise Frequency (time/ week)	exercise intensity	Exercise / times	muscular strength	body composition	
Chen et al., (2018)	2	medium intensity	3 × 8–12	Dorsal strength, RT, CG were unchanged	Skeletal muscle mass RT and CG, and body fat mass RT and CG were the changes	CRP,IL6, TNF-α
Chupel et al., (2017)	2–3	medium intensity	1–2 × 10–12	the power of gripping RT↑=CG	NS	CRP,TNF-α
Cunha et al., (2019)	3	NS	8 × 10–15	NS	NS	CRP
Deiber et al., (2011)	2	medium intensity	1 × 25–10	Strength test RT =CG	Lean body weight RT=CG, and body fat mass RT=CG	CRP,IL6
Hsieh et al. (2016)	3	high strength	3 × 8–10	RT =CG on the chest and RT =CG	Skeletal muscle mass is RT=CG, and RT =CG	CRP
Karabulut et al., (2013)	3	high strength	3 × 8	NS	Muscle cross-sectional area RT =CG	IL6
Martins et al., (2010)	3	medium intensity	3 × 8–15	RT of upper limb strength, no change in CG	NS	CRP
Strandberg et al., (2015)	2	high strength	3 × 15–8	Leg extension RT, CG	Leg lean body weight RT was unchanged with CG, and leg fat mass RT was unchanged with CG	CRP,IL6
Theodorou et al., (2016)	3	medium intensity	2 × 12–15	Leg peak moment RT =CG	Body fat mass, RT =CG	CRP
Tomeleri et al., (2016)	3	medium intensity	3 × 10–15	Chest recommendation RT =CG, knee extension RT =CG, and arm muscle RT =CG	Skeletal muscle mass RT =CG, body fat mass RT =CG	CRP,IL6, TNF-α
C M Tomeleri et al., (2018)	3	medium intensity	3 × 10–15	Total force, RT =CG	Skeletal muscle mass RT =CG, body fat mass RT =CG	CRP,IL6, TNF-α
Wanderley et al., (2013)	3	high strength	2 × 10–15	NS	Lean body weight RT=CG, and body fat mass RT =CG	TNF-α

RT: Resistance training; CG:, control group.

more than 85 % of subjects (Tomeleri et al., 2016; Hsieh et al., 2016). Among these, only the study by Chen et al. and Tomeleri (Chen et al., 2018; C M Tomeleri et al., 2018) reported that all subjects received intervention or control by assigned condition (Table 3).

Table 3
The PEDro score tables of the included literature.

Author and year / project	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩	⑪	total points
Chen et al., (2018)	1	1	1	1	0	0	0	1	1	1	1	8
Chupel et al., (2017)	1	1	0	1	0	0	0	0	0	1	1	5
Cunha et al., (2019)	1	1	1	1	0	0	0	1	0	1	1	7
Deiber et al., (2011)	1	1	0	1	0	0	0	1	0	0	1	5
Hsieh et al. (2016)	1	1	1	1	0	0	1	1	0	1	1	8
Karabulut et al., (2013)	1	0	0	1	0	0	0	1	0	1	1	5
Martins et al., (2010)	1	1	0	1	0	0	0	0	0	1	1	5
Strandberg et al., (2015)	1	1	0	1	0	0	0	1	0	0	1	5
Theodorou et al., (2016)	1	1	0	1	0	0	0	1	0	1	1	6
Tomeleri et al., (2016)	1	1	0	1	0	0	0	1	1	1	1	7
C M Tomeleri et al., (2018)	1	1	1	1	0	0	1	1	0	1	1	8
Wanderley et al., (2013)	1	1	1	1	0	0	0	0	0	1	1	6

3.4. Meta-analysis results of resistance training

3.4.1. Effect of resistance training on CRP

Of the twelve papers that made up this analysis, ten tested the effect of resistance schooling on CRP tiers in middle-elderly and older adults, the usage of a pattern size of 185 individuals within the trial organization and 180 in the control organization. A constant-effect model was decided on for analysis because of the low degree of heterogeneity across the research in the literature, as validated using the meta-evaluation's $I^2 = 48$ %. The consequences of the research validated that resistance training notably reduced CRP protein degrees in middle-and elderly-aged individuals (SMD = −0.56, 95 % confidence interval was −0.78, −0.34 and $P < 0.00001$) (Fig. 2).

3.4.2. Effect of resistance training on IL 6

Among the 12 articles included in this study, 6 articles compared the difference in IL 6 levels between the resistance training group and the human control group, with a sample size of 115 people in the experimental group and 105 people in the control group. As shown in the meta-analysis, $I^2 = 44$ % indicates a low degree of heterogeneity among studies, and a fixed-effects model should be selected for analysis. The results showed that SMD = −0.25, 95 %CI was −0.54, 0.04, $P = 0.09$, indicating that resistance training reduced IL 6 protein level in middle-aged people, but the anti-inflammatory effect was not significant (Fig. 3).

3.4.3. Effect of resistance training on TNF- α

Out of the twelve publications that made up this analysis, five of them examined how resistance training affected middle-aged and older people's TNF-α levels. The study had 85 participants in the experimental group and 94 participants in the control group. Since there was little variation between the studies, as Fig. $I^2 = 30$ % illustrates, a fixed-effects model was selected for analysis. After doing resistance training, middle-aged and elderly persons' TNF-α protein levels did not significantly alter, according to the study findings, which indicated SMD = −0.07, 95 %CI of −0.37, 0.23 and $P = 0.64$ (Fig. 4).

3.5. Publication bias analysis

To explore the publication bias, the funnel plots of the Meta-analysis of more than 10 included studies should be made and analyzed (Liu, 2011). One study-based Meta-analysis included more than 10 studies and required funnel plot analysis for publication bias.

The influence of resistance training on CRP concentration in middle-aged and elderly people. According to the figure, the left and right sides can be better symmetrical distribution. Fig. 5 shows that there is no publication bias.

3.6. Subgroup analysis of CRP concentration in middle-aged and elderly adults by resistance training

To explore the source of heterogeneity, this study conducted a subgroup analysis of CRP protein levels. After analysis, the reduction of CRP concentration in resistance and elderly people may be affected by exercise intensity, exercise frequency, exercise cycle, muscle mass and fat volume.

The included studies were divided into health status and could be divided into healthy and non-healthy groups. Subgroup analysis showed that resistance training could effectively reduce CRP concentration levels in healthy and non-healthy older people. In terms of muscle mass and fat mass, the subgroup analysis showed that the significant improvement in muscle mass and fat mass was associated with a significant decrease of CRP. In terms of the exercise cycle, the CRP concentrations were reduced at either 6 – 12 weeks or 16 – 32 weeks. In terms of exercise frequency, three weekly resistance training was effective in improving CRP concentration. In subgroup analysis according to exercise intensity, the analysis of moderate intensity resistance training showed that there was heterogeneity among studies, and the difference was statistically significant, indicating that moderate-intensity resistance training could significantly improve the CRP concentration in middle-aged and elderly people, while the improvement effect of high-intensity resistance training was not obvious (Table 4).

4. Discussion

4.1. Included in the literature quality evaluation and analysis

The PEDro scale was used to assess the quality of the 12 included papers, and the average score was 6.25, indicating good literature quality. Twelve papers employed moderate and high-intensity resistance training as an experimental intervention, but none of them were blinded to researchers or interventionists, and just two were blinded to assessors. The primary explanations for the drop in PEDro ratings were a lack of allocation concealment, participant blindness, intervention instructor blindness, evaluator blindness, and intention-to-treat analysis in the majority of the included trials. To increase research quality, late-stage studies may choose to conceal participants and interveners while blinding assessors. Regarding publishing bias, the left and right sides of the funnel map are evenly dispersed, and there is no clear danger of publication bias. Moreover, the basic information about the resistance training reprograms, including the number of exercises, sets, repetitions, execution speed, weekly frequency, protocol duration, and program intensity, are similar that of reported works by Bavaresco (Bavaresco Gambassi et al., 2019).

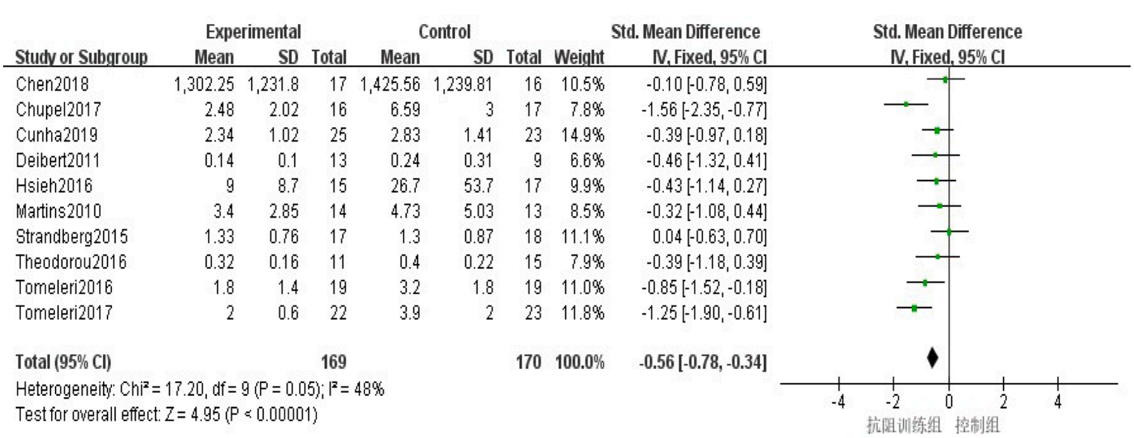

Fig. 2. Effect of resistance training on CRP in older adults.

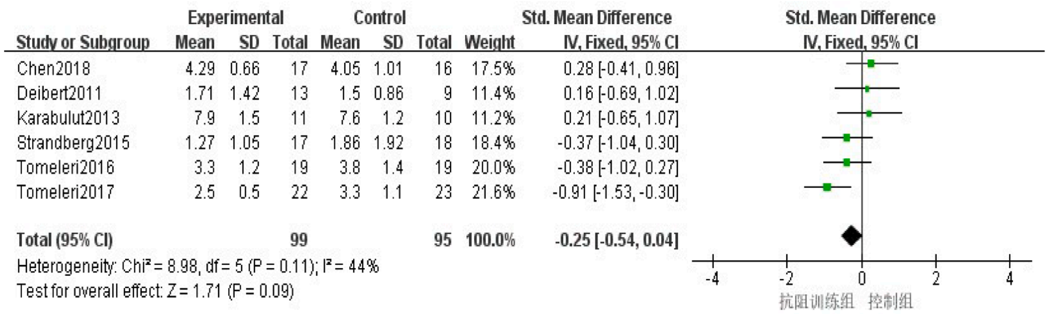

Fig. 3. Effect of resistance training on IL 6 in older adults.

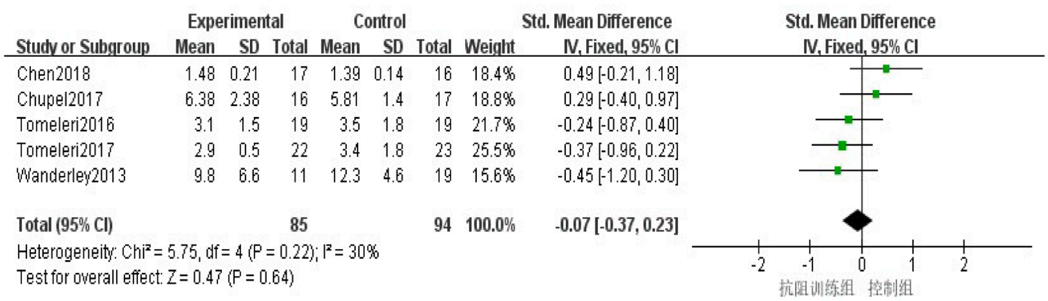

Fig. 4. Effects of resistance training on TNF- α in older adults.

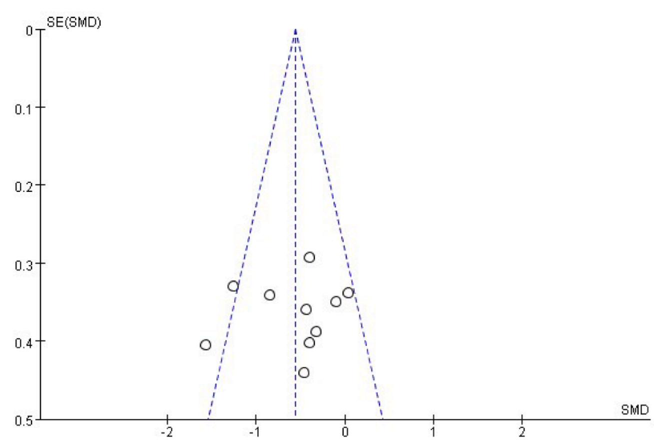

Fig. 5. Funnel plot of the effect of resistance training on CRP levels in middle-aged and elderly people.

4.2. Overall meta-analysis of the effects of resistance training on inflammatory markers in middle-aged and elderly people

This study is a meta-analysis of the effect of inflammatory markers in the elderly with resistance training intervention, mainly to analyze the effects of resistance training on inflammatory markers and provide a scientific training program for the elderly population. The results of Meta-analysis confirmed the effectiveness of resistance training as a partial inflammatory marker in middle-aged and elderly people, which was able to significantly reduce CRP concentration and improve IL 6 concentration to some extent, but did not change TNF- α concentration.

After short-term resistance training 2 times / week in middle-aged and elderly people, CRP levels were significantly reduced, but there were no significant changes in IL-6 and TNF-a levels (Liu, 2011). Similarly, a meta-analysis study reported that middle-aged and elderly adults undergoing regular exercise significantly reduced CRP levels, partly IL 6 concentrations, but did not change TNF- α protein levels (A V Sardeli et al., 2018). However, some scholars have presented different research results. Libardi et al. randomized 47 sedentary healthy men with a mean age of 49 years into combined resistance training, endurance training and resistance + endurance training. After 16 weeks of intervention, the

Table 4
Subgroup analysis of CRP concentration in middle-aged and elderly adults.

Research characteristics	divide into groups	sample capacity	MD	95 %CI	P	I^2/%
health condition	Health	6(215)	−0.55	−0.83, −0.28	<0.0001	45
	Non-healthy	4(124)	−0.57	−0.94,−0.20	0.002	63
Muscle volume	Increase	3(116)	−0.74	−1.40, −0.08	0.03	66
	keep	3(89)	−0.25	−0.67,0.17	0.24	0
fat mass	reduce	4(141)	−0.78	−1.12, −0.43	<0.0001	24
	keep	3(90)	−0.13	−0.55,0.29	0.55	0
period of motion	6–12 Weeks	6(218)	−0.59	−0.87, −0.32	<0.0001	32
	16–32 Weeks	4(121)	−0.50	−0.87, −0.13	0.009	69
Exercise frequency	2	3(90)	−0.13	−0.55, 0.29	0.55	0
	3	6(216)	−0.63	−0.90, −0.35	<0.00001	16
exercise intensity	medium intensity	7(224)	−0.72	−1.00, −0.44	<0.00001	51
	high strength	2(67)	−0.19	−0.67,0.30	0.45	

results showed no significant change in IL-6, CRP or TNF-A in the three groups (Libardi et al., 2012). Phillips et al. performed 10 weeks of resistance training in sedentary older women and detected a 37 % reduction in serum TNF- α levels after training (Phillips et al., 2010). The reasons for the different results may be related to the different intervention programs (training frequency, intensity, and volume), subject characteristics (inflammation level, training status, body composition, etc.) and data analysis methods. However, according to existing studies, the participation of middle-aged and elderly people in resistance training can significantly reduce the CRP level, but there is no significant effect in changing IL-6 or TNF- α levels.

These findings help to explore effective resistance training programs specifically tailored for the elderly, aiming to reduce inflammatory markers. By identifying and understanding the most beneficial training regimens, this work provides valuable clinical recommendations for elderly individuals. It encourages their participation in resistance training, with the goal of lowering the concentration of inflammatory markers, thereby potentially improving their overall health and reducing the risk of inflammation-related diseases.

4.3. Subgroup meta-analysis of the effects of resistance training on inflammatory markers in middle-aged and elderly adults

To explore inter-study heterogeneity, subgroup analysis was conducted based on the study of CRP concentration in the elderly in the resistance training intervention. The possible sources of heterogeneity included health status, exercise intensity, exercise frequency, number of exercise groups, exercise cycle, muscle mass and fat mass. Subgroup analysis showed that:

The results showed that resistance training could significantly improve CRP concentration in both healthy and non-healthy elderly people. However, there are few studies on the relationship between CRP concentration and resistance training in older people in different health conditions. White et al. conducted resistance training of 8 weeks, 250 times / week, 50–70 % maximum voluntary contraction (MVC). The exercises included knee flexion and extension, spinal flexion and extension. After training, the CRP level of chronic inflammation markers decreased significantly in the subjects (White et al., 2006). In addition, it has been shown that resistance training also improves CRP levels in patients with sarcopenia, cognitive impairment, type 2 diabetes, as well as coronary heart disease (Hsieh et al., 2016; Liu, 2011; Chupel et al., 2017; Theodorou et al., 2016). However, there are still different opinions on the conclusion that resistance training can improve CRP levels in people with different health conditions. Farinha et al. used a total of 10 weeks, 3 times / week of high-intensity resistance training in nine type 1 diabetes patients aged 18–40 years, and the subjects did not significantly reduce CRP levels after the training (Farinha et al., 2018). A study on the effects of acute and long-term training intervention on systemic chronic inflammation, the effect of resistance training and endurance training on inflammatory markers, mild inflammatory markers to acute resistance training is different from healthy individuals, long-term resistance training in improving inflammatory markers, but the effect of resistance training to improve inflammatory markers may depend on the type of disease and the degree of disease and the training program (Ploeger et al., 2009). Later studies require longer intervention duration, larger sample size, and older populations with different health conditions to explore the effect of resistance training on CRP levels. However, the particularity and physiological mechanism of CRP response caused by resistance training in elderly people with different health conditions deserve further study.

In a subgroup analysis to explore heterogeneity, CRP levels were not altered in RCT studies that kept fat mass constant, while significant improvement in CRP levels in middle-aged and elderly adults was found in RCT studies with significantly reduced fat mass. This may be related to the fact that adipose tissue is the main tissue that releases pro-inflammatory cytokines. Studies have confirmed that adipose tissue is the main stimulus leading to low-grade inflammation, and the reduction of fat mass is one of the key factors in the anti-inflammatory effect of resistance training (Coppack, 2001; Mora et al., 2006). The study of Tomileri reported that adipose tissue may affect the production of proinflammatory cytokines, and its results confirmed a positive correlation between the changes in fat mass and the reduction of inflammatory markers, and the correlation was higher in trunk fat (Tomeleri et al., 2016). However, Nicklas et al. observed that regular physical activity reduced the concentration of systemic inflammatory biomarkers even in the absence of weight loss (Nicklas et al., 2008). The reduction in the level of the inflammatory marker CRP may not be affected only by altered fat mass but may be other independent physiological mechanisms involved, for example, the increase of muscle mass can also significantly reduce CRP levels.

The results of the subgroup analysis found that resistance training did not change CRP levels in the randomized controlled trial study, and found a significant decrease in CRP levels in middle-aged and elderly people in the randomized controlled trial study promoting muscle hypertrophy. This may be related to the effects of two physiological mechanisms. First, muscle hypertrophy caused by resistance training increases energy consumption and insulin sensitivity in middle-aged and elderly people, which then reduces CRP levels (Calle & Fernandez, 2010). Secondly, skeletal muscle contraction during resistance training can directly produce cytokines with anti-inflammatory effects to reduce the level of inflammatory markers, which is beneficial to alleviating low-grade chronic inflammation (Pedersen & Febbraio, 2008). Mavros et al. performed progressive resistance training in 47 elderly people, which significantly reduced CRP levels in vivo and confirmed that the improvement in CRP concentration was associated with increased muscle mass (Mavros et al., 2014). Similarly, Ogawa trained 21 sedentary adults over 80 years showed that the results showed a negative correlation of muscle thickness with percentage change in CRP levels and that resistance training-induced muscle hypertrophy was associated with reduced inflammatory markers and levels (Ogawa et al., 2010). However, there are few studies on the relationship between muscle mass and CRP concentration in resistance training in middle-aged and elderly people, and future studies still need to explore the connection between the two.

Exercise intensity is an important variable of resistance training, which can interfere with the magnitude of structural adaptations in the organism. Currently, most studies have used moderate and high intensity as inflammatory markers in middle-aged and elderly people in exercise intensity intervention. Previous studies have shown that both moderate-intensity and high-intensity resistance training can reduce the level of CRP in middle-aged and elderly people with no adverse events. In this study, the moderate-intensity resistance training group reduced the CRP concentration better than the high intensity, which may be associated with a significant increase in muscle mass. Studies have confirmed that CRP levels are negatively correlated with muscle mass, while resistance training with 51–60 % of 1 RM has the greatest effect on muscle morphology, with an average SMDbs of 0.43 (Schaap et al., 2013; Borde et al., 2015). Different from the results of this study, Calle et al. and others found that high-intensity resistance training improved CRP levels in young people and exercise people (Calle & Fernandez, 2010). The reasons for the above two different results may be related to the age of the subjects and the excessive intensity of the tissue damage and elevated inflammatory markers in the middle-aged and elderly people (AV Sardeli et al., 2018). There has been much discussion about the intensity of resistance training in middle-aged and elderly people, but the optimal intensity of the effect of reducing CRP concentration in middle-aged and elderly people has not been determined. According to existing studies, medium-intensity resistance training can effectively reduce CRP levels.

According to the results of subgroup analysis, it was found that 6–12 weeks and 16–32 weeks of resistance training can effectively improve CRP levels in middle-aged and elderly people. CRP levels were significantly reduced even with shorter exercise periods (10–16 weeks) (Phillips et al., 2012; Donges et al., 2010). Studies have shown that longer exercise periods (> 20 weeks) are more effective in reducing body mass index (Phillips et al., 2012; Wilmore et al., 1999). However, weight loss was negatively correlated with inflammatory markers. Selvin et al. found that for every 1 kg of weight loss, CRP concentration decreased by 0.13 mg/L^{-1} (Selvin et al., 2007). In conclusion, according to existing studies, resistance training in different exercise cycles can produce beneficial effects on CRP. Considering the individual differences in middle-aged and elderly people and the effect of resistance training intervention on inflammatory markers, it is suggested that elderly people choose longer resistance training to achieve a higher training effect.

Subgroup analysis of CRP effects in older adults in resistance training interventions found that most studies used 2 times / week and 3 times / week as exercise frequency in the intervention program, and exercise frequency may be an important modulator of CRP effect in middle-aged and older adults. This study found that the CRP effect was not obvious in the elderly, and the three weekly resistance training could significantly improve CRP levels in middle-aged and elderly people. In a recent meta-analysis, Sardeli et al. reported that resistance training at a higher weekly frequency (3 times / week) significantly reduced CRP levels and was better than the 2 times / week resistance training group (Selvin et al., 2007). This may be related to a decrease in fat mass. Eklund et al. found that even with the same amount of training, the 4 times / week resistance training was significantly better than the 2 times / week group (Eklund et al., 2014). However, one study that randomized 92 healthy seniors aged 65 – 75 years to 1 times / week, 2 times / week and 3 times / week as well as the non-exercise group found that there was no evidence of high training frequency for greater improvement in CRP levels in healthy older adults (Halainen et al., 2018). Future studies could address the optimal frequency of CRP concentrations in older adults in a resistance training intervention.

In addition, these mentioned conclusions are of great significance in various clinical applications. For instance, in treating chronic inflammation-related diseases such as arthritis and diabetes, resistance training has been shown to effectively lower levels of CRP, IL-6, and TNF-α in patients. This not only helps to alleviate the inflammatory response but also improves overall health and quality of life. Additionally, for older adults, using resistance training to reduce chronic inflammation can prevent the decline in muscle mass and related physical deterioration, helping them maintain independence and physical function.

4.4. Limitations of the study

1) Only the search and inclusion of Chinese and English literature were conducted, and the comprehensiveness of the study was limited to some extent. 2) Resistance training has few studies on CRP in healthy middle-aged and elderly people. Four randomized controlled trials of non-healthy middle and elderly people were included, which affected homogeneity to some extent, but finally a subgroup analysis of the health status of the participants. 3) No subgroup analysis of muscle strength was performed, although many studies have reported the relationship between increased muscle strength and decreased inflammatory markers after resistance training (Tomeleri et al., 2016; Borde et al., 2015; Hagstrom et al., 2016). However, the included literature reported different methods of testing muscle strength and muscle strength at different sites, thus preventing a valid meta-analysis of it. 4) Study results and recommendations are only apply to middle-aged and elderly people aged 50 and older, and may not be applicable to other age groups. 5) Because resistance training had no significant change in IL 6 and TNF- α in middle-aged and elderly people, and the number of inclusions was small, no subgroup analysis was done.

5. Conclusion

Resistance training can effectively improve CRP levels and reduce IL-6 levels in middle-aged and elderly adults, though it does not have an anti-inflammatory effect on TNF-α pro-inflammatory cytokines. The reduction in CRP concentration is associated with improvements in both fat mass and muscle mass after resistance training in this population. Moderate-intensity resistance training, performed 3 times / week for a duration of 6–12 weeks or 16–32 weeks, has been shown to be particularly effective in reducing CRP levels. These findings suggest that a structured resistance training regimen can play a crucial role in enhancing inflammatory profiles and overall health in middle-aged and elderly individuals. By tailoring the intensity and duration of the training, clinicians can help mitigate age-related inflammation, improve body composition, and promote healthier aging.

Further, researches on the resistance training of middle-aged and elderly individuals also has significant applications and implications in clinical practice. Firstly, a scientifically designed resistance training program can effectively increase muscle mass and strength, which is particularly beneficial for middle-aged and elderly individuals, improving physical function and reducing the risk of falls and fractures. Secondly, resistance training has been shown to significantly reduce inflammatory markers such as CRP, helping to prevent and manage chronic inflammation-related diseases. Additionally, studies indicate that moderate-intensity resistance training is more suitable for the elderly than high-intensity training, providing specific guidance for clinical practice. With well-designed training programs, clinicians can help patients improve their quality of life, delay the aging process, and promote overall health.

In the future, studies may choose to blind subjects, interveners, and assessors to improve study quality. Increase the intervention of resistance training in different healthy people; increase the influence of different intensities of resistance training on CRP in middle-aged and elderly people; increase the relationship between strength and CRP in middle-aged and elderly people after resistance training, and improve the dose relationship of resistance training on inflammation markers in middle-aged and elderly people.

CRediT authorship contribution statement

Xinnian Cheng: Funding acquisition, Resources, Software, Visualization, Writing – review & editing, Writing – original draft. **Zhiqiang Yang:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software.

Declaration of competing interest

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

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