Meta-Analysis

The Impact of Exercise and Protein Intake on Inflammaging: A Meta-Analysis and Systematic Review of Randomized Controlled Trials

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Context: *Sarcopenia and cachexia lead to muscle wasting and increased health risks in older adults. Both sarcopenia and cachexia are associated with inflammaging, a chronic low-grade inflammatory state linked to aging. Strategies to preserve muscle mass and function are crucial for maintaining independence and quality of life among the elderly.* ***Objective:*** *This meta-analysis and systematic review was conducted to comprehensively assess the individual and combined effects of exercise training and protein supplementation on circulatory markers of inflammation in older adults.* ***Data Sources:*** *A systematic search of the PubMed, Scopus, Cochrane CENTRAL, and SPORTDiscus databases was conducted to identify relevant studies published until January 2024.* ***Data Extraction:*** *The search focused on randomized controlled trials examining the impact of exercise training (Ex), protein consumption (Pro), or their combination (Ex-Pro) on inflammatory factors, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) compared with a control (Con).* ***Data Analysis:*** *The meta-analysis revealed a significant decrease in CRP levels in the Ex vs Pro ($P = .0003$) and the Ex-Pro ($P < .00001$) group compared with the Ex group and in overall experimental (EXPL) subgroups ($P = .0002$) compared with the Con group. A similar reduction was found in IL-6 in the Ex group ($P = .001$), Ex-Pro group ($P = .05$), and EXPL ($P = .0002$) subgroup compared with the Pro group. However, for TNF-α levels, a significant reduction was noted only in the Ex-Pro group compared with the Ex group ($P < .00001$).* ***Conclusion:*** *Exercise training and protein supplementation, particularly when combined, show greater benefits in mitigating inflammaging. These findings highlight the importance of combined interventions against muscle wasting. Future studies and meta-analyses should further address the effects of Ex and Pro and Ex-Pro on inflammatory markers of older adults, considering specific conditions and larger sample sizes to identify optimal strategies for the aging population.*

Key words: *exercise training, protein supplementation, inflammatory markers, C-reactive protein, interleukin-6, tumor necrosis factor-α, meta-analysis.*

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INTRODUCTION

The dysregulation of inflammatory factors, leading to a chronic inflammatory state, plays a significant role in the onset and progression of many age-related diseases (ARDs) and muscle-wasting diseases.[1,2] The aging population in developed countries poses a significant public health and economic burden on society. It is estimated that approximately 5% to 13% of individuals aged 60-70 years experience sarcopenia.[3,4] Conditions such as sarcopenia and cachexia are closely associated with chronic low-grade inflammation, particularly in the context of aging, where it is referred to as "inflammaging." This condition is characterized by higher levels of serum C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) in middle-aged and older adults.[5,6] It remains unclear whether the imbalance of inflammatory responses is a cause or a consequence of the aging process itself, and a significant gap persists in our understanding of factors driving inflammaging.[2,5,7] However, exercise training and protein supplements are both considered promising strategies for combating ARDs, although the question remains about which part can be more effective.[8,9]

Exercise is widely recognized as part of healthy aging; it enhances muscle function and physical performance.[8,10] Although different types of exercise, such as aerobic training (AT), resistance training (RT), and concurrent training (CT), promote distinct adaptations in muscle morphology and physiology,[10,11] the anti-inflammatory benefits of chronic regular exercise, regardless of modality, intensity, or sex, have been widely reported.[2,7,9,12–15] However, findings regarding the acute effects of exercise and the impact of advanced training levels in athletes on inflammatory markers have been more varied.[12] Aerobic training is well-known for its effects on metabolic homeostasis by improving mitochondrial and cardiovascular activity, whereas RT enhances ribosomal biogenesis and protein synthesis to promote hypertrophy.[16,17] Concurrent training combines the advantages of both.[18] Each of these exercise types appears to reduce visceral adipose tissue and, subsequently, decrease inflammatory conditions, likely due to the reduction in visceral adipose tissue, decreased adipokine release, increased myokine production,[2,16,19] and the overall induction of an anti-inflammatory environment, although the exact mechanisms remain unclear.[9] Although regular exercise is considered a cornerstone strategy to prevent muscle loss and improve muscle function in combating ARDs and other muscle-wasting diseases, increasing protein intake, whether on its own or in conjunction with exercise, may promote protein synthesis, increase skeletal muscle mass, and enhance muscle function.[9,20]

Protein supplementation, often in the form of dietary proteins and protein supplements, provides essential amino acids necessary for muscle repair and growth, offering a more concentrated source compared with other dietary options.[21–23] Compared with young adults, a larger dose of protein intake is necessary for muscle protein synthesis in older adults, a condition called anabolic resistance.[24,25] Dietary protein may help combat or slow age-related changes, such as the decline in levels of anabolic hormones in men or the effects of menopause in women.[26] Moreover, most studies support the claim that protein supplements combined with RT can enhance the anabolic response, facilitating muscle adaptation and recovery after exercise. Similar findings have also been observed with other exercise modalities, although to a lesser extent.[27] Additionally, certain protein sources, such as whey protein, contain bioactive peptides that may have anti-inflammatory properties, contributing to muscle function and helping to combat inflammaging.[28]

The efficacy of exercise, protein ingestion, and exercise and protein ingestion together on muscle preservation, especially in older adult societies, however, is controversial and needs more research.[29] Some argue that catabolism in muscle protein followed by exercise can elevate the levels of CRP, IL-6, and TNF-α.[7] Additionally, chronic low-grade inflammaging may be accelerated by immunosenescence and ARDs.[7] Although acute inflammatory reactions are crucial for recovery after injury,[30] older adults often have chronic low-grade inflammation at their basal level.[30] Hence, understanding the mechanism involved in exercise, protein supplementation, and their combined efficacy in ARDs prevention and management among the elderly is important for developing strategies to ameliorate muscle mass and function. The current investigation is the first, to our knowledge, to examine the combined effects of exercise and protein supplements on inflammatory markers in this population.

METHODS

Search Strategy and Study Selection

This systematic review and meta-analysis followed the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting standards.[31,32]

A comprehensive systematic search was conducted of the PubMed, Scopus, Cochrane CENTRAL, and SPORTDiscus databases from inception until January 2024 to identify articles reporting on studies examining the effect of exercise training (Ex), protein consumption

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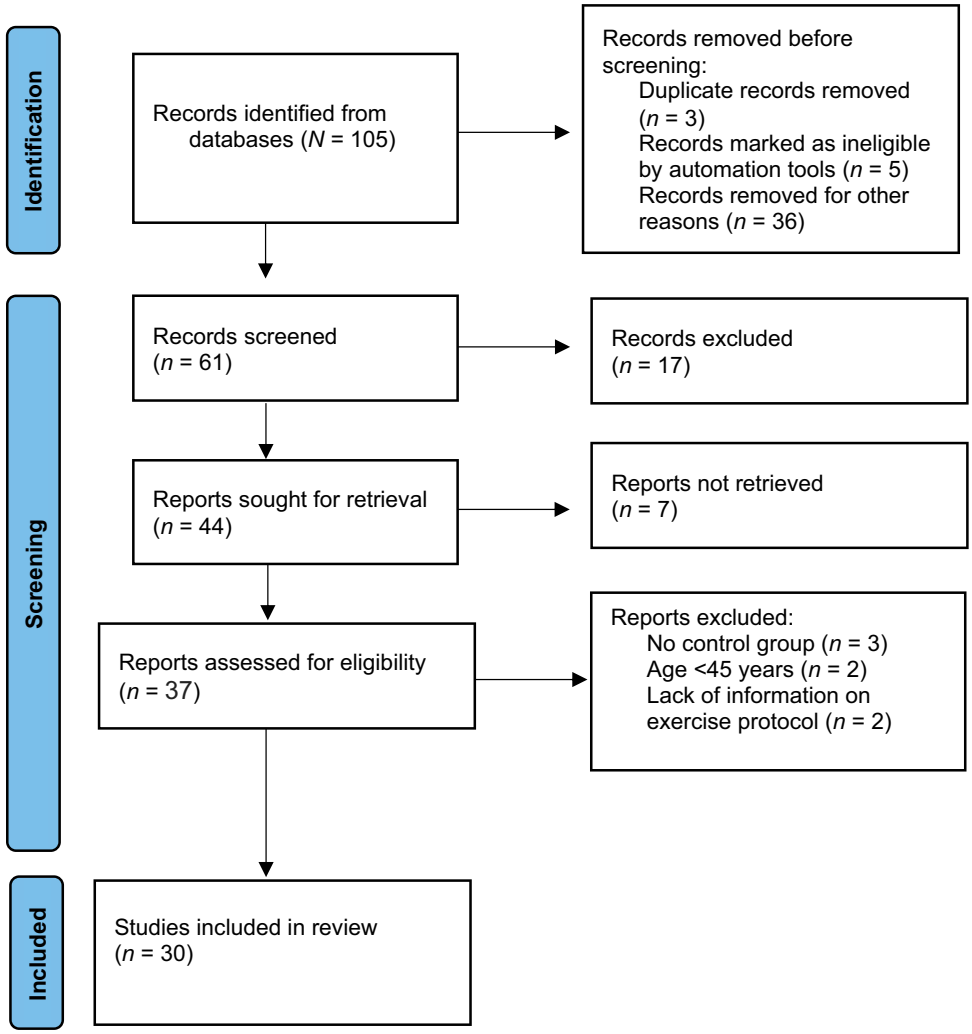

Figure 1. Flow Diagram Illustrating the Systematic Literature Search Process

(Pro), or a combination of both (Ex-Pro) on circulating levels of CRP, TNF-α, and IL-6 in older adults, specifically focusing on their impact on sarcopenia and cachexia. The search strategy involved combining Medical Subject Headings, free terms, and matching synonyms. Keywords included "exercise," "protein consumption," "inflammation," "sarcopenia," "cachexia," and variations of these terms. Additionally, manual screening of reference lists of selected articles was performed to identify additional relevant studies. The full search strategy is provided in Figure 1.

Eligibility Criteria

Two independent investigators screened the titles and abstracts of the articles obtained from the search to identify potentially eligible studies. Full-text screening was conducted for studies deemed relevant based on their titles and abstracts. The inclusion criteria were as follows (Table 1): (1) randomized controlled trials (RCTs) and controlled trials published in English; (2) interventions involving Ex and/or Pro; (3) outcomes including CRP, IL-6, TNF-α, and their impact on sarcopenia and cachexia. Any discrepancies between the investigators were resolved through discussion.

Data Extraction and Risk-of-Bias Assessment

Two authors (M.M.R. and R.N.B.) extracted data from the included studies, including study characteristics (author, publication year, country), participant demographics (age, sex), intervention details (type of Ex or Pro), outcome measures (inflammation factors, sarcopenia, cachexia), and study findings. The methodological quality of the included studies was assessed using the PEDro scale (score range 1–11), adapted to assess the quality of RCTs. The score for the present review was 9[33,34] (Table S3).

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Table 1. PICOS Criteria for Inclusion and Exclusion of Studies

Parameter	Inclusion criterion	Exclusion criterion
Population	Middle-aged and older adults in human studies	Studies involving nonhuman subjects, children, adolescents, or adults
Intervention	Exercise training (resistance, aerobic, or combination) and/or protein consumption	Studies without clear exercise or protein consumption interventions or those using unrelated interventions
Comparison	Control group with no intervention or placebo	Studies without a control group
Outcomes	C-reactive protein, interleukin-6, tumor necrosis factor-α levels	Studies without available data
Study design	Interventional trials (including randomized controlled trials and controlled trials)	Nonrandomized controlled trials, noncontrolled trials, observational studies, case studies, systematic reviews, meta-analyses, reviews, and articles not published in English

Data Analysis

The effect size of the outcomes was calculated by assessing the mean difference (MD) between intervention and control groups (Con) by subtracting the pretest mean from the post-test mean for all included studies. Review Manager, version 5.4 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used for all analyses. The pooled MD was calculated using the random-effects model with 95% CIs. In instances where outcome data were missing, attribute methods were used to estimate changes in mean and SD values. This estimation involved calculating the difference between the baseline and postintervention means. If this information was not explicitly provided in a study, these values were derived based on the available data, such as the sample size of the intervention group, group P values, or 95% CIs. Additionally, if studies reported the SEM rather than SD, SEM was converted to SD for consistency in the analysis.

The Q test, I^2, and meta-regression analysis were used to explore potential sources of heterogeneity. The results of the meta-analysis are displayed in forest plots, and funnel plots were used to assess the risk of publication bias (Figures S1-S24).

Study Quality

To assess the quality of the studies, the Tool for the Assessment of Study Quality and Reporting in Exercise (TESTEX) was used (Table S2).[35–62] This tool is a validated measure that totals 15 points, with a maximum of 4 points allocated to research quality and all points allocated to reporting quality in exercise research. Two investigators (M.M.R. and S.R.A.H.) independently evaluated the quality of the included studies, with disagreements resolved through consensus. Lastly, 2 authors (N.H. and V.C.F.) contributed to the revision and oversight of the entire research process, ensuring the accuracy and integrity of the study findings.

RESULTS

Study Selection

Initially, a total of 105 published articles were identified through systematic searches of the PubMed, Scopus, Cochrane CENTRAL, and SPORTDiscus databases, along with manual searching. After removing duplicate titles and excluding animal studies, 61 full-text articles remained for screening. Following a thorough review of abstracts and titles, 44 articles were eliminated based on predetermined criteria. Subsequently, the full text of 37 potentially eligible studies was retrieved for further assessment. Consequently, a final selection of 30 full-text articles met the eligibility criteria and were included in the comprehensive meta-analysis, as illustrated in the PRISMA flow diagram (Figure 1).

Study Characteristics

The details of the included RCTs are summarized in Table 2,[35–62] categorized by their respective countries of origin. The distribution of studies is as follows: 5 were conducted in the United States; 4 in Brazil; 3 each in Iran and Italy; 2 each in the United Kingdom, China, Finland, and Sweden; and 1 each in Thailand, Japan, Denmark, Belgium, Korea, and Slovenia.

The study included participants with a mean age of 67.64 ± 2.59 years and comprised 546 men, 1342 women, and 66 participants whose sex was not specified, as detailed in Table 2. The age range for female participants was between 58 and 88 years, which indicates they were considered menopausal.

Regarding participant allocation in the CRP analysis, the number of participants (reported respective to

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Table 2. Summary of Demographic Characteristics of Participants and Interventions

First author, year	Sex (M/F)	Groups (sample size)	Age, y	BMI (± SD), kg/m^2	Interventions	Participant health status	Outcomes assessed
Kirk et al (2021)[35]	F	Ex: 24 Con: 31 Ex-Pro: 22 Pro: 23	Ex: 66.63 ± 3.92 Con: 68.16 ± 5.85 Ex-Con: 68.59 ± 5.70 Pro: 71.83 ± 6.51	27.06 ± 5.18	16 w CT (2 d w^{-1} RT and 1 d w^{-1} AT) Protein: 1.55 ± 0.69 g kg^{-1} d^{-1}	Healthy	CRP TNF-α IL-6
Bo et al (2019)[36]	M	Pro: 30 Con: 30	Pro: 73.2 ± 6.5 Con: 74.8 ± 5.9	21.34 ± 2.47	Protein: 6 mo; 0.76 g kg^{-1} d^{-1}	Sarcopenia	CRP TNF-α IL-6
Nabuco et al (2019)[37]	F	Ex-Pro: 13 Ex: 13	Ex-Pro: 68.0 ± 4.2 Ex: 70.1 ± 3.9	27.4 ± 3.0	12 w RT (3 d w^{-1}, 8 movements, 3 sets × 8-12 R) Protein: 1.0 ± 0.23 g kg^{-1} d^{-1}	Sarcopenia	CRP TNF-α IL-6
Fernandes et al (2018)[38]	F	Pro: 16 Con: 16	Pro: 67.3 ± 4.1 Con: 67.8 ± 4.0	25.9 ± 2.7	Protein: 12 w, 89.3 ± 9.5 g d^{-1}	Healthy	CRP
Stojkovic et al (2017)[39]	F	Pro: 38 Con: 46	Pro: 68.9 ± 0.9 Con: 6.3 ± 0.9	26.0 ± 0.6	Protein: 18 w, 98.5 ± 2.8 g/d	Healthy	CRP IL-6
Griffen et al (2022)[40]	M	Pro: 9 Con: 9 Ex: 9 Ex-Pro: 9	Pro: 66 ± 2 Con: 67 ± 2 Ex-Pro: 68 ± 1 Ex: 67 + 1	26.6 ± 0.8	12 w RT (60%-80 % 1 RM, 3 sets × 10-12 R) Protein: 1.0 g kg^{-1} d^{-1}	Healthy	CRP TNF-α IL-6
Alghadir et al (2016)[41]	M/F	Con: 50 Ex: 100	Con: 66.8 ± 3.47 Ex: 67.3 ± 2.8	23.5 ± 1.7	24 w moderate continuous AT (MICT, 60%-70% MHR for 45-60 min)	Healthy	CRP
Beltran Valls et al (2014)[42]	M/F	Con: 10 Ex: 13	Con: 72.0 ± 3.16 Ex: 72.0 ± 3.65	25 ± 1	12 w RT (40%-50% 1 RM, 3-4 sets 15 R)	Healthy	TNF-α IL-6
Derosa et al (2020)[43]	M/F	Pro: 59 Con: 58	Pro: 59.7 ± 9.1 Con: 58.6 ± 8.8	22.7 ± 2.1	Protein: 12 w 2.7% of body weight	T2DM	CRP TNF-α IL-6
Li et al (2019)[44]	M/F	Pro-Ex: 56 Con: 56	Pro-Ex: 72.05 ± 6.54 Pro: 65.24 ± 4.05	24.69 ± 3.02	12 w RT (3 d w^{-1} 20 min intensive RT) Protein: 1.5 g kg^{-1} d^{-1}	Sarcopenia	TNF-α Il-6 CRP
Ahmadi et al (2020)[45]	M	Con: 21 Pro: 23	Con: 63.5 + 7.2 Pro: 62.1 + 7	21.53 ± 2.59	Protein: 55.55 ± 28.03 g d^{-1}	COPD	TNF-α Il-6
Bumrungpert et al (2018)[46]	M/F	Pro: 23 Con: 19	Pro: 54.1 + 9.3 Con: 51.5 + 9.6	24.9 ± 5.7	Protein: 1.6 g kg^{-1} d^{-1}	Cancer	CRP
Sohrabi et al (2016)[47]	M	Pro: 23 Con: 23	Pro: 57 + 9.6 Con: 55 + 6.5	24.3 ± 4.20	Protein: 18.5 g d^{-1}	Hemodialysis	CRP IL-6
Sugawara et al (2012)[48]	M/F	Ex-Pro: 15 Con: 14	Ex-Pro: 77.4 ± 5.2 Con: 77.1 ± 5.8	–	12 w AT (MICT, 40%-50% Vo_2max for 45 min) Protein: 1.5 ± 0.5 g kg^{-1} d^{-1}	COPD	CRP TNF-α IL-6
Madzima et al (2017)[49]	F	Ex: 16 Ex+Pro: 17	Ex: 59 + 9 Ex+Pro: 59 + 7	27.2 ± 5.6	12 w CT (1 d w^{-1} RT 65% 1 RM with 10 R and 2 d w^{-1} AT) Protein: 1.8 g kg^{-1} d^{-1}	Breast cancer survivor	CRP
Biesek et al (2021)[50]	F	Con: 18 Ex: 18 Ex-Pro: 18 Pro: 18	Con: 70.4 ± 3.9 Ex: 71.2 ± 4.2 Ex-Pro: 71.7 ± 4.8 Pro: 73.1 ± 5.3	27.1 ± 4.3	12 w CT (20 min AT + 20 min RT) Protein: 81.5 g d^{-1}	Pre-frail	IL-6

(continued)

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Table 2. Continued

First author, year	Sex (M/F)	Groups (sample size)	Age, y	BMI (± SD), kg/m^2	Interventions	Participant health status	Outcomes assessed
Forti et al (2014)[51]	M/F	Ex: 20 Con: 20	Ex: 65.69 ± 7 Con: 67.14 ± 5	27.30 ± 4.1	12 w RT (30%-80% 1 RM, 2 d w^{-1}, 3 sets × 10 R)	Community dwelling	IL-6
Ihalainen et al (2019)[52]	M	Ex: 26 Con: 20	Ex: 69.5 ± 2.2 Con: 69.4 ± 2.2	29.0 ± 4.1	6 mo RT (3 d w^{-1}, 70%-90% 1 RM, 2-5 sets × 4-12 R)	Healthy	CRP IL-6
Libardi et al (2012)[53]	M	Ex RT: 11 Ex ET: 12 Ex CT: 11 Con: 13	Ex: RT: 49.27 ± 4.81 Ex: ET: 49.25 ± 5.42 Ex: CT: 48.54 ± 5.35 Con: 49.10 ± 5.78	28.37 ± 3.0	16 w RT (50% 1 RM, 3 sets × 8-10 R) AT (60 min of walking or running at 55%-85% MHR) CT	Healthy inactive	IL-6 TNF-α
Masala et al (2020)[54]	F	Ex: 113 Con: 117	Ex: 58.7 (4.9) Con: 58.6 (5.5)	24.4 ± 3.4	24 mo of AT (6-10 MET)	Healthy	CRP TNF-α IL-6
Nicklas et al (2008)[55]	F	Ex: 183 Con: 186	Ex: 76.4 ± 4.1 Con: 77.0 ± 4.4	30.7 ± 6.0	12 mo CT (3 d w^{-1} 40-60 min AT + RT)	Healthy, community dwelling	TNF-α IL-6
Phillips et al (2010)[56]	F	Ex: 7 Con: 7	Ex: 71.1 + 6.2 Con: 73.1 + 6	26.0 ± 4.7	10 w RT (50% 1 RM, 3 d w^{-1}, 3 sets × 8-10 R)	Healthy	TNF-α IL-6
Rodriguez et al (2014)[57]	M/F	Ex: 16 Con: 10	Ex: 70.0 ± 0.9 Con: 69.1 ± 1.1	27.08 ± 0.8	8 w RT (60-80% of 1 RM, 2 d w^{-1})	Healthy	CRP IL-6
So et al (2013)[58]	M/F	Ex: 18 Con: 22	Ex: 71.6 ± 5.5 Con: 68.4 ± 5.8	25.9 ± 3.0	12 w RT (3 d w^{-1}, 2-3 sets × 12-25 R)	Healthy	CRP TNF-α IL-6
Strandberg et al (2015)[59]	F	Ex: 17 Con: 18	Ex: 68 ± 2 Con: 68 ± 1	24.5 ± 2.8	24 w RT (55%- 80% 1 RM, 3 sets × 8 -12 R)	Healthy	CRP IL-6
Tomeleri et al (2018)[60]	F	Ex: 22 Con: 23	Ex: 72.1 ± 6.3 Con: 68.8 ± 4.9	26.6 ± 3	12 w RT (3 d w^{-1}, 3 sets 10-15 R)	Healthy	CRP TNF-α IL-6
Urzi et al (2019)[61]	F	Ex: 11 Con: 9	Ex: 84.4 (7.7) Con: 88.9 (5.3)	28.0 ± 5.5	12 w of RT (3 d w^{-1}, 3 sets × 8-12 R)	Nursing home residents	CRP
Ward et al (2020)[62]	F	Ex: 26 Con: 29	Ex: 55.7 (5.1) Con: 55.4 (5.0)	28.1 ± 3.8	15 w RT (3 d w^{-1}, 2 sets × 8-12 R)	Healthy	CRP TNF-α

Data are reported as mean ± SD.

Abbreviations: AT, aerobic training; BMI, body mass index; Con, control; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CT, concurrent training; ET, exercise training; Ex, exercise; Ex-Pro, combined exercise and protein supplementation; F, female; IL-6, interleukin-6; M, male; MICT, moderate-intensity continuous training; Pro, protein supplementation; R, repetition; RM, repetition maximum; RT, resistance training; T2DM, type 2 diabetes mellitus; TNF-α, tumor necrosis factor α.

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the order of the listed groups) in the Ex vs Con groups was 523 and 518; in the Pro vs Con groups, 191 and 202; in the Ex-Pro vs Con groups, 89 and 98; in subtotal groups (ie, Ex and Pro, Ex-Pro vs Con) it was 803 and 818; in the Ex vs Pro groups, 33 and 32; in the Ex-Pro vs Pro groups, 87 and 88; in subtotal groups (Ex and Ex-Pro vs Pro), 64 and 64; and in the Ex-Pro vs Ex groups it was 61 and 62.

For IL-6 analysis, the distribution (reported respective to the order of the listed groups) was as follows: in the Ex vs Con groups, there were 520 and 504 participants; in the Pro vs Con groups, there were 208 and 220; in the Ex-Pro vs Con groups, 62 and 71; in subtotal groups (Ex and Pro, and Ex-Pro vs Con), 790 and 795; in the Ex vs Pro groups, 51 and 50 participants; in the Ex-Pro vs Pro groups, 121 and 122; in subtotal groups (Ex and Ex-Pro vs Pro), 172 and 172; and in the Ex-Pro vs Ex groups, there were 62 and 64 participants.

In TNF-α analysis, the participant allocation (reported respective to the order of the listed groups) was as follows: in the Ex vs Con groups, there were 266 and 261 participants; in the Pro vs Con groups, 114 and 119; in the Ex-Pro vs Con groups, 89 and 97; in subtotal groups (Ex and Pro, and Ex-Pro vs Con), 469 and 477; in the Ex vs Pro groups, 33 and 32 participants; in the Ex-Pro vs Pro groups, 103 and 104; in subtotal groups (Ex and Ex-Pro vs Pro), 136 and 136; and in the Ex-Pro vs Ex groups, there were 44 and 46 participants.

Intervention Characteristics

The intervention duration of RCTs varied from 8 weeks to 24 months. The weekly training sessions ranged from 2 to 3 times per week. Based on the classification of the training protocol criteria, the included articles utilized RT, AT, or CT. Additionally, some articles incorporated stretching and other types of training, as detailed in Table 2, where the intensity of the exercises is also specified. The protein supplementation protocols also are reported in Table 2, and the detailed daily nutritional profiles of the protein supplementation groups are provided in Table S4.[35–40,43–50,60]

Meta-Analysis Results

C-Reactive Protein. Based on 15 studies, the comparison of CRP levels between the Ex and Con groups did not show a significant difference (WMD: 0.09 μg/mL [95% CI, −0.12 to 0.31]; $P = .39$). However, there was significantly high heterogeneity ($I^2 = 95\%$; $P < .00001$) among the included studies (Figure S25).[35,40,41,52–55,57–62] Similarly, the comparison of CRP levels between the Pro and Con groups, based on 7 studies, showed no significant result (WMD: 0.38 μg/mL [95% CI, −0.07 to 0.83]; $P = .10$). There was significant heterogeneity across the studies ($I^2 = 97\%$; $P < .00001$) (Figure S26).[35,38,40,43,46,47] The comparison between the Ex-Pro and Con groups, based on 5 studies, also revealed no significant difference (WMD: 0.64 μg/mL [95% CI, −0.20 to 1.47]; $P = .13$), with high heterogeneity ($I^2 = 97\%$; $P < .00001$) (Figure S27).[35,36,40,48]

When comparing the overall EXPL groups (Ex and Pro, and Ex-Pro) with the Con group, no significant subgroup differences in CRP levels were found (WMD: 0.34 μg/mL [95% CI, 0.16-0.52]; $P = .19$). However, significantly high heterogeneity was observed across the studies ($I^2 = 97\%$; $P < .00001$) (Figure 2).[35,36,38–41,43,46–48,52–55,57–62] On the other hand, the comparison of CRP levels between the Ex and the Pro groups, including 2 studies, showed a significant reduction in the Ex group (WMD: −0.10 μg/mL [95% CI, −0.16 to −0.05]; $P = .0003$). Notably, the heterogeneity between these studies was low and not significant ($I^2 = 0\%$; $P = .37$) (Figure 3).[35,40] In contrast, the comparison of CRP levels between the Ex-Pro and Pro groups, based on 3 studies, did not show a significant difference (WMD: −0.37 μg/mL [95% CI, −1.01 to 0.26]; $P = .25$), though significant heterogeneity was observed ($I^2 = 94\%$; $P < .00001$) (Figure S28).[35,40,44]

The comparison results between the overall EXPL groups (Ex and Ex-Pro) and the Pro group did not yield significant results (WMD: −0.20 μg/mL [95% CI, −0.41 to 0.02]; $P = .07$) with high heterogeneity observed ($I^2 = 93\%$; $P < .00001$) (Figure S29).[35,40]

Finally, the comparison of CRP levels between the Ex-Pro and Ex groups, based on 4 studies, revealed a significant reduction in the Ex group (WMD: 0.21 μg/mL [95% CI, 0.12-0.29]; $P < .00001$). There was low but significant heterogeneity ($I^2 = 0\%$; $P < .00001$) among the included studies (Figure 4).[35,37,40,49]

Interleukin-6. Based on 16 studies, the comparison of IL-6 levels between the Ex and Con groups did not show significant differences (WMD: 0.06 μg/mL [95% CI, −0.32 to 0.44]; $P = .75$). However, significant high heterogeneity was observed ($I^2 = 99\%$; $P < .00001$) among the included studies (Figure S30).[35,40,42,50–60] The comparison between the Pro and Con groups, based on 8 studies, also did not show significant results (WMD: −0.03 μg/mL [95% CI, −0.12 to 0.06]; $P = .50$), with moderate heterogeneity among studies ($I^2 = 47\%$; $P = .07$) (Figure S31).[35,39,40,43,45,47,48,50] Similarly, the comparison between the Ex-Pro and Con groups, based on 4 studies, showed no significant result (WMD: −0.31 μg/mL [95% CI, −0.98 to 0.36]; $P = .36$), with significant high heterogeneity observed ($I^2 = 92\%$; $P < .00001$) (Figure S32).[35,40,50]

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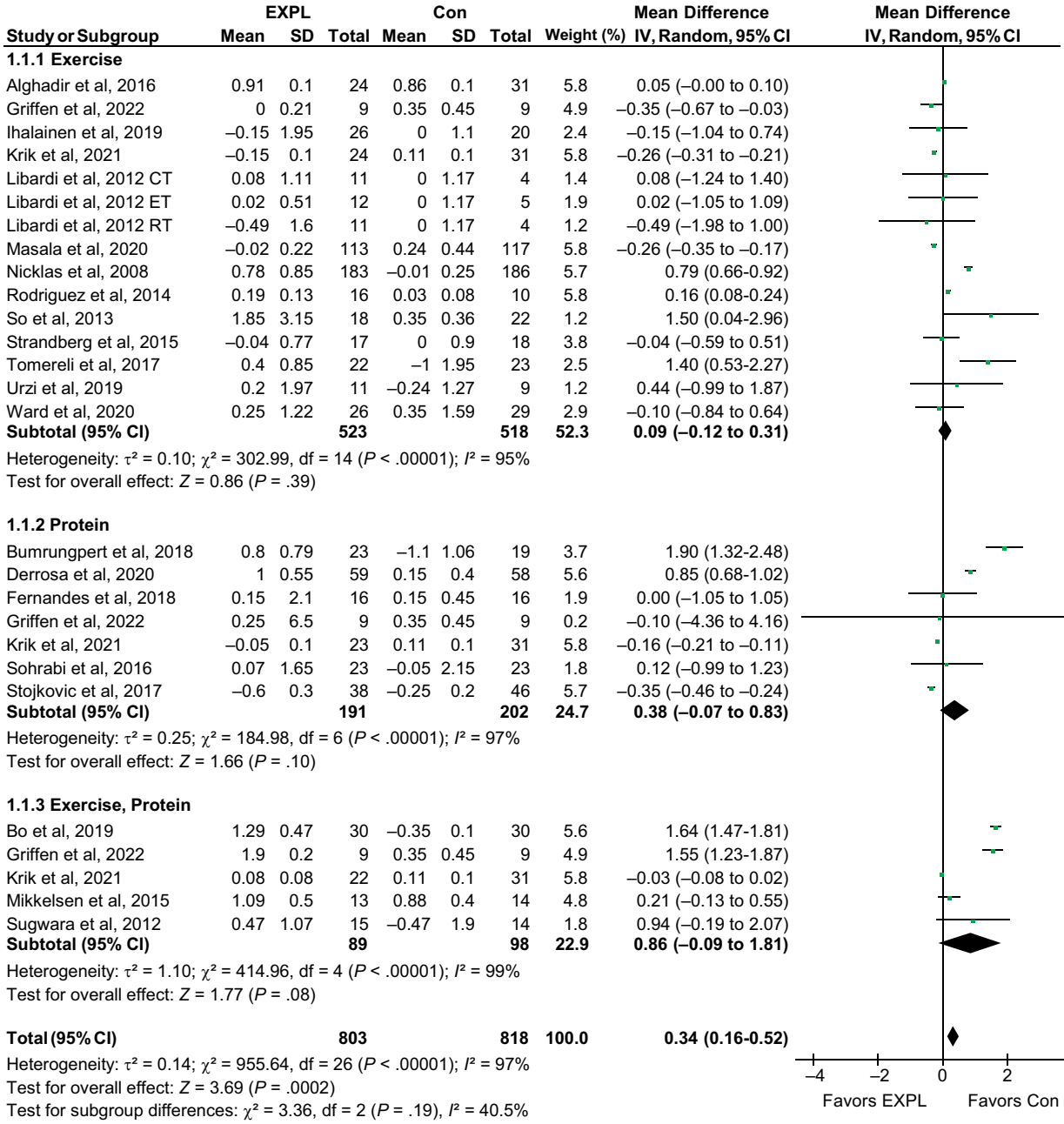

Figure 2. Forest Plot Illustrating the Effects of Total Subgroups (exercise and protein supplementation, and those 2 combined vs the control [Con] group) on C-reactive Protein. EXPL, experimental; IV, inverse variance.

The comparison results among the overall EXPL groups (Ex and Pro, and Ex-Pro) vs the Con group did not provide significant results (WMD: 0.04 μg/mL [95% CI, −0.19 to 0.27]; $P = .72$), with high heterogeneity ($I^2 = 98\%$; $P < .00001$) (Figure S33).[35,39,40,42,43,45,47,48,50–60] The comparison between the Ex and Pro groups, based on 2 studies, showed a significant reduction in the Ex group (WMD: −1.01 μg/mL [95% CI, −1.63 to −0.40]; $P = .001$), with moderate heterogeneity among studies ($I^2 = 43\%$; $P = .17$) (Figure 5).[35,40,50] The comparison among 5 studies between the Ex-Pro and Pro groups displayed a significant reduction in the Ex-Pro group (WMD: −0.54 μg/mL [95% CI, −1.07 to −0.01]; $P = .05$), though high heterogeneity was observed ($I^2 = 94\%$; $P < .00001$) (Figure 6).[35,40,44,50]

The comparison of IL-6 concentrations among the EXPL groups (Ex and Ex-Pro) compared with the Pro group revealed a significant reduction in EXPL (WMD: −0.70 μg/mL [95% CI, −1.16 to −0.25]; $P = .0002$) along with substantial high heterogeneity ($I^2 = 98\%$; $P < .00001$) (Figure 7).[35,40,44,50] Lastly, the comparison between the Ex-Pro and Ex groups, based on 4 studies,

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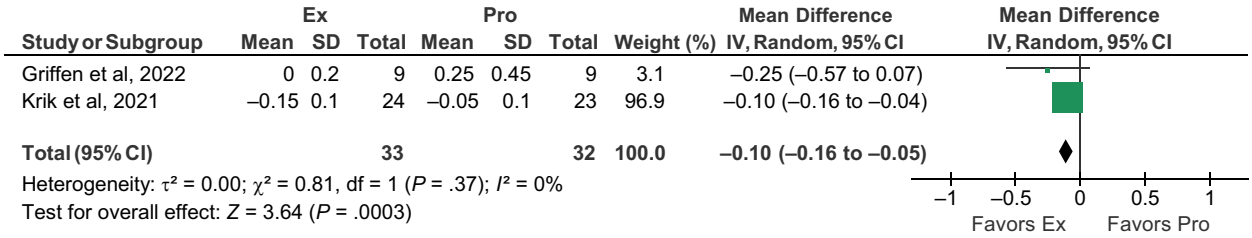

Figure 3. Forest Plot Illustrating the Effects of Exercise (Ex) vs Protein Supplementation (Pro) on C-reactive Protein. IV, inverse variance.

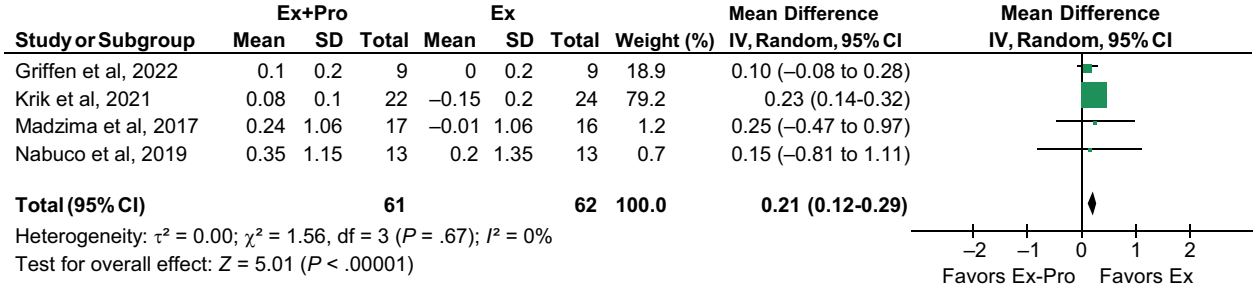

Figure 4. Forest Plot Illustrating the Effects of Combined Exercise (Ex) and Protein Supplementation (Pro) vs Ex Alone on C-reactive Protein. IV, inverse variance.

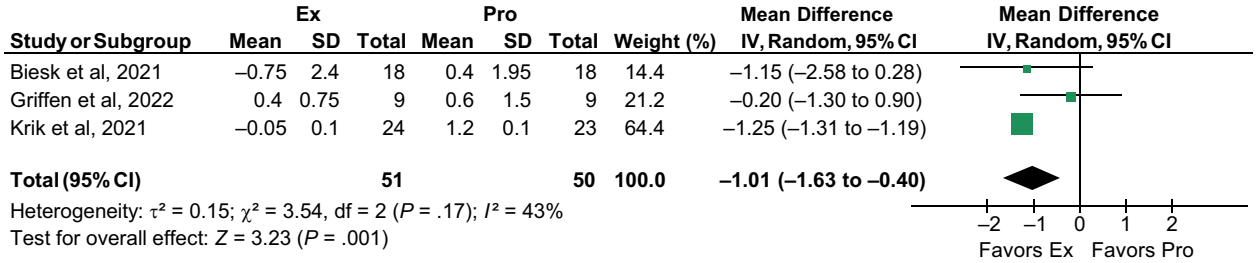

Figure 5. Forest Plot Illustrating the Effects of Exercise (Ex) vs Protein Supplementation (Pro) on Interleukin-6. IV, inverse variance.

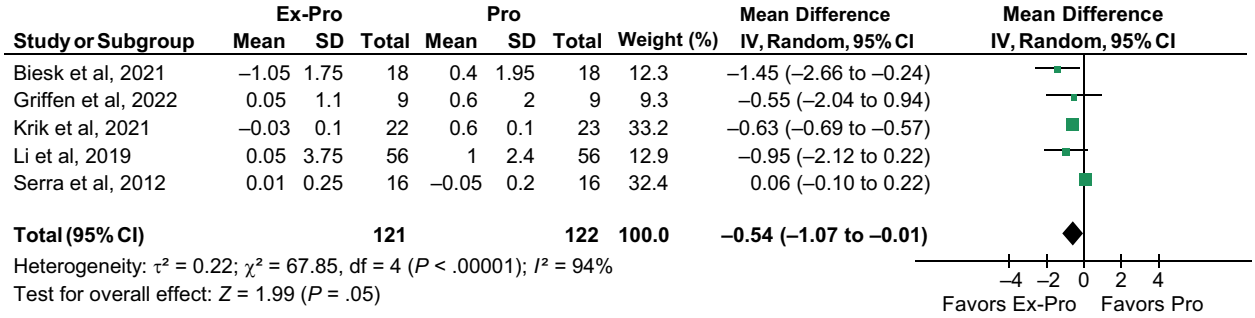

Figure 6. Forest Plot Illustrating the Effects of Combined Exercise (Ex) and Protein Supplementation (Pro) (Ex-Pro) vs Pro on Interleukin-6. IV, inverse variance.

did not show significant results (WMD: −0.01 μg/mL [95% CI, −0.07 to 0.05]; $P = .77$), with low and non-significant heterogeneity ($I^2 = 0\%$; $P = .66$) among the included studies (Figure S34).[35,37,40,50]

Tumor Necrosis Factor-α. Based on 11 studies, the comparison of TNF-α levels between the Ex and Con groups did not show significant results (WMD: 0.22 μg/mL [95% CI, −0.12 to 0.56]; $P = .20$). However, significantly high

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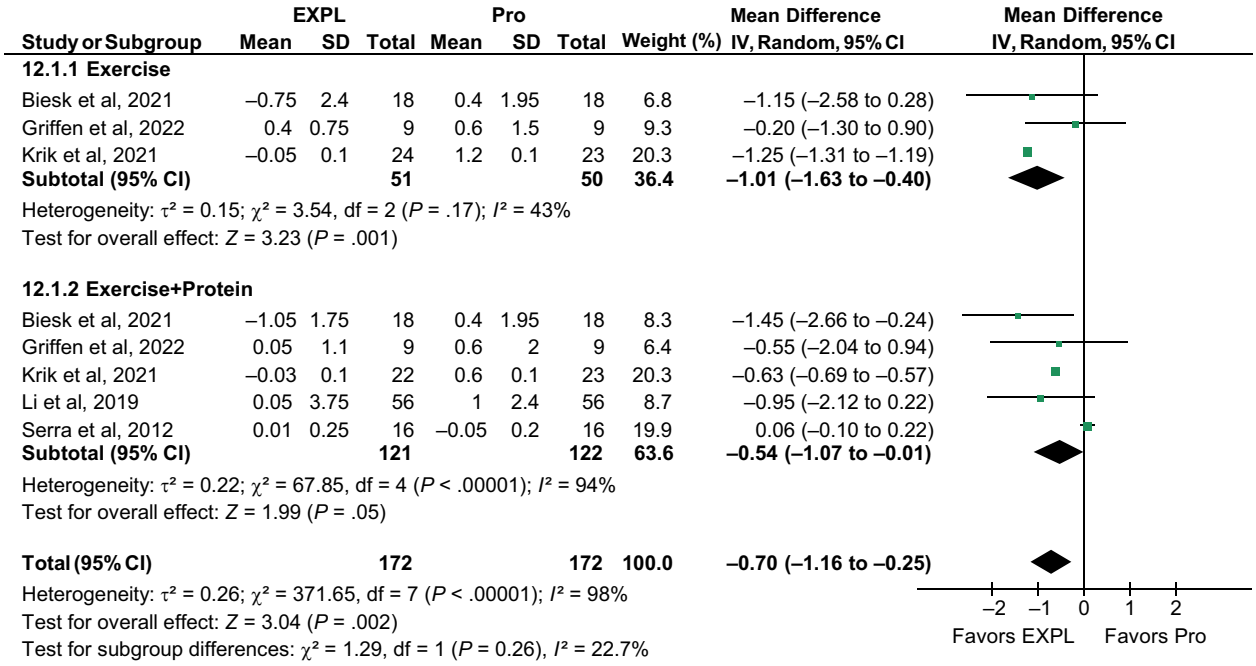

Figure 7. Forest Plot Illustrating the Effects of Total Subgroups (Exercise and Exercise + Protein Supplementation [Pro] vs Pro) on Interleukin-6. EXPL, experimental; IV, inverse variance.

heterogeneity was observed ($I^2 = 89\%$; $P < .00001$) among the included studies (Figure S35).[35,40,42,53,54,56,58,60,62] The comparison between the Pro and Con groups, based on 4 studies, did not yield significant results (WMD: 0.18 μg/mL [95% CI, −0.38 to 0.75]; $P = .52$), with high heterogeneity present among the studies ($I^2 = 95\%$; $P < .00001$) (Figure S36).[35,40,43,45] Similarly, the comparison between the Ex-Pro and Con groups, based on 5 studies, showed no significant results (WMD: −0.05 μg/mL [95% CI, −0.51 to 0.41]; $P = .84$), with significant high heterogeneity ($I^2 = 96\%$; $P < .00001$) among these studies (Figure S37).[35,36,40,48]

The comparison results among the overall EXPL groups (Ex and Pro, and Ex-Pro) compared with the Con group did not show significant results (WMD: 0.06 μg/mL [95% CI, −0.11 to 0.23]; $P = .48$), along with significant high heterogeneity (I2 = 93%; $P < .00001$) (Figure S38).[35,36,40,42,43,45,48,53,54,56,58,60,62] The comparison between the Ex and Pro groups, based on 2 studies, also did not show significant results (WMD: 0.16 μg/mL [95% CI, −0.77 to 1.09]; $P = .74$), with significantly high heterogeneity observed among the studies ($I^2 = 96\%$; $P < .00001$) (Figure S39).[35,40] The comparison between the Ex-Pro and Pro groups, based on 4 studies, did not show significant results (WMD: 0.21 μg/mL [95% CI, −0.44 to 0.85]; $P = .53$), with significantly high heterogeneity ($I^2 = 99\%$; $P < .00001$) among the studies (Figure S40).[35,40,44]

Similarly, the comparison results among EXPL groups (Ex and Ex-Pro) vs the Pro group did not show significant results (WMD: 0.19 μg/mL [95% CI, −0.22 to 0.59]; $P = .37$). There was a significantly high heterogeneity ($I^2 = 99\%$; $P < .00001$) (Figure S41).[35,40,44] Lastly, the comparison of TNF-α levels between the Ex-Pro and Ex groups, based on 3 studies, showed a significant reduction in the Ex-Pro group (WMD: −0.15 μg/mL [95% CI, −0.20 to 0.09]; $P < .00001$), with low heterogeneity observed among the studies ($I^2 = 0\%$; $P = .74$) (Figure 8).[35,37,40]

DISCUSSION

This comprehensive meta-analysis explores the complex relationship among exercise, protein supplementation, and inflammatory markers in the context of aging. In particular, the focus was on CRP, IL-6, and TNF-α levels, because they have been associated with several health outcomes.[63–65]

In the analysis across different comparison groups, CRP levels decreased significantly with Ex intervention compared with Pro. This reduction was also observed between the Ex group and both the Pro group and the Ex-Pro group, indicating that the reduction in CRP levels is more reliable with Ex intervention. There was no significant change in IL-6 levels between all intervention groups when compared with the Con group. Although some comparisons between Ex-Pro and Con revealed a trend favoring the Ex-Pro group and Pro group, this effect was not significant. However, the analysis revealed a significant reduction in lL-6 levels in Ex

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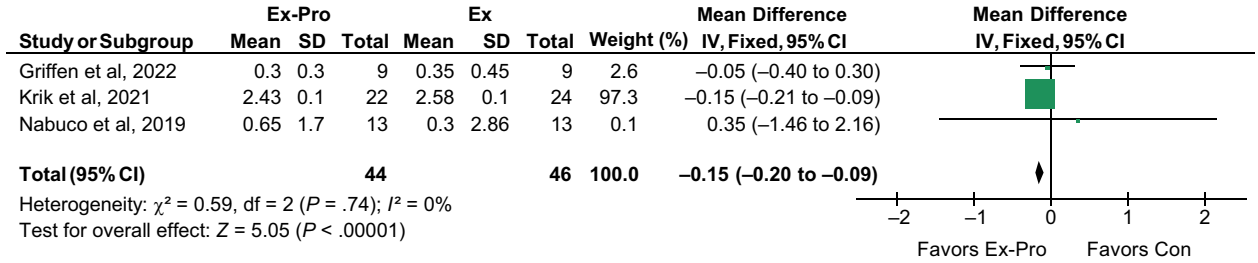

Figure 8. Forest Plot Illustrating the Effects of combined Exercise + Protein Supplementation (Ex-Pro) vs Ex on Tumor Necrosis Factor-α. IV, inverse variance.

group compared with the Pro group, suggesting a potential effect of Ex on IL-6. Additionally, the comparison of Ex-Pro and Pro showed a significant reduction in the Ex-Pro group on IL-6, highlighting the significant impact of Ex combined with Pro. Furthermore, the significant reduction in the EXPL group compared with the Pro group may indicate the effectiveness of the Ex intervention. For TNF-α levels, most comparisons did not show significant differences across groups. However, the Ex-Pro group, compared with the Ex group, showed a significant reduction in TNF-α levels, indicating the potential combined effects of Ex and Pro.

One potential strategy that offers health benefits is Ex, irrespective of age. Reduced physical activity is a key factor contributing to muscle loss in ARDs[66,67] and is often linked to chronic illness and aging. Increasing physical activity, therefore, may help slow, prevent, or even reverse muscle loss.[68] Bowen et al[68] argued that Ex promotes an anti-inflammatory environment by reducing local expression of TNF-α, IL-1β, and IL-6. Although the analysis focused on circulatory markers of inflammation, the findings support the view that Ex is an effective measure in reducing CRP when compared with Pro and Ex-Pro groups. For IL-6, these levels changed significantly in the Ex, Ex-Pro, and EXPL groups compared with the Pro group.

A recent meta-analysis on whey and soy protein supplementation showed significant reductions in IL-6 and TNF-α levels, with whey protein particularly effective for participants younger than 60 years and those with sarcopenia.[69] The analysis also indicated a reduction in IL-6 in the Pro group, though this reduction was significantly more pronounced in the Ex-Pro group. Subgroup analyses by Prokopidis et al[69] of TNF-α levels in individuals aged 60 years or older showed inconsistent results across different treatment durations. Similarly, soy protein decreased TNF-α levels,[69] aligning with the findings we report here that demonstrated a reduction in TNF-α levels in the Pro and Ex-Pro groups compared with the Ex group. Whey protein appears beneficial for sarcopenia and frailty, possibly due to its antioxidant properties.[69]

Variations in participant characteristics, such as age, health status, and baseline inflammatory profiles, may influence the responsiveness to protein supplementation.[70] Moreover, differences in methodology, such as sample size and statistical power, as well as the management of heterogeneity, may have affected these findings.[71] Therefore, whereas the Prokopidis et al[69] meta-analysis highlights the potential anti-inflammatory effects of whey and soy protein supplementation, the present study emphasizes the importance of considering both Pro and Ex interventions as an anti-inflammatory approach to combat ARDS.

Finally, similar to this meta-analysis, Woods et al[72] reported a moderate decrease in CRP levels in older adults after RT. The intervention group EXPL had reduced CRP levels compared with the Con group, and we note particularly that Ex was more effective in decreasing CRP levels than was Pro alone.

Limitations

It is important to acknowledge several limitations to this study. First, there was some inconsistency in heterogeneity among the few studies. Despite conducting subgroup analyses to address this inconsistency, the small number of studies in each category may have affected the conclusions, which is important for additional research in this field. However, most of our analysis indicates overall consistency in our findings.

The number of studies examining different types of Ex, their intensity, and duration was limited. The focus was on the chronic phase of Ex over the long term. It is recommended that future research investigate each type of Ex, along with its intensity, in this population.

Furthermore, although we tried to examine baseline characteristics in subgroup analyses to see how factors such as age, health condition, and initial inflammation might affect the anti-inflammatory effects of Ex in older adults, the differences among study populations remain a constraint.

Moreover, a significant limitation of the RCTs included in the analysis was the absence of details about

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the timing between the final Ex session and blood sample collection and the collection time; these can affect the levels of these inflammatory markers. This oversight could introduce bias because the acute effects of Ex may change inflammatory marker levels.

Additionally, although we had wanted to perform a subgroup analysis based on sex, the limited number of studies providing sex-specific data prevented this and restricted our ability to fully explore the differential effects of interventions on men and women.

CONCLUSION

The findings of this systematic review and meta-analysis demonstrate that both Ex and Pro, particularly when combined, show promise in reducing inflammatory markers and mitigating the effects of ARDs. Although valuable studies have advanced understanding of muscle wasting in sarcopenia and cachexia through Ex, more research is needed to validate these findings and explore various Ex intervention strategies on inflammatory markers. Given that aging often leads to muscle loss, it is crucial to understand how Ex and nutrition affect the progression of sarcopenia. Exercise training and Pro have shown promising results in combating muscle wasting, but the molecular mechanisms by which these interventions decrease inflammatory markers require further investigation. This meta-analysis provides important insights into the effect of Ex and Pro on inflammatory markers in older adults. However, more research is warranted to elucidate the underlying mechanisms and enhance strategies for addressing age-related muscle issues and improving overall health in older populations.

Acknowledgments

We are deeply saddened to announce that our coauthor Seyyed Reza Attarzadeh Hosseini has passed away, and we deeply appreciate all of his contributions to science. We specifically thank Barbara Ukropcova and Jozef Ukropec from the Biomedical Research Center of the Slovak Academy of Sciences for their invaluable support and assistance in conducting the research and preparing the manuscript.

Author Contributions

M.M.R. and R.N.B. searched the literature and extracted data from the included studies, including study characteristics, participant demographics, intervention details, and study outcomes. M.M.R. and S.R.A.H. assessed the methodological quality of the studies using the TESTEX tool. N.H. and V.C.F. contributed to the revision and oversight of the entire research process, ensuring the accuracy and integrity of the study findings. All authors participated in the manuscript revision and approved the final version.

Supplementary Material

Supplementary Material is available at *Nutrition Reviews* online.

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Conflict of Interest

None declared.

REFERENCES

1. Rüegg MA, Glass DJ. Molecular mechanisms and treatment options for muscle wasting diseases. *Annu Rev Pharmacol Toxicol*. 2011;51:373-395. https://doi.org/10.1146/annurevpharmtox-010510-100537
2. Liang Z, Zhang T, Liu H, et al. Inflammaging: the ground for sarcopenia? *Exp Gerontol*. 2022;168:111931. https://doi.org/10.1016/j.exger.2022.111931
3. Wang T. Searching for the link between inflammaging and sarcopenia. *Ageing Res Rev*. 2022;77:101611. https://doi.org/10.1016/j.arr.2022.101611
4. Degens H, McPhee JS. Muscle wasting, dysfunction, and inflammaging. In: Rahman I, Bagchi D, eds. *Inflammation, Advancing Age and Nutrition*. Academic Press; 2014:247-254.
5. Thomas R, Wang W, Su D-M. Contributions of age-related thymic involution to immunosenescence and inflammaging. *Immun Ageing*. 2020;17:2. https://doi.org/10.1186/s12979-020-0173-8
6. Bauer ME, De la Fuente M. Chapter 4—Oxidative stress, inflammaging and immunosenescence. In: Rahman I, Bagchi D, eds. *Inflammation, Advancing Age and Nutrition*. Academic Press; 2014:39-47.
7. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune–metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol*. 2018;14:576-590. https://doi.org/10.1038/s41574-018-0059-4
8. Bao W, Sun Y, Zhang T, et al. Exercise programs for muscle mass, muscle strength and physical performance in older adults with sarcopenia: a systematic review and meta-analysis. *Aging Dis*. 2020;11:863-873. https://doi.org/10.14336/ad.2019.1012
9. Morawin B, Tylutka A, Bielewicz F, Zembron-Lacny A. Diagnostics of inflammaging in relation to sarcopenia. *Front Public Health*. 2023;11:1162385. https://doi.org/10.3389/fpubh.2023.1162385
10. Vikberg S, Sörlén N, Brandén L, et al. Effects of resistance training on functional strength and muscle mass in 70-year-old individuals with pre-sarcopenia: a randomized controlled trial. *J Am Med Dir Assoc*. 2019;20:28-34. https://doi.org/10.1016/j.jamda.2018.09.011
11. Mao J, Wang T, Wang Y, Kuan G. Effect of resistance training programs differing in set structure on muscular hypertrophy and performance in untrained young men. *Front Physiol*. 2023;14:1301535. https://doi.org/10.3389/fphys.2023.1301535
12. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol*. 2011;11:607-615. https://doi.org/10.1038/nri3041
13. Wawrzyniak-Gramacka E, Hertmanowska N, Tylutka A, et al. The association of anti-inflammatory diet ingredients and lifestyle exercise with inflammaging. *Nutrients*. 2021;13:3696. https://doi.org/10.3390/nu13113696
14. de Lemos Muller CH, de Matos JR, Grigolo GB, Schroeder HT, Rodrigues-Krause J, Krause M. Exercise training for the elderly: inflammaging and the central role for HSP70. *J Sci Sport Exerc*. 2019;1:97-115. https://doi.org/10.1007/s42978-019-0015-6
15. Nilsson MI, Bourgeois JM, Nederveen JP, et al. Lifelong aerobic exercise protects against inflammaging and cancer. *PLoS One*. 2019;14:e0210863. https://doi.org/10.1371/journal.pone.0210863

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16. Smith JAB, Murach KA, Dyar KA, Zierath JR. Exercise metabolism and adaptation in skeletal muscle. *Nat Rev Mol Cell Biol*. 2023;24:607-632. https://doi.org/10.1038/s41580-023-00606-x
17. Nejati R, Bijeh N, Rad MM, Hosseini SRA. The impact of different modes of exercise training on GLP-1: a systematic review and meta-analysis research. *Int J Diabetes Dev Ctries*. 2022;42:40-48. https://doi.org/10.1007/s13410-021-00950-8
18. Motahari Rad M, Bijeh N, Attarzadeh Hosseini SR, Raouf Saeb A. The effect of two concurrent exercise modalities on serum concentrations of FGF21, irisin, follistatin, and myostatin in men with type 2 diabetes mellitus. *Arch Physiol Biochem*. 2023;129:424-433. https://doi.org/10.1080/13813455.2020.1829649
19. Motahari Rad M, Bijeh N, Attarzadeh Hosseini SR, Raouf Saeb A. The impact of different modes of exercise training on Irisin: a systematic review and meta-analysis research. review article. *J Adv Med Biomed Res*. 2021;29:125-138. https://doi.org/10.30699/jambs.29.134.125
20. Nasimi N, Sohrabi Z, Nunes EA, et al. Whey protein supplementation with or without vitamin D on sarcopenia-related measures: a systematic review and meta-analysis. *Adv Nutr*. 2023;14:762-773. https://doi.org/10.1016/j.advnut.2023.05.011
21. Allerton DM, West DJ, Stevenson EJ. Whey protein consumption following fasted exercise reduces early postprandial glycaemia in centrally obese males: a randomised controlled trial. *Eur J Nutr*. 2021;60:999-1011. https://doi.org/10.1007/s00394-020-02304-2
22. Cuyul-Vásquez I, Pezo-Navarrete J, Vargas-Arriagada C, et al. Effectiveness of whey protein supplementation during resistance exercise training on skeletal muscle mass and strength in older people with sarcopenia: a systematic review and meta-analysis. *Nutrients*. 2023;15:3424. https://doi.org/10.3390/nu15153424
23. McKendry J, Currier BS, Lim C, Mcleod JC, Thomas ACQ, Phillips SM. Nutritional supplements to support resistance exercise in countering the sarcopenia of aging. *Nutrients*. 2020;12:2057. https://doi.org/10.3390/nu12072057
24. Naseeb MA, Volpe SL. Protein and exercise in the prevention of sarcopenia and aging. *Nutr Res*. 2017;40:1-20. https://doi.org/10.1016/j.nutres.2017.01.001
25. Burd NA, Gorissen SH, van Loon LJC. Anabolic resistance of muscle protein synthesis with aging. *Exerc Sport Sci Rev*. 2013;41:169-173. https://doi.org/10.1097/JES.0b013e318292f3d5
26. Wang D, Ye J, Shi R, et al. Dietary protein and amino acid restriction: roles in metabolic health and aging-related diseases. *Free Radic Biol Med*. 2022;178:226-242. https://doi.org/10.1016/j.freeradbiomed.2021.12.009
27. Makanae Y, Fujita S. Role of exercise and nutrition in the prevention of sarcopenia. *J Nutr Sci Vitaminol (Tokyo)*. 2015;61 suppl:S125-S127. https://doi.org/10.3177/jnsv.61.S125
28. Park J, Bae J, Lee J. Complex exercise improves anti-inflammatory and anabolic effects in osteoarthritis-induced sarcopenia in elderly women. *Healthcare (Basel)*. 2021;9:711. https://doi.org/10.3390/healthcare9060711
29. Montero-Fernández N, Serra-Rexach JA. Role of exercise on sarcopenia in the elderly. *Eur J Phys Rehabil Med*. 2013;49:131-143.
30. Kunz HE, Lanza IR. Age-associated inflammation and implications for skeletal muscle responses to exercise. *Exp Gerontol*. 2023;177:112177. https://doi.org/10.1016/j.exger.2023.112177
31. Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane Collaboration and John Wiley & Sons Ltd; 2008. https://doi.org/10.1002/9780470712184
32. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264-269. https://doi.org/10.3736/jcim20090918
33. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther*. 2003;83:713-721. https://doi.org/10.1093/ptj/83.8.713
34. De Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Aust J Physiother*. 2009;55:129-133. https://doi.org/10.1016/S0004-9514(09)70043-1
35. Kirk B, Mooney K, Vogrin S, et al. Leucine-enriched whey protein supplementation, resistance-based exercise, and cardiometabolic health in older adults: a randomized controlled trial. *J Cachexia Sarcopenia Muscle*. 2021;12:2022-2033. https://doi.org/10.1002/jcsm.12805
36. Bo Y, Liu C, Ji Z, et al. A high whey protein, vitamin D and E supplement preserves muscle mass, strength, and quality of life in sarcopenic older adults: a double-blind randomized controlled trial. *Clin Nutr*. 2019;38:159-164. https://doi.org/10.1016/j.clnu.2017.12.020
37. Nabuco HCG, Tomeleri CM, Fernandes RR, et al. Effect of whey protein supplementation combined with resistance training on body composition, muscular strength, functional capacity, and plasma-metabolism biomarkers in older women with sarcopenic obesity: a randomized, double-blind, placebo-controlled trial. *Clin Nutr ESPEN*. 2019;32:88-95. https://doi.org/10.1016/j.clnesp.2019.04.007
38. Fernandes RR, Nabuco HCG, Sugihara Junior P, et al. Effect of protein intake beyond habitual intakes following resistance training on cardiometabolic risk disease parameters in pre-conditioned older women. *Exp Gerontol*. 2018;110:9-14. https://doi.org/10.1016/j.exger.2018.05.003
39. Stojkovic V, Simpson CA, Sullivan RR, et al. The effect of dietary glycemic properties on markers of inflammation, insulin resistance, and body composition in postmenopausal american women: an ancillary study from a multicenter protein supplementation trial. *Nutrients*. 2017;9:484. https://doi.org/10.3390/nu9050484
40. Griffen C, Duncan M, Hattersley J, Weickert MO, Dallaway A, Renshaw D. Effects of resistance exercise and whey protein supplementation on skeletal muscle strength, mass, physical function, and hormonal and inflammatory biomarkers in healthy active older men: a randomised, double-blind, placebo-controlled trial. *Exp Gerontol*. 2022;158:111651. https://doi.org/10.1016/j.exger.2021.111651
41. Alghadir AH, Gabr SA, Al-Eisa ES. Effects of moderate aerobic exercise on cognitive abilities and redox state biomarkers in older adults. *Oxid Med Cell Longev*. 2016;2016:2545168. https://doi.org/10.1155/2016/2545168
42. Beltran Valls MR, Dimauro I, Brunelli A, et al. Explosive type of moderate-resistance training induces functional, cardiovascular, and molecular adaptations in the elderly. *Age (Dordr)*. 2014;36:759-772. https://doi.org/10.1007/s11357-013-9584-1
43. Derosa G, D'Angelo A, Maffioli P. Change of some oxidative stress parameters after supplementation with whey protein isolate in patients with type 2 diabetes. *Nutrition*. 2020;73:110700. https://doi.org/10.1016/j.nut.2019.110700
44. Li C-w, Yu K, Shyh-Chang N, et al. Circulating factors associated with sarcopenia during ageing and after intensive lifestyle intervention. *J Cachexia Sarcopenia Muscle*. 2019;10:586-600. https://doi.org/10.1002/jcsm.12417
45. Ahmadi A, Eftekhari MH, Mazloom Z, et al. Fortified whey beverage for improving muscle mass in chronic obstructive pulmonary disease: a single-blind, randomized clinical trial. *Respir Res*. 2020;21:216. https://doi.org/10.1186/s12931-020-01466-1
46. Bumrungpert A, Pavadhgul P, Nunthanawanich P, Sirikanchanarod A, Adulbhan A. Whey protein supplementation improves nutritional status, glutathione levels, and immune function in cancer patients: a randomized, double-blind controlled trial. *J Med Food*. 2018;21:612-616. https://doi.org/10.1089/jmf.2017.4080
47. Sohrabi Z, Eftekhari MH, Eskandari MH, Rezaianzadeh A, Sagheb MM. Intradialytic oral protein supplementation and nutritional and inflammation outcomes in hemodialysis: a randomized controlled trial. *Am J Kidney Dis*. 2016;68:122-130. https://doi.org/10.1053/j.ajkd.2016.02.050
48. Sugawara K, Takahashi H, Kashiwagura T, et al. Effect of anti-inflammatory supplementation with whey peptide and exercise therapy in patients with COPD. *Respir Med*. 2012;106:1526-1534. https://doi.org/10.1016/j.rmed.2012.07.001
49. Madzima TA, Ormsbee MJ, Schleicher EA, Moffatt RJ, Panton LB. Effects of resistance training and protein supplementation in breast cancer survivors. *Med Sci Sports Exerc*. 2017;49:1283-1292. https://doi.org/10.1249/mss.0000000000001250
50. Biesek S, Vojciechowski AS, Filho JM, et al. Effects of exergames and protein supplementation on body composition and musculoskeletal function of prefrail community-dwelling older women: a randomized, controlled clinical trial. *Int J Environ Res Public Health*. 2021;18:9324. https://doi.org/10.3390/ijerph18179324
51. Forti LN, Njemini R, Beyer I, et al. Strength training reduces circulating interleukin-6 but not brain-derived neurotrophic factor in community-dwelling elderly individuals. *Age (Dordr)*. 2014;36:9704. https://doi.org/10.1007/s11357-014-9704-6
52. Ihalainen JK, Inglis A, Mäkinen T, et al. Strength training improves metabolic health markers in older individual regardless of training frequency. *Front Physiol*. 2019;10:32. https://doi.org/10.3389/fphys.2019.00032
53. Libardi CA, De Souza GV, Cavaglieri CR, Madruga VA, Chacon-Mikahil M. Effect of resistance, endurance, and concurrent training on TNF-a, IL-6, and CRP. *Med Sci Sports Exerc*. 2012;44:50-56. https://doi.org/10.1249/MSS.0b013e318229d2e9
54. Masala G, Bendinelli B, Della Bella C, et al. Inflammatory marker changes in a 24-month dietary and physical activity randomised intervention trial in postmenopausal women. *Sci Rep*. 2020;10:21845. https://doi.org/10.1038/s41598-020-78796-z
55. Nicklas BJ, Hsu F-C, Brinkley TJ, et al. Exercise training and plasma C-reactive protein and interleukin-6 in elderly people. *J Am Geriatr Soc*. 2008;56:2045-2052. https://doi.org/10.1111/j.1532-5415.2008.01994.x
56. Phillips MD, Flynn MG, McFarlin BK, Stewart LK, Timmerman KL. Resistance training at eight-repetition maximum reduces the inflammatory milieu in elderly women. *Med Sci Sports Exerc*. 2010;42:314-325. https://doi.org/10.1249/mss.0b013e3181b11ab7
57. Rodriguez-Miguelez P, Fernandez-Gonzalo R, Almar M, et al. Role of Toll-like receptor 2 and 4 signaling pathways on the inflammatory response to resistance training in elderly subjects. *Age (Dordr)*. 2014;36:9734. https://doi.org/10.1007/s11357-014-9734-0
58. So W-y, Song M, Park Y-h, et al. Body composition, fitness level, anabolic hormones, and inflammatory cytokines in the elderly: a randomized controlled trial. *Aging Clin Exp Res*. 2013;25:167-174. https://doi.org/10.1007/s40520-013-0032-y
59. Strandberg E, Edholm P, Ponsot E, et al. Influence of combined resistance training and healthy diet on muscle mass in healthy elderly women: a randomized controlled trial. *J Appl Physiol (1985)*. 2015;119:918-925. https://doi.org/10.1152/japplphysiol.00066.2015
60. Tomeleri CM, Souza MF, Burini RC, et al. Resistance training reduces metabolic syndrome and inflammatory markers in older women: a randomized controlled trial. *J Diabetes*. 2018;10:328-337. https://doi.org/10.1111/1753-0407.12614
61. Urzi F, Marusic U, Ličen S, Buzan E. Effects of elastic resistance training on functional performance and myokines in older women—a randomized controlled

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trial. *J Am Med Dir Assoc*. 2019;20:830-834.e2. https://doi.org/10.1016/j.jamda.2019.01.151
62. Ward LJ, Nilsson S, Hammar M, et al. Resistance training decreases plasma levels of adipokines in postmenopausal women. *Sci Rep*. 2020;10:19837. https://doi.org/10.1038/s41598-020-76901-w
63. Lavillegrand J-R, Garnier M, Spaeth A, et al. Elevated plasma IL-6 and CRP levels are associated with adverse clinical outcomes and death in critically ill SARS-CoV-2 patients: inflammatory response of SARS-CoV-2 patients. *Ann Intensive Care*. 2021;11:9. https://doi.org/10.1186/s13613-020-00798-x
64. Bermudez EA, Rifai N, Buring J, Manson JE, Ridker PM. Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. *Arterioscler Thromb Vasc Biol*. 2002;22:1668-1673. https://doi.org/10.1161/01.ATV.0000029781.31325.66
65. Puzianowska-Kuźnicka M, Owczarz M, Wieczorowska-Tobis K, et al. Interleukin-6 and C-reactive protein, successful aging, and mortality: the PolSenior study. *Immun Ageing*. 2016;13:21. https://doi.org/10.1186/s12979-016-0076-x
66. Bowden Davies KA, Pickles S, Sprung VS, et al. Reduced physical activity in young and older adults: metabolic and musculoskeletal implications. *Ther Adv Endocrinol Metab*. 2019;10:2042018819888824. https://doi.org/10.1177/2042018819888824
67. English KL, Paddon-Jones D. Protecting muscle mass and function in older adults during bed rest. *Curr Opin Clin Nutr Metab Care*. 2010;13:34-39. https://doi.org/10.1097/MCO.0b013e328333aa66
68. Bowen TS, Schuler G, Adams V. Skeletal muscle wasting in cachexia and sarcopenia: molecular pathophysiology and impact of exercise training. *J Cachexia Sarcopenia Muscle*. 2015;6:197-207. https://doi.org/10.1002/jcsm.12043
69. Prokopidis K, Mazidi M, Sankaranarayanan R, Tajik B, McArdle A, Isanejad M. Effects of whey and soy protein supplementation on inflammatory cytokines in older adults: a systematic review and meta-analysis. *Br J Nutr*. 2023;129:759-770. https://doi.org/10.1017/S0007114522001787
70. Liao Y, Peng Z, Chen L, et al. Prospective views for whey protein and/or resistance training against age-related sarcopenia. *Aging Dis*. 2019;10:157-173. https://doi.org/10.14336/ad.2018.0325
71. Valentine JC, Pigott TD, Rothstein HR. How many studies do you need? A primer on statistical power for meta-analysis. *J Educ Behav Stat*. 2010;35:215-247. https://doi.org/10.3102/1076998609346961
72. Woods JA, Wilund KR, Martin SA, Kistler BM. Exercise, inflammation and aging. *Aging Dis*. 2012;3:130-140.

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