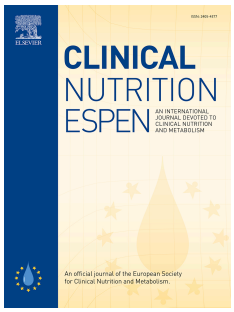

The combined effects of omega-3 polyunsaturated fatty acid supplementation and exercise training on body composition and cardiometabolic health in adults: a systematic review and meta-analysis

Mousa Khalafi, Aref Habibi Maleki, Michael E. Symonds, Sara K. Rosenkranz, Mahsa Ehsanifar, Sanaz Mohammadi Dinani

PII: S2405-4577(25)00022-1

DOI: https://doi.org/10.1016/j.clnesp.2025.01.022

Reference: CLNESP 2364

To appear in: *Clinical Nutrition ESPEN*

Received Date: 30 April 2024

Revised Date: 19 November 2024

Accepted Date: 3 January 2025

Please cite this article as: Khalafi M, Maleki AH, Symonds ME, Rosenkranz SK, Ehsanifar M, Dinani SM, The combined effects of omega-3 polyunsaturated fatty acid supplementation and exercise training on body composition and cardiometabolic health in adults: a systematic review and meta-analysis, *Clinical Nutrition ESPEN*, https://doi.org/10.1016/j.clnesp.2025.01.022.

The combined effects of omega-3 polyunsaturated fatty acid supplementation and exercise training on body composition and cardiometabolic health in adults: a systematic review and meta-analysis

Mousa Khalafi[*1], Aref Habibi Maleki[2], Michael E Symonds[3], Sara K Rosenkranz[4], Mahsa Ehsanifar[2], Sanaz Mohammadi Dinani[1]

1- Department of Sport Sciences, Faculty of Humanities, University of Kashan, Kashan, Iran
2- Department of Exercise Physiology and Corrective Exercises, Faculty of Sport Sciences, Urmia University, Urmia, Iran
3- Academic Unit of Population and Lifespan Sciences, Centre for Perinatal Research, School of Medicine, University of Nottingham, Nottingham, United Kingdom
4- Department of Kinesiology and Nutrition Sciences, University of Nevada Las Vegas, Las Vegas, NV, USA

*Corresponding author: Department of Sport Sciences, Faculty of Humanities, University of Kashan, Kashan, Iran, Email: mousa.khalafi@kashanu.ac.ir

Abstract

Introduction. We performed a systematic review and meta-analysis to investigate the effects of combining omega-3 polyunsaturated fatty acids (n-3 PUFAs) supplementation with exercise training, as compared to exercise training alone, on body composition measures including body weight, body mass index (BMI), fat mass, body fat percentage, and lean body mass. Additionally, we determined the effects on cardiometabolic health outcomes including lipid profiles, blood pressure, glycemic markers, and inflammatory markers.

Method. Three primary electronic databases including PubMed, Web of Science, and Scopus were searched from inception to April 5th, 2023 to identify original articles comparing n-3 PUFA supplementation plus exercise training versus exercise training alone, that investigated at least one of the following outcomes: fat mass, body fat percentage, lean body mass, triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), systolic (SBP) and diastolic (DBP) blood pressures, fasting glucose and insulin, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). Standardized mean differences (SMD) or weighted mean differences (WMD), and 95% confidence intervals (CIs) were calculated using random-effects models.

Results. A total of 21 studies involving 673 participants with BMIs ranging from 24-37 kg.m2 and ages ranging from 30–70 years were included in the meta-analysis. Overall, the results indicated that as compared with exercise training alone, adding omega-3 supplementation to exercise training decreased fat mass [WMD: -1.05 kg (95% CI: -1.88 to -0.22), p = 0.01], TG [WMD: -0.10 mmol/L (95% CI: -0.19 to -0.02)], SBP [WMD: -4.09 mmHg (95% CI: -7.79 to -2.16), p = 0.03], DBP [WMD: -4.26 mmHg (95% CI: -6.46 to -2.07), p = 0.001], and TNF-α [SMD: -0.35 (95% CI: -0.70 to -0.00), p = 0.04], and increased LDL [WMD: 0.14 mmol/L (95% CI: 0.02 to 0.26), p = 0.01] and lower-

body muscular strength [SMD: 0.42 (95% CI: 0.01 to 0.84), p = 0.04]. However, omega-3 supplementation with exercise training had no additional effects compared with training alone, for other body composition or cardiometabolic outcomes.

Conclusion. This systematic review and meta-analyses suggestes that adding omega-3 supplementation to exercise training may augment some effects of exercise training on body composition and cardiometabolic health in adults, although such effects appear to be modest.

Key words. Omega-3, exercise training, body composition, cardiometabolic health

Introduction

Exercise training and regular physical activity are effective strategies for promoting health and the prevention and treatment of several chronic diseases [1, 2]. Physical activity guidelines recommend both aerobic and resistance-based physical activity for people of all ages and abilities [3]. Exercise training also leads to a wide range of beneficial physiological adaptions such as improving dyslipidemia, insulin resistance, liver function, hypertension, chronic low-grade inflammation, plus body composition, together with complementary effects on overall cardiometabolic health [4-9].

Omega-3 polyunsaturated fatty acids (n-3 PUFAs), primarily docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and alpha-linolenic acid (ALA), play a clinically important role in promoting health and prevention of chronic diseases [10]. They have cardiometabolic health benefits including improving lipid profiles, blood pressure, liver fat, pro-inflammatory cytokines, and glycemic markers [11-14]. In addition, n-3 PUFAs can reduce the risks of sarcopenia through improved muscle strength and function due to anti-inflammatory, anti-catabolic effects, anabolic effects, and improved insulin sensitivity [15, 16]. Therefore, n-3 PUFAs supplementation may be clinically effective in management of cardiometabolic diseases such as type 2 diabetes, and in the treatment and prevention of sarcopenia. Both the cardiometabolic and anti-sarcopenic effects are associated with improved body composition.

Although several systematic reviews and meta-analyses have investigated the potential role of n-3 PUFAs to independently improve cardiometabolic risk factors [11, 17-22], no comprehensive meta-analysis has investigated the effects of n-3 PUFAs supplementation and exercise training. Previous results from randomized clinical trials have shown that n-3 PUFAs supplementation may have synergetic beneficial effects on cardiometabolic risk markers and body composition, although there are conflicting results [23-33]. Due to the proposed mechanisms by which n-3 PUFAs may improve cardiometabolic health, we hypothesized that n-3 PUFAs supplementation to exercise training would be a beneficial intervention for improving body composition measures including body weight, body mass index (BMI), fat mass, body fat percentage, and lean body mass. Additionally, we hypothesized further advantagous effects on cardiometabolic health outcomes including improved lipid profiles, blood pressure, glycemic markers, and inflammatory markers.

Methods

Study protocols

The current study followed the Cochrane Handbook for Systematic reviews of Interventions Guidelines and was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). This study was registered at www.crd.york.ac.uk/prospero with the ID number: CRD42024512182

Data Source and Search Strategy

We systematically searched three primary electronic databases including PubMed, Scopus, and Web of Science, from their inception through April 5th, 2023 to identify published studies that investigated the effects of n-3 PUFAs supplementation to exercise training on body composition and cardiometabolic health in adults. In order to conduct the systematic search, the following search terms and Boolean operators were used: ("omega-3" OR "omega 3" OR "n-3" OR "n-3 polyunsaturated fatty acid" OR "n-3 PUFA" OR "fishoil" OR "fish oil" OR "ALA" OR "DHA" OR "EPA" OR "alpha-linolenic acid" OR "acid α-linolenic acid" OR "docosahexaenoic acid" OR "eicosapentaenoic acid") AND ("exercise" OR "exercise training" OR "physical activity") AND ("randomized control trial" OR "randomized clinical trial" OR "randomized" OR "random*" OR "randomly"). The filter for the English language was applied. In addition, Google Scholar and the reference lists of selected studies were manually searched to ensure that all relevant studies were included in the meta-analysis. The search was performed by two independent reviewer (M Kh and A H M) and any disagreements were resolved by discussion with other reviewers.

Study Selection and Inclusion and Exclusion Criteria

All relevant studies were imported to Endnote 20 software for removing duplicate references. Subsequently, two reviewers (A H M and M E) independently screened them based on the titles and/or abstracts to identify studies potentially meeting the inclusion criteria. They then independently assessed the full-texts for eligibility, as is summarized in Figure 1. We included randomized parallel trials that were published in peer-reviewed articles written in the English language. Our search and screening strategies were based on the following PICO (Population, Intervention, Comparison, Outcome) process as follows: 1) Population: studies with human participants aged ≥ 18 years, regardless of sex assigned at birth or health status including individuals who are healthy, overweight/obese, and elderly participants, as well as those with various comorbidities (such as metabolic syndrome, cardiovascular diseases, non-alcoholic fatty liver disease, or diabetes). This diversity in health status reflects the high variability among study populations; 2) Intervention: studies that investigated the chronic effects of n-3 PUFAs supplementation plus exercise training with intervention durations of ≥ 2 weeks, with no limitations on the maximum duration of the interventions; 3) Comparison: studies that included an exercise training arm with the same exercise training as the n-3 PUFAs supplementation plus exercise training arm; 4) Outcome: studies that included any of the following measures related to body composition including body weight, BMI, fat mass, body fat percentage, and lean body mass; or cardiometabolic health markers including lipid profiles (triglycerides (TG), total cholesterol (TC), low density lipoprotein (LDL), and high density lipoprotein (HDL), blood pressure (systolic (SBP) and diastolic (DBP) blood pressure), glycemic markers (fasting glucose and insulin), and inflammatory markers including interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α). If required, lipid profiles and glycemic markers expressed in mg/dL were converted to mmol/L [34]. For n-3 fatty acid supplementation, all n-3 interventions in dietary or supplement form with reported dosages and duration of intervention were included [35].

For exercise training, any type from aerobic, resistance, interval, and combined training were included. The exclusion criteria were non-randomized trials and non-original studies, studies that included combining n-3 supplements with another supplement such as whey protein, and studies of trained subjects or athletes.

Data Extract and Synthesis and Quality Assessment

Two reviewers (M HS and A H M) independently extracted relevant data from all eligible studies, and any disagreements were resolved by discussion with other reviewers, first author, year of publication, study design, sample size, participant characteristics including sex assigned at birth, age, health status, n-3 characteristics including type, dosage, and time of consumption; and exercise training characteristics including training mode, duration, intensity, frequency, and time; and outcome variables. In addition, to calculate the effect sizes and generate forest plots, means and standard deviations (SDs) pre- and post- intervention and/or mean changes and their SDs were extracted. However, when required, these data were extracted from figures using GetData Graph Digitizer software, or were calculated from other data such as standard errors, medians, ranges and/or interquartile ranges (IQRs) [36-38]. The quality of the included studies was assessed using the 11-item Physiotherapy Evidence Database (PEDro) tool for risk of bias, for which scores are summarized in supplementary Table 1.

Data Analysis

Comprehensive Meta-analysis software (CMA3, version 3.0) was used to perform meta-analyses. Separate meta-analysies were conducted for each outcome to compare the effects of n-3 PUFAs plus exercise training, versus exercise training alone, to determine standardized means differences (SMD) and 95% confidence intervals (CIs) or weighted mean differences (WMD) and 95% CIs based on whether measurement units were the same or different. SMDs, WMDs and 95% CIs were calculated using random effects models and the DerSimonian and Laird approach due to the assumption that heterogeneity was likely between clinical studies [39]. The I^2 statistics was used to check for heterogeneity between studies, where I^2 values of ≥50% and ≥75% indicated significant and considerable heterogeneity, respectively; and I^2 values of <25% and 25–50% indicated low and moderate heterogeneity, respectively [40]. Visual interpretation of funnel plots and Egger's tests were used to determine whether publication bias was likely, where ap-value <0.10 was considered as significant. In addition, when publication bias was detected by visual interpretation of funnel plots, the trim and fill method was used, and any corrections reported [41].

Results

Characteristics of the included studies

The initial searches yielded 2,756 records through the electronic database searches. After removing duplicates, 1,993 articles remained for screening based on title and abstract of 70 articles remained for the full-text screen. Subsequently, 49 articles were removed for the reasons reported in Figure 1. Finally, 21 articles [23-29, 31-33, 42-52] met the eligibility criteria for meta-analysis. The extracted study characteristics are summarized in Table 1. Briefly, 673 participants with BMIs ranging from 24 to 37 kg.m2 and ages ranging from 30 to 70 years were included in the meta-analysis. In terms of health status, participants ranging from healthy to those with chronic cardiovascular and metabolic

disorders were included. Intervention durations ranged from six [24] to 48 [45] weeks. Ten studies used resistance training [23-28, 32, 42, 46, 48], six studies used aerobic training [29, 33, 44, 47, 49, 51], three studies used combined training [43, 50, 52], and two studies used high intensity interval training [31, 45]. For n-3 PUFAs, studies provided long-chain n-3 PUFAs (EPA and/or DHA) from fish oil or capsules, and ALA from flax oil.

Meta-analysis

Body Composition. Combined n-3 PUFAs supplementation and exercise training did not change body weight [WMD: -0.42 kg (95% CI: -1.31 to 0.47), p = 0.35; 11 trials], BMI [WMD: -0.36 kg.m2 (95% CI: -0.81 to 0.08), p = 0.12; 10 trials], body fat % [WMD: -0.54% (95% CI: -1.34 to 0.24), p = 0.17; 8 trials], or lean body mass [WMD: 0.20 kg (95% CI: -0.76 to 1.18), p = 0.67; 6 trials], but decreased fat mass [WMD: -1.05 kg (95% CI: -1.88 to -0.22), p = 0.01; 6 trials] significantly more than exercise training alone (Supplementary Figures 2-6). There was no significant heterogeneity among included studies for body weight (I^2=0.00, p =1.00), BMI (I^2=0.00, p =0.98), body fat% (I^2=0.00, p =0.99), fat mass (I^2=0.00, p =0.97) or lean body mass (I^2=0.00, p =1.00). Visual interpretation of funnel plots suggest publication bias for body weight, BMI, body fat %, fat mass, and lean body mass. However, Egger's tests did not confirm bias for body weight (p = 0.44), BMI (p = 0.14), body fat% (p = 0.78), fat mass (p = 0.38), or lean body mass (p = 0.79). The trim and fill method indicated missing studies on the right or left side of the mean, and after including the missing studies, the effect sizes were as follows: for body weight [WMD: -0.46 kg (95% CI: -1.35 to 0.42)], 2 trials from the left side of the mean], BMI [WMD: -0.42 kg.m2 (95% CI: -0.85 to 0.00), 4 trials from the left side of the mean], body fat % [WMD: -0.53% (95% CI: -1.33 to 0.25), 1 trial from the right side of the mean], fat mass [WMD: -1.12 kg.m2 (95% CI: -1.93 to -0.32), 2 trials from the left side of the mean] and lean body mass [WMD: 0.18 kg.m2 (95% CI: -0.76 to 1.14), 2 trials from the left side of the mean].

Lipid Profiles. Combined n-3 PUFAs supplementation and exercise training decreased TG [WMD: -0.10 mmol/L (95% CI: -0.19 to -0.02), p = 0.009; 9 trials] and increased LDL [WMD: 0.14 mmol/L (95% CI: 0.02 to 0.26), p = 0.01; 5 trials], but did not change TC [WMD: 0.07 mmol/L (95% CI: -0.01 to 0.17), p = 0.11; 7 trials] or HDL [WMD: 0.01 mmol/L (95% CI: -0.02 to 0.04), p = 0.53; 6 trials] comopared with exercise training alone (Supplementary figure 7-10). There was significant heterogeneity amongst included studies for TG (I^2=54.49, p =0.02) and HDL (I^2=27.87, p =0.22), but not for TC (I^2=0.00, p =0.54) or LDL (I^2=0.00, p =0.97). Visual interpretation of funnel plots suggest publication bias, but was not confirmed by Egger's test for TG (p = 0.53), TC (p = 0.45), LDL (p = 0.44), or HDL (p = 0.87). The trim and fill method indicated missing studies from the right or left side of the mean, and after including the missing studies, the effect sizes were as follows: for TG [WMD: -0.10 mmol/L (95% CI: -0.17 to -0.02), 2 trials from the right side of the mean], TC [WMD: 0.15 mmol/L (95% CI: 0.03 to 0.27), 4 trials from the right side of the mean], LDL [WMD: 0.14 mmol/L (95% CI: 0.03 to 0.26), 1 trial from the right side of the mean] and HDL [WMD: 0.01 mmol/L (95% CI: -0.01 to 0.03), 2 trials from the left side of the mean].

Blood Pressure. Combined n-3 PUFAs and exercise training decreased SBP [WMD: -4.09 mmHg (95% CI: -7.79 to -2.16), p = 0.03; 6 trials] and DBP [WMD: -4.26 mmHg (95% CI: -6.46 to -2.07), p = 0.001; 6 trials] than exercise training alone (Supplementary figure 11-12). There was no

significant heterogeneity among included studies for SBP (I^2=0.00, p =0.49) or DBP (I^2=0.00, p =0.69). Visual interpretation of funnel plots suggested publication bias, that was not confirmed by Eggers tests (SBP (p = 0.54) or DBP (p = 0.14)). The trim and fill method indicated missing studies from the right or left side of the mean, and after including the missing studies, the effect size for SBP was [WMD: -3.75 mmHg (95% CI: -7.33 to -0.17), 1 trial from the right side of the mean] and for DBP was [WMD: -4.81 mmHg (95% CI: -6.88 to -2.74), 2 trials from the left side of the mean].

Glycemic Markers. Combined n-3 PUFAs supplementation and exercise training did not change fasting glucose [WMD: 0.07 mmol/l (95% CI: -0.15 to 0.30), p = 0.50; 5 trials] or insulin [SMD: 0.10 (95% CI: -0.28 to 0.49), p = 0.60; 4 trials] compared with exercise training alone (Supplementary figure 13-14). There was no significant heterogeneity among included studies for fasting glucose (I^2=27.50, p =0.23) or insulin (I^2=0.00, p =0.77). Visual interpretation of funnel plots suggested publication bias and the Egger's tests confirmed bias for fasting insulin (p = 0.001), but not for fasting glucose (p = 0.45). The trim and fill method indicated missing studies from the right or left side of the mean, and after including the missing studies, the effect size for glucose was [WMD: 0.01 mmol/l (95% CI: -0.20 to 0.23), 1 trial from the left side of the mean] and for fasting insulin was [SMD: -0.03 (95% CI: -0.36 to 0.29), 2 trials from the left side of the mean].

Inflammatory Markers. Combined n-3 PUFAs supplementation and exercise training did not change IL-6 [SMD: -0.14 (95% CI: -0.38 to 0.10), p = 0.27; 10 trials], but decreased TNF-α [SMD: -0.35 (95% CI: -0.70 to -0.00), p = 0.04; 10 trials] compared with exercise training alone (Supplementary figure 15-16). There was no significant heterogeneity for IL-6 (I^2=0.00, p =0.76), but heterogeneity was significant for TNF-α (I^2=48.20, p =0.04). Visual interpretation of funnel plots suggested publication bias, but not confirmed by Egger's tests (IL-6 (p = 0.70) or TNF-α (p = 0.63)). The trim and fill method indicated missing studies from the right or left side of the mean, and after including the missing studies, the effect size for IL-6 was [SMD: -0.07 (95% CI: -0.30 to 0.15), 2 trials from the left side of the mean] and for TNF-α was [SMD: -0.44 (95% CI: -0.80 to -0.08), 1 trial from the left side of the mean].

Muscular Strength

Combined n-3 PUFAs and exercise training did not change upper-body muscular strength [SMD: 0.24 (95% CI: -0.16 to 0.64), p = 0.24; 6 trials] or hand grip strength [SMD: 0.09 (95% CI: -0.31 to 0.50), p = 0.64; 4 trials], but increased lower-body muscular strength [SMD: 0.42 (95% CI: 0.01 to 0.84), p = 0.04; 13 trials] compared with exercise training alone (Supplementary Figure 17-19). There was no significant heterogeneity studies for upper-body muscular strength (I^2=34.59, p =0.17), hand grip strength (I^2=0.00, p =0.98), but there was for lower-body muscular strength (I^2=69.17, p =0.001). Visual interpretation of funnel plots suggests publication bias, but Egger's tests confirmed publication bias only for lower-body muscular strength (p = 0.08), and not for upper-body muscular strength (p = 0.27) or hand grip strength (p = 0.52). The trim and fill method indicated missing studies from the right or left side of the mean, and after including the missing studies, the effect sizes were as follows: for upper-body muscular strength [SMD: 0.40 (95% CI: 0.04 to 0.75), 2 trials from the right side of the mean], hand grip strength [SMD: 0.06 (95% CI: -0.29 to 0.43), 1 trial from the left side of

the mean] and lower-body muscular strength [SMD: 0.70 (95% CI: 0.30 to 1.10), 4 trials from the right side of the mean].

Discussion

The primary results of this meta-analysis are that n-3 PUFAs supplementation to exercise training led to decreased TG, blood pressure, and TNF-α, and increased LDL and lower-body muscular strength, as compared with exercise training alone. However, n-3 PUFAs supplementation had no beneficial effect on body composition, glycemic markers, TC, , HDL, IL-6, or upper-body muscular strength. Consequently, adding n-3 PUFAs supplements to exercise training has modest benefits on some cardiometabolic health markers.

Several systematic reviews and meta-analyses have investigated the impact of n-3 supplementation but the results are mixed. For example, one meta-analysis showed a 0.59 kg reduction in body weight but no change in fat and lean body mass following n-3 supplementation [53], whilst another showed no effect [54]. Regarding the combination of n-3 PUFAs supplementation with exercise training, our results are consistent with a recent meta-analysis which showed no increase muscle mass in healthy young and older adults [55], or body mass in elderly subjects [15]. It has been suggested that n-3 leads to weight and fat loss via regulation fat oxidation, reducing food intake and increasing thermogenesis activity, and enhances muscle mass by increasing the rate of the muscle protein synthesis [15, 56-59]. Exercise training is the primary lifestyle intervention recommended to improve body composition by reducing body fat and increasing muscle mass (lean body mass). These benefits occur depending on the type of exercise training [60]. Based on our analysis and understanding of the literature, we propose that, given that exercise can improve body composition, n-3 PUFAs supplementation may not add further stimulation of muscle protein synthesis or fat oxidation.

Dyslipidemia is a primary and independent risk factor for CVDs [61-64], and is thereby considered as a main therapeutic target for prevention and treatment. Previuous meta-analyses have suggested that exercise training improves dyslipidemia as exhibited by increased HDL and decreased TG, TC, and LDL [65-70], adaptations mediated by weight and fat loss [71]. Additionally, exercise training may improve lipid metabolism in skeletal muscle, liver, and adipose tissue [72]. The potential for augmented benefits on dyslipidemia for adding n-3 PUFAs to exercise training are largely unknown. Our study indicates that n-3 PUFAs supplementation may reduce TG without influencing TC, LDL, and HDL, and may even occur when LDL concentrations are increased [19-22]. An improvement in lipid profiles with n-3 PUFA supplementation may act by increased LDL catabolism, decreased LDL synthesis, and increased the utilization of lipids in the liver through enhanced PPAR-α and reduced PPAR-γ action [73, 74]. We also show that adding n-3 PUFAs to exercise training does not improve fasting glucose and insulin, and is accord with previous meta-analyses [75, 76]. Our findings show that there is insufficient evidence to suggest that n-3 PUFAs may augment the effects of exercise training on glycemic markers and lipid profiles—except for TG— and may lead to increases in LDL. These results may be explained by the role of n-3 PUFAs in converting lipoprotein sub-units, VLDL to LDL [77].

Exercise training has been widely recognized as a safe and effective approach for reducing and controlling blood pressure [78, 79] that may be enhanced with n-3 PUFA supplementation as shown by others [80-82]. Possible mechanisms include improved endothelial function, stimulation of nitric oxide synthase, lowered vascular resistance, and increased anti-inflammatory and antioxidant activity

[83-87]. Even small beneficial effects from n-3 PUFA supplementation on blood pressure may be clinically important given small changes in blood pressure can increase CVD risk [88], whilst and modets reductions lower the risk of CVD and CVD-related mortality [89].

Exercise training and n-3 PUFA supplementation have well documented anti-inflammatory properties which are associated with reducing the effects of pro-inflammatory cytokines [90, 91], as confirmed by earlier meta-analyses showing reduced pro-inflammatory cytokines such as IL-6 and TNF-α under a range of health conditions [11, 17, 18], and with exercise training [92-95]. Our study shows a synergetic effect with combined n-3 PUFAs supplementation and exercise training on reducing TNF-α that may be important, since TNF-α contributes to the progression of CVDs and metabolic diseases such as diabetes mellitus [96-98]. Previous studies have indicated that n-3 fatty acids work mechanistically by displacing arachidonic acid in cell membranes, which leads to the production of eicosanoids known for their anti-inflammatory properties [99]. Additionally, n-3 fatty acids downregulate the expression of cyclooxygenase (COX), a crucial enzyme involved in the production of pro-inflammatory cytokines, through the inhibition of NF-kB signaling [100]. In this regard, it has been shown that the consumption of EPA and DHA decreases the expression of genes associated with inflammatory pathways, including the NF-kB signaling pathway and the synthesis of eicosanoids [101]. However, the decrease in TNF-α was small, and no significant differences in changes in IL-6 were observed. In future investigations, it is important to determine whether changes in inflammatory markers translate into improved insulin resistance, that was beyond the scope of our meta-analysis due to the small number of studies available.

In addition to effects of n-3 supplementation on body composition and cardiometabolic health, it can improve exercise performance, especially muscle strength [55]. In addition, in individuals with sarcopenia or at risk for sarcopenia, high dose n-3 PUFA supplementation was associated with improved muscle strength and physical function [15]. We confirm findings in older adults showing positive effects of n-3 PUFAs supplementation with resistance training on lower-body muscle strength [102], and may be mediated by improving anabolic and decreasing catabolic effects, improved insulin sensitivity, and neuroprotective properties [15]. However, it is not clear which of the mechanisms may be responsible for the beneficial effects of adding n-3 PUFAs to exercise, but it appears that benefits are more than just increased muscle mass, as we did not observe significantly larger changes in lean body mass with combined supplementation and exercise as compared with exercise alone.

Our study had several important limitations that should be considered. First, the number of studies that met our apriori inclusion criteria was limited, resulting in small sample sizes that did not allow us to perform subgroup analyses for several relevant outcomes, including fasting glucose and insulin levels. Second, the n-3 PUFAs supplementation included in our analysis varied widely in terms of dosage and EPA/DHA ratios, which may have moderated the effects of n-3 PUFAs. This variability could not be further examined due to the small number of available studies, along with the differing types of exercise adopted. Additionally, the overall variability within the study populations, including differences in age, biological sexes, and health statuses, was high, which may limit the generalizability of our findings to broader populations. Furthermore, the relatively small number of participants in each intervention group could potentially affect the robustness of our conclusions and the statistical power of our analyses. We recommend that future research should aim to include larger samples and consider subgroup analyses to address the identified limitations more effectively. Therefore, our

findings should be interpreted with caution, as the results may be applicable only to specific groups or under certain conditions.

In conclusion, we show that n-3 PUFAs supplementation to exercise training may be have slightly superior effects on reducing TG, blood pressure, and TNF-α, and increasing lower-body muscular strength when compared with exercise training alone. However, these results should be considered with caution given the high heterogeneity and potential publication bias for some outcomes, and given the fact that for several health outcomes considered, there was no significant difference between combined n-3 PUFAs supplementation with exercise as compared with exercise training only. This is particularly true for body composition measures, limiting our enthusiasm regarding the effectiveness of prescribing this supplement for improving body composition and for many cardiometabolic health markers.

Availability of data and materials. All data generated or analyzed during this study are included in this published article and supplementary tables. Other data can be made available upon reasonable request to the corresponding author.

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.

Funding. This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions: M Kh, M E S and S K R conceptualization of the systematic review and meta-analysis. M Kh, A H M, M E, and S M D carried out the screenings and reviews. M Kh and A H M analyzed the data and performed meta-analyses. M Kh, M E S, and S K R drafted the manuscript. M Kh, S K R, and M E S revised the manuscript. All authors read and approved the final manuscript.

References

1. Warburton, D.E., C.W. Nicol, and S.S. Bredin, Health benefits of physical activity: the evidence. Cmaj, 2006. **174**(6): p. 801-809.

2. McGee, S.L. and M. Hargreaves, Exercise adaptations: molecular mechanisms and potential targets for therapeutic benefit. Nature Reviews Endocrinology, 2020. **16**(9): p. 495-505.
3. Bull, F.C., et al., World Health Organization 2020 guidelines on physical activity and sedentary behaviour. British journal of sports medicine, 2020. **54**(24): p. 1451-1462.
4. Lin, X., et al., Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. Journal of the American heart association, 2015. **4**(7): p. e002014.
5. Battista, F., et al., Effect of exercise on cardiometabolic health of adults with overweight or obesity: Focus on blood pressure, insulin resistance, and intrahepatic fat—A systematic review and meta-analysis. Obesity Reviews, 2021. **22**: p. e13269.
6. Batacan, R.B., et al., Effects of high-intensity interval training on cardiometabolic health: a systematic review and meta-analysis of intervention studies. British journal of sports medicine, 2016.
7. Ashcroft, S.P., et al., Exercise induces tissue-specific adaptations to enhance cardiometabolic health. Cell Metabolism, 2023.
8. Keating, S.E., et al., Effect of aerobic exercise training dose on liver fat and visceral adiposity. Journal of hepatology, 2015. **63**(1): p. 174-182.
9. You, T., et al., Effects of exercise training on chronic inflammation in obesity: current evidence and potential mechanisms. Sports Medicine, 2013. **43**: p. 243-256.
10. Shahidi, F. and P. Ambigaipalan, Omega-3 polyunsaturated fatty acids and their health benefits. Annual review of food science and technology, 2018. **9**: p. 345-381.
11. O'Mahoney, L.L., et al., Omega-3 polyunsaturated fatty acids favourably modulate cardiometabolic biomarkers in type 2 diabetes: a meta-analysis and meta-regression of randomized controlled trials. Cardiovascular diabetology, 2018. **17**: p. 1-13.
12. Ebrahimi, M., et al., Omega-3 fatty acid supplements improve the cardiovascular risk profile of subjects with metabolic syndrome, including markers of inflammation and auto-immunity. Acta cardiologica, 2009. **64**(3): p. 321-327.
13. Cicero, A.F., S. Ertek, and C. Borghi, Omega-3 polyunsaturated fatty acids: their potential role in blood pressure prevention and management. Current vascular pharmacology, 2009. **7**(3): p. 330-337.
14. Šmíd, V., et al., Effect of Omega-3 Polyunsaturated Fatty Acids on Lipid Metabolism in Patients With Metabolic Syndrome and NAFLD. Hepatology Communications, 2022. **6**(6): p. 1336-1349.
15. Tseng, P.-T., et al., Omega-3 polyunsaturated fatty acids in sarcopenia management: a network meta-analysis of randomized controlled trials. Ageing Research Reviews, 2023: p. 102014.
16. Bird, J.K., et al., The effect of long chain omega-3 polyunsaturated fatty acids on muscle mass and function in sarcopenia: A scoping systematic review and meta-analysis. Clinical Nutrition ESPEN, 2021. **46**: p. 73-86.
17. Kavyani, Z., et al., Efficacy of the omega-3 fatty acids supplementation on inflammatory biomarkers: An umbrella meta-analysis. International Immunopharmacology, 2022. **111**: p. 109104.
18. Mocellin, M.C., et al., A meta-analysis of n-3 polyunsaturated fatty acids effects on circulating acute-phase protein and cytokines in gastric cancer. Clinical Nutrition, 2018. **37**(3): p. 840-850.
19. Wang, J., et al., Does Omega-3 Fatty Acid Supplementation Have Favorable Effects on the Lipid Profile in Postmenopausal Women? A Systematic Review and Dose–Response Meta-Analysis of Randomized Controlled Trials. Clinical Therapeutics, 2023.
20. Natto, Z.S., et al., Omega-3 fatty acids effects on inflammatory biomarkers and lipid profiles among diabetic and cardiovascular disease patients: a systematic review and meta-analysis. Scientific reports, 2019. **9**(1): p. 18867.

21. Khorshidi, M., et al., Effect of omega-3 supplementation on lipid profile in children and adolescents: a systematic review and meta-analysis of randomized clinical trials. Nutrition journal, 2023. **22**(1): p. 1-11.
22. Yang, Y., et al., The effect of omega-3 fatty acids and its combination with statins on lipid profile in patients with hypertriglyceridemia: A systematic review and meta-analysis of randomized controlled trials. Frontiers in Nutrition, 2022. **9**: p. 1039056.
23. Alves, N.M.D., et al., Randomised Controlled Trial of Fish Oil Supplementation on Responsiveness to Resistance Exercise Training in Sarcopenic Older Women. Nutrients, 2022. **14**(14).
24. Brook, M.S., et al., Omega-3 supplementation during unilateral resistance exercise training in older women: A within subject and double-blind placebo-controlled trial. Clin Nutr ESPEN, 2021. **46**: p. 394-404.
25. Cornish, S.M. and P.D. Chilibeck, Alpha-linolenic acid supplementation and resistance training in older adults. Applied Physiology, Nutrition and Metabolism, 2009. **34**(1): p. 49-59.
26. Cornish, S.M., et al., Omega-3 supplementation with resistance training does not improve body composition or lower biomarkers of inflammation more so than resistance training alone in older men. Nutr Res, 2018. **60**: p. 87-95.
27. Dalle, S., et al., Omega-3 Supplementation Improves Isometric Strength But Not Muscle Anabolic and Catabolic Signaling in Response to Resistance Exercise in Healthy Older Adults. J Gerontol A Biol Sci Med Sci, 2021. **76**(3): p. 406-414.
28. Félix-Soriano, E., et al., Effects of dha-rich n-3 fatty acid supplementation and/or resistance training on body composition and cardiometabolic biomarkers in overweight and obese post-menopausal women. Nutrients, 2021. **13**(7).
29. Hill, A.M., et al., Combining fish-oil supplements with regular aerobic exercise improves body composition and cardiovascular disease risk factors. Am J Clin Nutr, 2007. **85**(5): p. 1267-74.
30. Lee, S.R., E. Jo, and A.V. Khamoui, Chronic Fish Oil Consumption with Resistance Training Improves Grip Strength, Physical Function, and Blood Pressure in Community-Dwelling Older Adults. Sports (Basel), 2019. **7**(7).
31. Nayebifar, S.H., E. Ghasemi, and S. Karimipour, Effect of high-intensity interval training and omega-3 supplementation on liver enzymes and lipid profile of young men. Science and Sports, 2020. **35**(1): p. e1-e9.
32. Rodacki, C.L.N., et al., Fish-oil supplementation enhances the effects of strength training in elderly women. American Journal of Clinical Nutrition, 2012. **95**(2): p. 428-436.
33. Tartibian, B., et al., Long-term aerobic exercise and omega-3 supplementation modulate osteoporosis through inflammatory mechanisms in post-menopausal women: A randomized, repeated measures study. Nutrition and Metabolism, 2011. **8**.
34. Guo, Z., et al., Influence of consumption of probiotics on the plasma lipid profile: a meta-analysis of randomised controlled trials. Nutrition, Metabolism and Cardiovascular Diseases, 2011. **21**(11): p. 844-850.
35. Huang, L., et al., Effect of omega-3 polyunsaturated fatty acids on cardiovascular outcomes in patients with diabetes: A meta-analysis of randomized controlled trials. Advances in Nutrition, 2023.
36. Wan, X., et al., Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC medical research methodology, 2014. **14**: p. 1-13.
37. Hozo, S.P., B. Djulbegovic, and I. Hozo, Estimating the mean and variance from the median, range, and the size of a sample. BMC medical research methodology, 2005. **5**(1): p. 1-10.
38. Higgins, J.P., Cochrane handbook for systematic reviews of interventions version 5.0. 1. The Cochrane Collaboration. http://www. cochrane-handbook. org, 2008.

39. Tufanaru, C., et al., Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. JBI Evidence Implementation, 2015. **13**(3): p. 196-207.
40. Higgins, J.P., et al., Measuring inconsistency in meta-analyses. Bmj, 2003. **327**(7414): p. 557-560.
41. Duval, S. and R. Tweedie, Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. Biometrics, 2000. **56**(2): p. 455-463.
42. Da Boit, M., et al., Sex differences in the effect of fish-oil supplementation on the adaptive response to resistance exercise training in older people: a randomized controlled trial. Am J Clin Nutr, 2017. **105**(1): p. 151-158.
43. Daďová, K., et al., Calanus Oil Supplementation Does Not Further Improve Short-Term Memory or Brain-Derived Neurotrophic Factor in Older Women Who Underwent Exercise Training. Clin Interv Aging, 2022. **17**: p. 1227-1236.
44. Haghravan, S., et al., Impact of Omega-3 PUFAs supplementation with lifestyle modification on anthropometric indices and Vo2 max in overweight women. Archives of Iranian Medicine, 2016. **19**(5): p. 342-347.
45. Hearon, C.M., Jr., et al., 1 Year HIIT and Omega-3 Fatty Acids to Improve Cardiometabolic Risk in Stage-A Heart Failure. JACC Heart Fail, 2022. **10**(4): p. 238-249.
46. Heileson, J.L., et al., The effect of fish oil supplementation on resistance training-induced adaptations. J Int Soc Sports Nutr, 2023. **20**(1): p. 2174704.
47. Hill, A.M., et al., n-3 Fatty acid supplementation and regular moderate exercise: Differential effects of a combined intervention on neutrophil function. British Journal of Nutrition, 2007. **98**(2): p. 300-309.
48. Lee, S.R., D. Directo, and A.V. Khamoui, Fish oil administration combined with resistance exercise training improves strength, resting metabolic rate, and inflammation in older adults. Aging Clin Exp Res, 2022. **34**(12): p. 3073-3081.
49. Slivkoff-Clark, K.M., A.P. James, and J.C.L. Mamo, The chronic effects of fish oil with exercise on postprandial lipaemia and chylomicron homeostasis in insulin resistant viscerally obese men. Nutrition and Metabolism, 2012. **9**.
50. Stepan, M., et al., Exercise Training Combined with Calanus Oil Supplementation Improves the Central Cardiodynamic Function in Older Women. Nutrients, 2022. **14**(1).
51. Taheri, M., et al., The effect of omega-3 fatty acid supplement and aerobic exercise on lipid profile and depression in obese women. Acta Medica Mediterranea, 2018. **34**(3): p. 865-870.
52. Wei, M., et al., Perilla oil and exercise decrease expressions of tumor necrosis factor-alpha, plasminogen activator inhibitor-1 and highly sensitive C-reactive protein in patients with hyperlipidemia. J Tradit Chin Med, 2013. **33**(2): p. 170-5.
53. Bender, N., et al., Fish or n3-PUFA intake and body composition: a systematic review and meta-analysis. Obesity reviews, 2014. **15**(8): p. 657-665.
54. Du, S., et al., Does fish oil have an anti-obesity effect in overweight/obese adults? A meta-analysis of randomized controlled trials. PLoS One, 2015. **10**(11): p. e0142652.
55. Esteves, G.P., et al., The influence of n-3pufa supplementation on muscle strength, mass, and function: a systematic review and meta-analysis. Advances in Nutrition, 2023. **14**(1): p. 115-127.
56. Delpino, F.M., L.M. Figueiredo, and B.G.C. da Silva, Effects of omega-3 supplementation on body weight and body fat mass: A systematic review. Clinical Nutrition Espen, 2021. **44**: p. 122-129.
57. Huang, Y.-H., et al., Effects of omega-3 fatty acids on muscle mass, muscle strength and muscle performance among the elderly: a meta-analysis. Nutrients, 2020. **12**(12): p. 3739.
58. Gray, S.R. and B. Mittendorfer, Fish oil-derived n-3 polyunsaturated fatty acids for the prevention and treatment of sarcopenia. Current Opinion in Clinical Nutrition & Metabolic Care, 2018. **21**(2): p. 104-109.

59. Buckley, J.D. and P.R. Howe, Long-chain omega-3 polyunsaturated fatty acids may be beneficial for reducing obesity—a review. Nutrients, 2010. **2**(12): p. 1212-1230.
60. Willis, L.H., et al., Effects of aerobic and/or resistance training on body mass and fat mass in overweight or obese adults. Journal of applied physiology, 2012.
61. Arsenault, B.J., S.M. Boekholdt, and J.J. Kastelein, Lipid parameters for measuring risk of cardiovascular disease. Nature Reviews Cardiology, 2011. **8**(4): p. 197-206.
62. McQueen, M.J., et al., Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. The lancet, 2008. **372**(9634): p. 224-233.
63. Jacobsen, A.P., et al., Dyslipidemia, in Hypertension. 2024, Elsevier. p. 476-488.
64. Miller, M., Dyslipidemia and cardiovascular risk: the importance of early prevention. QJM: An International Journal of Medicine, 2009. **102**(9): p. 657-667.
65. Kodama, S., et al., Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: a meta-analysis. Archives of internal medicine, 2007. **167**(10): p. 999-1008.
66. Wood, G., et al., Determining the effect size of aerobic exercise training on the standard lipid profile in sedentary adults with three or more metabolic syndrome factors: a systematic review and meta-analysis of randomised controlled trials. British Journal of Sports Medicine, 2022. **56**(18): p. 1032-1041.
67. Halbert, J., et al., Exercise training and blood lipids in hyperlipidemic and normolipidemic adults: a meta-analysis of randomized, controlled trials. European journal of clinical nutrition, 1999. **53**(7): p. 514-522.
68. Kelley, G.A., K.S. Kelley, and B. Franklin, Aerobic exercise and lipids and lipoproteins in patients with cardiovascular disease: a meta-analysis of randomized controlled trials. Journal of cardiopulmonary rehabilitation, 2006. **26**(3): p. 131.
69. Hayashino, Y., et al., Effects of supervised exercise on lipid profiles and blood pressure control in people with type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. Diabetes research and clinical practice, 2012. **98**(3): p. 349-360.
70. Khalafi, M., et al., Exercise training, dietary intervention, or combined interventions and their effects on lipid profiles in adults with overweight and obesity: a systematic review and meta-analysis of randomized clinical trials. Nutrition, Metabolism and Cardiovascular Diseases, 2023.
71. DeFronzo, R.A. and E. Ferrannini, Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes care, 1991. **14**(3): p. 173-194.
72. Krüger, K., P. Tirekoglou, and C. Weyh, Immunological mechanisms of exercise therapy in dyslipidemia. Frontiers in Physiology, 2022. **13**: p. 903713.
73. Kim, D.Y., et al., Effects of d-α-tocopherol supplements on lipid metabolism in a high-fat diet-fed animal model. Nutrition research and practice, 2013. **7**(6): p. 481-487.
74. Nestel, P.J., Fish oil and cardiovascular disease: lipids and arterial function. The American journal of clinical nutrition, 2000. **71**(1): p. 228S-231S.
75. Brown, T.J., et al., Omega-3, omega-6, and total dietary polyunsaturated fat for prevention and treatment of type 2 diabetes mellitus: systematic review and meta-analysis of randomised controlled trials. bmj, 2019. **366**.
76. Akinkuolie, A.O., et al., Omega-3 polyunsaturated fatty acid and insulin sensitivity: a meta-analysis of randomized controlled trials. Clinical nutrition, 2011. **30**(6): p. 702-707.
77. Lu, G., S.L. Windsor, and W.S. Harris, Omega-3 fatty acids alter lipoprotein subfraction distributions and the in vitro conversion of very low density lipoproteins to low density lipoproteins. The Journal of Nutritional Biochemistry, 1999. **10**(3): p. 151-158.

78. Cornelissen, V.A. and N.A. Smart, Exercise training for blood pressure: a systematic review and meta-analysis. Journal of the American heart association, 2013. **2**(1): p. e004473.
79. Halbert, J.A., et al., The effectiveness of exercise training in lowering blood pressure: a meta-analysis of randomised controlled trials of 4 weeks or longer. Journal of human hypertension, 1997. **11**(10): p. 641-649.
80. Miller, P.E., M. Van Elswyk, and D.D. Alexander, Long-chain omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and blood pressure: a meta-analysis of randomized controlled trials. American journal of hypertension, 2014. **27**(7): p. 885-896.
81. Musazadeh, V., et al., The beneficial effects of omega-3 polyunsaturated fatty acids on controlling blood pressure: An umbrella meta-analysis. Frontiers in nutrition, 2022. **9**: p. 985451.
82. Zhang, X., et al., Omega-3 polyunsaturated fatty acids intake and blood pressure: a dose-response meta-analysis of randomized controlled trials. Journal of the American Heart Association, 2022. **11**(11): p. e025071.
83. Mozaffarian, D., Fish, n-3 fatty acids, and cardiovascular haemodynamics. Journal of Cardiovascular Medicine, 2007. **8**: p. S23-S26.
84. Gousset-Dupont, A., et al., The effect of n-3 PUFA on eNOS activity and expression in Ea hy 926 cells. Prostaglandins, leukotrienes and essential fatty acids, 2007. **76**(3): p. 131-139.
85. Mori, T.A., et al., Differential effects of eicosapentaenoic acid and docosahexaenoic acid on vascular reactivity of the forearm microcirculation in hyperlipidemic, overweight men. Circulation, 2000. **102**(11): p. 1264-1269.
86. Colussi, G., et al., Impact of omega-3 polyunsaturated fatty acids on vascular function and blood pressure: relevance for cardiovascular outcomes. Nutrition, Metabolism and Cardiovascular Diseases, 2017. **27**(3): p. 191-200.
87. Wang, H., et al., Omega-3 polyunsaturated fatty acids: versatile roles in blood pressure regulation. Antioxidants & Redox Signaling, 2021. **34**(10): p. 800-810.
88. Consortium, C., et al., Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature, 2011. **478**(7367): p. 103-109.
89. Ettehad, D., et al., Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. The Lancet, 2016. **387**(10022): p. 957-967.
90. Yates, C.M., P.C. Calder, and G.E. Rainger, Pharmacology and therapeutics of omega-3 polyunsaturated fatty acids in chronic inflammatory disease. Pharmacology & therapeutics, 2014. **141**(3): p. 272-282.
91. Kang, J.X. and K.H. Weylandt, Modulation of inflammatory cytokines by omega-3 fatty acids. Lipids in health and disease, 2008: p. 133-143.
92. Khosravi, N., et al., Exercise training, circulating cytokine levels and immune function in cancer survivors: a meta-analysis. Brain, behavior, and immunity, 2019. **81**: p. 92-104.
93. Khalafi, M., A. Malandish, and S.K. Rosenkranz, The impact of exercise training on inflammatory markers in postmenopausal women: A systemic review and meta-analysis. Experimental Gerontology, 2021. **150**: p. 111398.
94. Khalafi, M., et al., Influence of different modes of exercise training on inflammatory markers in older adults with and without chronic diseases: a systematic review and meta-analysis. Cytokine, 2023. **169**: p. 156303.
95. Khalafi, M., M.E. Symonds, and A. Akbari, The impact of exercise training versus caloric restriction on inflammation markers: a systemic review and meta-analysis. Critical Reviews in Food Science and Nutrition, 2022. **62**(15): p. 4226-4241.
96. Hotamisligil, G.S. and B.M. Spiegelman, Tumor necrosis factor α: a key component of the obesity-diabetes link. Diabetes, 1994. **43**(11): p. 1271-1278.

97. Hotamisligil, G., Mechanisms of TNF-α-induced insulin resistance. Experimental and clinical endocrinology & diabetes, 1999. **107**(02): p. 119-125.
98. Bennet, A., et al., Association of TNF-α serum levels and TNFA promoter polymorphisms with risk of myocardial infarction. Atherosclerosis, 2006. **187**(2): p. 408-414.
99. Simonetto, M., et al., A Novel Anti-Inflammatory Role of Omega-3 PUFAs in Prevention and Treatment of Atherosclerosis and Vascular Cognitive Impairment and Dementia. Nutrients, 2019. **11**(10).
100. Massaro, M., et al., The omega-3 fatty acid docosahexaenoate attenuates endothelial cyclooxygenase-2 induction through both NADP(H) oxidase and PKC epsilon inhibition. Proc Natl Acad Sci U S A, 2006. **103**(41): p. 15184-9.
101. Yusof, H.M., E.A. Miles, and P. Calder, Influence of very long-chain n-3 fatty acids on plasma markers of inflammation in middle-aged men. Prostaglandins Leukot Essent Fatty Acids, 2008. **78**(3): p. 219-28.
102. Cornish, S.M., et al., Effects of omega-3 supplementation alone and combined with resistance exercise on skeletal muscle in older adults: a systematic review and meta-analysis. Nutrients, 2022. **14**(11): p. 2221.

Table 1. Intervention Characteristics

Source, year	Participant characteristics				Exercise and supplement intervention characteristics					Outcomes
	Sample size (sex)	Health status	Age (years)	BMI (kg/m^2)	Design	Duration (weeks)	Exercise mode; weekly sessions	Exercise protocol	Supplement protocol	
Alves et al, 2022 [1]	32 (F)	Sarcopenic	EX:71.4±6.2 EX+SU:70.6±3.9	EX:24.7±3.5 EX+SU:25.6±3.1	Double-blind RCT	14	Resistance; 3 Supervised sessions	3 sets, 12 reps, 50-80% 1RM	4 g/day, fish oil capsule (440 mg EPA, 220 mg DHA)	Weight, BMI, IL-6, TNF-a, Lower body strength, Hand grip
Brook et al, 2021 [2]	16 (F)	Healthy	EX:66.5±4.0 EX+SU:64.4±2.3	EX:25.8±2.5 EX+SU:26.0±2.0	Double-blind RCT	6	Resistance, 3 Supervised sessions	6 sets, 8 reps, 75% 1RM	3680 mg/day· n-3 PUFA pill (1860 mg EPA, 1540 mg DHA)	LBM, BF, Lower body strength
Cornish and Chilibeck, 2009 [3]	51 (M & F)	Healthy	EX:65.4±6.2 EX+SU:65.4±6.2	ND	Double-blind RCT	12	Resistance, 3 Supervised sessions	2-4 sets, 6-12 reps, 60-85% 1RM	30 ml/day, Flax oil (14 g ALA)	TNF-a, IL-6, Upper & Lower body strength, LBM, FM
Cornish et al, 2018 [4]	23 (M)	Older	EX:70.9±5.0 EX+SU:71.4±6.2	EX:27.7±3.5 EX+SU:27.5±4.2	Double-blind RCT	12	Resistance, 3 Supervised sessions	2-4 sets, 6-12 reps, 60-85% 1RM	3 g/day· omega-3 capsule (1.98 g EPA, 0.99 g DHA)	Weight, LBM, BF, Upper & Lower body strength, IL-6, TNF-a
Da Boit et al, 2017 [5]	50 (M & F)	Older	EX:70.6±4.5 EX+SU:70.6±4.5	EX:25.6±4.2 EX+SU:25.6±4.2	Double-blind RCT	18	Resistance, 2 Supervised sessions	4 sets, 9 reps, 70% 1RM	3 g/day, n-3 PUFA capsule (2.1 g EPA, 0.6 g DHA)	Weight, BMI, Glucose, TG, Insulin, IL-6, TNF-a, SBP, DBP, Lower body strength
Dalle et al, 2021 [6]	22 (M & F)	Non-sarcopenic older	EX:70.6±1.5 EX+SU:71.2±1.0	EX:26.7±0.4 EX+SU:27.1±0.7	Double-blind RCT	12	Resistance; 3 Supervised sessions	first 6 weeks: 2 sets, 12-15 reps, ~70% 1RM last 6 weeks: 3 sets, 10-12 reps, ~80% 1RM	1100 mg/day, n-3 PUFA softgels (540 mg EPA, 410 mg DHA, 4 mg vitamin E)	Weight, BMI, HDL, LDL, TG, TC, Insulin, Glucose, BF, Lower body strength, Hand grip, IL-6
Félix-Soriano et al, 2021 [7]	36 (F)	Overweight and obesity	EX:59.0±3.5 EX+SU:58.1±3.1	EX:30.8±2.3 EX+SU:31.1±1.8	Double-blind RCT	16	Resistance, 2 Supervised sessions	3-4 sets, 8-15 reps, 50-80% 1RM	3 g/day, omega-3 capsule (150 mg EPA, 1650 mg DHA)	Weight, BMI, Upper & Lower body strength, BF, SBP, DBP, TC, TG, LDL, HDL, Glucose, Insulin
Haghravan et al, 2016 [8]	44 (F)	Overweight	20 to 45 years old	EX:27.6±1.3 EX+SU:27.9±1.5	Double-blind RCT	8	Aerobic, Supervised sessions	supervised exercise sessions	1 capsules/day, omega-3 (600 mg EPA, 300 mg DHA)	Weight, BMI, BF, VO_{2max}
Hearon et al, 2022 [9]	29 (M & F)	Obese with high-risk of heart failure	EX:50.0±6.0 EX+SU:50.0±6.0	EX: 36.7±5.0 EX+SU: 36.7±5.3	Double-blind RCT	48	HIIT, 3-4 Supervised sessions	5-8 sets, 30-120 s, cycling, >95% HR_{peak}	1.6 g/day EPA, omega-3	Weight, BMI, FM, LBM, VO_{2max}
Heileson et al, 2023 [10]	21 (M & F)	Healthy	EX:30.5±5.7 EX+SU:28.0±7.4	EX:26.6±4.3 EX+SU:25.8±3.5	Double-blind RCT	10	Resistance, 2 Unsupervised and 1 Supervised session	3-4 sets, 8-12 reps, 70% 1RM	4.5 g/day, omega-3 capsule (2.3 mg EPA, 1.6 mg DHA)	Upper & Lower body strength, LBM, FM, BF
Hill et al, 2007a [11]	30 (M & F)	Overweight with high blood pressure, cholesterol, or triacylglycerols	EX:51.0±7.5 EX+SU:47.0±8.0	EX:32.7±3.0 EX+SU:34.5±6.0	Double-blind RCT	12	Aerobic, 3 Supervised sessions	45 min, walking, 75% HR_{max}	1.9 g/day, n-3 PUFA capsule (60 mg EPA, 260 mg DHA)	Weight, BMI, BF, FM, LBM, TG, TC, HDL, SBP, DBP
Lee et al, 2019 [12]	20 (M & F)	Healthy	EX:66.6±7.3 EX+SU:67.1±4.4	EX:23.5±3.6 EX+SU:24.0±3.2	RCT	12	Resistance, 2 Supervised sessions	2 sets, 10 reps, 50-70% 1RM	3 capsules/day, n-3 PUFA (2.1 g EPA, 0.72 g DHA)	SBP, DBP, Hand grip
Lee et al, 2022 [13]	20 (M & F)	Healthy	EX:66.6±7.3 EX+SU:67.1±4.4	EX:23.5±3.6 EX+SU:24.0±3.2	RCT	12	Resistance, 2 Supervised sessions	2 sets, 10 reps, 50-70% 1RM	3 capsules/day, n-3 PUFA (2.1 g EPA, 0.72 g DHA)	Upper & Lower body strength, IL-6, TNF-a
Lee et al, 2023 [14]	20 (F)	Healthy	EX:65.4±2.3 EX+SU:65.9±4.3	EX:24.4±3.0 EX+SU:23.9±1.5	RCT	8	Resistance, 2 Supervised sessions	3 sets, 10 reps, 50-70% 1RM	3 capsules/day, n-3 PUFA (2.1 g EPA, 0.72 g DHA)	SBP, DBP, TG, IL-6, TNF-a, Lower body strength, Hand grip
Nayebifar et al, 2020 [15]	32 (M)	Healthy	20 to 30 years old	ND	RCT	6	HIIT, 3 Supervised sessions	4-8 reps, 30-s, 85-95% HR_{max}, 30-s recovery	Two 1000 mg tablets of omega-3	TG, TC
Rodacki et al, 2012 [16]	30 (F)	Elderly	EX:64.9±1.0 EX+SU:63.8±1.4	EX:25.4±1.6 EX+SU:27.7±1.3	RCT	12	Resistance, 3 Supervised sessions	3 sets, 8 reps, 70-80% 1RM	2 g/day, n-3 PUFA capsule (0.4 g EPA, 0.3 g DHA)	Weight, BMI, Lower body strength
Slivkoff-Clark et al, 2012 [17]	29 (M)	Overweight and obesity	EX:56.2±5.2 EX+SU:49.2±7.2	EX:31.9±5.2 EX+SU:32.5±2.9	Single-blind RCT	12	Aerobic, 2-5 Supervised sessions	Walking at 50-65% HR	4 capsules/day, fish oil (1000 mg EPA, 700mg DHA)	BMI, Glucose, TG, LDL, HDL, TC
Stepan et al, 2022 [18]	51 (F)	Elderly	EX:70.0±4.0 EX+SU:71.0±4.0	EX:19.0–37.0 EX+SU:19.0–37.0	RCT	16	Combined, 3 Supervised sessions	Twice a week (60 min, strength training, moderate intensity of BRPE 13–14) + once a week (50 min, walking, 60%–85% VO_{2peak})	5 capsules/day, omega-3 (230 mg EPA+DHA)	Weight, BF, FM, , LBM, VO_{2max}
Taheri et al, 2018 [19]	16 (F)	Obese with mild to moderate depression	EX:45.0±5.1 EX+SU:45.0±5.1	EX:32.4±1.3 EX+SU:32.4±1.3	RCT	8	Aerobic, 5 Supervised sessions	Jogging, 30 min, 65-75% HR_{max}	2 capsules/day, omega-3 (180 mg EPA, 120mg DHA)	HDL, LDL, TC
Tartibian et al, 2011 [20]	38 (F)	Healthy	EX:61.4±6.9 EX+SU:59.7±2.3	EX:25.1±7.1 EX+SU:26.3±4.8	RCT	24	Aerobic, 3-4 Supervised sessions	Walking and jogging; 25-45 min, 45-65% of HR_{max}	1000 mg/day, n-3 PUFA, capsule (180 mg EPA, 120mg DHA)	TNF-a, IL-6
Wei et al, 2013 [21]	24 (M & F)	Hyperlipidemic	18 to 75 years old	ND	RCT	8	Combined, 4 Supervised sessions	60 min, walking, cycling and calisthenics; 50-70% VO_{2peak}	Perilla oil capsules were taken 4 grain/time, twice/day	TC, TG, HDL, LDL, TNF-a

Abbreviations: ***SU*** omega 3 supplement; ***BMI*** body mass index ***EX*** exercise intervention; ***F*** female, ***M*** male; ***BF*** body fat; ***LBM*** lean body mass; ***FM*** fat mass; ***SBP*** systolic blood pressure; ***DBP*** diastolic blood pressure; ***TC*** total cholesterol; ***TG*** triglyceride; ***LDL*** low-density lipoprotein; ***HDL*** high-density lipoprotein; ***IL-6*** Interleukin-6; ***TNF-a*** tumor necrosis factor alpha; ***HIIT*** high-intensity interval training; ***$VO_{2max/peak}$*** maximal or peak oxygen uptake***;*** ***$HR_{max/peak}$*** maximal or peak heart rate; ***R*** resistance; ***A*** aerobic; ***C*** combined; ***reps*** repetitions; ***1RM*** one-repetition maximum; ***BRPE*** borg rating of perceived exertion; ***CSA*** cross-sectional area; ***ND*** not-described

1. Alves, N.M.D., et al., *Randomised Controlled Trial of Fish Oil Supplementation on Responsiveness to Resistance Exercise Training in Sarcopenic Older Women.* Nutrients, 2022. **14**(14).
2. Brook, M.S., et al., *Omega-3 supplementation during unilateral resistance exercise training in older women: A within subject and double-blind placebo-controlled trial.* Clin Nutr ESPEN, 2021. **46**: p. 394-404.
3. Cornish, S.M. and P.D. Chilibeck, *Alpha-linolenic acid supplementation and resistance training in older adults.* Applied Physiology, Nutrition and Metabolism, 2009. **34**(1): p. 49-59.
4. Cornish, S.M., et al., *Omega-3 supplementation with resistance training does not improve body composition or lower biomarkers of inflammation more so than resistance training alone in older men.* Nutr Res, 2018. **60**: p. 87-95.
5. Da Boit, M., et al., *Sex differences in the effect of fish-oil supplementation on the adaptive response to resistance exercise training in older people: a randomized controlled trial.* Am J Clin Nutr, 2017. **105**(1): p. 151-158.
6. Dalle, S., et al., *Omega-3 Supplementation Improves Isometric Strength But Not Muscle Anabolic and Catabolic Signaling in Response to Resistance Exercise in Healthy Older Adults.* J Gerontol A Biol Sci Med Sci, 2021. **76**(3): p. 406-414.
7. Félix-Soriano, E., et al., *Effects of dha-rich n-3 fatty acid supplementation and/or resistance training on body composition and cardiometabolic biomarkers in overweight and obese post-menopausal women.* Nutrients, 2021. **13**(7).
8. Haghravan, S., et al., *Impact of Omega-3 PUFAs supplementation with lifestyle modification on anthropometric indices and Vo2 max in overweight women.* Archives of Iranian Medicine, 2016. **19**(5): p. 342-347.
9. Hearon, C.M., Jr., et al., *1 Year HIIT and Omega-3 Fatty Acids to Improve Cardiometabolic Risk in Stage-A Heart Failure.* JACC Heart Fail, 2022. **10**(4): p. 238-249.
10. Heileson, J.L., et al., *The effect of fish oil supplementation on resistance training-induced adaptations.* J Int Soc Sports Nutr, 2023. **20**(1): p. 2174704.
11. Hill, A.M., et al., *Combining fish-oil supplements with regular aerobic exercise improves body composition and cardiovascular disease risk factors.* Am J Clin Nutr, 2007. **85**(5): p. 1267-74.
12. Lee, S.R., E. Jo, and A.V. Khamoui, *Chronic Fish Oil Consumption with Resistance Training Improves Grip Strength, Physical Function, and Blood Pressure in Community-Dwelling Older Adults.* Sports (Basel), 2019. **7**(7).
13. Lee, S.R., D. Directo, and A.V. Khamoui, *Fish oil administration combined with resistance exercise training improves strength, resting metabolic rate, and inflammation in older adults.* Aging Clin Exp Res, 2022. **34**(12): p. 3073-3081.
14. Lee, S.R. and D. Directo, *Fish Oil Supplementation with Resistance Exercise Training Enhances Physical Function and Cardiometabolic Health in Postmenopausal Women.* Nutrients, 2023. **15**(21).
15. Nayebifar, S.H., E. Ghasemi, and S. Karimipour, *Effect of high-intensity interval training and omega-3 supplementation on liver enzymes and lipid profile of young men.* Science and Sports, 2020. **35**(1): p. e1-e9.
16. Rodacki, C.L.N., et al., *Fish-oil supplementation enhances the effects of strength training in elderly women.* American Journal of Clinical Nutrition, 2012. **95**(2): p. 428-436.
17. Slivkoff-Clark, K.M., A.P. James, and J.C.L. Mamo, *The chronic effects of fish oil with exercise on postprandial lipaemia and chylomicron homeostasis in insulin resistant viscerally obese men.* Nutrition and Metabolism, 2012. **9**.
18. Stepan, M., et al., *Exercise Training Combined with Calanus Oil Supplementation Improves the Central Cardiodynamic Function in Older Women.* Nutrients, 2022. **14**(1).
19. Taheri, M., et al., *The effect of omega-3 fatty acid supplement and aerobic exercise on lipid profile and depression in obese women.* Acta Medica Mediterranea, 2018. **34**(3): p. 865-870.
20. Tartibian, B., et al., *Long-term aerobic exercise and omega-3 supplementation modulate osteoporosis through inflammatory mechanisms in post-menopausal women: A randomized, repeated measures study.* Nutrition and Metabolism, 2011. **8**.
21. Wei, M., et al., *Perilla oil and exercise decrease expressions of tumor necrosis factor-alpha, plasminogen activator inhibitor-1 and highly sensitive C-reactive protein in patients with hyperlipidemia.* J Tradit Chin Med, 2013. **33**(2): p. 170-5.

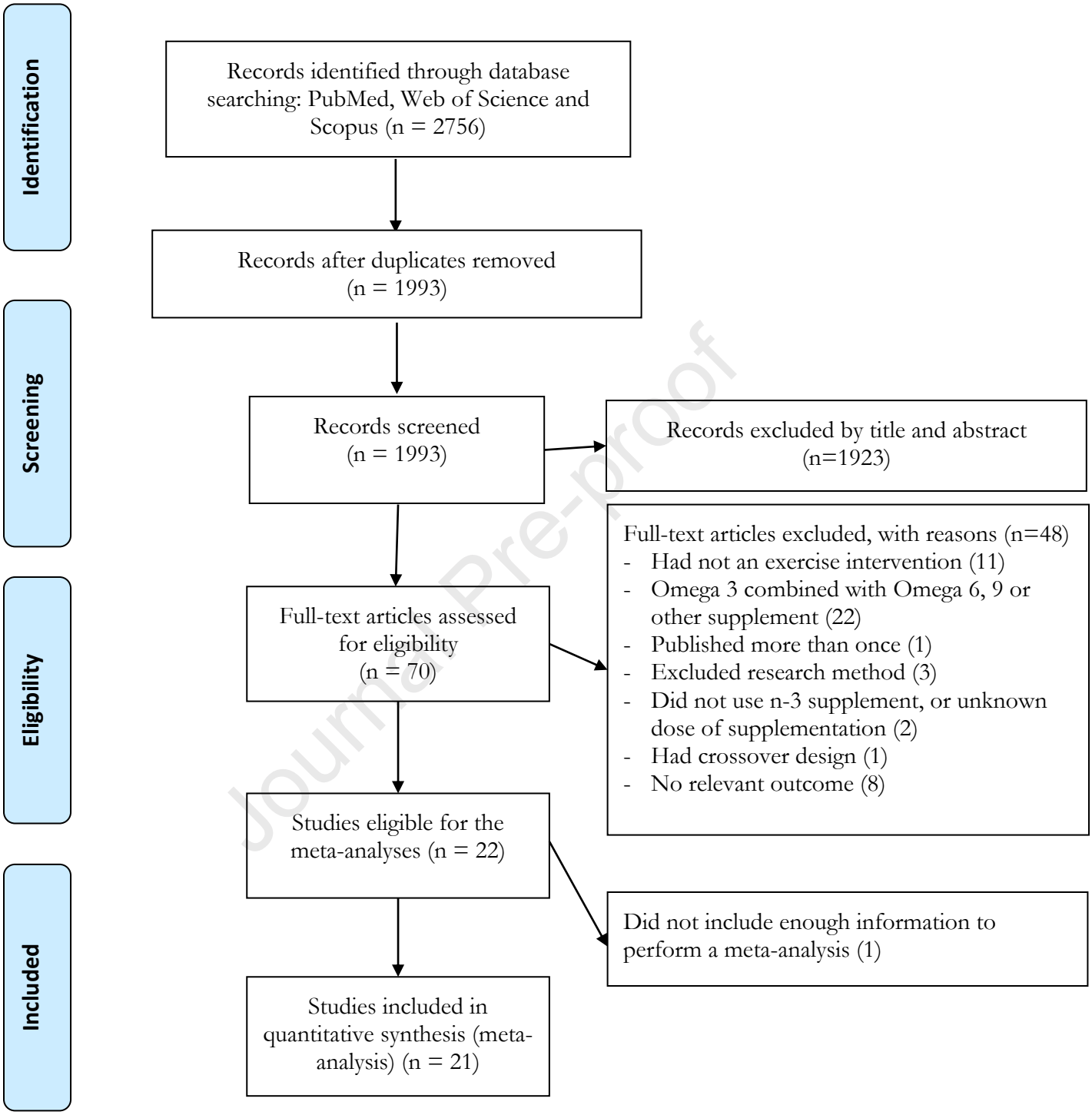

Figure 1. Flow diagram of systematic literature search