REVIEW

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Does omega-3 supplementation added to exercise attenuate inflammaging? Effects on circulating interleukin-6 in older adults: A meta-analysis of randomized controlled trials

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ABSTRACT

Background: Low-grade systemic inflammation (inflammaging) characterizes older adults, with circulating interleukin-6 (IL-6) as a key biomarker linked to frailty, physical decline, and cardiometabolic risk. Exercise repeatedly elicits anti-inflammatory myokine responses, while long-chain omega-3 (eicosapentaenoic Acid (EPA)/ docosahexaenoic acid (DHA)) promotes resolution of inflammation via membrane remodelling and specialized pro-resolving mediators. This study aimed to determine whether adding omega-3 supplementation to structured exercise reduces resting IL-6 more than exercise alone in older adults.

Methods: A systematic search was undertaken in PubMed using a pre-specified medical subject headings (MeSH) strategy that combined terms for long-chain omega-3 fatty acids, structured exercise/physical activity, Interleukin-6, the aged population, and randomized/clinical trial filters; animal-only studies were excluded. This search yielded 22 records. Complementary searches in Scopus (14 records) and ResearchGate (18 records) were pooled with PubMed results and deduplicated prior to screening. Four RCTs (duration 8–18 weeks) met all criteria. Pooled effects were estimated with a random-effects model using restricted maximum likelihood (REML). Between-study heterogeneity was summarized by Q, I^2, and τ^2 summarized between-study heterogeneity. Potential small-study effects were explored visually using a funnel plot.

Results: Pooled analysis using a REML model shows that post-intervention IL-6 was lower by 0.77 pg/mL when omega-3 supplementation was added to exercise versus exercise alone (MD = −0.77 pg/mL; 95% CI −1.46 to −0.08; p = 0.03; k = 4), indicating a statistically significant, directionally consistent attenuation of resting inflammation. Between-study heterogeneity was moderate (Q = 7.04, df = 3, p = 0.07; I^2 = 55%; τ^2 = 0.26), suggesting that differences in trial characteristics (e.g., duration 8–18 weeks, exercise mode, and omega-3 dose/form) contributed to variability in effect sizes. Funnel-plot analysis did not reveal marked asymmetry.

Conclusion: Across randomized trials in older adults, omega-3 supplementation added to exercise achieves a modest but statistically significant reduction in resting IL-6 versus exercise alone, consistent with attenuation of inflammaging.

Keywords: exercise, interleukin-6, inflammaging, older adults, omega-3.
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INTRODUCTION

Ageing is accompanied by a chronic, low-grade, systemic inflammatory state (inflammaging) that is thought to arise from multiple, converging drivers including immune remodelling, accumulation of senescent cells with a pro-inflammatory secretome (SASP), metabolic dysregulation, and impaired resolution pathways.[1,2] Among circulating mediators implicated in inflammaging, interleukin-6 (IL-6) occupies a central position. Higher resting IL-6 concentrations in older adults correlate with poorer physical performance and strength, increased frailty risk, cardiometabolic morbidity, and mortality.[1,3] IL-6 is produced by innate immune cells, adipose tissue, endothelial cells, and other parenchymal tissues in response to oxidative, metabolic, and infectious stressors, and it amplifies downstream inflammatory signalling and hepatic acute-phase responses (e.g., C-reactive protein).[1,3] Thus, lowering resting IL-6 is commonly interpreted as a shift toward a less inflammatory internal milieu in older people.

Paradoxically, exercise acutely raises IL-6 as a myokine released from contracting skeletal muscle. This short-lived surge is part of an anti-inflammatory reflex that increases IL-10 and IL-1 receptor antagonist and suppresses TNF-α, helping to resolve inflammation after each bout.[4] Repeated training, especially when it reduces visceral adiposity and improves mitochondrial function, is associated with lower basal IL-6 over time,

reflecting improved immune-metabolic homeostasis. Exercise, therefore, acts both as an acute pro-resolving stimulus and a chronic modifier of inflammatory set-points in older adults. Long-chain omega-3 polyunsaturated fatty acids (LC n-3 PUFA; eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) constitute a complementary, mechanistically distinct lever on inflammaging.[6,7] By incorporating into cell membranes in place of arachidonic acid, EPA/DHA alter lipid raft composition and eicosanoid profiles and serve as substrates for specialized pro-resolving mediators (SPMs) such as resolvins, protectins, and maresins.[5,6] These mediators actively promote the resolution of inflammation, limiting neutrophil infiltration, enhancing efferocytosis, and restraining NF-κB–dependent transcription of pro-inflammatory genes, including IL6.[5-7] Experimental and clinical data also indicate that omega-3 fatty acids can modulate Toll-like receptor signalling, macrophage polarization, and insulin sensitivity, all of which are relevant to the inflammatory phenotype of late life.[6,7]

Given these complementary mechanisms, exercise as a repeated pro-resolving trigger and omega-3 as a substrate and signal for resolution biology, it is biologically plausible that combining omega-3 supplementation with structured exercise would yield greater reductions in resting IL-6 than exercise alone in older adults. However, trials in this area have varied in omega-3 formulations and doses, exercise modalities and durations, participant sex and age distributions, and IL-6 assay methods, leading to uncertainty about the magnitude and consistency of any added benefit.[6-11]

Randomized controlled trials (RCTs) have begun to test this combined approach. In older men and women undertaking resistance exercise, fish-oil supplementation has been evaluated for its capacity to modify training adaptations and circulating cytokines.[8] Other trials in healthy older adults report that omega-3 provided alongside resistance or mixed-mode exercise, with inflammatory markers including IL-6 as secondary outcomes.[9-11] While individual studies suggest directionally favourable changes in IL-6 with the combination strategy, confidence intervals are often wide and sample sizes modest—typical features of intervention research in gerontology.

In order to address this evidence gap, the present work synthesizes available RCTs to quantify the added effect of omega-3 supplementation on circulating IL-6 when layered onto structured exercise in older adults. Exercise training and omega-3 supplementation each target complementary nodes of the inflammatory network, resolution physiology and immune-metabolic tuning, with IL-6 serving as a pragmatic, integrative biomarker. The present meta-analysis, therefore, aims to evaluate whether omega-3 added to exercise attenuates inflammaging by reducing resting circulating IL-6 in older adults and assesses the robustness and translational significance of this effect.

METHODS

This study was designed as a systematic review and meta-analysis examining whether adding omega-3 supplementation to structured exercise reduces resting circulating interleukin-6 (IL-6) in older adults. The protocol followed PRISMA recommendations for study identification, screening, eligibility assessment, and quantitative synthesis.

Search Strategy and Article Eligibility

A comprehensive search was conducted in three sources. First, PubMed was queried using a predefined MeSH-based strategy combining terms for long-chain omega-3 fatty acids (e.g., Fatty Acids, Omega-3, Fish Oils, EPA, DHA, α-linolenic acid), structured exercise/physical activity (e.g., Exercise, Exercise Therapy, Resistance Training, HIIT, and walking), systemic

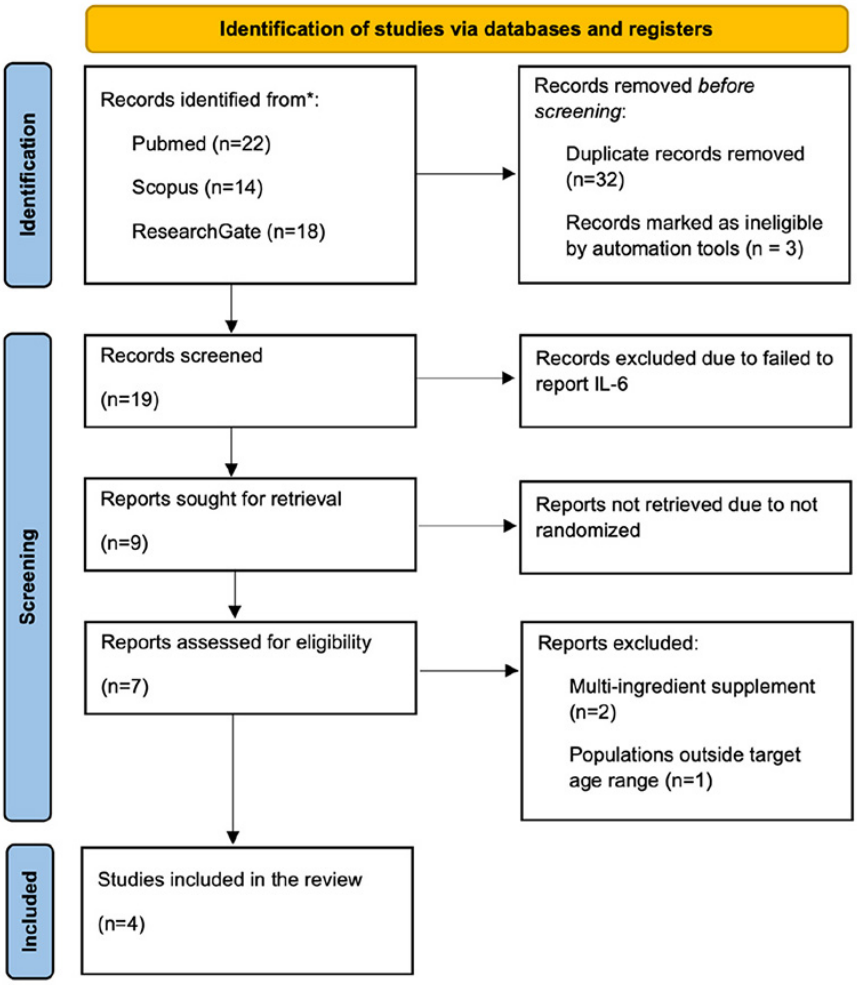

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram for the systematic review

inflammation (e.g., Interleukin-6, C-reactive protein, and Tumor Necrosis Factor-alpha), the aged population (Aged and 60 or over), and randomized/clinical trial filters while excluding animal-only articles. This PubMed search retrieved 22 articles. Second, complementary searches were performed in Scopus (14 articles) and ResearchGate (18 articles) to broaden coverage. All records were exported, merged, and deduplicated prior to screening.

Following title/abstract screening, potentially relevant articles underwent full-text assessment against prespecified eligibility criteria. Studies were excluded if they were not randomized, did not evaluate the combination of omega-3 plus exercise (e.g., omega-3 alone or exercise alone), enrolled ineligible populations, or failed to report IL-6 with extractable/convertible data. After full-text review and exclusions, four randomized controlled trials (RCTs) met the inclusion criteria for the quantitative synthesis (**Figure 1**).

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Inclusion and Exclusion Criteria

Eligible studies met all of the following criteria based on PICO: (1) Population: older adults (approximately ≥60 years; trials in postmenopausal women with mean age ~65 years were eligible); (2) Intervention: oral omega-3 supplementation (fish oil or equivalent EPA/DHA formulations) added to a structured exercise program (e.g., resistance or mixed-mode training); (3) Comparator**:** exercise alone; (4) Outcome: circulating IL-6 measured in serum or plasma and reported as post-intervention with mean and standard deviation (SD) or convertible summary statistics; and (5) Design: parallel-group RCTs with intervention duration ≥4 weeks. Exclusion criteria comprised: non-randomized designs; protocols, cross-sectional, or animal studies; multi-ingredient supplements where the specific effect of omega-3 could not be isolated (non-factorial blends); populations clearly outside the target age range or with conditions not generalizable to community-dwelling older adults; absence of IL-6 data or insufficient quantitative detail; and duplicate publications or secondary analyses of the same cohort (to avoid double counting).

Data Collection, Data Extraction, and Quality Assessment

Screening and data extraction were conducted independently by two reviewers using a standardized form. Extracted variables included study identifiers (first author, year, journal), setting, participant characteristics (age, sex), intervention details (omega-3 source, EPA/DHA dose, regimen; exercise modality, frequency, and duration), comparator characteristics, IL-6 matrix and units, and post-intervention IL-6 means, SDs, and sample sizes for each arm. Where arms were reported separately by sex, male and female strata were pooled using standard formulas for combining means and variances to yield a single value per randomized group. In multi-arm trials with more than one eligible control, control groups were appropriately combined to preserve independence of comparisons.

In order to harmonize the standard unit, all IL-6 values were expressed in pg/mL. When dispersion was provided as the standard error of the mean (SEM), SD was computed as SEM × $\sqrt{n}$. If only median and interquartile range (IQR) were reported, conversion to mean ± SD followed established estimation methods, assuming approximate symmetry in the absence of minimum/maximum values. In cases where outcomes were presented only as figures, data were graphically digitized to estimate post-intervention means and dispersion; such estimates were flagged and later addressed in sensitivity analyses. Risk of bias was appraised using the Cochrane Risk of Bias 2 tool across domains of randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting; disagreements were resolved by consensus.

Data Analysis

All analyses were performed in IBM SPSS Statistics, version 29 for macOS. The primary effect measure was the unstandardized mean difference (MD) in post-intervention IL-6 (pg/mL) between omega-3+exercise and exercise-only arms. For each study, MD and its standard error were computed from group means, SDs, and sample sizes. We generated fixed-effects (inverse-variance) and random-effects summary estimates; the principal model was random effects using the DerSimonian–Laird method for τ^2 with inverse-variance weighting. Between-study heterogeneity was quantified using Cochran's Q, I^2 (proportion of total variability due to heterogeneity), and τ^2 (between-study variance). Where informative, a 95% prediction interval was derived from the random effects estimate and τ^2 to indicate the range of true effects expected across settings comparable to the included trials. Funnel plots were visually inspected to explore small-study effects. Forest and funnel plots, as well as study-level and pooled tables (including Q, I^2, τ^2, and prediction intervals), were produced directly from SPSS version 29.0 for Mac.

RESULTS

Across the four randomized controlled trials included in this meta-analysis (total n = 176), participants were predominantly healthy older adults aged ≥65 years, comprising mixed-sex cohorts and postmenopausal women. Omega-3 supplementation doses were broadly comparable, ranging from approximately 2.0 to 3.0 g/day of combined EPA and DHA, delivered mainly as fish oil, with one study using algae oil. However, EPA and DHA proportions varied across trials. Exercise interventions were consistently resistance-based but differed in modality and structure, including supervised resistance training, combined aerobic–resistance programs, and vibration plus home-based resistance exercise, with intervention durations spanning 8 to 18 weeks (**Table 1**). Despite this clinical and methodological diversity, all studies assessed post-intervention circulating IL-6, and three of four trials showed directionally lower IL-6 with omega-3 supplementation added to exercise compared with exercise alone, with no study reporting an adverse increase (**Table 1**). Collectively, these data indicate that the pooled IL-6 reduction was observed across heterogeneous yet biologically coherent intervention strategies, supporting the robustness of the combined omega-3 and exercise effect and justifying the use of a random-effects model.

Table 1. Characteristics of included randomized controlled trials

Author (Year)	Population	Omega-3 Intervention	Exercise Modality	Study Duration
Da Boit et al., 2017[8]	Healthy older adults ≥65 years (n=45, men and women)	Fish oil 3 g/day (1.86 g EPA + 1.5 g DHA)	Resistance training, twice weekly	12 weeks
Dalle et al., 2021[9]	Healthy postmenopausal women (n=50)	Omega-3 2 g/day (EPA + DHA)	Combined aerobic and resistance training	18 weeks
Haß et al., 2022[10]	Community-dwelling older adults 65–85 years (n=61)	Algae oil 3.5 mL/day (2.2 g n-3: 1.4 g DHA + 0.75 g EPA)	Vibration exercise plus home-based resistance training	8 weeks
Lee et al., 2023[11]	Healthy postmenopausal women (n=20)	Fish oil providing 2.1 g EPA + 0.72 g DHA/day	Resistance training, twice weekly	8 weeks

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; g, gram; mL, millilitter; n, number of participants.

The forest plot (**Figure 2**) summarizes the mean differences (MDs) in post-intervention IL-6 comparing omega-3 add to exercise versus exercise alone across the four included randomized trials. Three of the four studies favoured the combined intervention, and one showed a slight, imprecise difference. Study-specific estimates were −0.19 pg/mL for DaBoit 2017, −1.51 pg/mL for Dalle 2021, −0.54 pg/mL for Haß 2022, and −0.70 pg/mL for Lee 2023, with corresponding 95% CIs shown in Figure 2. Using a random-effects model (REML), the pooled MD was −0.77 pg/mL (95% CI −1.46 to −0.08; p = 0.03), indicating a statistically significant reduction in resting IL-6 when omega-3 supplementation is added to structured exercise. The choice of a random-effects model was appropriate given moderate heterogeneity (Q = 7.04, df = 3, p = 0.07; I^2 = 55%; τ^2 = 0.26), which likely reflects differences in intervention duration (8–18 weeks), exercise modalities, and omega-3 dose/formulation among trials. (**Figure 2**).

A funnel plot was used to check whether small studies might be skewing the results (**Figure 3**). Points are balanced around the overall effect. The two larger/more precise trials (Dalle 2021 and DaBoit 2017) are located near the top of the plot on opposite sides of the vertical line, which indicates that the publication bias is low. The two smaller/less precise trials (Haß 2022 and Lee 2023) sit lower and slightly to the left, giving a mild leftward lean. All four points fall inside the dashed 95% lines, and there is no apparent gap that would suggest strong publication bias as well as by Egger's test and Funnel Plot (**Figure 3**).

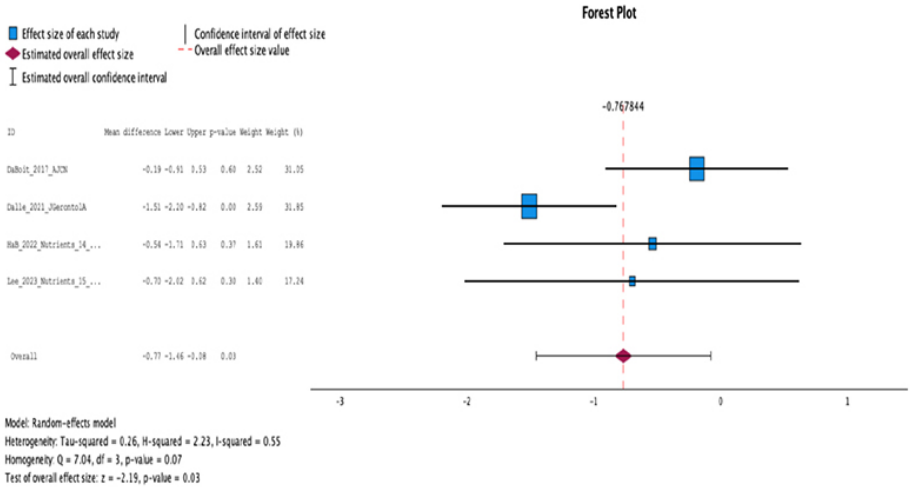

Figure 2. Forest plot of four studies evaluating omega-3 supplementation added to exercise attenuates the interleukin-6

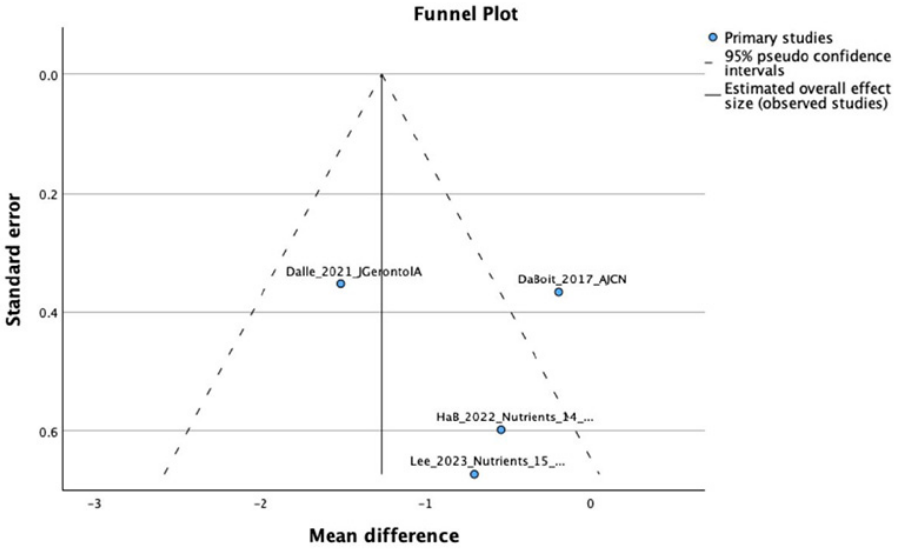

Figure 3. Funnel plot of four studies regarding the publication bias

DISCUSSION

Although IL-6 is the most visible cytokine signal in inflammaging, ageing-related inflammation is not solely a Th1/innate program, type-2 immune circuits, such as IL-33, ILC2, IL-5, and eosinophil axis in adipose tissue, wane with age and help set the metabolic–inflammatory "tone" of late life.[1,12,13] With advancing age, adipose tissue shows immune remodeling characterized by loss/dysfunction of ILC2s, disturbed eosinophil homeostasis, and a drift away from M2-like macrophage programs that normally sustain repair and insulin sensitivity, changes that foster sterile, low-grade inflammation and metabolic decline.[14,15] In mice and humans, adipose ILC2s are a key source of IL-5; their attrition during ageing or metabolic stress is linked to reduced eosinophil support, impaired adipose "beiging," and thermogenic failure. Although IL-33 can expand ILC2 numbers, aged ILC2s are intrinsically hypofunctional, indicating qualitative as well as quantitative defects with age.[12,13] Consequently, IL-5 has a bidirectional role: physiological IL-5 supports eosinophil-mediated tissue homeostasis and an anti-inflammatory adipose niche, whereas loss of IL-5–dependent circuits permits pro-inflammatory macrophage programs and IL-6-dominant signaling to prevail.[16] Attempts to pharmacologically elevate IL-5 to rescue adipose eosinophils in obesity models have yielded mixed metabolic outcomes, underscoring that IL-5 operates within a broader tissue ecology and that age-related defects are not easily corrected by ligand replacement alone.[17] Taken together, these observations suggest that inflammaging reflects erosion of type-2, pro-resolving tone (IL-33/IL-5/ILC2/eosinophils) alongside elevation of canonical mediators; this provides a biologic rationale for interventions such as exercise and omega-3 fatty acids that can help re-establish resolution biology and thereby lower basal IL-6 in older adults.[16-18]

During exercise, contracting skeletal muscle releases IL-6 as a myokine; this transient surge functions as an anti-inflammatory signal that up-regulates IL-10 and IL-1 receptor antagonist, dampens TNF-α signaling, improves substrate metabolism, and when repeated with training, shifts the basal inflammatory set-point downward rather than provoking chronic inflammation.[18,19] With sustained programs, training also reduces visceral adiposity and enhances mitochondrial function, thereby removing adipose-derived inflammatory drive common in later life.[20] In parallel, omega-3 fatty acids (EPA/DHA) modulate inflammation through complementary mechanisms: they remodel membrane phospholipids, blunt TLR/NF-κB activation, and, critically, serve as substrates for specialized pro-resolving mediators (SPMs), resolvins, protectins, and maresins, that actively terminate inflammation, promote efferocytosis, and restore tissue homeostasis.[5,7] Contemporary consensus further underscores that SPM biosynthesis and receptor signaling directly restrain IL-6 and related cytokines, fostering resolution rather than broad immunosuppression.[21,22] Taken together, exercise supplies a recurrent myokine-driven anti-inflammatory impulse, while omega-3s provide both the substrate and signal for resolution biology; mechanistically, this pairing is expected to lower resting circulating IL-6 more than exercise alone, via enhanced SPM generation with training, improved macrophage polarization, and protection against endotoxin-triggered innate activation typical of older adults, an integrated rationale aligns with the direction of effect observed in our meta-analysis.[17-21]

Pooled across four randomized trials, adding omega-3 to structured exercise lowered post-intervention IL-6 by 0.77 pg/mL versus exercise alone (95% CI −1.46 to −0.08; p=0.03), with moderate between-study heterogeneity (I^2=55%; τ^2=0.26), as expected under a random-effects framework for clinically diverse trials.[23] The prediction interval (−1.99 to 0.45 pg/mL) indicates that most comparable settings are likely to observe reductions. However, small null effects remain plausible given variation in EPA/DHA dose/formulation, intervention length (8–18 weeks), and assay methods.[24] The funnel plot was broadly symmetric among the more precise studies, and the slight leftward scatter of less precise trials is compatible with sampling variability; with 4 studies, formal tests for asymmetry are underpowered, so absence of a signal should not be over-interpreted.[25] Overall, these findings are directionally consistent with prior work showing that chronic training can lower basal inflammatory markers and that omega-3–derived resolution pathways (including SPMs) restrain cytokine signaling, helping explain the modest, coherent downward shift in resting IL-6 we observed.[19]

This review is limited by a small evidence base (n=4) and methodological diversity across trials. Omega-3 protocols differed in dose, duration, and formulation (e.g., EPA:DHA ratios; ethyl ester vs triglyceride) and were seldom titrated to a target omega-3 index or accompanied by SPM profiling, plausibly inflating between-study variance in IL-6 responses.[6,26] Exercise prescriptions also varied in modality, frequency, supervision, and adherence reporting, typical challenges for non-pharmacologic RCTs that can introduce deviations from intended interventions and affect cytokine outcomes.[27] Measurement methods for IL-6 were not harmonized (plasma vs serum; different high-sensitivity platforms; variable pre-analytical handling), and in some reports only graphical summaries were available, necessitating figure extraction or conversions (SEM to SD; median to mean/SD) that add uncertainty.[28] Risk-of-bias appraisal frequently lacked detail on allocation concealment and blinding of outcome assessment, common sources of concern in exercise–nutrition trials and reflected in RoB 2 guidance.[29] Short intervention windows (8–18 weeks) may also be insufficient to fully remodel inflammatory networks in older adults, limiting detectable changes in resting IL-6 and precluding analysis of dose–response, sex-specific effects, or modification by baseline inflammatory status and comorbidities. Future studies should standardize omega-3 dosing to achieve prespecified omega-3 index targets, quantify SPMs, harmonize IL-6 assays and pre-analytics, ensure robust allocation concealment with transparent adherence/co-intervention reporting, and extend follow-up to strengthen causal inference and reduce heterogeneity.[26-29]

From a clinical translation perspective, the observed fall in resting IL-6 suggests

that combining exercise with omega-3 shifts older adults toward a more pro-resolving inflammatory set-point, with potential downstream benefits for frailty progression, mobility, and cardiometabolic risk. Because higher IL-6 is consistently linked to poorer function and survival in ageing cohorts, even modest, sustained reductions may be meaningful. To turn this biomarker change into patient-centered gains, future RCTs should be larger and longer, include functional outcomes (e.g., gait speed, chair rise, grip strength), and test mechanistic hypotheses, for example, whether reaching a target EPA and DHA blood index or SPM profile mediates IL-6 lowering and functional improvements, and whether omega-3 plus progressive resistance training outperforms aerobic-dominant regimens for inflammatory control in older adults. Trials should also stratify by adiposity and metabolic health, given age-sensitive adipose ILC2/eosinophil pathways that interact with systemic inflammation. Finally, integrating omics (e.g., SPM lipidomics, cytokinomics) with rigorous trial design will help identify who benefits most, the optimal dose, and the durability of effects after supplementation or supervised training ends, evidence needed to inform geriatric guidelines.

Several limitations of this meta-analysis warrant consideration. First, the number of included randomized controlled trials was small, limiting statistical power and precluding formal subgroup or meta-regression analyses to explore effect modification by sex, baseline inflammatory status, omega-3 dose, or exercise modality. Second, there was moderate clinical and methodological heterogeneity across studies, including differences in omega-3 source and formulation (fish oil vs algae oil), EPA:DHA ratios, intervention duration (8–18 weeks), and exercise prescriptions, which may have contributed to the observed between-study variability. Third, IL-6 measurement was not fully standardized across trials, with differences in biological matrices (serum vs plasma), assay platforms, and pre-analytical handling, introducing potential measurement variability. In addition, IL-6 was often a secondary outcome, and in some studies, data extraction required statistical conversions or graphical estimation, which may have added imprecision. Fourth, the relatively short intervention periods may be insufficient to capture longer-term remodelling of age-related inflammatory networks. Finally, with a limited number of studies, the assessment of publication bias was underpowered, and the absence of marked funnel plot asymmetry should be interpreted cautiously. Collectively, these limitations suggest that while the observed reduction in resting IL-6 is biologically plausible and directionally consistent, the magnitude of effect should be interpreted conservatively pending confirmation from larger, longer, and more standardized trials.

CONCLUSION

In this meta-analysis adding omega-3 supplementation to structured exercise produced a statistically significant reduction in resting circulating IL-6 versus exercise alone. This effect is directionally consistent across studies and aligned with mechanistic pathways of myokine-driven anti-inflammatory signalling and omega-3, derived resolution biology. While limited by small study numbers and moderate heterogeneity, these findings support the hypothesis that the combination strategy attenuates inflammaging. Well-designed, longer, and standardized trials that couple biomarker endpoints with functional outcomes are warranted to confirm durability and translate reductions in IL-6 into significant benefits for frailty and cardiometabolic health in older adults.

ETHICAL CONSIDERATIONS

This study was conducted as a systematic review and meta-analysis based exclusively on data extracted from previously published studies. No new human or animal participants were recruited, and no individual-level identifiable data were accessed. Therefore, ethical approval and informed consent were not required for this study, in accordance with institutional and international guidelines for secondary analyses of published data.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to this study.

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AUTHOR CONTRIBUTIONS

NMH conceptualized the study, performed the literature search, data extraction, and drafted the manuscript. DMW and IMWR contributed to the study design, interpretation of findings, and critical revision of the manuscript. IPYP contributed to the methodological framework, statistical analysis, and interpretation of meta-analytic results. All authors reviewed, revised, and approved the final version of the manuscript.

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