Diabetes, Metabolic Syndrome and Obesity

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REVIEW

The Impact of Omega-3 Fatty Acids on Triglyceride Levels in Patients with Metabolic Dysfunction–Associated Steatotic Liver Disease: A Meta-Analysis of Randomized Controlled Trials with Subgroup Analysis by Diabetes Status

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Background: The rising global burden of metabolic dysfunction–associated steatotic liver disease (MASLD) necessitates effective therapies. This meta-analysis therefore assesses the efficacy of omega-3 PUFAs in reducing triglycerides in MASLD patients and examines how diabetes status modulates this effect.

Purpose: To resolve existing uncertainties, this systematic review and meta-analysis was conducted to evaluate the efficacy of omega-3 PUFAs in reducing TG among MASLD patients, with a prespecified analysis to elucidate the role of diabetes status.

Patients and Methods: We systematically searched PubMed, Web of Science, Embase, and the Cochrane Library (up to Sep 22, 2025) for randomized controlled trials assessing omega-3 PUFA supplementation on triglyceride levels in MASLD patients, with subgroup analysis by diabetes status.

Results: Pooled data from 9 studies (n=528) revealed that omega-3 PUFA supplementation was associated with a significant reduction in triglyceride (TG) levels in MASLD patients (MD: −13.81 mg/dL; 95% CI: −24.56, −3.06); however, considerable heterogeneity (I^2=22.5%) suggests that the true effect may be inconsistent across different patient populations. Subgroup analysis delineated a stark contrast: while a beneficial effect was confirmed in non-diabetic MASLD patients (MD: −15.78 mg/dL), it was absent in those with comorbid type 2 diabetes (P = 0.33). Meta-regression further confirmed that the prevalence of diabetes within study populations did not linearly influence the TG-lowering outcome (P = 0.752). Finally, the intervention showed no significant impact on other metabolic parameters such as ALT, HDL, or LDL.

Conclusion: This meta-analysis suggests that omega-3 fatty acids are associated with reduced TG levels in MASLD patients on average, but the effect is inconsistent and influenced by diabetes status. The non-significant effect in diabetic patients and the wide prediction intervals call for caution in interpreting these findings, and further research is needed to identify subgroups that may benefit.

Keywords: metabolic dysfunction–associated steatotic liver disease, omega-3 polyunsaturated fatty acids, triglycerides, type 2 diabetes

Introduction

The growing yearly prevalence of Metabolic Dysfunction–non-alcoholic fatty liver disease (MASLD) has emerged as a worldwide public health concern, driven by improved living conditions, evolving lifestyle habits, and the widespread occurrence

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of obesity, diabetes, and metabolic syndrome.[1] Metabolic dysfunction-associated fatty liver disease (MASLD)—the term newly established by international consensus to replace previous designations including NAFLD and MAFLD—represents a major global health challenge associated with obesity and diabetes, as evidenced by its rising prevalence.[2,3] This manuscript adopts the MASLD nomenclature in alignment with this current international consensus.

Currently, no approved drugs exist for treating MASLD, a condition that may progress to cirrhosis and hepatocellular carcinoma. The urgency for treatment is further heightened by its strong bidirectional association with type 2 diabetes (T2D)—each disease independently increases the risk of developing the other and exacerbates its severity.[4,5]

The accumulation of TG in hepatocytes, stemming from disrupted lipid homeostasis, forms the basis of MASLD patholog.[6,7] These lipids are not inert; through lipotoxicity, they transmit cellular stress and inflammation, thereby driving the progression of more severe diseases.[6] The current lack of approved drugs, coupled with the limitations of lifestyle interventions, necessitates new therapeutic approaches targeting these fundamental processes.[7,8]

Omega-3 polyunsaturated fatty acids (PUFAs) are compelling candidates for MASLD treatment due to their targeted mechanisms, including promoting fatty acid oxidation through Peroxisome Proliferator–Activated Receptor Alpha (PPARα) activation and inhibiting lipogenesis by suppressing Sterol Regulatory Element–Binding Protein 1c (SREBP-1c).[9,10] Although their efficacy in lowering serum triglycerides is widely recognized, their effects on other metabolic and hepatic parameters remain inconsistent across studies.[11–13] This inconsistency obscures the true therapeutic value of omega-3 polyunsaturated fatty acids and suggests the presence of key effect-modifying factors.

The metabolic heterogeneity of study populations, particularly regarding T2D comorbidity, remains an unexplored source of the inconsistent outcomes with omega-3 PUFA therapy.[13,14] Patients with both MASLD and T2DM exhibit a more severe disease phenotype and pronounced insulin resistance, which may fundamentally alter their response to PUFAinterventions.[15] Filling this gap is crucial for determining whether diabetic status is a key effect modifier, thereby explaining inconsistent results in the literature and advancing toward more personalized therapeutic approaches.

Therefore, we conducted a systematic review and meta-analysis of randomized controlled trials with the following objectives: 1) to quantitatively synthesize evidence and determine the overall effect of omega-3 PUFAs on TG levels in patients with (MASLD; 2) to perform subgroup analyses comparing efficacy in patients with and without T2DM; 3) to use meta-regression to explore whether the proportion of diabetic patients within study populations influences the magnitude of TG-lowering effects. This study aims to resolve existing controversies, clarify the role of diabetic status in influencing treatment response, and provide high-level evidence to guide the precise application of omega-3 PUFAs in MASLD management.

Methodology

Literature Search

To identify all relevant RCTs evaluating the effect of omega-3 fatty acids on triglyceride levels in MASLD, we comprehensively searched four databases (PubMed, Embase, Cochrane Library, Web of Science) through September 22, 2025. Our search strategy was constructed to balance sensitivity and precision. It incorporated controlled vocabulary alongside an extensive list of free-text keywords covering key concepts: the disease "non-alcoholic fatty liver disease", "NAFLD", "hepatic steatosis"), the intervention ("omega-3 fatty acids", "n-3 PUFA", "eicosapentaenoic acid", "docosahexaenoic acid", "fish oil"), and the study design ("randomized controlled trial", "clinical trial"). In accordance with the latest international nomenclature consensus, the term "non-alcoholic fatty liver disease (NAFLD)" is hereafter referred to as "metabolic dysfunction–associated steatotic liver disease (MASLD)" throughout this manuscript.[3] Boolean operators (AND, OR) were applied to logically combine these terms. The full, database-specific search queries are available in Appendix 1. This review was conducted in accordance with the PRISMA guidelines, and the study protocol was prospectively registered with PROSPERO (CRD420251160035) to ensure methodological rigor and minimize reporting bias.[16]

Selection and Eligibility Criteria

Studies included in this meta-analysis must meet the following PICOS criteria: (1) Participants (P): Adult patients (aged ≥18 years) with a confirmed diagnosis of MASLD, without restriction on the presence of diabetes, as this factor will be explored

through subgroup analysis; (2) Intervention (I) and Control (C): The intervention group received omega-3 fatty acid supplementation (any source or dose); the control group received placebo or standard care; (3) Outcome (O): Changes in serum triglyceride levels or endpoint values before and after intervention must be reported; (4) Study Type (S): Included randomized controlled trials (RCTs) in our meta-analysis.

Data Extraction and Quality Assessment

After the conclusive selection of studies, a systematic data extraction procedure was launched. Two reviewers, Li and Cong, autonomously completed a pre-tested, standardized data collection template using Microsoft Excel.[17] This form was designed to capture the following key elements from each eligible trial: (1) Study Characteristics: first author, publication year, country, and trial duration; (2) Participant Profile: sample size, baseline characteristics (eg, age, sex, diabetes status), and MASLD diagnostic criteria; (3) Intervention and Comparator: specific type, dosage, and administration schedule of omega-3 supplementation, alongside details of the control/placebo regimen; (4) Outcome Data: primary and secondary outcomes of interest, specifically pre- and post-intervention means, standard deviations (SDs), or change scores for TG levels and other relevant indicators.

The methodological quality of the included RCTs was independently appraised by two authors using the Cochrane RoB 2 tool, which evaluates five domains—randomization, intervention deviations, missing outcome data, outcome measurement, and result selection—and categorizes each as "low risk", "some concerns", or "high risk" of bias.[18]

A two-stage resolution process was employed for disagreements in data extraction and quality assessment: initial discussion between the two independent reviewers was followed by arbitration from a third senior investigator (Zhang) for unresolved issues, whose decision was final.

Statistical Analysis

The quantitative synthesis of data across the included studies was performed using meta-analytic techniques. For the primary outcome of triglyceride level change, we calculated the pooled effect size as the mean difference (MD) along with its 95% confidence interval (CI). Assessment of publication bias was not conducted due to the limited number of studies, which precludes reliable evaluation using standard methods.

Statistical heterogeneity was quantified using Cochran's Q test ($P < 0.10$) and the I^2 statistic. We employed a random-effects model for all meta-analyses, as this approach provides more conservative estimates by accounting for both within-study and between-study variability. This choice was made a priori, regardless of the observed heterogeneity levels, to ensure robust and generalizable results.

To investigate a pre-specified hypothesis, we conducted a meta-regression analysis to examine whether the proportion of diabetic patients within each study (a continuous covariate) explained a significant portion of the observed heterogeneity in the triglyceride outcome. This analysis was fitted using the Restricted Maximum Likelihood (REML) method under a random-effects framework. A P-value of less than 0.05 for the regression coefficient was considered statistically significant.

In addition to the conventional random-effects meta-analysis, we calculated 95% prediction intervals (PIs) to estimate the range within which the true effects of future studies are expected to fall, accounting for between-study heterogeneity. Prediction intervals were computed based on the method described by Riley 2011,[19] incorporating both the estimated between-study variance (τ^2) and the uncertainty in the pooled effect estimate. For subgroups with fewer than 3 studies, prediction intervals were not calculated due to limited degrees of freedom. The between-study variance τ^2 was estimated using the DerSimonian-Laird method, consistent with the primary random-effects model. Prediction intervals were calculated for the overall analysis to provide a more comprehensive interpretation of the potential variability in treatment effects across different settings.

All primary meta-analyses and meta-regression were conducted using the metafor package in R (v4.3.2); the robustness of these primary findings was further validated through a sensitivity analysis performed with Review Manager (RevMan v5.4.1).

Results

Study Selection

Nine studies met the eligibility criteria for inclusion in the meta-analysis (Figure 1). The systematic search initially yielded 2630 records. After the removal of 571 duplicates, 2059 records were screened by title and abstract. Of these, 1238 were excluded for being irrelevant to the research topic, and a further 795 were excluded for being non-conforming publication types (eg, reviews, conference abstracts), leaving 26 reports for which full-text articles were sought. Of these, 13 reports could not be retrieved. The remaining 13 full-text articles were assessed for eligibility, and 4 were excluded because data could not be extracted, resulting in the final inclusion of 9 studies.

Study Characteristics

This meta-analysis encompassed 9 randomized controlled trials published between 2007 and 2021, which were conducted across several countries (eg, USA, China, Poland, UK). The studies involved cohorts with ages ranging from 13.0 to 50.73 years and male proportions between 29.63% and 85.33%. Sample sizes varied from 34 to 111 participants, and the intervention duration spanned from 3 months to one year (with one cohort extending to 11 years). Various omega-3 formulations, including pure PUFAs and fish oil, were compared against placebo. Two studies specifically targeted

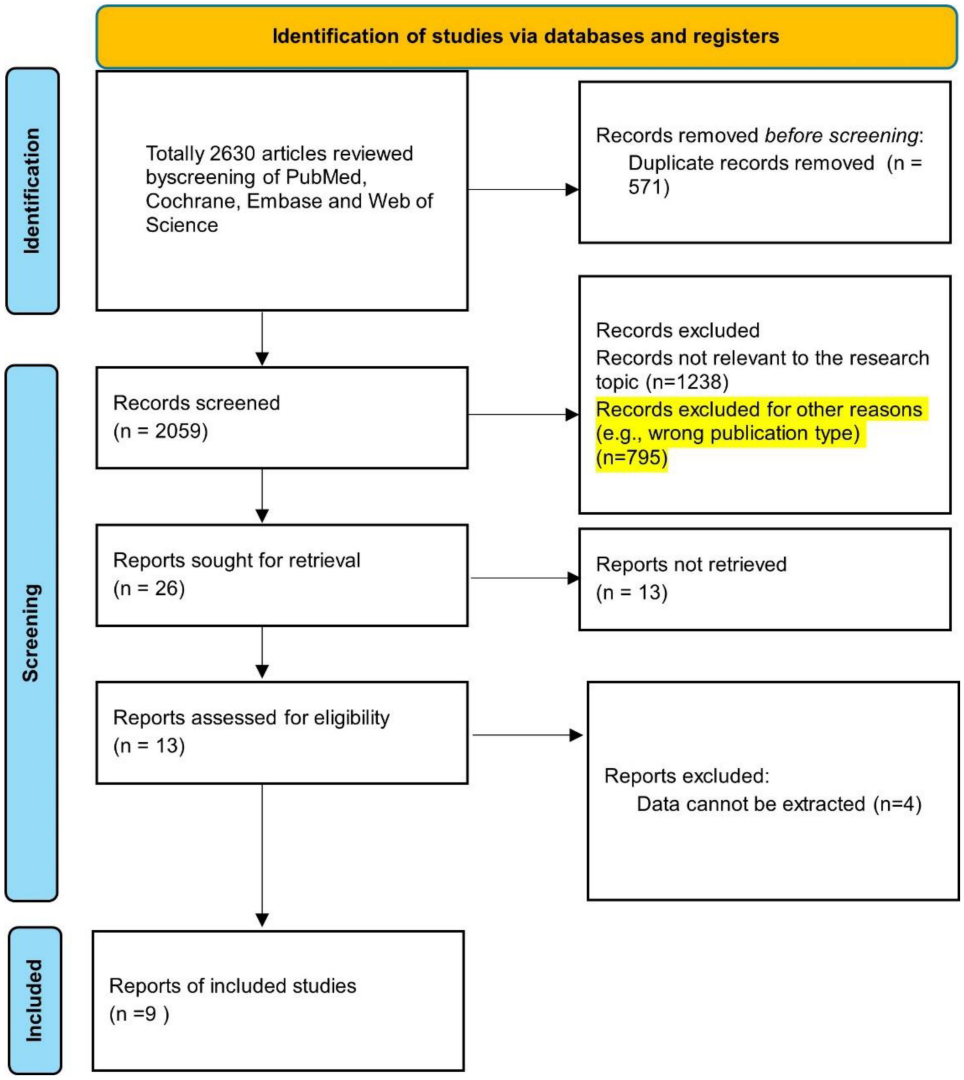

Figure 1 Flowchart of the study selection process for the systematic review and meta-analysis.

MASLD patients with concomitant diabetes (diabetes prevalence 100%). All studies reported TG as the primary outcome measure, with seven articles additionally reporting ALT, HDL, and LDL (Tables 1 and 2).

Bias Risk Assessment Results

The findings from the bias risk evaluation for the studies included are outlined in Figure 2. In general, the majority of the studies (7 out of 9) exhibited a low risk of bias. Two studies presented certain concerns, mainly because of insufficient details regarding the randomization procedure and the application of blinding.

Overall Effect of Omega-3 Fatty Acids on TG in Patients with MASLD

A total of nine RTCs involving 528 participants were analyzed to assess the impact of omega-3 on triglyceride concentrations. The analysis indicated a moderate degree of heterogeneity (I^2=22.5%). According to the random-effects meta-analysis, omega-3 fatty acids is associated with reduction in triglyceride levels among patients with MASLD (mean difference = −13.81 mg/dL, 95% confidence interval [−24.56, −3.06]). Comprehensive findings are displayed in Figure 3. For this purpose, we calculated a 95% prediction interval of [−35.36, 7.74] mg/dL. This interval encompasses zero, indicating that the actual effect of omega-3 fatty acids on triglycerides may vary significantly across different clinical settings or patient populations. The range of outcomes could span from clinically meaningful reductions to no discernible effect, or even slight increases.

Exploratory Subgroup Analysis Based on Diabetes Status

Stratified by diabetic status, the triglyceride-lowering effect of omega-3 was confined to patients without diabetes. In the non-diabetic MASLD subgroup (4 studies, n=214), a significant reduction was observed (MD = −15.78 mg/dL, 95% CI: −27.25, −4.31. However, due to the limited number of studies in each subgroup (only 2 studies in the diabetic subgroup), prediction intervals were not calculated as they would not provide meaningful estimates of the expected range of effects in future studies. In contrast, this effect was abolished in diabetic patients (2 studies, n=97), where the result was non-significant (MD = −16.71 mg/dL, 95% CI: −50.28, 16.85; P = 0.33) (Figure 4).

Meta-Regression Analysis of the Proportion of Individuals with Diabetes

To investigate whether the proportion of diabetic patients in studies influences effect sizes, we conducted a meta-regression analysis with this proportion as a covariate. Results revealed nonlinear relationship between the proportion of diabetic patients and the triglyceride-lowering effect of omega-3 (regression coefficient = 15.703, 95% CI [−81.8, 113.2], P = 0.752). This indicates that the prevalence of diabetes in study populations cannot explain the heterogeneity in omega-3 efficacy. This covariate explains an extremely low proportion of the heterogeneity between studies ($R^2 \approx 0\%$) (Figure 5).

Impact of Omega-3 on Other Metabolic Indicators in Patients with MASLD

This study additionally examined how omega-3 fatty acids influence liver enzyme concentrations and additional markers of lipid metabolism in MASLD. According to the meta-analysis findings, supplementation with omega-3 did not produce a significant change in ALT, HDL, or LDL values (Figure 6). In the ALT analysis, which included seven studies with 428 participants, no notable variation in ALT levels was observed between the omega-3 and control groups (mean difference = −1.44 IU/L, 95% CI [−7.89, 5.02]). A moderate level of heterogeneity was present across the studies (I^2 = 63%, P = 0.66). Regarding HDL, an evaluation of seven studies involving 454 patients found no significant impact of omega-3 supplementation on HDL concentrations (mean difference = −0.06 mg/dL, 95% CI [−2.79, 2.67]). There was substantial heterogeneity among the included studies (I^2 = 70%, P = 0.97). For LDL, the analysis of seven studies (452 patients) revealed no statistically significant difference in LDL levels between the omega-3 and control groups (mean difference = 0.26 mg/dL, 95% CI [−4.73, 5.24]). The analysis indicated minimal heterogeneity (I^2 = 14%, P = 0.92).

Table 1 Basic Characteristics of the Research Subjects

No.	Research Basic Information						Characteristics of the Study Population							
	Author	Year	Country	Study Design	Study Period	Follow-Up Period for Data Extraction	Total Sample Size (N)	Intervention Group Sample Size (N_I)	Control Group Sample Size (N_C)	Age (Years)	Male (%)	BMI (kg/m²)	Diabetes Prevalence Rate (%)	Provide T2DM Subgroup Data
1	Curtis K Argo[20]	2015.1	USA	Parallel trial	1 year	1 year	34	17	17	46.8	13 (38.2)	N/A	32.4	NO
2	John Climax[21]	2020.8	UK	Parallel trial	16 weeks	16 weeks	93	31	30	48.5 ± 12.4	63 (66.7)	32.8 ± 4.2	36.88	NO
3	Wojciech Janczyk[22]	2015.6	Polish	Parallel trial	24 weeks	24 weeks	64	30	34	13.0 ± 3.04	65 (85.53)	28.7 ± 4.44	N/A	NO
4	Vali Musazade[23]	2021.8	N/A	Parallel trial	12 weeks	12 weeks	43	21	21	44.09±5.27	22 (51.16)	N/A	N/A	NO
5	Arun J. Sanyal[24]	2014.8	USA	Parallel trial	12 months	12 months	174	64	55	48.63 ± 12.04	95 (54.60)	34.87 ± 6.36	34.98	NO
6	Fatemeh Shojasaadat[25]	2018.12	Iran	Parallel trial	12 weeks	12 weeks	104	38	34	41.71 ± 8.81	57 (54.81)	31.27 ± 3.61	N/A	NO
7	L. Spadaro[26]	2007.12	N/A	Parallel trial	6 months	6 months	36	18	18	50.73 ± 11.31	19 (52.78)	30.55 ± 4.07	N/A	NO
8	Srinivasan Dasarathy[27]	2015.2	N/A	Parallel trial	48 weeks	48 weeks	37	18	19	50.6±9.8	8 (29.63)	26.8±3.0	100	Yes
9	Zahra Orang[28]	2018.11	N/A	Parallel trial	12 weeks	12 weeks	60	30	30	48.72±8.23	15 (50.0)	30.03±3.94	100	Yes

Table 2 Intervention Characteristics and Outcomes of the Study Population

No.	Research Basic Information	Interventions and Control Measures			Outcome Metric Data							
	Author	Omega-3'tape	Total Daily Dose (mg/day)	Control Group Type	TG_E_M/SD (IG)	TG_E_M/SD (CG)	ALT_E_M/SD (IG)	ALT_E_M/SD (CG)	HDL-C_E_M/SD (IG)	HDL-C_E_M/SD (CG)	LDL-C_E_M/SD (IG)	LDL-C_E_M/SD (CG)
1	Curtis K Argo[20]	n-3 fish oil	3000 mg / day	Capsules containing predominantly soybean oil	132.2 ±45.4mg/dl	187.7 ±89.2mg/dl	56.7 ±28.3U/L	52.8±31.0U/L	N/A	N/A	128.2 ±34.8mg/dl	124.1 ±36.3mg/dl
2	John Climax[21]	Epeleuton	2g/day	Light liquid paraffin	208.4 ± 103.2mg/dl	186.2 ± 92.5mg/dl	83.2±47.6U/L	81.8±35.0U/L	41.0 ± 14.1mg/dl	42.0 ± 8.1mg/dl	132.3 ± 36.3mg/dl	135.7 ± 43.0mg/dl
3	Wojciech Janczyk[22]	EPA+DHA	450-1300 mg/day	Sunflower oil	91.0±35.6mg/dl	97.5±34.1mg/dl	48.5±23.0U/L	53.5±44.4U/L	44±8.9mg/dl	39.5±8.9mg/dl	122±40.0mg/dl	109.5±31.1mg/dl
4	Vali Musazade[23]	Camelina sativa oil	20g	Sunflower oil	158.27±30.21mg/dl	180.76±36.36mg/dl	29.09±5.65IU/L	32.33±3.86IU/L	44.40±7.18mg/dl	40.57±4.16mg/dl	82.84±21.91mg/dl	102.94±42.20mg/dl
5	Arun J. Sanyal[24]	EPA	2700 mg/d	N/A	146.5±43.41mg/dl	151±45.19mg/dl	70.5±37.26Iu/L	59.0±33.33IU/L	43.5±5.04mg/dl	45±7.41mg/dl	123±22.96mg/dl	124±22.96mg/dl
6	Fatemeh Shojasaadat[25]	PUFA	1500 mg/day	No intervention	165.85±80.75mg/dl	189.35±88.7mg/dl	35.28±21.0IU/L	31.06±15.49UI/L	45.14±5.75mg/dl	44.32±8.0mg/dl	107.94±22.8mg/dl	102.70±21.90mg/dl
7	L. Spadaro[26]	PUFA	2 g/day	N/A	110 ± 39.1mg/dl	135 ± 52mg/dl	39.5 ± 14U/l	55.5 ± 31U/l	46.8 ± 12.9mg/dl	48 ± 8.7mg/dl	N/A	N/A
8	Srinivasan Dasarathy[27]	PUFA	N/A	Corn oil	211.5±160.8mg/dl	177.4±66.0mg/dl	N/A	N/A	N/A	N/A	N/A	N/A
9	Zahra Orang[28]	Omega-3 supplement	2g/d	Placebo capsules	124.75 ± 63.52mg/dl	152.32 ± 81.49mg/dl	N/A	N/A	46.60 ± 7.82mg/dl	53.28 ± 9.26mg/dl	92.23 ± 22.25mg/dl	94.00 ± 25.49mg/dl

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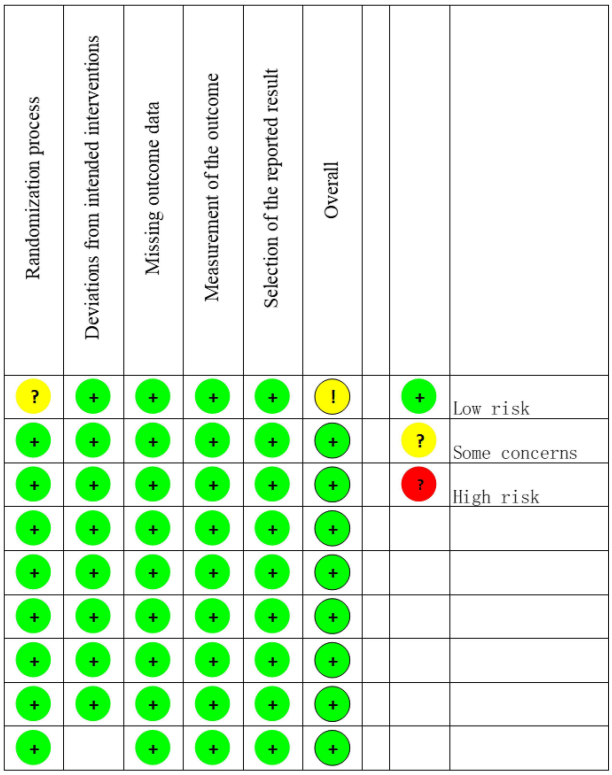

Figure 2 Risk of bias summary for the included randomized controlled trials.

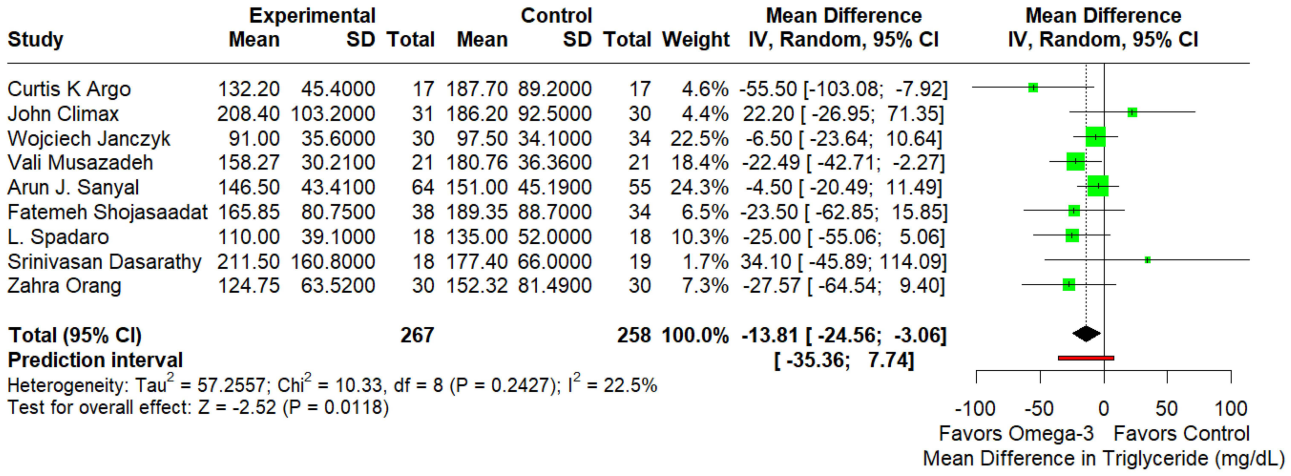

Figure 3 Forest plot for the effect of omega-3 supplementation on triglyceride levels in patients with MASLD. The 95% prediction interval is shown, indicating the expected range of true effects in future study settings.
Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; MD, mean difference; CI, confidence interval.

Discussion

Key Findings Summary

This review found that although omega-3 supplementation was associated with reduced triglyceride levels in the overall MASLD population, the wide 95% prediction intervals spanning the zero effect line preclude definitive conclusions regarding its efficacy in future clinical settings. The moderate overall reduction in triglycerides observed in our analysis aligns with the 2021 meta-analysis, which reported a similar effect size (MD: −28.57 mg/dL) across a broader MASLD cohort.[29] However,

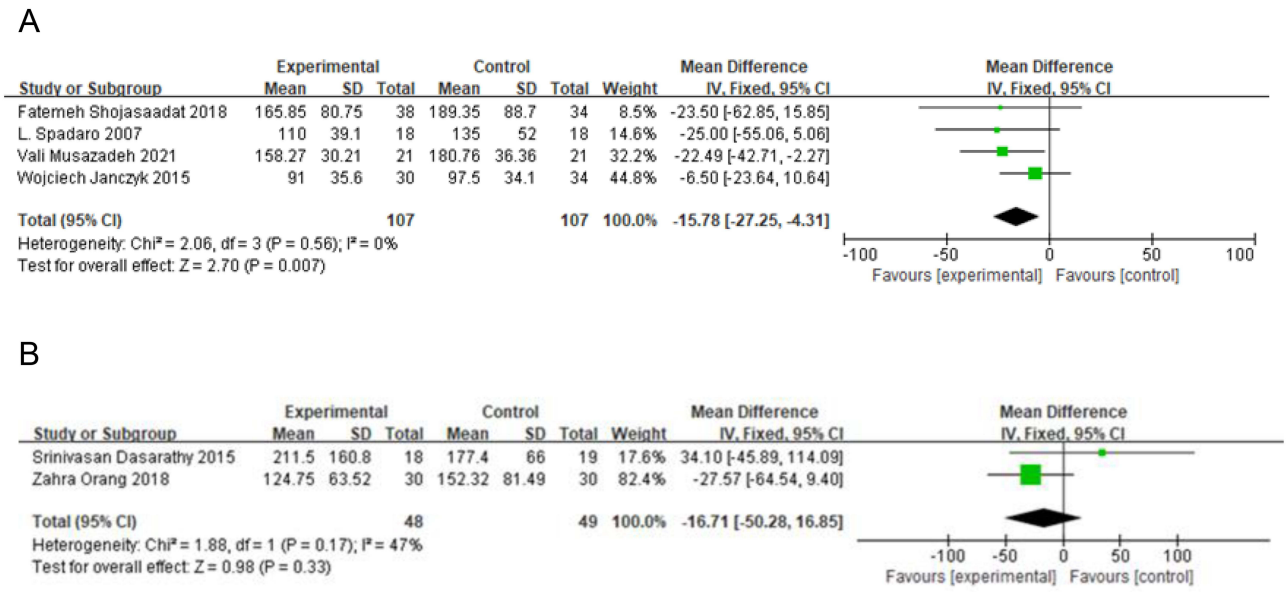

Figure 4 Forest plot of subgroup analysis based on diabetic status for the effect of omega-3 supplementation on triglyceride levels. Subgroups: (**A**) patients with MASLD without diabetes; (**B**) patients with MASLD and concomitant diabetes.

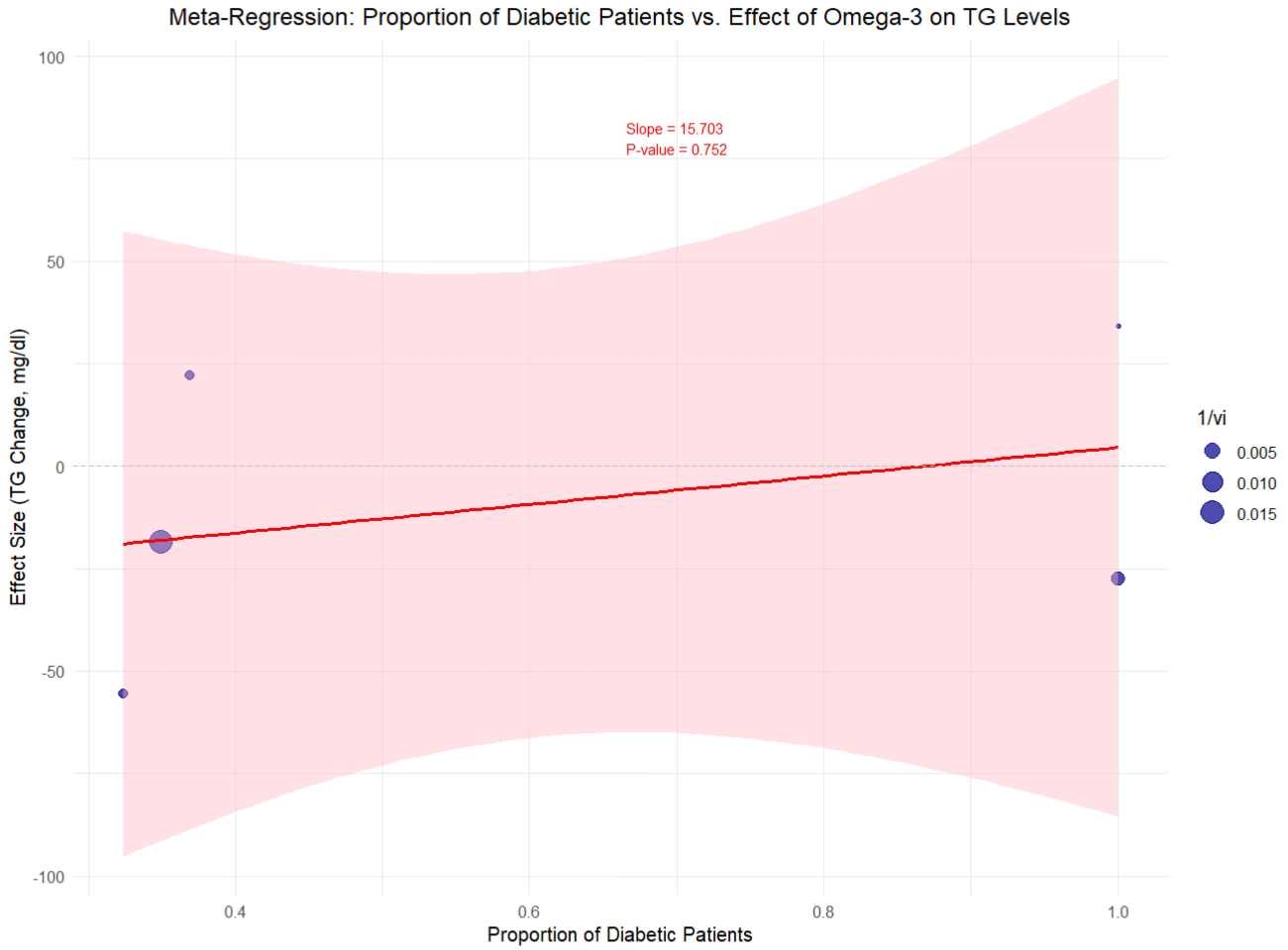

Figure 5 Meta-regression bubble plot evaluating the association between the proportion of participants with diabetes and the effect size (mean difference in triglyceride levels). The size of the bubbles corresponds to the weight of each study in the analysis.

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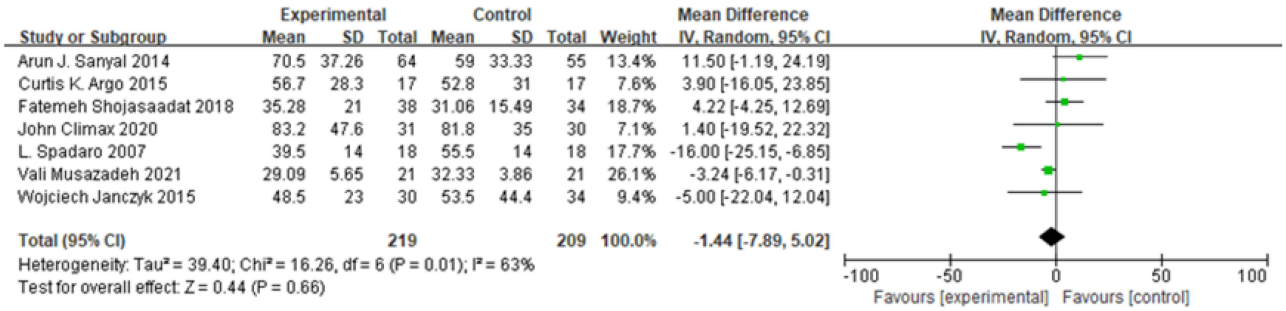
A



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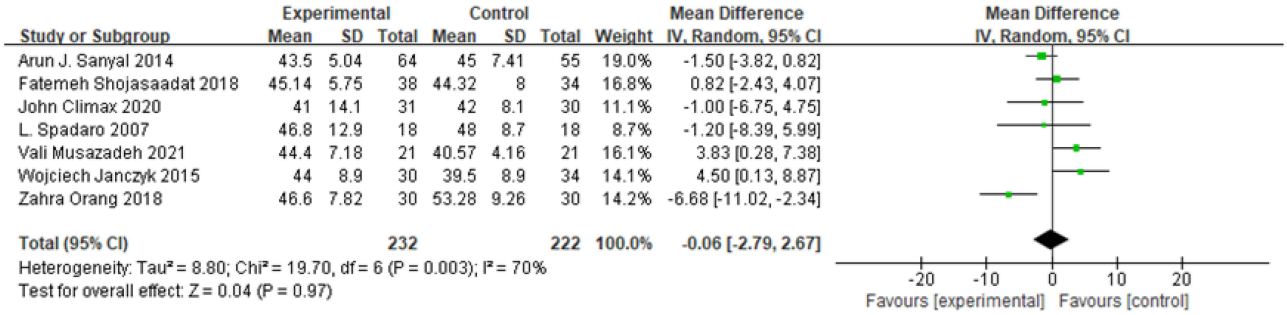

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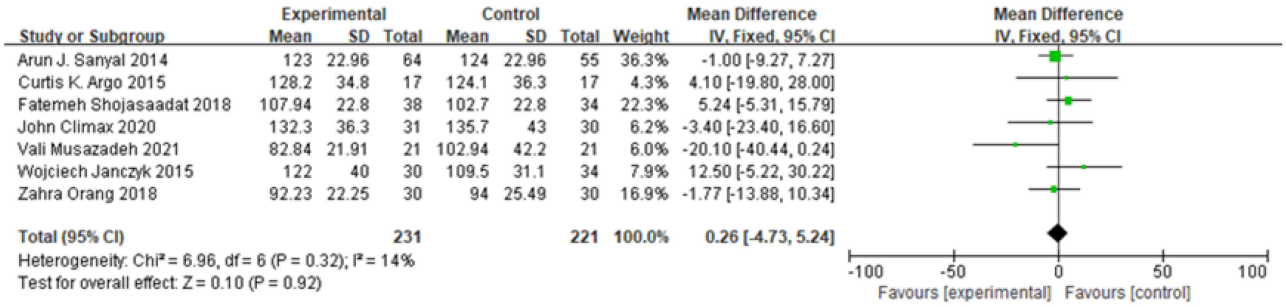

Figure 6 Forest plots for the effects of omega-3 supplementation on secondary outcomes. (**A**) alanine aminotransferase (ALT) levels; (**B**) high-density lipoprotein (HDL) cholesterol levels; (**C**) low-density lipoprotein (LDL) cholesterol levels.

our study extends this understanding by specifically examining the role of diabetic status as a potential effect modifier—an aspect not thoroughly investigated in prior syntheses. This association was not observed in the diabetic subgroup. Meta-regression analysis failed to confirm a significant modifying effect of diabetes prevalence, and no improvements in ALT or other lipid markers were noted.[30] These findings suggest that the potential role of omega-3 fatty acids in MASLD may not be universal but rather influenced by underlying metabolic states, with the specific mechanisms requiring comprehensive elucidation.

Interpretation of Results and Discussion of Mechanisms

The triglyceride-lowering effect of omega-3 fatty acids in MASLD is attributed to their influence on master transcriptional regulators—including PPARα, PPARγ, SREBP-1, and ChREBP—that orchestrate fundamental hepatic lipid metabolic pathways.[31,32] Specifically, n-3 PUFAs act as potent ligands for PPARα, triggering its activation and the subsequent upregulation of genes involved in fatty acid oxidation.[32,33] Beyond enhancing β-oxidation, n-3 PUFAs concurrently suppress

de novo lipogenesis by inhibiting the expression and maturation of SREBP-1, and by reducing the activity of ChREBP, thereby curbing hepatic glycolysis and lipid synthesis.[34–37] Additionally, ω-3 fatty acids are rich in ALA, which may increase resting energy expenditure by upregulating uncoupling protein 3 mRNA and peroxisomal acyl-CoA oxidase expression.[38] However, in diabetic MASLD patients, severe insulin resistance, chronic inflammation, and oxidative stress may impair these pathways, leading to the failure of omega-3 therapy.[39] The use of n-3 PUFA may also result in the failure of beneficial effects by activating PPARα, increasing oxidative stress, and thereby enhancing hepatic mitochondrial fatty acid oxidation.[40,41]

The lack of effects on ALT, HDL, and LDL may reflect the selective action of omega-3 fatty acids. Their lipid-lowering effects primarily target the triglyceride metabolic pathway, including promoting fatty acid oxidation and reducing lipogenesis by activating PPAR-α and inhibiting SREBP-1c,[42,43] while exerting weaker direct effects on cholesterol reverse transport and synthesis.[44,45] ALT levels exhibit spontaneous fluctuations and may not respond significantly to short-term intervention.[46] Furthermore, prior studies suggest that the beneficial effects of omega-3 on liver enzymes may require longer treatment durations to manifest,[47] and the average treatment duration in the trials included in this study may have been insufficient to capture such changes. Additionally, the effects of omega-3 on HDL and LDL may be influenced by numerous factors, such as the different types of omega-3 supplements used and the varying types of control groups employed.[48] The studies included in this meta-analysis exhibited differences in these factors, which may explain why no significant overall effect on the aforementioned indicators was detected.

Comparison with Existing Evidence

Our findings partially align with existing evidence. Similar to meta-analyses by Lee et al and Liu et al, we observed that omega-3 significantly reduces triglyceride levels in MASLD patients.[29,49] For NAFD patients with concomitant diabetes, no relevant meta-analysis literature was identified at present, and our meta-analysis included only two articles. However, our meta-regression explicitly demonstrated that the proportion of diabetic patients was not a significant effect modifier, offering a new perspective for understanding the heterogeneity observed in previous meta-analyses. Regarding liver enzyme improvement, our negative findings align with those of Kim et al, who also reported heterogeneity in the efficacy of omega-3 for ALT improvement across studies.[50] This inconsistency may stem from differences in study population characteristics, omega-3 formulation type (EPA/DHA ratio), or baseline MASLD severity.

Clinical Significance and Application

This analysis provides evidence supporting the adjunctive use of omega-3 fatty acids for triglyceride management in non-diabetic MASLD patients, aligning with the American Heart Association's recommendations for managing hypertriglyceridemia.[42] For MASLD patients with comorbid diabetes, a therapeutic strategy combining omega-3 fatty acids with agents like GLP-1 receptor agonists—which robustly improve metabolic and hepatic parameters—may be warranted, as omega-3 monotherapy appears insufficient.[51] Consistent with EASL guidelines, our results indicate that omega-3 is not a first-line option for MASLD, given its lack of efficacy on ALT and key lipid parameters (HDL, LDL), which are crucial for comprehensive metabolic and inflammatory control.[52] Overall, while our meta-analysis indicates a beneficial association between the two, interpretation of these findings requires caution. Some studies yielded neutral results. Furthermore, the clinical relevance of the observed reduction in TG levels warrants further investigation in long-term outcome studies.

Research Limitations

This study has several limitations. First, the limited number of included studies, particularly the small sample size in the diabetes subgroup, may have affected statistical power. Second, heterogeneity existed across studies regarding omega-3 dosage, treatment duration, and patient characteristics. Although random-effects models and meta-regression were employed for adjustment, residual confounding may still exist. Third, primary outcomes were based on laboratory markers rather than clinical endpoints (eg, liver fibrosis progression or cardiovascular events), leaving long-term benefits uncertain. Finally, incomplete reporting of baseline metabolic characteristics in some studies limited more refined subgroup analyses.

Future Research Directions

Future research should focus on the following areas: (1) Exploring high-dose omega-3 therapy or combination therapy with other medications (such as insulin sensitizers) in diabetic MASLD patients; (2) Evaluating the impact of omega-3 on hepatic histological outcomes through meta-analyses of individual participant data; (3) Predicting omega-3 response based on biomarkers (such as baseline triglyceride levels or genotypes) to enable personalized treatment.

Conclusion

In conclusion, this meta-analysis demonstrates that omega-3 supplementation is associated with reduced TG levels specifically in non-diabetic patients with MASLD, while current evidence remains insufficient to support its efficacy in those with coexisting diabetes. Therefore, clinicians might consider omega-3 primarily for triglyceride management in non-diabetic MASLD patients, whereas its routine use in diabetic MASLD is not supported by current evidence and requires further investigation.

Data Sharing Statement

Data sharing is not applicable to this article as no new datasets were generated or analyzed during this meta-analysis.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Specifically, the individual contributions are as follows:

[Lan Li]: Conceptualization, Methodology, Formal Analysis, Writing - Original Draft.

[Cong Cong]: Data Curation, Investigation, Software, Validation.

[Xiaolan Zhang]: Writing - Review & Editing, Supervision, Project Administration.

[Xiaoxia Zhang]: Resources, Visualization.

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Disclosure

The authors declare that they have no competing interests.

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