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Review

Effectiveness of ω-3 Supplementation on Biochemical, Clinical, and Inflammatory Parameters in Patients with Diabetes: A Systematic Review and Meta-analysis

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A B S T R A C T

Omega-3 (*n*–3) polyunsaturated fatty acids, including marine-derived eicosapentaenoic acid and docosahexaenoic acid, as well as plant-derived formulations rich in α-linolenic acid, have been proposed as adjunctive therapy in diabetes because of their potential effects on lipid metabolism, inflammation, oxidative stress, and neuroprotection. Searches were performed in MEDLINE, EMBASE, SCOPUS, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, and Web of Science through January 2026. Outcomes included lipid parameters, glycemic markers, inflammatory and oxidative stress biomarkers, and corneal nerve branch density (CNBD). Random-effects models were applied. Eleven trials met the criteria for quantitative synthesis. Pooled analyses showed no significant effects on triglycerides, low-density or high-density lipoprotein cholesterol, glycated hemoglobin, fasting plasma glucose, or inflammatory and oxidative stress biomarkers, with substantial heterogeneity across several outcomes. In contrast, fasting insulin and homeostasis model assessment of insulin resistance were significantly reduced with low heterogeneity, and CNBD showed a consistent improvement with no detectable heterogeneity, suggesting potential benefits for insulin sensitivity and small-fiber nerve integrity. Overall, the certainty of evidence ranged from very low to low, mainly because of heterogeneity, imprecision, and small sample sizes. ω-3 supplementation demonstrated limited effects on most metabolic and inflammatory outcomes in diabetes. Observed improvements in insulin sensitivity indices and CNBD warrant further investigation in adequately powered trials with longer follow-up. These findings should be interpreted as hypothesis-generating rather than confirmatory.

Keywords: omega-3 fatty acids, diabetes mellitus, insulin sensitivity, lipid metabolism, glycemic control, inflammation, corneal nerve branch density, systematic review, meta-analysis

Abbreviations: CNBD, corneal nerve branch density; CRP, C-reactive protein; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; GSH, glutathione; hs-CRP, high-sensitivity C-reactive protein; MD, mean difference; MDA, malondialdehyde; NO, nitric oxide; QUICKI, Quantitative Insulin Sensitivity Check Index; SMD, standardized mean difference; TAC, total antioxidant capacity.

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Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin resistance, or a combination of both mechanisms [1]. This metabolic dysregulation affects not only glucose homeostasis but also lipid and protein metabolism, contributing to systemic metabolic dysfunction. When inadequately controlled, diabetes leads to progressive, often asymptomatic, damage to multiple organs and systems [2]. Long-term complications most commonly involve the kidneys (diabetic nephropathy), retina (diabetic retinopathy), peripheral and autonomic nervous systems (diabetic neuropathy), and the cardiovascular system, with cardiovascular disease remaining the leading cause of morbidity and mortality among individuals with diabetes [3].

The global burden of diabetes has increased markedly over the past few decades. By 2022, >800 million individuals worldwide were living with diabetes, compared with ~200 million in 1990 [4]. During this period, adult prevalence nearly doubled, rising from 7% to 14%, with a disproportionate impact observed in low- and middle-income countries [5]. This rapid increase underscores the urgent need for effective preventive strategies and adjunctive therapeutic approaches applicable across different types of diabetes. The cornerstone of diabetes management remains nonpharmacological intervention, including dietary modification to optimize glycemic control, lipid profiles, and blood pressure, as well as regular physical activity to improve insulin sensitivity, manage body weight, and reduce the risk of complications [6]. When glycemic targets are not achieved, pharmacological therapy is initiated. This includes insulin therapy—essential in type 1 diabetes and advanced type 2 diabetes—as well as oral and injectable glucose-lowering agents, such as metformin, sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, and incretin-based therapies [7,8]. Treatment selection is guided by individual patient characteristics, diabetes subtype, and comorbidities. Long-chain omega-3 (*n*–3) PUFAs, specifically EPA and DHA, are predominantly obtained from fatty fish such as salmon, tuna, and mackerel, or from purified fish oil supplements [9]. Upon ingestion, EPA and DHA are incorporated into cell membrane phospholipids and metabolized through cyclooxygenase and lipoxygenase pathways into specialized proresolving lipid mediators, including resolvins and protectins. These mediators exert anti-inflammatory, antioxidant, and cytoprotective effects, modulating inflammatory signaling pathways implicated in the pathogenesis of chronic metabolic diseases [10]. Given the central roles of chronic low-grade inflammation and oxidative stress in the development and progression of diabetes and its associated complications, ω-3 fatty acids have attracted significant interest as a potential adjunctive therapy. In addition to marine-derived EPA and DHA, ω-3 fatty acids also include plant-derived α-linolenic acid (ALA), which is present in sources such as flaxseed and perilla oils. Although the biological effects of ALA may differ from those of EPA and DHA because of limited conversion to long-chain metabolites, these formulations have also been investigated in patients with diabetes and were therefore included in the present review.

International guidelines generally recommend an intake of ~250 to 500 mg/d of EPA and DHA for the general population to support cardiovascular health, whereas higher pharmacological doses may be used under clinical supervision for specific indications, such as severe hypertriglyceridemia. [11]. Supplementation enables standardized dosing and may reduce exposure to environmental contaminants in certain fish species, provided high-quality preparations are used [12]. In patients with diabetes, particularly those with type 2 diabetes, ω-3 supplementation has been associated with improvements in lipid profiles, and most consistently reductions in triglyceride concentrations, with modest or neutral effects on other lipid fractions [13]. ω-3 fatty acids have also been reported to exert anti-inflammatory effects by downregulating proinflammatory cytokines, such as TNF-α, and by enhancing antioxidant capacity, potentially mitigating oxidative stress [14]. However, evidence regarding their effects on glycemic control, including fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c), remains inconsistent and appears to vary by diabetes subtype, dosage, formulation, and duration of supplementation [15].

Despite increasing interest, the clinical effects of ω-3 supplementation on biochemical, inflammatory, and functional outcomes across different forms of diabetes remain heterogeneous and incompletely understood. Existing trials differ substantially with respect to diabetes type (type 1, type 2, or gestational diabetes), ω-3 formulation (EPA, DHA, or mixed), dosage, cosupplementation strategies, and follow-up duration, resulting in marked clinical and methodological heterogeneity. Therefore, systematic review and meta-analysis are warranted to synthesize the available evidence regarding the effects of ω-3 supplementation on metabolic, inflammatory, and clinical parameters in patients with diabetes [16]. Given the heterogeneity of populations and interventions, the present synthesis is intended to be exploratory and hypothesis-generating, with the aim of clarifying current evidence and informing the design of adequately powered clinical trials.

Methods

Protocol and registration

This systematic review and meta-analysis were conducted and reported in accordance with the PRISMA 2020 guidelines [17]. The study protocol was prospectively registered in PROSPERO under the registration number CRD420250655364.

Literature search

A comprehensive and systematic literature search was performed across multiple electronic databases, including MEDLINE (via PubMed), EMBASE, SCOPUS, the Cochrane Central Register of Controlled Trials, the Cumulative Index to Nursing and Allied Health Literature, and Web of Science. The search covered all records from database inception through January 2026. Randomized controlled trials and controlled clinical trials published in English or Spanish were considered eligible.

Search terms were applied in various combinations and included: "omega-3 supplementation," "omega-3 therapy," "omega-3 fatty acids," "eicosapentaenoic acid," "docosahexaenoic acid," "type 1 diabetes," "type 2 diabetes," and "gestational diabetes." The complete search strategy for each database is provided in Supplemental Table 2. Two reviewers (JJV-F and ML-C) independently screened titles and abstracts of all

retrieved records. Full-text articles were obtained for studies considered potentially eligible by either reviewer. Discrepancies were resolved by discussion, and when consensus could not be reached, a third reviewer (MB-V) adjudicated.

Study selection

Studies were considered eligible for inclusion if they met the following criteria:

1. Population: adults or pregnant women diagnosed with type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes mellitus, or individuals at high risk of diabetes, according to established diagnostic criteria.
2. Intervention: supplementation with ω-3 PUFAs, including EPA, DHA, or combined formulations, administered at any dose or duration.
3. Comparator: placebo, standard care, or control intervention without ω-3 supplementation.
4. Outcomes: at least one reported biochemical, metabolic, inflammatory, oxidative stress, or functional outcome, including lipid parameters, glycemic markers, insulin resistance indices, inflammatory or oxidative stress biomarkers, or corneal nerve parameters.
5. Study design: randomized controlled trials or controlled clinical trials.

Studies were excluded if they met any of the following criteria: narrative or systematic reviews, meta-analyses, case reports or case series, editorials, letters to the editor, conference abstracts without full data, or nonhuman studies; inclusion of participants without diabetes or with metabolic disorders unrelated to diabetes; interventions not involving ω-3 fatty acids or where the effect of ω-3 supplementation could not be isolated; absence of a comparator group; or insufficient quantitative data to permit extraction.

Data extraction and risk of bias assessment

Two reviewers (MB-V and ML-C) independently extracted data from each included study using a standardized data extraction form. Extracted information included author(s) and year of publication; study design; sample size; geographic location; participant characteristics (age, sex distribution, and diabetes type); details of the intervention (ω-3 formulation, dose, duration, and route of administration); comparator characteristics; outcome measures; and corresponding statistical data.

Methodological quality and risk of bias were assessed using the Cochrane Risk of Bias (RoB) tool [18], which evaluates the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. Each domain was classified as low, unclear, or high risk of bias. Disagreements were resolved by discussion or consultation with a third reviewer (JPL-G). Interrater agreement was quantified using Cohen's kappa statistic, indicating substantial agreement ($\kappa = 0.79$).

Data synthesis and statistical analysis

Data synthesis focused on biochemical, metabolic, inflammatory, and functional outcomes most frequently reported across studies, including triglycerides, LDL cholesterol, HDL cholesterol, VLDL cholesterol, non-HDL cholesterol (mg/dL), FPG (mg/dL), glycated hemoglobin (HbA1c, %), fasting insulin (μIU/mL), HOMA-IR, Quantitative Insulin Sensitivity Check Index (QUICKI), inflammatory and oxidative stress biomarkers [C-reactive protein (CRP)/high-sensitivity CRP (hs-CRP), malondialdehyde (MDA), total antioxidant capacity (TAC), glutathione (GSH), nitric oxide (NO)], and corneal nerve branch density (CNBD, branches/mm^2).

Clinical heterogeneity was anticipated because of differences in diabetes subtype, ω-3 formulation (EPA, DHA, or mixed), dosage (0.5–8 g/d), cosupplementation strategies (e.g., vitamin D, curcumin, aspirin, and vitamin E), and intervention duration (6 wk to 5 y). For outcomes reported in identical units, treatment effects were expressed as mean differences (MDs). The standardized mean difference (SMD) was used only for outcomes measured with different scales, such as CNBD. Pooled estimates were calculated using a random-effects model (DerSimonian–Laird method) to account for expected clinical and methodological heterogeneity.

Statistical heterogeneity was assessed using the χ^2 test and quantified with the I^2 statistic; values >75% were interpreted as indicating substantial heterogeneity. When 10 or more studies were available, funnel plots were visually inspected to explore potential publication bias. Exploratory subgroup analyses were conducted according to intervention duration (short: 1–12 wk; intermediate: 13–26 wk) when data permitted. Exploratory metaregression analyses were performed to assess the potential influence of age, ω-3 dose, intake frequency, and sex distribution; these analyses were explicitly considered hypothesis-generating because of the limited number of studies, potential collinearity among predictors, and absence of correction for multiple testing.

All statistical analyses were performed using Review Manager (RevMan) version 5.4 (Cochrane Collaboration) and Comprehensive Meta-Analysis software. Given the substantial clinical and methodological heterogeneity across included trials, all pooled analyses were prespecified as exploratory and hypothesis-generating, and results should be interpreted with caution regarding clinical significance and generalizability.

Certainty of evidence assessment

The certainty of evidence for each meta-analyzed outcome was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [19]. Evidence was rated as high, moderate, low, or very low based on RoB, inconsistency, indirectness, imprecision, and publication bias. Although several trials demonstrated acceptable methodological quality, certainty was frequently downgraded because of extreme inconsistency (I^2 >75%), serious imprecision related to small sample sizes and wide confidence intervals (CIs), and indirectness arising from heterogeneous populations, formulations, and intervention durations. Consequently, the overall certainty of evidence for most biochemical and inflammatory outcomes ranged from low to very low, whereas CNBD achieved low certainty with consistent findings across studies. GRADE assessments were conducted using GRADEpro, with results summarized in the "Summary of Findings" table (Supplemental Table 3) [19,20].

Results

Study selection

The electronic search identified 268 records, of which 22 articles were retrieved for full-text assessment [21–42]. The study selection process is presented in Figure 1. No additional eligible studies were identified through clinical trial registers. A total of 11 randomized controlled trials met the inclusion criteria and were included in the quantitative synthesis [23,27,28,30,33–35,37,40–42]. Excluded full-text studies and reasons for exclusion are provided in Supplemental Table 1. An updated search through January 2026 did not identify any additional studies meeting the eligibility criteria for quantitative synthesis. A total of 268 records were identified through database searching, and 2 additional records were identified through other sources. After screening and eligibility assessment, 22 studies were included in the systematic review, of which 11 were eligible for quantitative synthesis.

Study characteristics

Table 1 summarizes the characteristics of the 22 included studies [21–42], which evaluated ω-3 fatty acids administered alone or in combination with cointerventions (e.g., vitamin D, curcumin, aspirin, or vitamin E) compared with placebo or standard care in participants with type 1 diabetes, type 2 diabetes, gestational diabetes, or individuals at high risk of diabetes.

Among the 22 included studies, 1 study exclusively enrolled individuals with type 1 diabetes, 10 enrolled individuals with type 2 diabetes, 4 enrolled women with gestational diabetes, 2 included individuals with prediabetes or at high risk of developing type 2 diabetes, and 1 large trial enrolled participants with diabetes irrespective of subtype. The studies were conducted between 1992 and 2022 across several countries, including the United States, Germany, Australia, Iran, the United Kingdom, China, Canada, Brazil, and South Korea. Overall, 20,013 participants were enrolled (experimental, n = 10,013; control, n = 10,000), with mean ages ranging from 30 to 65 y and follow-up durations ranging from 6 wk to 5 y. Interventions included marine-derived EPA/DHA preparations as well as plant-derived ω-3 formulations, including perilla oil and flaxseed oil, administered at doses ranging from 500 mg/d to 8 g/d. Control interventions included olive oil, sunflower oil, liquid paraffin, and cornstarch. Outcomes assessed across studies included glycemic indices, lipid parameters, inflammatory and oxidative stress biomarkers, vascular and renal outcomes, periodontal outcomes, corneal nerve measures, and patient-reported outcomes. Eleven studies provided sufficient comparable data for quantitative synthesis [23,27,28,30,33–35,37,40–42], whereas the remaining studies contributed to the qualitative synthesis.

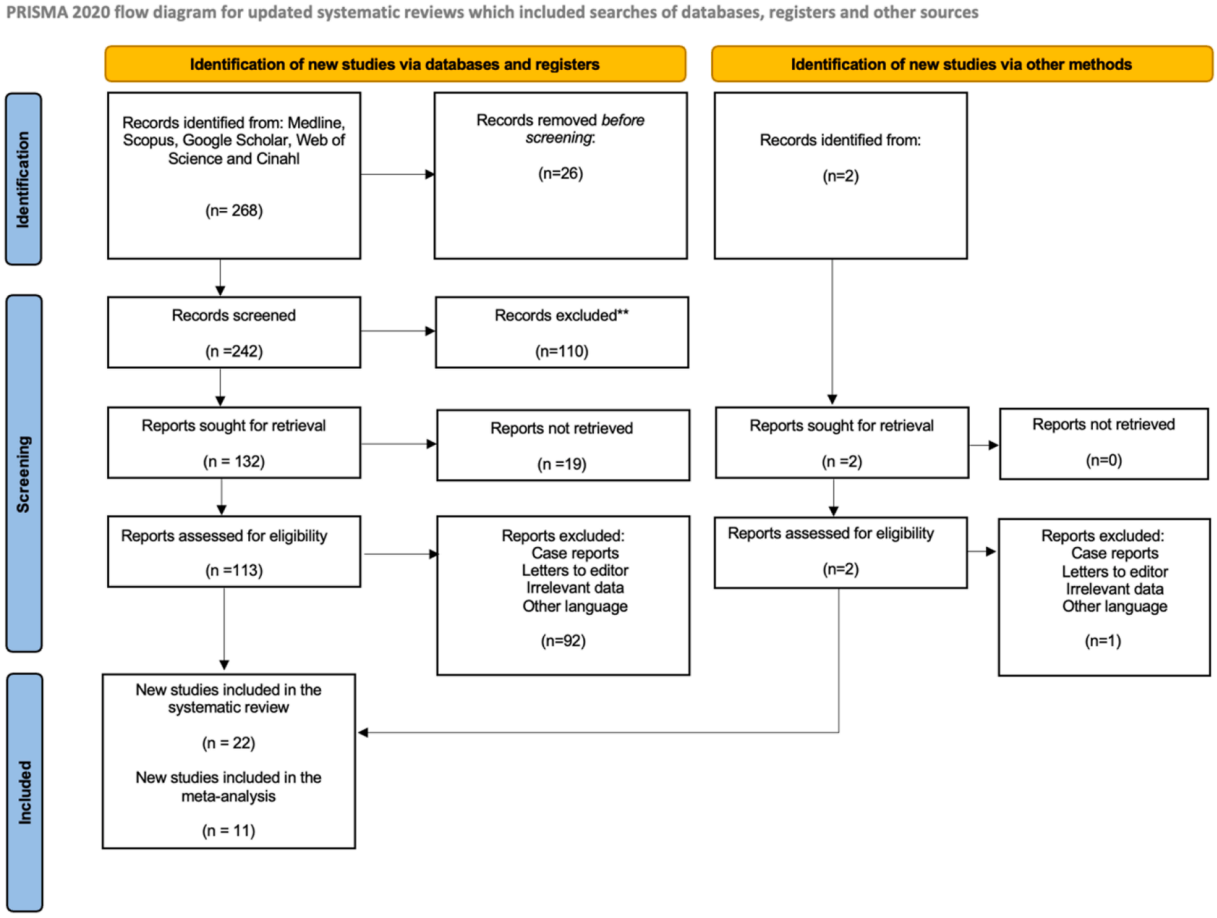


FIGURE 1. PRISMA flow diagram of study selection for the systematic review and meta-analysis of ω-3 supplementation in individuals with diabetes.

TABLE 1
Characteristics of the included studies

Author	Country	Population		Intervention		Outcomes	Follow -up	Results
		Sample size (*n*)	Patients mean (SD)	Intervention	Characteristics/dose			
De Boer et al. [21]	United States	CG:320 EG:370	CG: 67.5 (6.9) EG: 67.4 (7.3) Adult patients with type 2 diabetes Adults diagnosed with type 2 diabetes mellitus (T2DM)	CG: 2 placebos EG: vitamin D3 and ω-3 fatty acids	CG: Inert placebo for 5 y. EG: vitamin D3 (cholecalciferol, 2000 IU) and ω-3 fatty acids (fish oil, 1-g capsules containing 465 mg EPA and 375 mg DHA), administered for 5 y	eGFR change ≥40% eGFR decline/ kidney failure/death ≥40% eGFR decline Doubling of ACR ≥30 mg/g Adverse events	5 y	EGFR: $P = 0.26$ Not significant (Vit D vs. P: –12.3 vs. –13.1; ω-3 vs. *P*: −12.2 vs. –13.1) Not significant (Vit D HR 0.92; ω-3 HR 1.11) Not significant Vit D trend 1.34 ($P = 0.05$); ω-3 NS Kidney stones: Vit D 32 vs. P 26; GI bleeding: ω-3 28 vs. P 17
Stirban et al. [22]	Germany	CG:17 EG:17	CG: 56.8 (8.3) EG: 56.8 (8.3) Subjects with type 2 diabetes mellitus and no history of major cardiovascular events	CG: placebo EG: ω-3 fatty acids	CG: placebo capsules containing olive oil and 4 mg (6 IU) of vitamin E per capsule, for 6 wk. EG: 2 capsules of n23 FA capsules daily; the 1-g gel capsules were oral and liquid-filled and contained 460 mg EPA ethyl ester, 380 mg DHA ethyl ester, and 60 mg of other n23 FAs for a total of 900 mg n23 FAs and 4 mg (6 IU) of vitamin E per capsule, for 6 wk.	FMD RH	6 wk	FMD: $P = 0.03$ RH: $P = 0.04$
Thota et al. [23]	Australia	PL:19 CC:20 FO:20 CC-FO:22	PL:50 (2.5) CC:55 (2.8) FO:58 (2.5) CC-FO: 57 (2.2) Participants with a high risk of developing diabetes or with impaired fasting glucose or impaired glucose tolerance	PL: placebo tablets CC: curcumin tablets FO: LC*n*–3 PUFA CC-FO: double active (curcumin plus LC*n*–3 PUFA)	PL: 2 × placebo tablets matching for curcumin Plus 2 × 1000 mg corn oil capsules per day CC: 2 × 500 mg curcumin (Meriva) tablets, providing 180 mg curcumin plus 2 × 1000 mg corn oil capsules per day FO: 2 × 1000 mg fish oil (EPAX 1050 TG) capsules providing 1.2 g DHA + EPA plus 2× placebo tablets, matching the curcumin dose, per day	Fasting plasma glucose (%) HbA1c (%) Fructosamine (μmol/L) Total cholesterol (mmol/L) LDL cholesterol (mmol/L) HDL cholesterol (mmol/L) Total: HDL cholesterol I CRP (mg/L) White blood cells Neutrophils Lymphocytes Monocytes Platelets	12 wk	Fasting plasma glucose (%): $P = 0.851$ HbA1c (%): $P = 0.765$ Fructosamine (μmol/L): $P = 0.776$ Total cholesterol (mmol/L): $P = 0.767$ LDL cholesterol (mmol/L): $P = 0.120$ HDL cholesterol (mmol/L): $P = 0.333$ Total: HDL cholesterol: $P = 0.180$ CRP (mg/L): $P = 0.080$ White blood cells: $P = 0.339$ Neutrophils: $P = 0.070$ Lymphocytes: $P = 0.024$ Monocytes: $P = 0.290$ Platelets: $P = 0.618$

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TABLE 1 (*continued*)

Author	Country	Population		Intervention		Outcomes	Follow -up	Results
		Sample size (*n*)	Patients mean (SD)	Intervention	Characteristics/dose			
Zare et al. [24]	Iran	CG: 12 I1: 12 I2: 12 I3: 12	CG: 53.60 (6.23) I1: 57.75 (8.58) I2: 57.88 (6.03) I3: 53.14 (6.91) Patients with type 2 diabetes and periodontal disease	CG: nothing I1: ω 3 I2: cranberry juice I3: cranberry juice enriched with ω-3 Nonsurgical Periodontal therapy was provided for all patients during the study.	CG: nonsurgical periodontal therapy alone; ω-3 supplementation (1 g twice daily containing 180 mg EPA and 120 mg DHA), cranberry juice, or cranberry juice enriched with ω-3 fatty acids for 8 wk.	PD	8 wk	PD: $P = 0.31$
Zambon et al. [25]	United States	CG: None EG:10	CG: glyburide alone (within-subject control; crossover design). EG: fish oil (ω-3 fatty acids, 8 g/d EPA + DHA) for 8 wk (randomized crossover).	EG: *n*–3 fatty acid	EG: ~8 g *n*–3 fatty acids/ d were provided for 8 wk in 15 marine lipid capsules. Five capsules were taken at breakfast, lunch, and dinner. Each capsule contained 1000 mg ethyl ester fatty acids, providing 1 mg cholesterol, 200 mg DHA (22:6*n*–3), and 300 mg EPA.	Fasting plasma Glucose Postprandial insulin Insulin response to IV arginine Glucagon response to IV arginine Total cholesterol VLDL cholesterol LDL cholesterol Apolipoprotein B HDL cholesterol VLDL	8 wk	Fasting glucose: ↑ with *n*–3 FA; partially ↓ with glyburide + *n*–3 FA, not to glyburide alone level Postprandial insulin: ↓ with *n*–3 FA ± glyburide IV arginine insulin response: no significant change IV arginine glucagon: ↑ with *n*–3 FA alone; moderated with glyburide Total cholesterol: no change VLDL cholesterol: slight ↓ with *n*–3 FA alone; no change with glyburide + *n*–3 FA LDL cholesterol: ↑ with *n*–3 FA; glyburide did not prevent Apolipoprotein B: ↑ with *n*–3 FA; glyburide did not prevent HDL cholesterol: no consistent change Triglycerides (total and VLDL): no further reduction with *n*–3 FA ± glyburide
The ASCEND Study Collaborative Group [26]	United Kingdom	CG:7740 EG: 7740	CG: 63.3 (9.2) EG: 63.3 (9.2) Patients with diabetes mellitus (any type) who did not have evidence of cardiovascular disease.	CG: placebo EG: *n*–3 fatty acids	CG: placebo capsule (olive oil) to be taken once daily. EG: 1-g capsules containing either 840 mg marine *n*−3 fatty acids acids (460 mg EPA and 380 mg DHA) to be taken once daily.	First serious vascular event	< 3 y 3 to < 5 y 5 to < 7 y > 7 y	First serious vascular event: $P = 0.55$
Jamilian et al. [27]	Iran	CG:35 EG:35	CG:30.7 (4.1) EG:30.7 (3.5) Adults with gestational diabetes mellitus (GDM) Pregnant females diagnosed with	CG: placebo EG: ω 3	CG:1000 mg ω-3 fatty acids containing 360 mg EPA and 240 mg DHA twice a day 1 vitamin D placebo (n 5 35); EG: 50,000 IU vitamin D every 2 wk plus 1000 mg ω-3 fatty acids containing 360 mg	Vitamina D FPG Insulin HOMA-IR HOMA-B QUICKI Triglycerides	6 wk	Vitamina D, $P = 0.07$ FPG, $P = 0.24$ Insulin, $P = 0.62$ HOMA-IR, $P = 0.6$ HOMA-B, $P = 0.67$ QUICKI, $P = 0.9$ Triglycerides, $P = 0.23$

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TABLE 1 (*continued*)

Author	Country	Population		Intervention		Outcomes	Follow -up	Results
		Sample size (*n*)	Patients mean (SD)	Intervention	Characteristics/dose			
			gestational diabetes mellitus		EPA and 240 mg DHA, administered twice daily.	VLDL cholesterol Total cholesterol LDL cholesterol HDL cholesterol Total-/HDL cholesterol		VLDL cholesterol, $P = 0.23$ Total cholesterol, $P = 0.25$ LDL cholesterol, $P = 0.5$ HDL cholesterol, $P = 0.55$ Total-/HDL cholesterol, $P = 0.34$
Jamilian et al. [28]	Iran	CG:27 EG:27	CG: 30.0 (5,5) EG: 30.1 (5,3) Females with gestational diabetes	CG: placebo EG: ω 3	CG: 1 placebo per day for 6 wk. EG:1000 mg ω-3 pearl (containing 180 mg EPA and 120 mg DHA) per day	Height (cm) Weight at study baseline (kg) Weight at end-of-trial (kg) Weight change (kg) BMI at study baseline (kg/m^2) BMI at end-of-trial (kg/m^2) Weight change (kg/m^2) hs-CRP (ng/mL) NO (mmol/L) TAC (mmol/L) GSH (mmol/L) MDA (mmol/L)	6 wk	Height, $P = 0.43$ Weight at study baseline, $P = 0.59$ Weight at end-of-trial, $P = 0.63$ Weight change, $P = 0.48$ BMI at study baseline, $P = 0.75$ BMI at end-of-trial, $P = 0.82$ Weight change, $P = 0.45$ NO, $P = 0.45$ TAC, $P = 0.52$ GSH, $P = 0.82$ MDA, $P = 0.04$
Liu et al. [29]	China	EG: ω-3 fatty acids of marine and plant origin FO:52 PO:50 LFO:48	FO: 62.45 (8.58) PO: 63.84 (9.67) LFO: 61.19 (8.38) Patients with type 2 diabetes mellitus and dyslipidemia	FO: fish oil PO: perilla oil LFO: mixed Linseed And Fish Oil	The FO, PO, and LFO capsules were standardized to 500 mg. Each FO capsule contained 143 mg EPA and 172 mg DHA. Each PO capsule contained 322 mg ALA. The major fatty acids in each LFO capsule were EPA (105 mg), DHA (60 mg), and ALA (140 mg)	EPA MUFAs/SFAs ratio b PUFAs/SFAs ratio ω-3 index (%) duda+	6 wk	EPA: $P < 0.001$ MUFAs/SFAs: $P = 0.124$ PUFAs/SFAs: $P = 0.542$ ω-3: $P < 0.001$
Lewis et al. [30]	Canada	CG: No reported EG:36	CG:-EG:48 (14) PUFAs in patients with neuropathy in type 1 diabetes	CG: not applicable (single-arm, open-label study). EG: seal oil ω-3 PUFAs, administered as 10 mL/d orally, providing a total of 2330 mg ω-3 fatty acids, including 750 mg EPA, 560 mg docosapentaenoic acid (DPA), and 1020 mg DHA, divided into 2 daily doses of 5 mL.	Oral 10 mL dose of seal oil v-3 PUFAs with 2330 mg essential fatty acids divided into 2 daily 5 mL doses with breakfast and dinner	CNFL, mm/mm^2 CNBD, br/mm^2 CNFD, fib/mm^2 CNFA, mm^2/mm^2	12 mo	CNFL, mm/mm^2: $P = 0.002$ CNBD, br/mm^2: $P = 0.03$ CNFD, fib/mm^2: $P = 0.07$ CNFA, mm^2/mm^2: $P = 0.07$

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TABLE 1 (*continued*)

Author	Country	Population		Intervention		Outcomes	Follow -up	Results
		Sample size (*n*)	Patients mean (SD)	Intervention	Characteristics/dose			
Jamilian et al. [31]	Iran	CG:30 EG:30	CG: 30.4 (4.2) EG: 29.7 (5.5) Females with gestational diabetes	CG: placebo EG: ω-3 fatty acids and vitamin E	CG: placebo EG: patients were randomly allocated to intake Either 1000 mg ω-3 fatty acids from flaxseed oil plus 400 IU vitamin E supplements for 6 wk	TAC (mmol/L) GSH (μmol/L) MDA (μmol/L) hs-CRP (ng/mL) NO (μmol/L)	6 wk	TAC (mmol/L): $P < 0.001$ GSH (μmol/L): $P = 0.96$ MDA (μmol/L): $P = 0.01$ hs-CRP (ng/mL): $P = 0.12$ NO (μmol/L): $P < 0.001$
Manson et al. [32]	United States	CG: 10,000 EG: 10,000	Male ≥50 Female ≥55	CG: placebo EG: ω-3 fatty acids and vitamin D	CG: vitamin D (2000 IU/d) EG: marine ω-3 fatty acids (EPA + DHA 1 g/d)		5 y	
Britten-Jones et al. [33]	Australia	CG:22 EG: 21	CG: 40.5 (19.6) EG: 48.1 (19.2)	CG: placebo EG: *n*–3 PUFAs	CG: placebo supplements (olive oil) EG: long-chain triglyceride *n*–3 PUFA supplements	CNF(mm/mm^2) CNBD (branches/mm^2) Central corneal sensitivity threshold (mbar) Room temperature stimulust Cooled stimulust	12 mo	CNFL (mm/mm^2): $P < 0.001$ CNBD (branches/mm^2): $P = 0.004$ Central corneal sensitivity threshold (mbar): $P = 0.002$ Room temperature stimulust: $P = 0.39$ Cooled stimulus: $P = 0.29$
Mozaffarian et al. [34]	United States	CG:148 EG:372	CG:53.9 (11.8) EG:55.3 (10.9) Adults aged ≥18 y with fasting TG concentrations from 500 to 1500 mg/dL	CG: placebo EG: ω-3–PL/FFA	CG: placebo EG: ω-3–PL/FFA, 4 g/d (including 1.24 g/d of EPA and DHA as FFAs or PLs and 2.4 g of total)	TG concentration, mg/dL Week 12 Week 26 Non-HDL cholesterol concentration, mg/dL Week 12 Week 26 VLDL cholesterol concentration, mg/dL Week 12 Week 26 HDL cholesterol concentration, mg/dL Week 12 Week 26 LDL cholesterol concentration, mg/dL Week 12 Week 26	26 wk	TG concentration, mg/dL Week 12: $P = 0.02$ Week 26: $P = 0.02$ Non-HDL cholesterol concentration, mg/dL Week 12: $P = 18$ Week 26: $P = 0.04$ VLDL cholesterol concentration, mg/dL Week 12: $P = 0.38$ Week 26: $P = 0.15$ HDL cholesterol concentration, mg/dL Week 12: $P = 0.77$ Week 26: $P = 0.57$ LDL cholesterol concentration, mg/dL Week 12: $P = 0.40$ Week 26: $P = 0.51$
Pooya et al. [35]	Iran	CG:40 EG:41	CG:52.7 (10.65) EG:56.38 (9.24) Patients were diagnosed (by health staff) with type 2 diabetes for ≥2 y	CG: control group EG: treatment group	CG: placebo capsules contained 2100 mg sunflower oil EG: ω-3 fatty acids were set at 3 capsules/d for 2 mo	HbA1C (%) homocysteine Malondialdehyde C-reactive protein (mg/L) Total cholesterol LDL cholesterol FBS (mg/dL)	12 wk	HbA1C (%): $P < 0.001$ Homocysteine: $P < 0.001$ Malondialdehyde: $P =$ NS C-reactive protein (mg/L): $P =$ NS Total cholesterol: $P =$ NS LDL cholesterol: $P =$ NS FBS (mg/dL): $P =$ NS

(*continued on next page*)

TABLE 1 (*continued*)

Author	Country	Population		Intervention		Outcomes	Follow -up	Results
		Sample size (*n*)	Patients mean (SD)	Intervention	Characteristics/dose			
Rajabi-Naeeni et al. [36]	Iran	CG:42 EG:42	CG: 30.3 (5.5) EG:29.8 (5.0) Females aged 15–50 y with prediabetes and hypovitaminosis D.	CG: placebo EG: ω-3 fatty acid	CG: placebo (500 mg liquid paraffin) vs. ω-3 supplementation (1000 mg/d containing 180 mg EPA and 120 mg DHA) for 8 wk.	Depression Anxiety Stress Sleep quality	8 wk	Depression: $P < 0.001$ Anxiety: $P < 0.001$ Stress: $P < 0.001$ Sleep quality: $P < 0.001$
Samimi et al. [37]	Iran	CG:28 EG:28	CG:30,3 (5.5) EG:29.8 (5.0) Pregnant females aged 18-40 y who have been diagnosed with GDM by "one-step" 2-h 75-g oral glucose tolerance test at 24–28 wk of gestation.	CG: placebo group EG: ω-3 fatty acid	The supplementation was started immediately after enrollment when the subjects were still at 24–28 wk of gestation. CG:1 placebo per day for 6 wk. EG: 1000 mg ω-3 pearl per day and individuals	FPG (mg/dL) Insulin (mIU/mL) HOMA-IRd HOMA-Be QUICKIf Total cholesterol (mg/dL) Triglycerides (mg/dL) LDL cholesterol g (mg/dL) HDL cholesterol h (mg/dL) Total: HDL cholesterol ratio	3 mo	FPGc (mg/dL) $P = 0.24$ Insulin (mIU/mL) $P = 0.02$ HOMA-IRd $P = 0.02$ HOMA-Be $P = 0.06$ QUICKIf $P = 0.18$ Total cholesterol (mg/dL) $P = 0.25$ Triglycerides (mg/dL) $P = 0.25$ LDL cholesterolg (mg/dL) $P = 0.46$ HDL cholesterolh (mg/dL) $P = 0.09$ Total: HDL cholesterol ratio $P = 0.97$
Sangouni et al. [38]	Iran	CG:30 EG:30	CG:48.8 (8.7) EG:48.6 (7.6) Patients with diabetes	CG: placebo EG: ω-3	CG: placebo EG: 2 g/d ω-3 as gel capsule (each 1000 mg capsule contained 180 mg EPA and 120 mg DHA)	FLI LAP VAI	12 wk	FLI: $P = 0.04$ LAP: $P = 0.002$ VAI: $P = 0.01$
Castro et al. [39]	Brasil	CG: 25 EG: 25	CG: 54.9 (9.7) EG: 54.4 (10.2) patients with type 2 diabetes.	CG: placebo EG: ASA + ω 3	CG: placebo EG: 3g fish oil (900 mg ω-3 PUFA) and 100 mg ASA daily for 2 mo	BoP (%) PI (%)	6 mo	BoP: $P = 0.05$ PI: $P = 0.05$
Chun et al. [40]	South Korea	CG:42 EG: 44 (1 g), 43 (2 g), 44 (4g)	CG: 54 (9) EG: 55 (9); 54 (9); 55 (8)	CG: placebo EG: omacor de 1 g, 2 g y 4 g in patient with hypertriglyceridemia	ω-3 fatty acids administered at doses of 1 g/d, 2 g/d, or 4 g/d vs. placebo for 2 mo.	Total cholesterol Triglycerides LDL cholesterol Apo B HDL cholesterol Apo A-I TG/HDL ratio Non-HDL FMD (%) NTG (%) hs-CRP (mg/L) Fibrinogen (mg/dL) ADP (μg/mL) Insulin (μU/mL) Glucose (mg/dL)	2 mo	Total cholesterol: $P = 0.403$ Triglycerides: $P = 0.021$ LDL cholesterol: $P = 0.743$ Apo B: $P = 0.358$ HDL cholesterol: $P = 0.050$ Apo A-I: $P = 0.096$ TG/HDL ratio: $P = 0.152$ Non-HDL: $P = 0.261$ FMD (%): $P \leq 0.001$ NTG (%): $P = 0.989$ hs-CRP (mg/L): $P = 0.401$ Fibrinogen (mg/dL): $P = 0.070$ ADP (μg/mL): $P = 0.375$ Insulin (μU/mL): $P = 0.078$

(*continued on next page*)

TABLE 1 (*continued*)

Author	Country	Population		Intervention		Outcomes	Follow -up	Results
		Sample size (*n*)	Patients mean (SD)	Intervention	Characteristics/dose			
						QUICKI HbA1c (%)		Glucose (mg/dL): $P = 0.397$ QUICKI: $P = 0.222$ HbA1c (%): $P = 0.389$
Holman et al. [41]	United Kingdom	CG: 202 EG: 200	CG: 65 (57–73) EG: 63 (57–72) patients with type 2 diabetes for ≥3 mo, aged ≥18 y, with no known CVD events,	CG: placebo EG: atorvastatin and ω-3	CG: placebo capsule and ω-3 EE90, 2 g/d containing 46% EPA and 38% DHA for 4 mo. EG: ω-3 EE90 2 g/d. Patients and study staff were masked to study medication group assignment, and patients were asked to swallow capsules whole to avoid unmasking	LDL cholesterol ≤2.6 mmol/l Triacylglycerol <1.5 mmol/L Estimated 10 y CVD risk <20% Total cholesterol (mmol/L) LDL cholesterol (mmol/L) HDL cholesterol (mmol/L) Triacylglycerol (mmol/L) Systolic blood pressure (mmHg) Diastolic blood pressure (mmHg) HbA1c (%)	4 mo	LDL cholesterol ≤2.6 mmol/L: $P \leq 0.001$ Triacylglycerol <1.5 mmol/L: $P = <0.001$ Estimated 10 y CVD risk <20%: $P = 0.18$ Total cholesterol (mmol/L): $P = 0.99$ LDL cholesterol (mmol/L): $P = 0.82$ HDL cholesterol (mmol/L): $P = 0.082$ Triacylglycerol (mmol/L): $P = 0.003$ Systolic blood pressure (mmHg) 0.83 Diastolic blood pressure (mmHg): $P = 0.34$ HbA1c (%): $P = 0.62$
Huang et al. [42]	China	CG: 70 EG: 80	CG: 31.3 (4.7) EG:31.5 (4.1) Patients with gestational diabetes	CG: placebo EG: vitamin D and ω-3	EG: the test group took 40,000 IU of vitamin D and 8000 mg ω-3 fatty acids twice daily.	FBG (mmol/L) Fasting insulin (uIU/mL) HOMA-IR HOMA-β TG (mmol/L) Total cholesterol (mmol/L) LDL (mmol/L) HDL (mmol/L) VLDL (mmol/L)	19 mo	FBG (mmol/L): $P = 0.42$ Fasting insulin (uIU/mL): $P = 0.32$ HOMA-IR: $P = 0.19$ HOMA-β: $P = 0.12$ TG (mmol/L): $P = 0.43$ Total cholesterol (mmol/L): $P = 0.56$ LDL (mmol/L): $P = 0.72$ HDL (mmol/L): $P = 0.86$ VLDL (mmol/L): $P = 0.91$

Abbreviations: ADP, adiponectin; ALA, alpha-lipoic acid; Apo A-I, apolipoprotein A-I; Apo B, apolipoprotein B; ASA, aspirin; BoP, bleeding on probing; CC, curcumin; CG, control group; CNBD, corneal nerve branch density; CNFA, corneal nerve fiber area; CNFD, corneal nerve fiber density; CNFL, corneal nerve fiber length; EG, experimental group; eGFR, estimated glomerular filtration rate; FA, Fatty acid; FBG, fasting blood glucose; FBS, fasting blood sugar; FLI, fatty liver index; FMD, flow-mediated dilation; FO, fish oil; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; GSH, total glutathione; HbA1c, glycated hemoglobin; hs-CRP, high-sensitivity C-reactive protein; I1, intervention group 1; I2, intervention group 2; I3, intervention group 3; LAP, lipid accumulation product; LFO, mixed linseed and fish oil; MDA, malondialdehyde; NO, nitric oxide; non-HDL, total cholesterol minus HDL; NTG, nitroglycerin-induced dilation; PD, periodontal status; PI, plaque index; PO, perilla oil; QUICKI, Quantitative Insulin Sensitivity Check Index; RH, reactive hyperemia; TAC, total antioxidant capacity; TDF, total dietary fiber; TG/HDL ratio, triglyceride-to-HDL ratio; TG, triglyceride; VAI, visceral adiposity index; WC, waist circumference.

RoB assessment in individual studies

RoB was assessed using the Cochrane RoB tool and showed mixed methodological quality across domains. Random sequence generation was judged to be of low risk in 10 studies [23,27,28,30,33–35,37,41,42], with 1 study unclear [40]. Allocation concealment was low risk in 4 studies [34,35,37,40] and high risk in 7 [23,27,28,30,33,41,42]. Blinding of participants and personnel was low risk in 9 studies [23,28,30,33,35,37,40–42] and high risk in 2 [27,34]. Blinding of outcome assessment was low risk in 4 studies [23,33,35,42] and high risk in 7 [27,28,30,34,37,40,41]. Attrition bias was low risk in 6 studies [27,28,30,35,37,41] and high risk in 5 [23,33,34,40,42]. Selective reporting was low risk in 9 studies [23,27,28,30,33,34,40–42] and high risk in 2 [35,37]. Other bias was low risk in 6 studies [28,30,33,34,40,41] and high risk in 5 [23,27,35,37,42]. Importantly, the certainty of evidence was frequently downgraded in the GRADE due to imprecision, indirectness, and substantial between-study heterogeneity, even when some RoB domains were rated as low risk (Figures 2 and 3)

Other methodological considerations: placebo selection

Control interventions exhibited considerable variability, encompassing inert agents such as liquid paraffin and cornstarch, as well as vegetable oils, including sunflower and olive oils, which may exert metabolic effects. Multiple trials employed matched placebo capsules to ensure blinding, as seen in the studies conducted by Jamilian et al. [28] Differences in placebo composition and their metabolic neutrality likely contributed to heterogeneity in outcomes, warranting consideration in the interpretation of pooled results.

Synthesis of results

Meta-analyses were performed in RevMan 5.4 using continuous outcome data and the inverse-variance method. When SDs were not reported, they were derived from CIs using SD = $\sqrt{n}$ × (upper limit − lower limit)/3.92. Effects were oriented so that reductions represented benefit where clinically appropriate. Given substantial clinical heterogeneity, pooled estimates were interpreted as exploratory/hypothesis-generating.

Blood and metabolic profile

Triglycerides

Across 5 studies [27,34,37,41,42], ω-3 supplementation did not significantly reduce triglycerides (MD: −20.34 mg/dL; 95% CI: −49.33, 8.64; $P = 0.17$), with considerable heterogeneity (I^2 = 99%) (Figure 4). In exploratory subgroup analyses, short-duration interventions (1–12 wk; 4 studies [27,34,37,42]) showed no significant effect (MD: −25.34 mg/dL; $P = 0.27$; I^2 = 100%). Interventions lasting 13–26 wk (2 studies [34,41]) were associated with a statistically significant reduction (MD: −9.99 mg/dL; $P = 0.0001$; $I^2 = 26\%$), although subgroup comparisons were underpowered. The certainty of the evidence was very low.

HbA1c

Across 4 studies [23,35,40,41], ω-3 supplementation showed no effect on HbA1c (MD: 0.00; 95% CI: −0.74, 0.74; $P = 1.00$) (Figure 5), with extreme heterogeneity (I^2 = 100%). The certainty of evidence was very low. HbA1c concentrations are elevated in patients with diabetes, reflecting mean blood glucose concentrations over the preceding 2–3 mo.

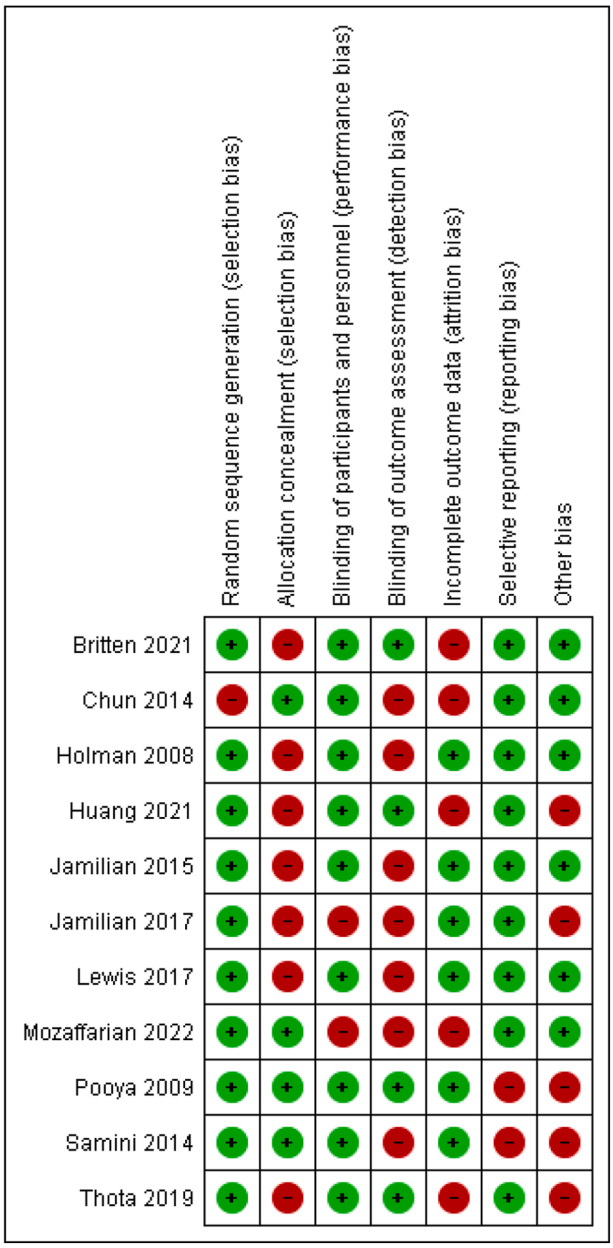


FIGURE 2. Risk of bias summary of included randomized controlled trials evaluating ω-3 supplementation in individuals with diabetes.

Fasting insulin

Two studies [27,37] showed a reduction in fasting insulin, favoring ω-3 supplementation (MD: −3.68 μIU/mL; 95% CI: −6.12, −1.24; $P = 0.003$) with no heterogeneity (I^2 = 0%) (Figure 6). Certainty of evidence was low.

LDL cholesterol

Across 8 studies [23,27,34,35,37,40,41,42], ω-3 supplementation had no significant effect on LDL cholesterol (MD: −8.38 mg/dL, 95% CI: −34.07, 17.31; $P = 0.52$) (Figure 7), with extreme heterogeneity (I^2 = 100%). Exploratory duration subgroups (1–12 compared with 13–26 wk) did not demonstrate

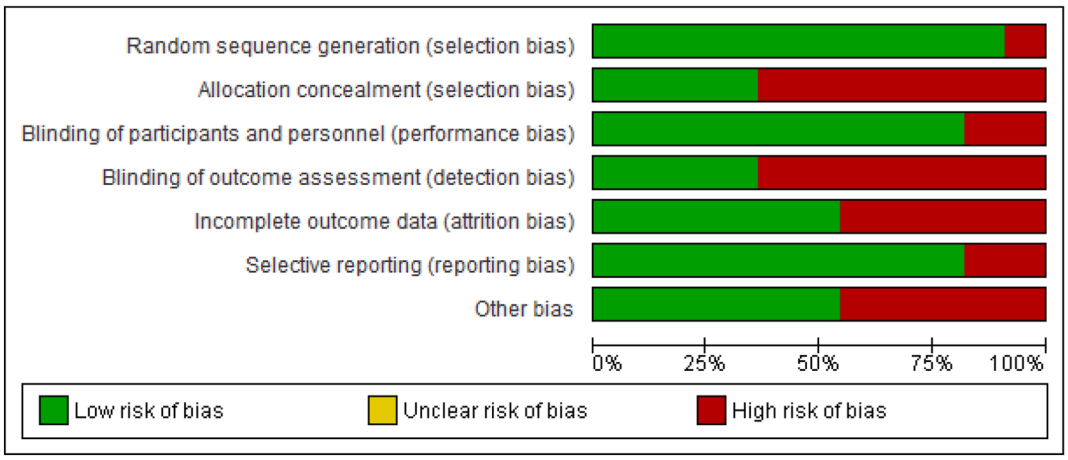


FIGURE 3. Risk of bias graph of included randomized controlled trials evaluating ω-3 supplementation in individuals with diabetes.

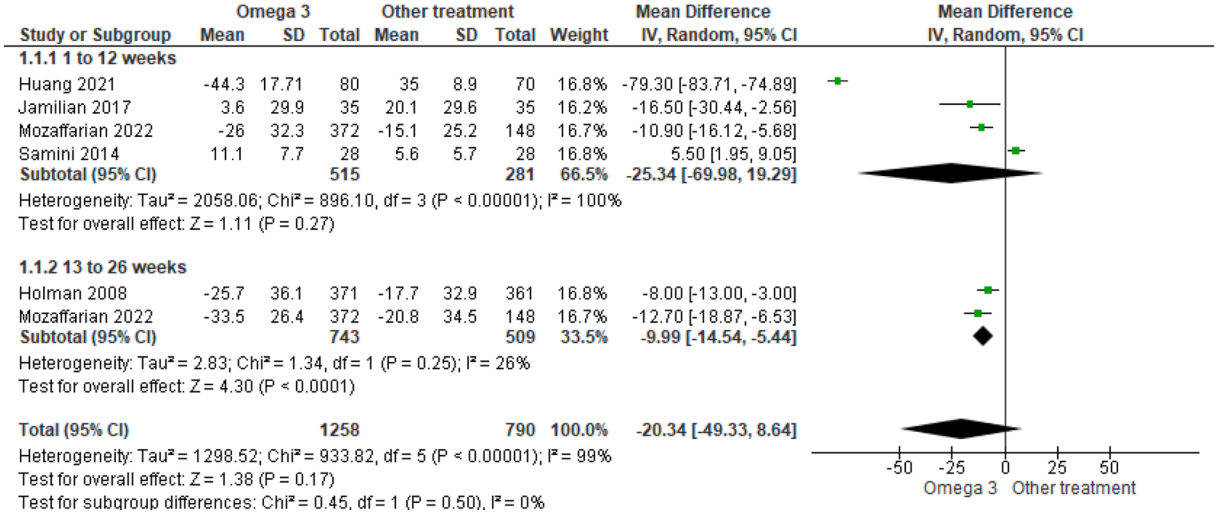


FIGURE 4. Forest plot of the effect of ω-3 fatty acids on triglyceride concentrations in individuals with diabetes. CI, confidence interval; IV, inverse variance.

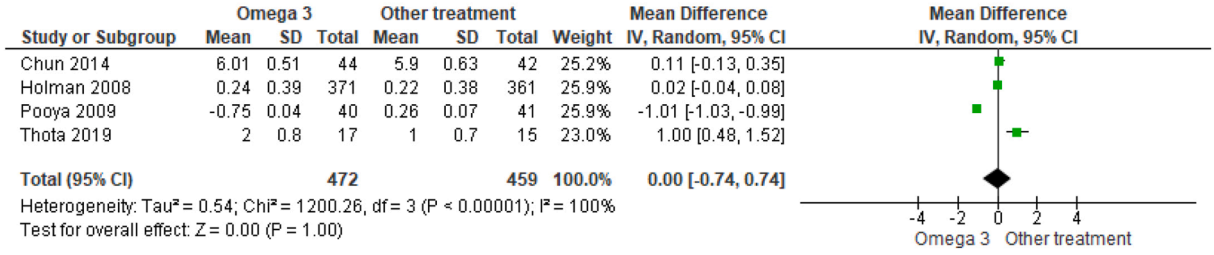


FIGURE 5. Forest plot of the effect of ω-3 fatty acids on glycated hemoglobin in individuals with diabetes. CI, confidence interval; IV, inverse variance.

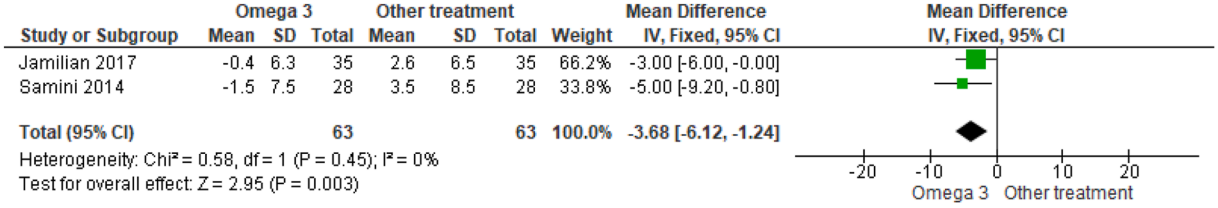


FIGURE 6. Forest plot of the effect of ω-3 fatty acids on fasting insulin concentrations in individuals with diabetes. CI, confidence interval; IV, inverse variance.

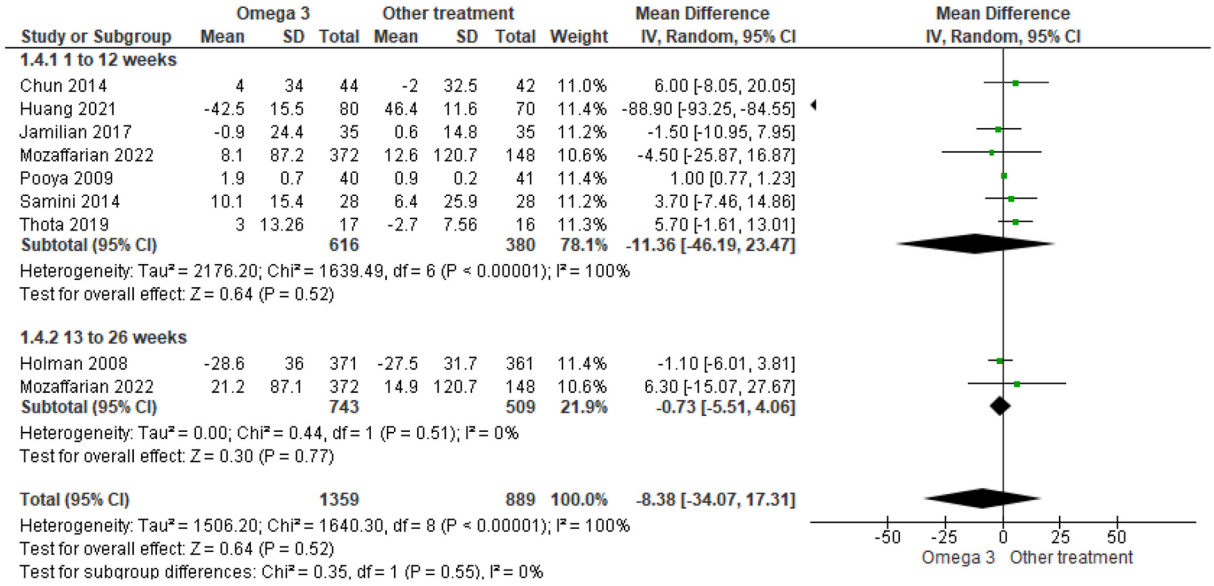


FIGURE 7. Forest plot of the effect of ω-3 fatty acids on LDL cholesterol concentrations in individuals with diabetes. CI, confidence interval; IV, inverse variance.

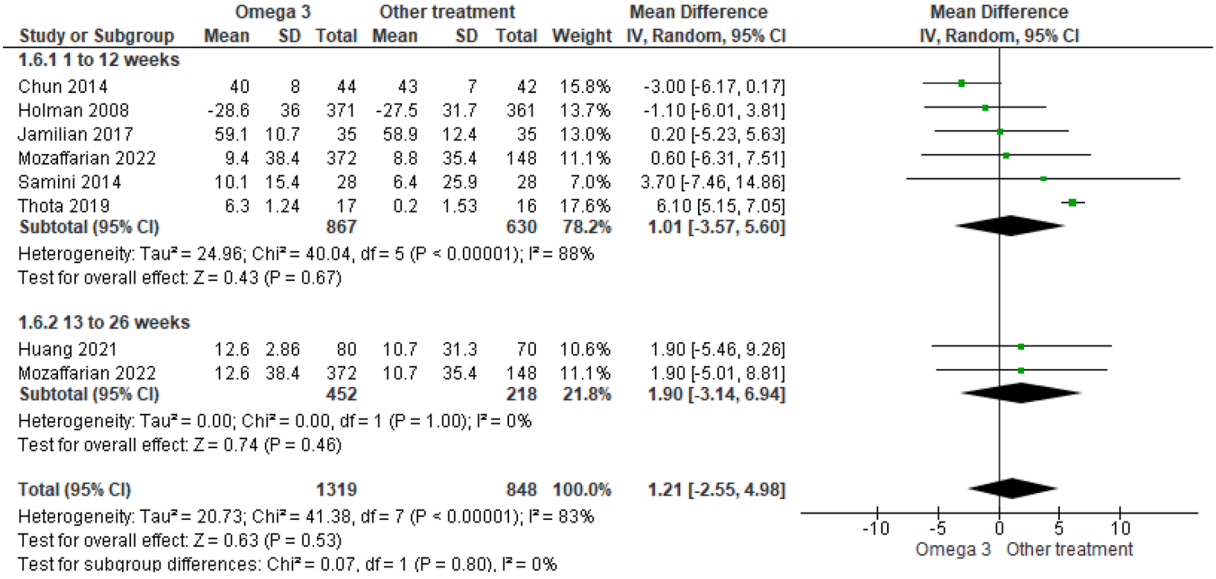


FIGURE 8. Forest plot of the effect of ω-3 fatty acids on HDL cholesterol concentrations in individuals with diabetes. CI, confidence interval; IV, inverse variance.

differences (P for subgroup difference = 0.55). The certainty of the evidence was very low.

HDL cholesterol

Across 7 studies [23,27,34,37,40,41,42], ω-3 supplementation showed no significant effect on HDL cholesterol (MD: 1.21 mg/dL, 95% CI: −2.55, 4.98; P = 0.53) (Figure 8), with substantial heterogeneity (I^2 = 83%). Duration subgroup analysis showed no evidence of effect modification (P = 0.80). The certainty of evidence was very low.

VLDL cholesterol

Two studies [27,34] showed a reduction in VLDL cholesterol in favor of ω-3 supplementation (MD: −3.23 mg/dL; 95% CI: −5.80, −0.66; P = 0.01) (Figure 9), with no heterogeneity (I^2 = 0%). The certainty of evidence was very low.

HOMA-IR

Three studies [27,37,42] showed a reduction in HOMA-IR favoring ω-3 supplementation (MD: −0.52, 95% CI: −0.64, −0.40; P < 0.00001) (Figure 10), with low heterogeneity (I^2 = 5%). The certainty of evidence was very low.

Total cholesterol ratio

Three studies [23,27,37] showed no significant effect on total cholesterol ratio (SMD: 1.07; 95% CI: −0.29, 2.43; P = 0.12) (Figure 11), with high heterogeneity (I^2 = 93%). The certainty of the evidence was very low.

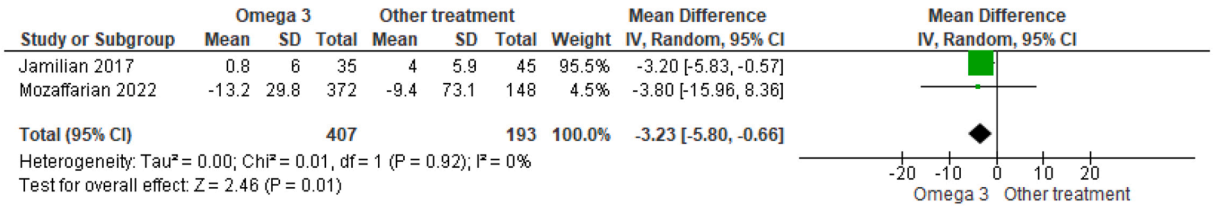


FIGURE 9. Forest plot of the effect of ω-3 fatty acids on VLDL cholesterol concentrations in individuals with diabetes. CI, confidence interval; IV, inverse variance.

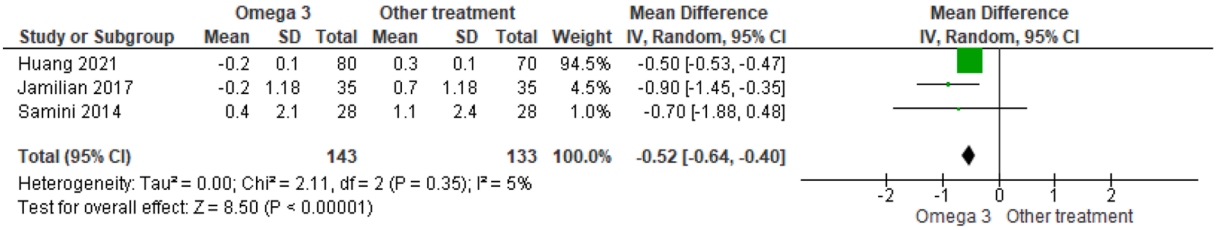


FIGURE 10. Forest plot of the effect of ω-3 fatty acids on HOMA-IR in individuals with diabetes. CI, confidence interval; IV, inverse variance.

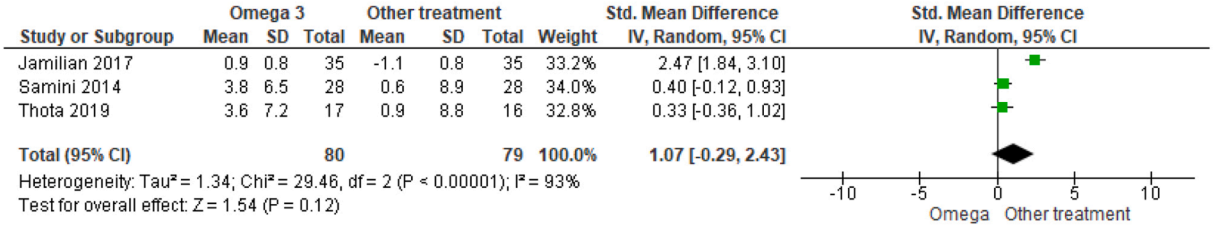


FIGURE 11. Forest plot of the effect of ω-3 fatty acids on total cholesterol to HDL cholesterol ratio in individuals with diabetes. CI, confidence interval; IV, inverse variance.

FPG

Three studies [23,27,37] showed no significant effect on FPG (MD: 5.78 mg/dL, 95% CI: −1.94, 13.50; $P = 0.14$) (Figure 12), with extreme heterogeneity ($I^2 = 99\%$). The certainty of evidence was very low.

QUICKI

Two studies [27,37] showed no significant effect on QUICKI (SMD: 0.10; 95% CI: −0.24, 0.44; $P = 0.55$) (Figure 13), with moderate heterogeneity ($I^2 = 64\%$). The certainty of evidence was very low.

Non-HDL cholesterol

Two studies [34,40] showed no significant effect on non-HDL cholesterol (MD: −2.47 mg/dL, 95% CI: −7.07, 2.13; $P = 0.29$) (Figure 14), with no heterogeneity ($I^2 = 0\%$). The certainty of evidence was very low.

Secondary outcomes

Functional outcomes

CNBD. Two studies [30,33] reported CNBD and showed a statistically significant improvement in favor of ω-3 supplementation (SMD: 0.54; 95% CI: 0.16, 0.91; $P = 0.005$) (Figure 15), with no heterogeneity ($I^2 = 0\%$). Certainty of evidence was low. CNBD was the most consistently reported functional outcome across the included trials, as explained in the discussion.

Inflammation and oxidative stress biomarkers

Across outcomes, ω-3 supplementation did not demonstrate statistically significant effects on inflammatory or oxidative stress biomarkers, and pooled estimates were imprecise with substantial heterogeneity.

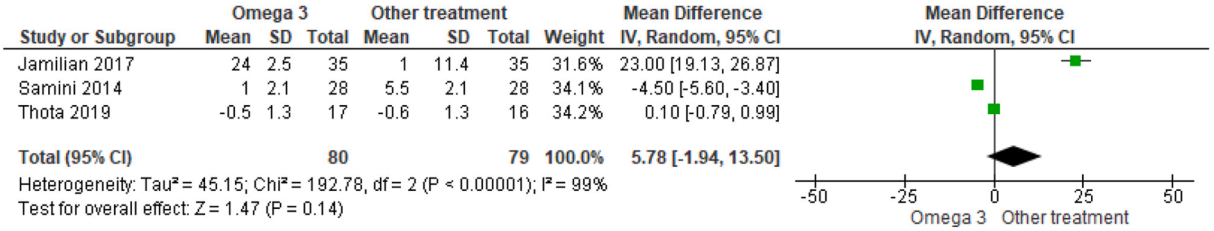


FIGURE 12. Forest plot of the effect of ω-3 fatty acids on fasting plasma glucose in individuals with diabetes. CI, confidence interval; IV, inverse variance.

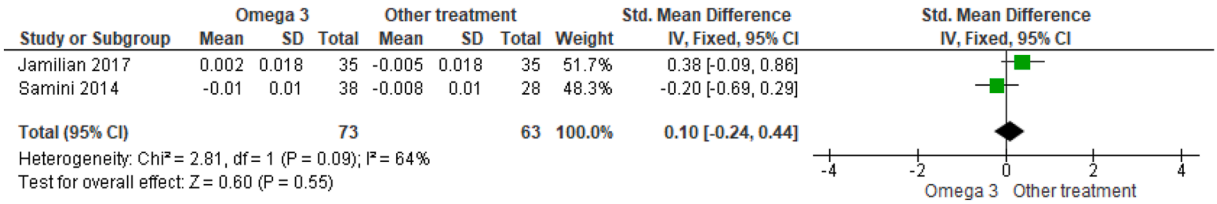


FIGURE 13. Forest plot of the effect of ω-3 fatty acids on QUICKI in individuals with diabetes. CI, confidence interval; QUICKI, Quantitative Insulin Sensitivity Check Index; IV, inverse variance.

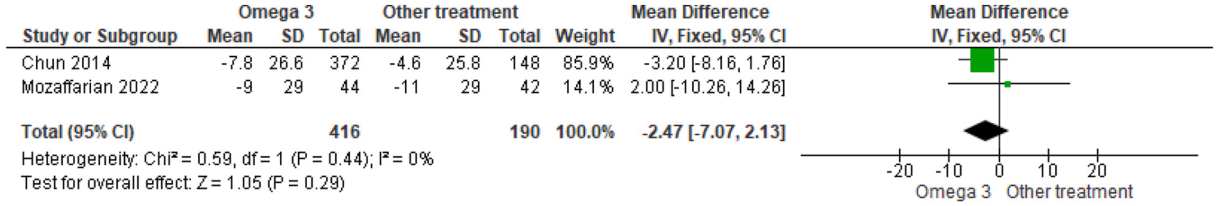


FIGURE 14. Forest plot of the effect of ω-3 fatty acids on non-HDL cholesterol concentrations in individuals with diabetes. CI, confidence interval; IV, inverse variance.

- MDA (2 studies [27,28]): SMD, −2.19; $P = 0.21$; $I^2 = 98\%$ (Figure 16); certainty of evidence: very low.
- TAC (2 studies [27,28]): SMD, 4.85; $P = 0.34$; $I^2 = 99\%$ (Figure 17); certainty of evidence: very low.
- CRP/hs-CRP (2 studies [35,40]): SMD, −2.97; $P = 0.33$; $I^2 = 99\%$ (Figure 18); certainty of evidence: very low.
- GSH (2 studies [27,28]): SMD, 0.75; $P = 0.58$; $I^2 = 97\%$ (Figure 19); certainty of evidence: very low.
- NO (2 studies [27,28]): SMD, 0.75; $P = 0.74$; $I^2 = 99\%$ (Figure 20); certainty of evidence: very low.

Adverse effects

Most trials did not report frequent or serious adverse effects. When reported, adverse events were generally mild and included gastrointestinal symptoms (e.g., nausea and diarrhea), headache,

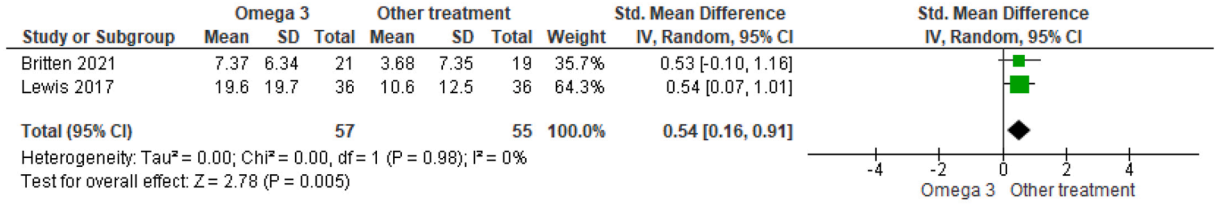


FIGURE 15. Forest plot of the effect of ω-3 fatty acids on corneal nerve branch density in individuals with diabetes. CI, confidence interval; IV, inverse variance.

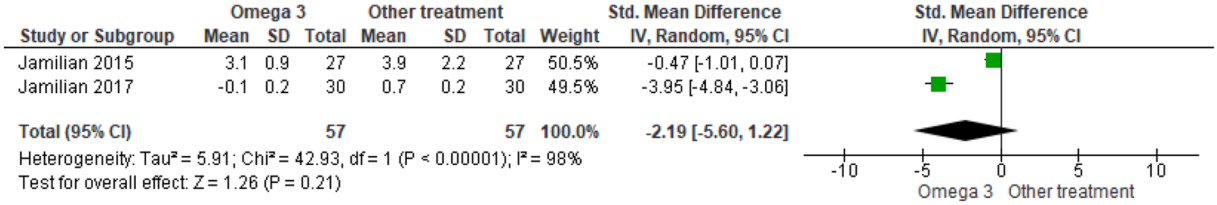


FIGURE 16. Forest plot of the effect of ω-3 fatty acids on malondialdehyde concentrations in individuals with diabetes. CI, confidence interval; IV, inverse variance.

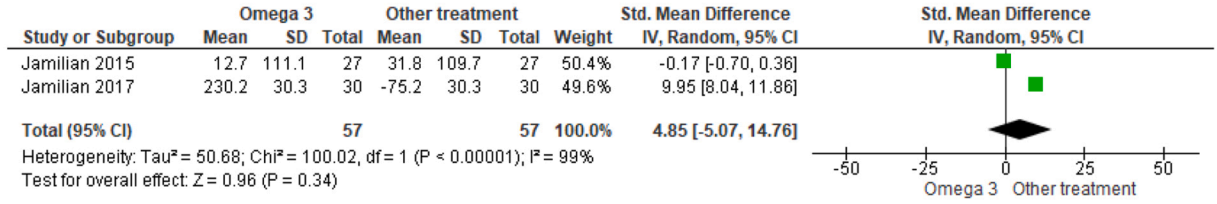


FIGURE 17. Forest plot of the effect of ω-3 fatty acids on total antioxidant capacity in individuals with diabetes. CI, confidence interval; IV, inverse variance.

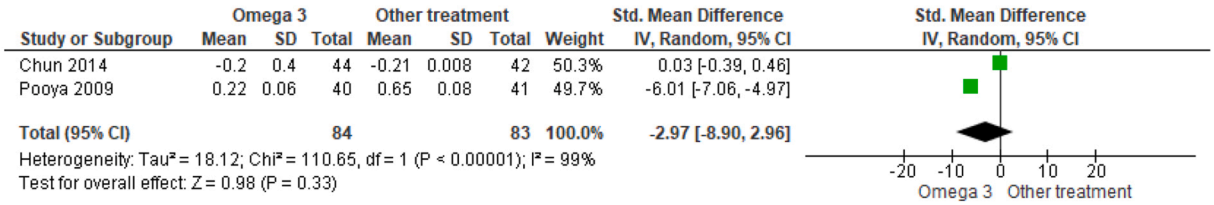


FIGURE 18. Forest plot of the effect of ω-3 fatty acids on C-reactive protein/high-sensitivity C-reactive protein concentrations in individuals with diabetes. CI, confidence interval.

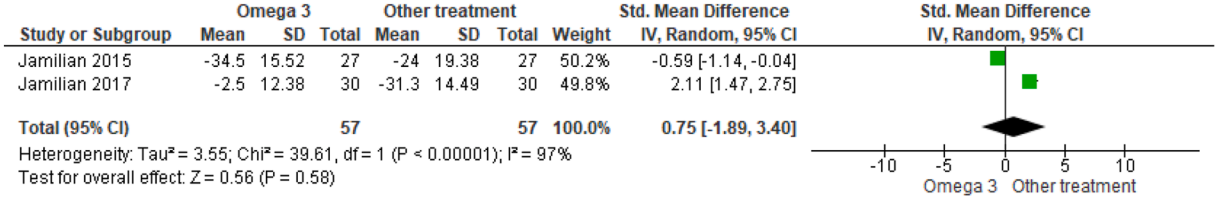


FIGURE 19. Forest plot of the effect of ω-3 fatty acids on glutathione concentrations in individuals with diabetes. CI, confidence interval; IV, inverse variance.

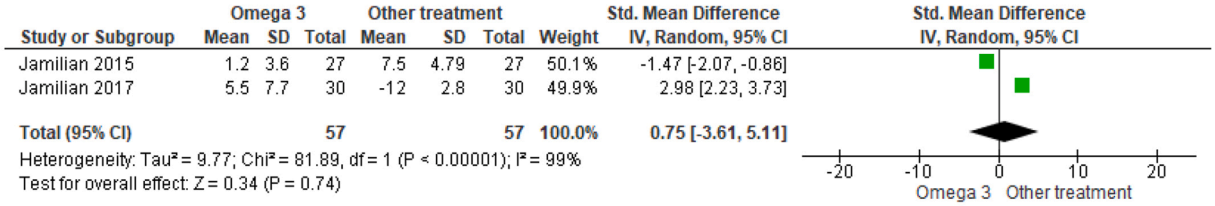


FIGURE 20. Forest plot of the effect of ω-3 fatty acids on nitric oxide concentrations in individuals with diabetes. CI, confidence interval; IV, inverse variance.

cough, and respiratory infections, observed in small proportions of participants in Mozaffarian et al. [34] and Holman et al. [41].

Exploratory metaregression

An exploratory metaregression assessed whether age, intervention duration, intake frequency, ω-3 dose, or sex distribution moderated metabolic outcomes. Given the limited number of studies per outcome, potential collinearity (dose–duration–frequency), and lack of multiplicity adjustment, results were interpreted as hypothesis-generating.

Associations were observed for FPG with weekly intake frequency ($\beta = 0.54$; 95% CI: 0.01, 1.07; $P = 0.04635$); LDL cholesterol with daily dose ($\beta = -0.47$; 95% CI: −0.61, −0.33; $P < 0.00001$); HDL cholesterol with weekly intake frequency ($\beta = 0.76$; 95% CI: 0.09, 1.44; $P = 0.02668$); total cholesterol ratio with daily dose ($\beta = 2.19$; 95% CI: 1.25, 3.14; $P = 0.00001$); triglycerides with daily dose ($\beta = -0.39$; 95% CI: −0.48, −0.30; $P < 0.00001$); HbA1c with weekly intake frequency ($\beta = -1.12$; 95% CI: −2.14, −0.09; $P = 0.03239$); HOMA-IR with age ($\beta = -4.43$; 95% CI: −5.28, −3.57; $P < 0.00001$); and daily dose ($\beta = -0.68$; 95% CI: −0.79, −0.56; $P < 0.00001$). These findings should be interpreted cautiously because of the limited number of studies and the exploratory nature of the analyses (Table 2).

Discussion

This systematic review and meta-analysis synthesized randomized evidence on the effects of ω-3 fatty acid supplementation on metabolic, inflammatory, oxidative stress, and functional outcomes in individuals with diabetes. Overall, the findings indicate that ω-3 supplementation does not consistently improve glycemic control or most lipid fractions, whereas selected outcomes, particularly insulin sensitivity indices and CNBDs, showed directionally favorable or statistically significant effects. However, the certainty of evidence was predominantly low to very low, and the quantitative synthesis should therefore be interpreted as exploratory and hypothesis-generating rather than confirmatory.

Metabolic and lipid outcomes

Across pooled analyses, ω-3 supplementation did not significantly improve HbA1c or FPG, suggesting that ω-3 fatty acids should not be considered a glucose-lowering intervention in diabetes management. These neutral findings are consistent with earlier systematic reviews in type 2 diabetes, which reported no meaningful effects on long-term glycemic control despite improvements in lipid concentrations [43,44]. With respect to lipid metabolism, triglyceride concentrations showed a directionally favorable reduction in the overall pooled analysis, but this effect did not reach statistical significance and was accompanied by substantial heterogeneity. Exploratory subgroup analyses suggested that interventions lasting 13 to 26 wk were associated with statistically significant reductions in triglycerides, whereas shorter interventions were not. This temporal pattern is biologically plausible because suppression of hepatic VLDL synthesis and enhanced clearance of triglyceride-rich lipoproteins may require prolonged exposure

TABLE 2
Exploratory metaregression analyses evaluating potential moderators of the effects of ω-3 supplementation in individuals with diabetes

Outcome	Moderator	B	95% LLCI	95% ULCI	p-value
Omega 3 FPG	Age (years)	-0.01	-0.34	0.32	0.95369
Omega 3 FPG	Treatment duration (weeks)	-0.04	-1.42	1.34	0.95369
Omega 3 FPG	Frequency per week	0.54	0.01	1.07	0.04635
Omega 3 FPG	Daily dose (grams)	3.91	-0.18	8	0.06102
Omega 3 FPG	Proportion of Women	0.6	-19.75	20.95	0.95369
Omega 3 LDL	Age (years)	0.09	-0.02	0.2	0.11302
Omega 3 LDL	Treatment duration (weeks)	0.07	-0.2	0.34	0.61376
Omega 3 LDL	Frequency per week	0.01	-0.37	0.39	0.95888
Omega 3 LDL	Daily dose (grams)	-0.47	-0.61	-0.33	0.00000
Omega 3 LDL	Proportion of Women	0.14	-0.51	0.79	0.67271
Omega 3 HDL	Age (years)	-0.03	-0.3	0.23	0.79715
Omega 3 HDL	Treatment duration (weeks)	0.01	-0.52	0.54	0.98043
Omega 3 HDL	Frequency per week	0.76	0.09	1.44	0.02668
Omega 3 HDL	Daily dose (grams)	-0.02	-0.77	0.73	0.96022
Omega 3 HDL	Proportion of Women	2.58	-15.27	20.44	0.77667
Omega 3 Total Cholesterol HDL	Age (years)	-0.04	-0.19	0.1	0.54272
Omega 3 Total Cholesterol HDL	Treatment duration (weeks)	-0.18	-0.77	0.41	0.54272
Omega 3 Total Cholesterol HDL	Frequency per week	0.14	-0.37	0.66	0.58540
Omega 3 Total Cholesterol HDL	Daily dose (grams)	2.19	1.25	3.14	0.00001
Omega 3 Total Cholesterol HDL	Proportion of Women	2.7	-6	11.4	0.54272
Omega 3 Triglycerides	Age (years)	0.04	-0.12	0.21	0.59073
Omega 3 Triglycerides	Treatment duration (weeks)	0.08	-0.22	0.38	0.60161
Omega 3 Triglycerides	Frequency per week	-0.44	-0.97	0.09	0.10451
Omega 3 Triglycerides	Daily dose (grams)	-0.39	-0.48	-0.3	0.00000
Omega 3 Triglycerides	Proportion of Women	0.73	-2.7	4.17	0.67582
Omega 3 HbA1c	Age (years)	-1.07	-2.77	0.62	0.21391
Omega 3 HbA1c	Treatment duration (weeks)	1.2	-1.58	3.98	0.39718
Omega 3 HbA1c	Frequency per week	-1.12	-2.14	-0.09	0.03239
Omega 3 HbA1c	Daily dose (grams)	-9.89	-23.38	3.61	0.15105
Omega 3 HOMA-IR	Age (years)	-4.43	-5.28	-3.57	0.00000
Omega 3 HOMA-IR	Frequency per week	-0.36	-1.39	0.66	0.48612
Omega 3 HOMA-IR	Daily dose (grams)	-0.68	-0.79	-0.56	0.00000

Abbreviations: B, regression coefficient; HbA1c, glycated hemoglobin; LLCI, lower limit of the 95% confidence interval; ULCI, upper limit of the 95% confidence interval.

[43]. Nevertheless, the small number of contributing studies and marked heterogeneity substantially limit confidence in the magnitude and generalizability of this effect. LDL and HDL cholesterol remained unchanged across both global and subgroup analyses, indicating that ω-3 supplementation does not consistently affect these lipid fractions in diabetic populations, in agreement with previous meta-analyses [43,44].

Insulin sensitivity

Despite neutral effects on HbA1c and fasting glucose, ω-3 supplementation was associated with statistically significant reductions in fasting insulin and HOMA-IR, with minimal heterogeneity across studies. These findings suggest a potential improvement in insulin sensitivity, possibly mediated through alterations in membrane lipid composition, modulation of intracellular insulin signaling pathways, or reductions in ectopic lipid accumulation [44]. Similar improvements in insulin resistance indices, without parallel reductions in HbA1c, have been reported in individuals with or at risk of diabetes [44]. However, these results were derived from a limited number of trials and were graded as low to very low certainty due to imprecision and small sample sizes. As such, although biologically plausible, they remain insufficient to support definitive therapeutic recommendations.

Inflammation and oxidative stress

Markers of systemic inflammation and oxidative stress, including CRP/hs-CRP, MDA, GSH, NO, and TAC, did not demonstrate statistically significant pooled effects. Most analyses were characterized by extreme heterogeneity, reflecting differences in baseline inflammatory status, biomarker assays, intervention duration, and cosupplementation strategies. Although

nonsignificant trends were often directionally consistent with the anti-inflammatory and antioxidant properties attributed to ω-3 fatty acids, the available evidence does not support reliable conclusions regarding these pathways in diabetes. Prior meta-analyses have similarly reported inconsistent effects on inflammatory biomarkers, with benefits appearing more pronounced in selected subgroups or under specific conditions [45]. Standardized biomarker assessment and adequately powered trials are required to clarify these mechanisms.

Functional outcomes and neuropathy

A notable and comparatively robust finding of this review was the improvement in CNBD with ω-3 supplementation. This outcome demonstrated a moderate effect size, with no detectable heterogeneity, and was assigned a low certainty rating by GRADE. Corneal nerve metrics are increasingly recognized as sensitive indicators of small-fiber neuropathy and early neuronal repair in diabetes. The homogeneous effect observed across studies suggests a potential neuroprotective role for ω-3 fatty acids, possibly related to membrane stabilization, axonal regeneration, or modulation of neuroinflammatory processes [30,33]. However, the limited number of trials and the absence of parallel improvements in neuropathic symptoms, functional impairment, or quality of life limit conclusions regarding clinical relevance. This is consistent with prior work reporting minimal effects of ω-3 supplementation on neuropathic symptoms despite structural nerve changes [33].

Sources of heterogeneity and certainty of evidence

Interpretation of pooled estimates is complicated by substantial clinical and methodological heterogeneity. Included trials varied widely in diabetes subtype (type 1, type 2, or gestational), ω-3 formulation (EPA, DHA, or mixed), dose, duration, baseline metabolic risk, and cosupplementation strategies. Evidence from gestational diabetes trials has shown more consistent improvements in metabolic biomarkers, although without clear effects on clinical outcomes [46,47]. Placebo selection also differed considerably, ranging from inert substances to vegetable oils with potential metabolic activity, further contributing to heterogeneity. These factors, combined with small sample sizes and short intervention durations, led to significant inconsistency, indirectness, and imprecision, which explains the frequent downgrading of certainty in GRADE assessments.

Implications for practice and research

From a clinical perspective, current evidence does not support routine ω-3 supplementation for improving glycemic control or most lipid parameters in people with diabetes. Importantly, the predominance of neutral findings across major metabolic, inflammatory, and oxidative outcomes suggests that ω-3 supplementation should not be considered a disease-modifying intervention for diabetes itself. Although improvements in selected surrogate markers of insulin sensitivity and nerve morphology were observed, these changes occurred in the absence of consistent improvements in major metabolic outcomes and cannot presently be assumed to translate into clinically meaningful long-term benefits. ω-3 supplementation may remain appropriate for indications supported by broader cardiovascular evidence, particularly in populations at high cardiovascular disease risk [48], but diabetes-specific benefits remain uncertain. Future research should prioritize adequately powered randomized trials with clearly defined diabetes subtypes, standardized ω-3 formulations with quantified EPA and DHA content, metabolically neutral placebos, and sufficient duration. Importantly, trials should extend beyond intermediate biomarkers and include clinically meaningful endpoints such as cardiovascular events, progression of diabetic complications, neuropathy-related disability, and patient-reported outcomes.

Strengths and limitations

Strengths

This systematic review and meta-analysis have several important strengths. First, it followed a prospectively registered protocol and was conducted in accordance with PRISMA guidelines, enhancing transparency and methodological rigor. Second, an extensive literature search across multiple major databases was conducted, minimizing the risk of missing relevant trials. Third, the analysis incorporated a broad range of outcomes, including lipid parameters, glycemic markers, insulin sensitivity indices, inflammatory and oxidative stress biomarkers, and functional outcomes such as CNBD, providing a comprehensive overview of potential metabolic and neuroprotective effects of ω-3 supplementation in diabetes. Methodologically, the use of MD for outcomes reported in the same units improved clinical interpretability, whereas the SMD was appropriately reserved for outcomes measured on different scales. The application of random-effects models prespecified subgroup analyses, and clearly labeled exploratory metaregression allowed for appropriate handling of anticipated heterogeneity. Importantly, the GRADE framework was systematically applied to assess the certainty of evidence, facilitating transparent interpretation of findings and preventing overstatement of results. Finally, the explicit framing of pooled analyses as exploratory and hypothesis-generating represents a methodological strength, aligning conclusions with the limitations of the underlying evidence.

Limitations

Several limitations should be considered when interpreting these findings. First, substantial clinical and methodological heterogeneity was present across most outcomes, driven by variation in diabetes subtypes (type 1, type 2, gestational, and high-risk populations), ω-3 formulation (EPA, DHA, or mixed), dosage, intervention duration, baseline metabolic status, and cosupplementation strategies. This heterogeneity frequently led to very high I^2 values and contributed to the downgrading of evidence certainty. Second, many pooled analyses were based on a small number of trials with limited sample sizes and short follow-up periods, leading to imprecision and wide CIs. As a result, several statistically significant findings, particularly for insulin sensitivity indices, were graded as low or very low certainty. Third, placebo selection varied considerably across studies, ranging from inert substances to vegetable oils with potential metabolic effects, which may have attenuated observed differences between intervention and control groups. Fourth, the evidence base relied predominantly on intermediate

biomarkers rather than hard clinical endpoints. None of the included trials evaluated outcomes such as cardiovascular events, progression of nephropathy or retinopathy, or neuropathy-related disability, limiting the ability to draw conclusions about long-term clinical benefit. Fifth, although exploratory metaregression analyses identified potential moderators of treatment effects, these analyses were constrained by low study counts, collinearity among predictors, and the lack of adjustment for multiple testing, and should therefore be interpreted cautiously. Finally, only studies published in English or Spanish were included, raising the possibility of language bias, and publication bias could not be reliably assessed for several outcomes because of the limited number of available trials.

In conclusion, this systematic review and meta-analysis indicate that ω-3 fatty acid supplementation does not consistently improve glycemic control, LDL or HDL cholesterol, or inflammatory and oxidative stress biomarkers in individuals with diabetes. Directionally favorable effects were observed for triglyceride concentrations, and statistically significant improvements were identified for fasting insulin, HOMA-IR, and CNBD. However, the overall certainty of evidence for most outcomes ranged from low to very low, largely because of substantial clinical and methodological heterogeneity, small sample sizes, short intervention durations, and imprecision. Importantly, none of the included trials evaluated hard clinical endpoints such as cardiovascular events, progression of diabetic complications, or neuropathy-related disability. As a result, it remains uncertain whether observed changes in intermediate biomarkers translate into meaningful long-term clinical benefits. Given these limitations, the present findings should be interpreted as exploratory and hypothesis-generating rather than confirmatory.

Future research should prioritize adequately powered randomized controlled trials with clearly defined diabetes subtypes, standardized ω-3 formulations (EPA, DHA, or mixed), sufficient intervention duration, and metabolically neutral placebos. Crucially, such trials should incorporate clinically relevant outcomes alongside mechanistic biomarkers to clarify whether ω-3 supplementation has a meaningful role as an adjunct to diabetes management. Until such evidence is available, ω-3 supplementation should be regarded as a complementary intervention rather than a routine therapeutic recommendation for people with diabetes.

Author Contribution

Jessica Paola Loaiza-Giraldo (JPLG), Rocío Valdivia-Arroyo (RVA), Valentina Greve-Quezada (VGQ), Alonso Quivira-Muñoz (AQM), Orlando Silva-Perez (OSP), Trinidad Soublette-Tocornal (TST), Alejandro Bruna-Mejias (ABM), Pablo Nova-Baeza (PNB), Mathias Orellana-Donoso (MOD), Maria P. Moya (MPM), Juan Sanchis-Gimeno (JSG), Vitor E. Valenti (VEV), Maria Piagkou (MP), Marko Konschake (MK), and Juan José Valenzuela-Fuenzalida (JJVF) contributed to the conception and design of the study. JPLG, RVA, VGQ, AQM, OSP, TST, ABM, and PNB conducted the literature search, screening, and data extraction. JPLG, MOD, MPM, and JJVF performed the data analysis and interpretation. JPLG and JJVF drafted the manuscript. JSG, VEV, MP, MK, and JJVF provided methodological expertise and critical intellectual input. MK served as the corresponding author and coordinated manuscript submission and correspondence. JJVF served as the senior author, supervised all stages of the project, and had primary responsibility for the final content. All authors critically revised the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors confirm that no generative AI or AI-assisted technologies were used in the writing, preparation, analysis, interpretation, revision, or editing of this manuscript.

Conflict of interest

The authors report no conflicts of interest.

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Appendix A. Supplementary data

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