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The Effects of Omega-3 Fatty Acids on Cardiometabolic Indices and Inflammatory Markers in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-analysis of Randomized Placebo-controlled Trials

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Abstrak:

Pendahuluan: Diabetes mellitus tipe 2 (T2DM) merupakan masalah kesehatan global yang terkait dengan risiko kardiovaskular. Studi ini bertujuan menilai efek asam lemak omega-3 (n3-FA) yang berasal dari laut, khususnya eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) terhadap indeks kardiometabolik dan penanda inflamasi pada pasien T2DM melalui tinjauan sistematis dan meta-analisis RCT. **Metode:** Tinjauan sistematis dilakukan terhadap RCT yang dipublikasikan di PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, dan Cochrane Library. Risiko bias dinilai dengan Cochrane RoB2. Analisis gabungan dilakukan dengan model efek acak dan dilaporkan sebagai *mean differences* (MD) atau *odds ratio* (OR) dengan interval kepercayaan (IK) 95%. Tingkat keyakinan bukti dievaluasi dengan pendekatan GRADE. **Hasil:** Sebanyak 37 RCT ($n=2.423$ pasien) diinklusi. n3-FA secara signifikan memperbaiki HbA1c (MD= -0,29 [IK 95%: -0,50, -0,08]; $I^2=92\%$), resistensi insulin (MD= -0,53 [-0,88, -0,18]; $I^2=70\%$), BMI (MD= -0,42 [-0,76, -0,08]; $I^2=0\%$), kolesterol total (MD= -6,39 [-12,57, -0,21]; $I^2=74\%$), HDL (MD= 1,37 [0,02, 2,73]; $I^2=59\%$), trigliserida (MD= -32,55 [-46,35, -18,74]; $I^2=84\%$), TNF- α (MD= -2,97 [-5,10, -0,84]; $I^2=86\%$), dan CRP (MD= -0,83 [-1,26, -0,40]; $I^2=70\%$) dibandingkan plasebo ($p < 0,05$). Tidak ditemukan efek bermakna pada glukosa darah, tekanan darah, LDL, dan IL-6. n3-FA ditoleransi baik dengan profil keamanan serupa plasebo (OR= 0,84; IK 95%: 0,41–1,72). Evaluasi GRADE menunjukkan tingkat bukti yang sedang hingga sangat rendah. **Kesimpulan:** n3-FA dikaitkan dengan perbaikan beberapa indeks kardiometabolik (HbA1c, resistensi insulin, BMI, kolesterol total, HDL, dan trigliserida) dan penanda inflamasi (TNF- α dan CRP) pada pasien T2DM. Interpretasi perlu kehati-hatian karena tingginya heterogenitas dan variasi kepastian bukti. Penelitian skala besar dengan metode ketat diperlukan untuk mendukung rekomendasi klinis.

Kata kunci: Asam lemak omega-3; Diabetes mellitus tipe 2; Inflamasi; Profil lipid; Resistensi insulin

Abstract:

Introduction: Type 2 diabetes mellitus (T2DM) remains a global health problem associated with cardiovascular risk. This study aims to study the effects of marine-derived omega-3 fatty acids (n3-FA), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), on cardiometabolic indices and inflammatory markers in patients with T2DM through systematic review and metaanalysis of RCTs. **Methods:** Systematic review was conducted on RCTs published in PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and Cochrane Library. Risk of bias was evaluated using Cochrane RoB2. Pooled analyses were performed using random-effects model and expressed as mean differences (MD) or odds ratio (OR) with 95% confidence intervals (CI). Evidence certainty was assessed using GRADE approach. **Results:** Thirty-seven RCTs ($n=2,423$ patients) were included. n3-FA significantly improved HbA1c (MD= -0.29 [95% CI: -0.50, -0.08]; $I^2=92\%$), insulin resistance (MD= -0.53 [-0.88, -0.18]; $I^2=70\%$), BMI (MD= -0.42 [-0.76, -0.08]; $I^2=0\%$), total cholesterol (MD= -6.39 [-12.57, -0.21]; $I^2=74\%$), HDL (MD= 1.37 [0.02, 2.73]; $I^2=59\%$), triglycerides (MD= -32.55 [-46.35, -18.74]; $I^2=84\%$), TNF- α (MD= -2.97 [-5.10, -0.84]; $I^2=86\%$), and CRP (MD= -0.83 [-1.26, -0.40]; $I^2=70\%$) compared with placebo ($p < 0.05$). No significant changes were observed in blood glucose, blood pressure, LDL, and IL-6. n3-FA was well tolerated with safety profile similar to placebo (OR= 0.84; 95% CI: 0.41–1.72). GRADE evaluation showed moderate-to-very low level of evidence. **Conclusion:** n3-FA associated with improvements on cardiometabolic indices (HbA1c, insulin resistance, BMI, total cholesterol, HDL, and triglycerides) and inflammatory markers (TNF- α and CRP) in T2DM patients. Interpretation should be cautious due to high heterogeneity and varying evidence certainty. Large-scale studies with rigorous methodology are needed to support clinical recommendations.

Keywords: Inflammation; Insulin resistance; Lipid profile; Omega-3 fatty acids; Type 2 diabetes mellitus

1. Introduction

Diabetes mellitus (DM) is a complex, multisystem metabolic disorder characterized by hyperglycemia that arises from insufficient insulin or action, resulting in impaired physiological glucose uptake and disrupted energy storage in muscle, adipose, and liver tissues (1). Several studies have shown that genetic factors and various risk factors, including obesity, smoking, dyslipidemia, hypertension, physical inactivity, age, unhealthy diet and sleep patterns, history of gestational diabetes, ethnicity, and stress or mental health, contribute to the development of DM (2–4). Type 2 DM (T2DM) is the most common types of DM in which insulin resistance and β -cell dysfunction are core pathophysiological mechanisms (5). By 2019, the global number of individuals with T2DM had increased to 437.9 million, compared with 148.4 million in 1990 (6). This underscores the urgency for comprehensive prevention and management strategies.

T2DM is associated with an increased risk of macro- and microvascular complications, especially cardiovascular disease, a leading causes of global morbidity and mortality in this population (7–9). Evidence suggests that these complications, including heart failure, ischemic heart disease, stroke, coronary artery disease, and peripheral artery disease, cause up to 50% of deaths among patients with T2DM (10). Insulin resistance, dyslipidemia, and chronic systemic inflammation are key mediators that accelerate the occurrence of atherosclerosis and cardiovascular disease (11–14). Since most of the morbidity and mortality in T2DM are thought to stem from cardiometabolic disorders and modifiable chronic inflammatory processes, interventions that target not only glycemic control but also lipid profiles and inflammatory markers are priorities for clinical research and disease control.

Marine-derived omega-3 fatty acids (n3-FA), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been extensively studied as adjunctive therapies in metabolic disorders due to their pleiotropic metabolic and anti-inflammatory effects. Mechanistic evidence indicates that n3-FA can improve insulin sensitivity, thereby influencing glucose uptake and lipid metabolism (15). They also suppress hepatic lipogenesis, regulate lipid metabolism, and increase fatty acid oxidation, which together contribute to improvement in lipid profiles (16). Beyond metabolic regulation, specialized pro-resolving mediators derived from n3-FA actively attenuate inflammatory pathways by inhibiting the NF- κ B signaling and reducing the production of pro-inflammatory cytokines (17,18). Additionally, marine-derived n3-FAs are generally more potent and have a direct impact on cardiovascular health and reducing inflammation than plant-based n3-FAs such as alpha-linolenic acid (ALA), as the human body is less efficient at converting ALA into EPA/DHA, so ALA is less recommended because it requires much larger doses to produce the same benefits as marine-derived EPA and DHA n3-FAs (19,20). These biological properties suggest that marine-derived n3-FA supplementation has the potential to simultaneously address dysglycemia, cardiometabolic risk factors, and chronic inflammation in T2DM.

Several RCTs have evaluated the effects of n3-FA for preventing cardiovascular disease and its complications in T2DM patients; however, inconsistent results remain observed, both in glycemic, cardiometabolic, and inflammatory outcomes. In the past five years, several meta-analyses have been published (21,22); however, updates are warranted to: 1) perform subgroup analyses by n3-FA dose to determine whether low and high doses have differences in the outcomes analyzed; 2) stratify by supplementation duration to evaluate whether the duration of supplementation influences clinically significant outcomes; 3) focus specifically on fish-oil-based or marine-derived n3-FA to reduce heterogeneity, as previous meta-analyses included n3-FA from mixed sources, including plant-based ones; and 4) include adverse events and safety analysis. Therefore, a comprehensive, focused, and homogeneous update of the evidence synthesis is needed, taking into account marine-based sources of n3-FA, clearly defined doses, and duration of supplementation as potential determinants of clinical effects.

Based on this background, this systematic review and meta-analysis aims to evaluate the effects of marine-derived n3-FA on glycemic control parameters, cardiometabolic indices, and inflammatory markers in patients with T2DM, using evidence from RCTs.

2. Materials and Methods

2.1. Protocol and Registration

This systematic review with meta-analysis followed the PRISMA 2020 guidelines (23). The study protocol has been registered prospectively in PROSPERO (registration number: CRD420261308693).

2.2. Eligibility Criteria

Research question formulated using the Population (P), Intervention (I), Comparison (C), Outcomes (O), and Study design (S) model is: “In patients with T2DM (P), does the administration of n3-FA (I), compared with placebo (C), provide beneficial effects on glycemic control, cardiometabolic risk factors, and inflammatory markers (O) based on evidence from RCTs (S)?”.

Based on the predefined PICOS model, studies were included if: 1) they were RCTs involving at least two arms consisting of an intervention with n3-FA and a control receiving a placebo; 2) studies were conducted in populations with a primary diagnosis of T2DM; 3) studies used marine-derived n3-FA limited to EPA and DHA content or based on fish oil; 4) RCTs reported ≥ 1 of the following outcomes: glycemic control parameters (fasting blood glucose [FBG], hemoglobin A1c [HbA1c], and insulin resistance [HOMA-IR]), cardiometabolic risk factors (body mass index [BMI], systolic/diastolic blood pressure [SBP/DBP], total cholesterol [TC], high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglycerides [TG]), and inflammatory markers (interleukin-6 [IL-6], tumor necrosis factor- α [TNF- α], and C-reactive protein [CRP]); 5) trials with at least 4 weeks of follow-up duration; 6) studies clearly reported numerical baseline and endpoint data for each outcome; and 7) publications were in English in peer-reviewed journals without year restriction.

RCTs were excluded if: 1) they were non-RCTs or studies with a pre-post design that did not involve a placebo control; 2) studies used plant-based n3-FA interventions; 3) RCTs reported clinical outcomes in data that could not be extracted, including data presented only in graphs, diagrams, and other illustrations without numerical information; 4) studies had follow-up period of < 4 weeks; and 5) articles were any type of review, case reports and case series, observational studies, preclinical studies based on computational approaches, animal model studies, preprints, and studies available only as abstracts without accessible full text.

2.3. Information Sources

Major databases were used in the literature search, including PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and Cochrane Library. The search was also expanded using backward and forward citation searching methods through Google Scholar to ensure all RCTs relevant to this meta-analysis were not missed. Included studies were published from the database's inception through January 2026.

2.4. Search Strategy

Search strategy was executed using MeSH terms combined with following basic keywords: (“omega-3” OR “omega-3 fatty acids” OR “eicosapentaenoic acid” OR “docosahexaenoic acid”) AND (“diabetes mellitus” OR “type 2 diabetes mellitus”) AND (“randomized controlled trial” OR “controlled clinical trial” OR “RCT”). The keywords were developed based on the database, which can be seen in detail in **Table 1**. This search process was executed by two authors (F.M.R. and A.P.W.) in January 2026.

Table 1. Search strategy.

Database	Queries
PubMed/MEDLINE	#1 ("fatty acids omega 3"[Supplementary Concept] OR "fatty acids omega 3"[All Fields] OR "omega 3"[All Fields] OR "fatty acids, omega 3"[MeSH Terms] OR ("fatty"[All Fields] AND "acids"[All Fields] AND "omega 3"[All Fields]) OR "omega 3 fatty acids"[All Fields]) #2 ("eicosapentaenoic acid"[Supplementary Concept] OR "eicosapentaenoic acid"[All Fields] OR "eicosapentaenoic acid"[MeSH Terms] OR ("eicosapentaenoic"[All Fields] AND "acid"[All Fields])) #3 ("docosahexaenoic acids"[Supplementary Concept] OR "docosahexaenoic acids"[All Fields] OR "docosahexaenoic acid"[All Fields] OR "docosahexaenoic acids"[MeSH Terms] OR ("docosahexaenoic"[All Fields] AND "acids"[All Fields]) OR ("docosahexaenoic"[All Fields] AND "acid"[All Fields]))

	#4 ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) #5 ("randomized controlled trial" OR "controlled clinical trial" OR "RCT") #6 ("review" OR "systematic review" OR "meta-analysis" OR "case study" OR "case report" OR "case series" OR "animal" OR "animal study" OR "animal model" OR "in vivo" OR "mouse" OR "murine" OR "mice") #7 (#1 OR #2 OR #3) AND #4 AND #5 NOT #6
Scopus	TITLE-ABS-KEY (omega-3 OR "omega-3 fatty acids" OR "eicosapentaenoic acid" OR "docosahexaenoic acid") AND TITLE-ABS-KEY (diabetes OR "diabetes mellitus" OR "type 2 diabetes mellitus") AND TITLE-ABS-KEY ("randomized controlled trial" OR "controlled clinical trial" OR RCT) AND NOT TITLE (review OR "systematic review" OR meta-analysis OR "case study" OR "case report" OR "case series" OR animal OR "animal study" OR "animal model" OR "in vivo" OR mouse OR murine OR mice) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (SRCTYPE , "j")) AND (LIMIT-TO (LANGUAGE , "English"))
Web of Science	#1 omega-3 OR "omega-3 fatty acids" OR "eicosapentaenoic acid" OR "docosahexaenoic acid" #2 diabetes OR "diabetes mellitus" OR "type 2 diabetes mellitus" #3 "randomized controlled trial" OR "controlled clinical trial" OR RCT #4 review OR "systematic review" OR meta-analysis OR "case study" OR "case report" OR "case series" OR animal OR "animal study" OR "animal model" OR "in vivo" OR mouse OR murine OR mice #5 #1 (Topic) AND #2 (Topic) AND #3 (Topic) NOT #4 (Title); Document types: Article
ScienceDirect	Title, abstract, keywords: (omega-3 OR "omega-3 fatty acids" OR "eicosapentaenoic acid" OR "docosahexaenoic acid") AND (diabetes OR "diabetes mellitus" OR "type 2 diabetes mellitus") AND ("randomized controlled trial" OR "controlled clinical trial")
Cochrane Library	Title Abstract Keyword: (omega-3 OR "omega-3 fatty acids" OR "eicosapentaenoic acid" OR "docosahexaenoic acid") AND (diabetes OR "diabetes mellitus" OR "type 2 diabetes mellitus") AND ("randomized controlled trial" OR "controlled clinical trial" OR RCT)

2.5. Selection Process

The process began by importing all raw records found through electronic database searches and citation searches into Zotero 8.0 for Windows. Using the software's automated tools, all duplicates were removed and manually validated to ensure no duplicates remain. Records without duplicates were then subjected to initial screening based on title and abstract, and all articles not relevant to the topic were excluded at this stage, leaving potentially eligible articles. These potential studies were then obtained in full text for a comprehensive evaluation, by applying the PICOS model along with the predetermined inclusion criteria. All RCTs deemed eligible were subjected to data extraction and synthesis. The entire selection process was documented in a PRISMA flowchart.

Selection process was conducted by two authors (F.M.R. and A.P.W.). Both authors previously conducted a calibration to achieve a common understanding of the eligibility criteria for selecting potentially eligible studies. If discrepancies emerged during the process, a third author (A.S.) was involved in the discussion to reach a unanimous consensus.

2.6. Data Collection Process

Data collection process was performed to extract all essential data and was carried out by two authors (A.P.W. and R.A.), and validated by the third author (A.S.). Data extracted from the full text of eligible studies were documented using Microsoft Excel 2016 for Windows. Extracted data included the following: author/study, country, number of patients, age, baseline diabetes criteria, study duration, intervention details, EPA and DHA dose, and control.

Meanwhile, several data points were extracted for quantitative synthesis, including author, number of patients analyzed in both arms, baseline (pre-intervention) and endpoint (post-intervention) data for each outcome, n3-FA (EPA and DHA) dosage, and intervention duration. Outcome data finally were extracted as mean and standard deviation (SD).

2.7. Study Risk of Bias Assessment

Risk of bias in studies was evaluated using the Cochrane RoB2 (24). This tool assessed five domains related to bias: randomization process, deviation from the intended intervention, missing outcome data, outcome

measurement, and selection of the reported result. Each domain was judged as low, some concerns, or high risk. The RobVis tool was used to visualize the results of the assessment (25).

This assessment was conducted independently by two reviewers (F.M.R. and R.A.), both of whom had calibrated the interpretation of the Cochrane RoB2 tool's signaling questions. Any discrepancies that emerged during the evaluation process were addressed through in-depth discussion, and, if necessary, a senior researcher (A.S.) was involved to reach a final consensus.

2.8. Statistical Synthesis Methods

Endpoint data in the form of mean and SD for each outcome were used to compare the final results of the intervention between the group of patients receiving n3-FA and the placebo control group. For studies reporting numerical data in the form of median with min–max values or first quartile–third quartile, if eligible, the data were converted into mean and SD using the conversion model by Wan et al. (26). If studies reported data as mean with standard error of the mean (SEM) or 95% CI, they were then converted into SD using the following formulations (27):

$$SD = SEM \times \sqrt{n}$$

$$SD = \frac{(Upper\ limit - Lower\ limit)}{3.92} \times \sqrt{n}$$

Additional analyses were also conducted for several outcomes to convert units in order to enable homogeneous pooled analysis. For the FBG outcome, studies that used units of mmol/L were first converted into mg/dL using the following equation (28):

$$Mean_{mg/dL} = Mean_{mmol/L} \times 18.018$$

$$SD_{mg/dL} = SD_{mmol/L} \times 18.018$$

For HbA1c outcome, studies with units in the form of IFCC units (mmol/mol) were converted into NGSP units (%) using the equation (29,30):

$$Mean_{\%} = (Mean_{mmol/mol} \times 0.09148) + 2.152$$

$$SD_{\%} = SD_{mmol/mol} \times 0.09148$$

For the TC, HDL, and LDL outcomes, studies that used units of mmol/L were converted into mg/dL using the following formula (31):

$$Mean_{mg/dL} = Mean_{mmol/L} \times 38.67$$

$$SD_{mg/dL} = SD_{mmol/L} \times 38.67$$

Meanwhile, specifically for the TG outcome, studies that used units of mmol/L were converted into mg/dL using the following formula (31):

$$Mean_{mg/dL} = Mean_{mmol/L} \times 88.57$$

$$SD_{mg/dL} = SD_{mmol/L} \times 88.57$$

Considering the variability in patient characteristics, n3-FA dosage, intervention duration, and baseline criteria across studies, a meta-analysis using a random-effects model of DerSimonian–Laird was implemented to pool effect estimates. Results for all outcomes were presented as mean differences (MD) with 95% confidence intervals (CI). Statistical significance was set at $p < 0.05$ and was inferred when 95% CI excluded zero. The χ^2 test and I^2 statistic were used to assess heterogeneity, indicated by $p < 0.10$, and degree of heterogeneity, categorized as low, moderate, and high ($I^2 < 25\%$, $25\text{--}75\%$, $> 75\%$, respectively) (32).

Subgroup analyses were conducted to further explore heterogeneity across studies, by stratifying the analyses based on EPA and DHA n3-FA dose ($< 2,000$ vs $\geq 2,000$ mg/day) and intervention duration (≤ 8 weeks vs > 8 weeks). The cut-off values for subgroup analyses based on dose and duration were determined based on previous meta-analyses (21,22). Finally, sensitivity analysis using leave-one-out method was performed to assess the robustness of the meta-analyses. Statistical analyses were conducted using StataMP 17.0 for Windows.

2.9. Reporting Bias Assessment

If the number of studies for a particular outcome reached ≥ 10 studies, publication bias was assessed using a funnel plot by plotting MD against standard error (33). Funnel plot visualization was performed by two authors

(F.M.R. and A.S.). For formal analysis, Egger's test (34) and Begg's test (35) were conducted, with $p < 0.10$ indicating a presence of publication bias. Publication bias analysis was performed using StataMP 17.0 for Windows.

2.10. Adverse Events and Safety Analysis

Analysis of any adverse events that occurred was conducted to determine the safety profile of n3-FA compared to placebo. Pooled analysis was run using a random-effects model of DerSimonian–Laird and was reported as odds ratio (OR) with 95% CI. To address studies reporting zero events in one or both arms, a treatment-arm continuity correction was implemented. The χ^2 test and I^2 statistic were used for heterogeneity evaluation. Adverse events analysis was conducted using StataMP 17.0 for Windows.

2.11. Certainty Assessment

Two authors (F.M.R. and A.S.) evaluated certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (36). This approach assesses the following: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Since this study included only RCTs, all outcomes were initially assigned a high level of certainty, and subsequently evidence certainty was evaluated for potential downgrading or upgrading based on the assessment of each domain. Results of the certainty of evidence evaluation for each outcome were presented in a summary of findings table.

3. Results

3.1. Study Selection

Database searches yielded 1,117 records. After removal of duplicates and retracted papers, 791 records remained. Initial screening based on titles and abstracts excluded 688 records, and 103 potentially eligible articles were further assessed for eligibility. At this stage, several articles were excluded due to noncompliance with the eligibility criteria; therefore, 35 articles were retrieved from the databases. Study identification was also performed through citation searching, yielding two eligible articles. Ultimately, 37 RCTs (37–73) were included in this study (Figure 1).

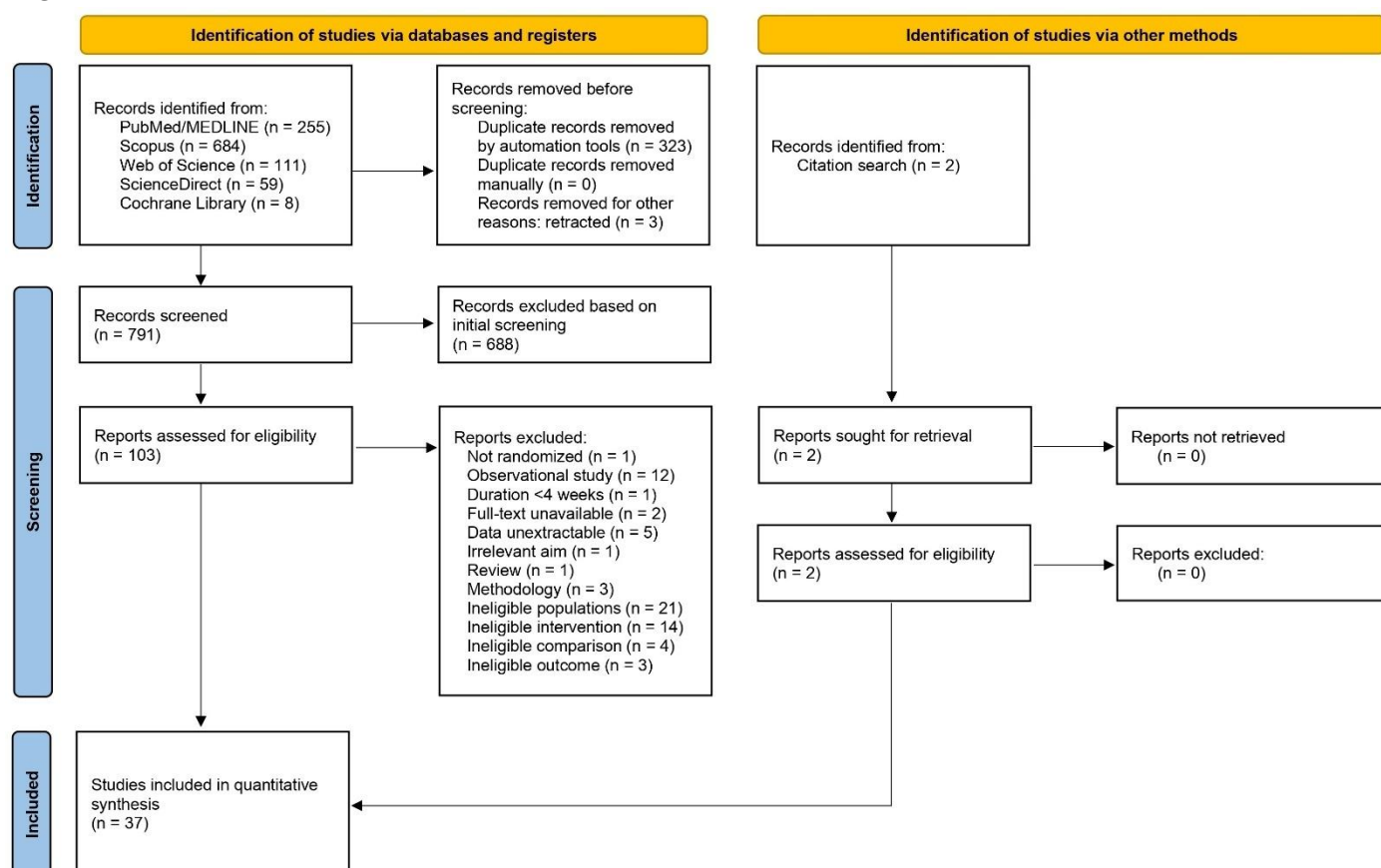


Figure 1. PRISMA flowchart.

3.2. Study Characteristics

Thirty-seven studies involving 2,423 adult patients (aged ≥ 18 years) with T2DM were included in this review. The studies were conducted in the following regions: Iran (37,38,40,42–45,49,54–57,59,62–65), China (47,52,53,67,68,70,72,73), Brazil (39,41), Japan (51,60), United Kingdom (46), Mexico (48), France (50), Norway (58), Denmark (61), Egypt (69), and Australia (71). The intervention duration varied across studies, ranging from 8 weeks or less (39,41,42,44–46,49–51,54–56,59,61,62,71) to more than 8 weeks (37,38,40,43,47,48,52,53,57,58,60,63–70,72,73) (**Table 2**).

Table 2. General study characteristics.

Study	Country	Participants			Baseline diabetes criteria	Study duration
		N ^a	Age ^b			
Asghari et al. (37)	Iran	50 (25/25)	>18	(56.88 ± 8.36/57.48 ± 11.27)	American Diabetes Association (ADA) criteria; taking antidiabetic medication for ≥4 months; HbA1c >5.8%	12 w
Azizi-Soleiman et al. (38)	Iran	45 (14/14/17) ^c	30–65	(51.4 ± 8.8/56.1 ± 9.7/56.9 ± 5.5) ^c	Taking oral antidiabetic medication; FBG <140 mg/dL	12 w
Crochemore et al. (39)	Brazil	41 (14/14/13) ^c	(60.64 ± 7.37/60.00 ± 7.49/61.83 ± 9.07)		Menopausal women with T2DM	4 w
Farsi et al. (40)	Iran	44 (22/22)	30–65	(54.23 ± 7.69/53.32 ± 6.80)	T2DM clinical criteria	10 w
Fayh et al. (41)	Brazil	30 (15/15)	≥18	(50.47 ± 6.06/50.67 ± 6.70)	HbA1c <9.0%	8 w
Ghaedi et al. (42)	Iran	36 (18/18)	35–50	(44.44 ± 3.79/44.72 ± 4.69)	ADA criteria; T2DM for ≥1 year; taking oral antidiabetic medication for ≥3 months	8 w
Golpour et al. (43)	Iran	61 (31/30)	30–65	(51.15 ± 7.45/50.56 ± 7.21)	ADA criteria; FBG >126 mg/dL without using antidiabetic medication	10 w
Golzari et al. (44)	Iran	36 (18/18)	35–50	(44.44 ± 3.79/44.72 ± 4.69)	ADA criteria; T2DM for ≥1 year; FBG ≥126 mg/dL or 2hPG ≥200 mg/dL	8 w
Hajianfar et al. (45)	Iran	71 (37/34)	45–65		T2DM for ≥5 years	8 w
Hendra et al. (46)	United Kingdom	80 (40/40)	(56.0 ± 8.07/55.8 ± 11.29)		T2DM clinical criteria	6 w
Hua et al. (47)	China	105 (54/51)	(45.6 ± 5.9/43.7 ± 8.6)		Newly diagnosed T2DM; HbA1c <7.8%	12 w
Jacobo-Cejudo et al. (48)	Mexico	54 (29/25)	25–60	(50.4 ± 6.3/48.1 ± 6.8)	T2DM with oral antidiabetic medication	24 w
Jazayery et al. (49)	Iran	33 (16/17)	33–65		Men with T2DM	8 w
Kabir et al. (50)	France	26 (12/14)	40–60	(55 ± 3.7/55 ± 6.9)	Postmenopausal women with T2DM; HbA1c ≥7.0%	8 w
Kondo et al. (51)	Japan	23 (11/12)	(69.5 ± 6.0/69.8 ± 7.3)		Postmenopausal women with T2DM; HbA1c <8.4%	4 w
Liu et al. (52)	China	61 (31/30)	40–60	(50.2 ± 5.9/49.7 ± 5.4)	ADA criteria; HbA1c 6.5–7.5%	12 w
Lu et al. (53)	China	309 (153/156)	20–75	(50.84 ± 9.97/50.56 ± 11.19)	1999 WHO criteria; stable condition under oral antidiabetic medication; HbA1c <7.5%	12 w
Mahmoudabadi et al. (54)	Iran	33 (16/17)	33–63	(54.2 ± 4.8/52.6 ± 5.4)	Men with T2DM	8 w
Malekshahi Moghadam et al. (55)	Iran	84 (42/42)	45–85	(55.36 ± 9.88/52.96 ± 10.72)	T2DM for ≥2 years; taking oral antidiabetic medication; FBG ≥140 mg/dL or RBG ≥200 mg/dL	8 w
Mansoori et al. (56)	Iran	68 (35/33)	30–70	(55.8 ± 7.6/56.0 ± 7.0)	FBG ≥126 mg/dL	8 w
Mazaherioun et al. (57)	Iran	85 (44/41)	30–65	(51.15 ± 7.45/50.56 ± 7.21)	ADA criteria	10 w

Study	Country	Participants		Baseline diabetes criteria	Study duration
		N ^a	Age ^b		
Mostad et al. (58)	Norway	26 (12/14)	40–75	T2DM clinical criteria	9 w
Naeini et al. (59)	Iran	50 (25/25)	30–70 (54.7 ± 7.6/56.3 ± 7.8)	FBG ≥126 mg/dL	8 w
Ogawa et al. (60)	Japan	26 (13/13)	(79.5 ± 8.6/81.2 ± 7.6)	Elderly T2DM exclusively fed by enteral nutrition	12 w
Pedersen et al. (61)	Denmark	44 (23/21)	38–85 (63/63)	T2DM for ≥1 year; T2DM onset at age >30 years	8 w
Pooya et al. (62)	Iran	81 (40/41)	45–85 (56.38 ± 9.24/52.7 ± 10.65)	T2DM for ≥2 years	8 w
Raygan et al. (63)	Iran	60 (30/30)	(64.1 ± 9.3/62.0 ± 13.0)	2014 ADA criteria	12 w
Sarbolouki et al. (64)	Iran	67 (32/35)	35–55 (43.03 ± 4.88/45.3 ± 3.93)	T2DM for 2–15 years; taking oral antidiabetic medication or FBG >7.0 mmol/L	12 w
Shidfar et al. (65)	Iran	50 (25/25)	33–75 (54.1 ± 11.1/53.4 ± 11.7)	T2DM for ≥6 years; taking oral antidiabetic medication; HbA1c <9.0%; FBG ≥126 mg/dL or 2hPG ≥200 mg/dL	10 w
Udupa et al. (66)	India	50 (25/25)	21–65 (54.9 ± 3.5/53.8 ± 2.1)	T2DM for 5–10 years; oral antidiabetic medication for ≥6 months; FBG 110–250 mg/dL	12 w
Wang et al. (67)	China	99 (49/50)	(64.6 ± 5.5/66.3 ± 5.1)	WHO criteria; FBG ≥7.0 mmol/L or 2hPG ≥11.1 mmol/L	24 w
Wang et al. (68)	China	63 (35/28)	51–65 (58.94 ± 7.21/56.18 ± 4.06)	2012 ADA criteria	12 w
Werida et al. (69)	Egypt	70 (35/35)	30–60 (50.51 ± 8.42/52.42 ± 7.64)	T2DM for ≥2 years; HbA1c ≥7.0%	12 w
Wong et al. (70)	China	97 (49/48)	(61.2 ± 9.0/59.0 ± 9.3)	WHO criteria; taking oral antidiabetic medication and/or insulin; HbA1c <11.0%	12 w
Woodman et al. (71)	Australia	51 (17/18/16) ^c	40–75 (61.2 ± 9.6/60.9 ± 8.2/61.5 ± 7.6) ^c	FBG >7.0 mmol/L or RBG >11.1 mmol/L or taking oral antidiabetic medication; HbA1c <9.0%	6 w
Xia et al. (72)	China	101 (52/49)	18–70 (53.37 ± 9.22/54.29 ± 8.45)	Very well controlled T2DM; HbA1c <9.0%	12 w
Zheng et al. (73)	China	113 (58/55)	35–80 (59.7 ± 8.8/59.1 ± 10)	FBG >7.0 mmol/L or on antidiabetic medication	24 w

RBG, random blood glucose; 2hPG, 2-hour plasma glucose; w, weeks.

^a Number of participants (intervention/control).

^b Age range (mean ± standard deviation [SD], intervention/control) in years.

^c Study using 2 included intervention group (intervention 1/intervention 2/control).

Based on the intervention characteristics, most studies administered n3-FA or fish oil capsules, except for two studies (51,60) that implemented fish-based dietary interventions rich in n3-FA with reported EPA and DHA content. Regarding the daily dosage, 21 studies (37–39,41,42,44,45,47–50,54,56,59,60,63,64,66,68,69,72) used EPA and DHA doses of less than 2,000 mg/day and 16 studies (40,43,46,51–53,55,57,58,61,62,65,67,70,71,73) administered doses of 2,000 mg/day or more (**Table 3**). All included RCTs used a placebo-controlled supplement similar to n3-FA intervention.

Table 3. Intervention and control details of included studies.

Study	Intervention	EPA + DHA dose (mg/day)	Control
Asghari et al. (37)	2,000 mg n3-FA (@1,000 mg: 500 mg EPA/200 mg DHA)	1,400	Placebo capsules
Azizi-Soleiman et al. (38)	980 mg EPA (245 mg EPA/30 mg DHA) or 964 mg DHA (33 mg EPA/241 mg DHA)	275/274	Placebo gel (canola oil)
Crochemore et al. (39)	2,500 mg fish oil (547.5 mg EPA/352.5 mg DHA) or 1,500 mg fish oil (328.5 mg EPA/211.5 mg DHA)	900/540	Placebo (gelatin)
Farsi et al. (40)	4,000 mg n3-FA (@1 capsule: 310 mg EPA/210 mg DHA)	2,080	Placebo (4,000 mg corn oil)
Fayh et al. (41)	300 mg n3-FA (180 mg EPA/120 mg DHA)	300	Placebo (500 mg gelatin)
Ghaedi et al. (42)	2,000 mg EPA soft gel (@1,000 mg: 75% EPA)	1,500	Placebo (edible paraffin)
Golpour et al. (43)	2,700 mg n3-FA soft gel (@900 mg: 600 mg EPA/300 mg DHA)	2,700	Placebo (900 mg edible paraffin)
Golzari et al. (44)	2,000 mg n3-FA (@1 capsule: 75% EPA)	1,500	Placebo (1,000 mg edible paraffin)
Hajianfar et al. (45)	2,000 mg n3-FA (@1,000 mg: 360 mg EPA/240 mg DHA)	1,200	Placebo (1,000 mg cornstarch)
Hendra et al. (46)	10,000 mg fish oil (1,800 mg EPA/1,200 mg DHA)	3,000	Placebo (olive oil)
Hua et al. (47)	2,000 mg fish oil (@1,000 mg: 500 mg EPA and DHA with ratio 3:2)	1,000	Placebo (1,000 mg corn oil)
Jacobo-Cejudo et al. (48)	2,400 mg fish oil (@1,400 mg: 160 mg EPA/100 mg DHA)	520	Placebo gel (cornstarch)
Jazayery et al. (49)	500 mg EPA	500	Placebo
Kabir et al. (50)	3,000 mg fish oil (1,080 mg EPA/720 mg DHA)	1,800	Placebo (paraffin oil)
Kondo et al. (51)	n3-FA-rich fish-based diet ($\geq 3,000$ mg EPA and DHA)	$\geq 3,000$	Placebo (control diet)
Liu et al. (52)	6,000 mg fish oil (2,460 mg EPA/690 mg DHA)	3,150	Placebo (6,000 mg corn oil)
Lu et al. (53)	4,000 mg n3-FA (@1,000 mg 465 mg EPA/375 mg DHA)	3,360	Placebo (corn oil)
Mahmoudabadi et al. (54)	500 mg EPA	500	Placebo
Malekshahi Moghadam et al. (55)	2,714 mg n3-FA (1,548 mg EPA/828 mg DHA/338 mg others)	2,376	Placebo (2,100 mg sunflower oil)
Mansoori et al. (56)	2,400 mg fish oil (@1 capsule: 362.5 mg EPA/600 mg DHA)	1,850	Placebo (2,400 mg paraffin oil)
Mazaherioun et al. (57)	2,700 mg n3-FA (@900 mg: 600 mg EPA/300 mg DHA)	2,700	Placebo (900 mg edible paraffin)
Mostad et al. (58)	17.6 mL fish oil (1,800 mg EPA/3,000 mg DHA)	4,800	Placebo (17.8 mL corn oil)
Naeini et al. (59)	2,400 mg fish oil (@600 mg: 100 mg EPA/362.5 mg DHA)	1,850	Placebo gels (600 mg paraffin oil)
Ogawa et al. (60)	Liquid diet rich in n3-FA (@100 kcal: 25 mg EPA/17 mg DHA)	427	Liquid diet without EPA and DHA
Pedersen et al. (61)	4,000 mg fish oil (2,600 mg EPA and DHA)	2,600	Placebo capsule (corn oil)
Pooya et al. (62)	2,714 mg n3-FA (1,548 mg EPA/828 mg DHA/338 mg others)	2,376	Placebo capsule (2,100 mg sunflower oil)
Raygan et al. (63)	1,000 mg fish oil (250 mg EPA/150 mg DHA)	400	Placebo (paraffin)
Sarbolouki et al. (64)	2,000 mg EPA (@500 mg: 95% EPA)	1,900	Placebo capsule (500 mg corn oil)
Shidfar et al. (65)	2,000 mg purified n3-FA (@1,000 mg: 520 mg EPA/480 mg DHA)	2,000	Placebo capsule
Udupa et al. (66)	300 mg n3-FA (@1 capsule: 180 mg EPA/120 mg DHA)	300	Placebo gelatin capsule
Wang et al. (67)	4,000 mg fish oil (1,340 mg EPA/1,070 mg DHA)	2,410	Placebo capsule (corn oil)
Wang et al. (68)	2,000 mg (@1 capsule: 1,000 mg EPA/400 mg DHA)	1,400	Placebo (soybean powder + placebo)

Study	Intervention	EPA + DHA dose (mg/day)	Control
Werida et al. (69)	1,000 mg fish oil (13% EPA/9% DHA)	220	Placebo (corn oil)
Wong et al. (70)	4,000 mg fish oil (42% EPA/25% DHA)	2,680	Placebo capsule (4,000 mg olive oil)
Woodman et al. (71)	4,000 mg EPA (@1 capsule: ~96% EPA) or 4,000 mg DHA (@1 capsule: ~92% EPA/~0.5% DHA)	3,840/3,700	Placebo capsule (4,000 mg olive oil)
Xia et al. (72)	3,000 mg fish oil (@100 g: 36.86 g EPA/17.47 g DHA)	1,630	Placebo capsules (corn oil)
Zheng et al. (73)	2,000 mg fish oil (@500 mg: 300 mg EPA/200 mg DHA)	2,000	Placebo capsule (corn oil)

3.3. Risk of Bias in Studies

Based on the evaluation, 18 studies (38,39,41,45–51,54,55,57,60,62,64,65,71) were judged some concerns, whereas the remaining 19 studies (37,40,42–44,52,53,56,58,59,61,63,66–70,72,73) were considered low risk of bias (**Figure 2**). Domain 1 (bias arising from the randomization process) was the domain most frequently rated as having some concerns, mainly because, although randomization was performed, the randomization method was not explicitly described. In addition, allocation concealment was not reported in most studies.

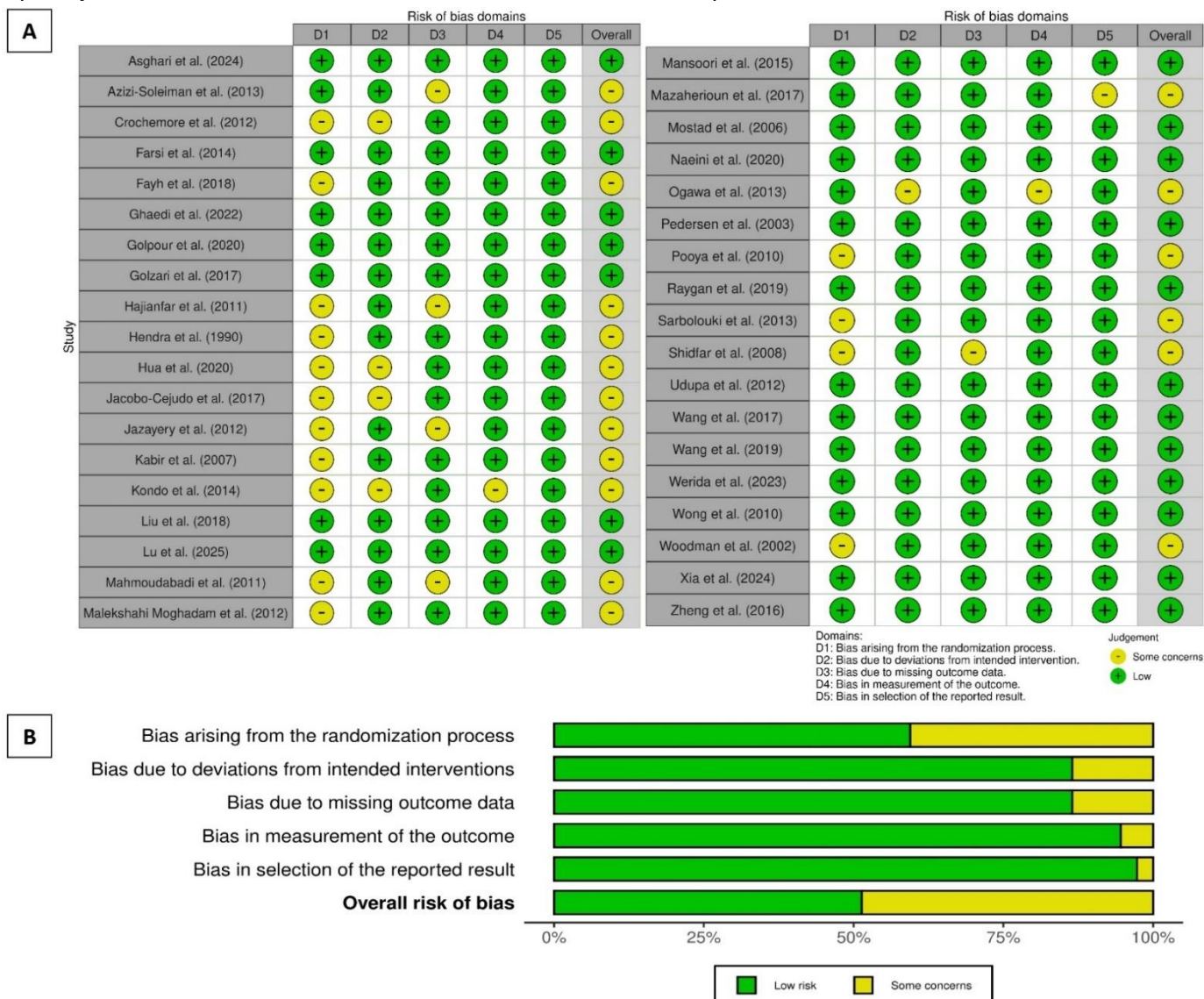


Figure 2. Risk of bias assessment using Cochrane RoB2 tool: (A) traffic light plot and (B) and graph.

3.4. Omega-3 Fatty Acids and Glycemic Control

Random-effects meta-analysis demonstrated that n3-FA significantly reduced HbA1c by 0.29% (number of studies [n_{studies}] = 27; MD = -0.29; 95% CI: -0.50, -0.08; $p = 0.01$) and HOMA-IR by 0.53 (n_{studies} = 16; MD = -0.53; 95% CI: -

0.88, -0.18; $p < 0.01$) compared with placebo, with heterogeneity that was high (HbA1c: $p < 0.01$; $I^2 = 92\%$) and moderate ($p < 0.01$; $I^2 = 70\%$), respectively (**Figure 3B-C**). However, n3-FA did not significantly reduce FBG levels ($n_{\text{studies}} = 33$; MD = -2.78; 95% CI: -7.53, 1.97; $p = 0.25$) (**Figure 3A**).

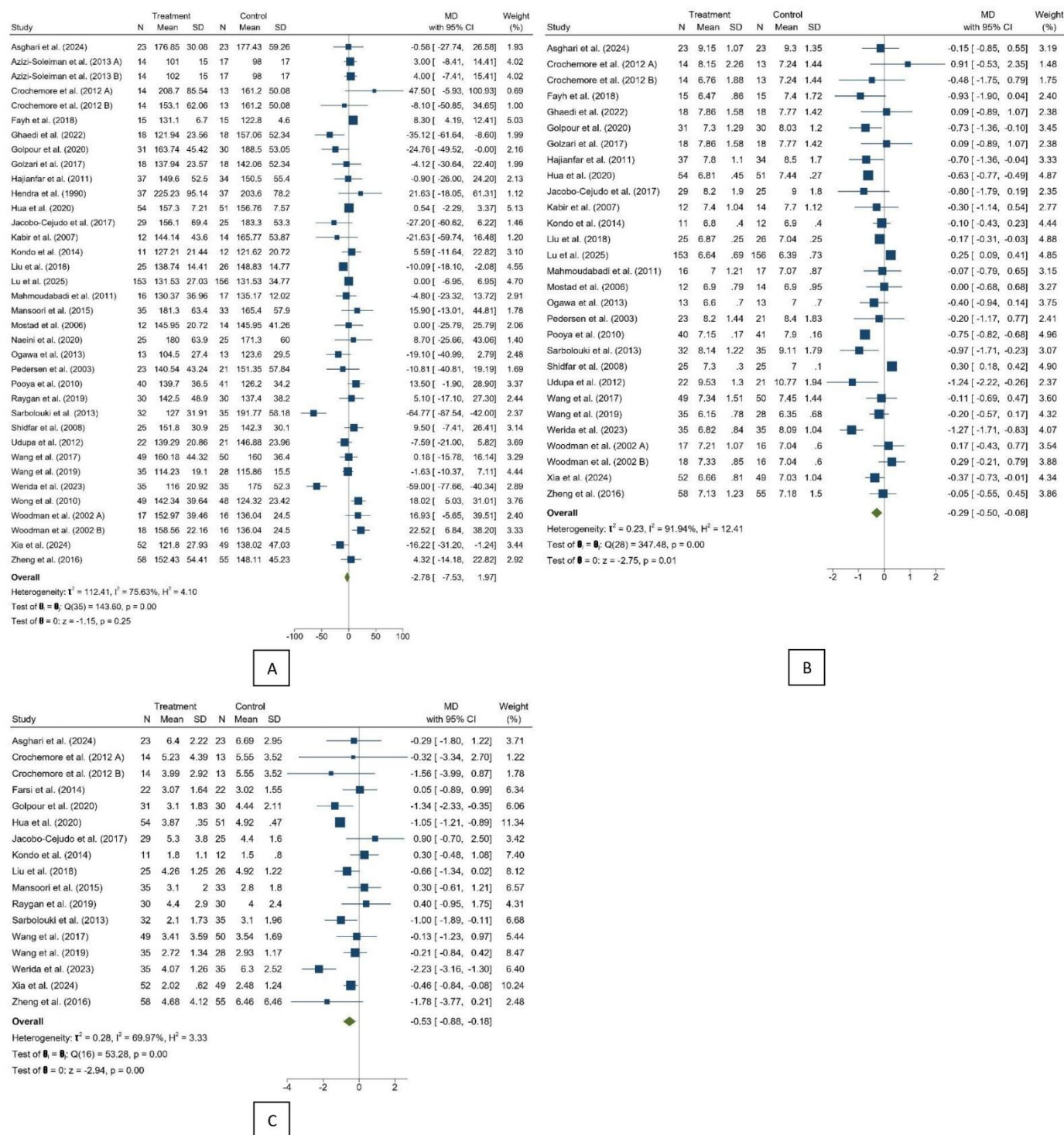


Figure 3. Forest plot of the efficacy of n3-FA supplementation on glycemic control: (A) FBG; (B) HbA1c; and (C) HOMA-IR.

3.5. Omega-3 Fatty Acids and Cardiometabolic Indices

Compared with placebo, the analysis showed that n3-FA significantly reduced BMI by 0.42 kg/m^2 ($n_{\text{studies}} = 18$; MD = -0.42; 95% CI: -0.76, -0.08; $p = 0.02$) with no detected heterogeneity ($p = 0.49$; $I^2 = 0\%$) (**Figure 4A**). However, n3-FA supplementation had no effect on either SBP ($n_{\text{studies}} = 6$; MD = 1.26; 95% CI: -1.21, 3.72; $p = 0.32$) or DBP ($n_{\text{studies}} = 6$; MD = 0.10; 95% CI: -1.23, 1.44; $p = 0.88$) (**Figure 4B-C**).

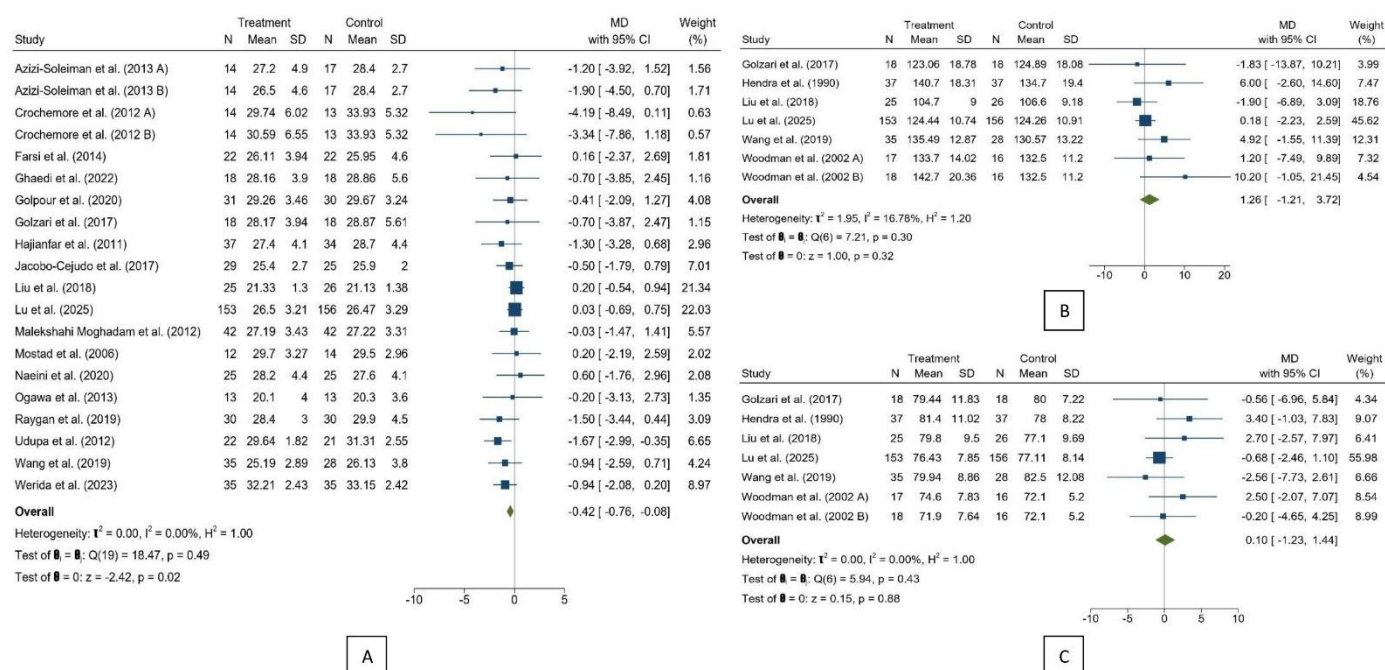
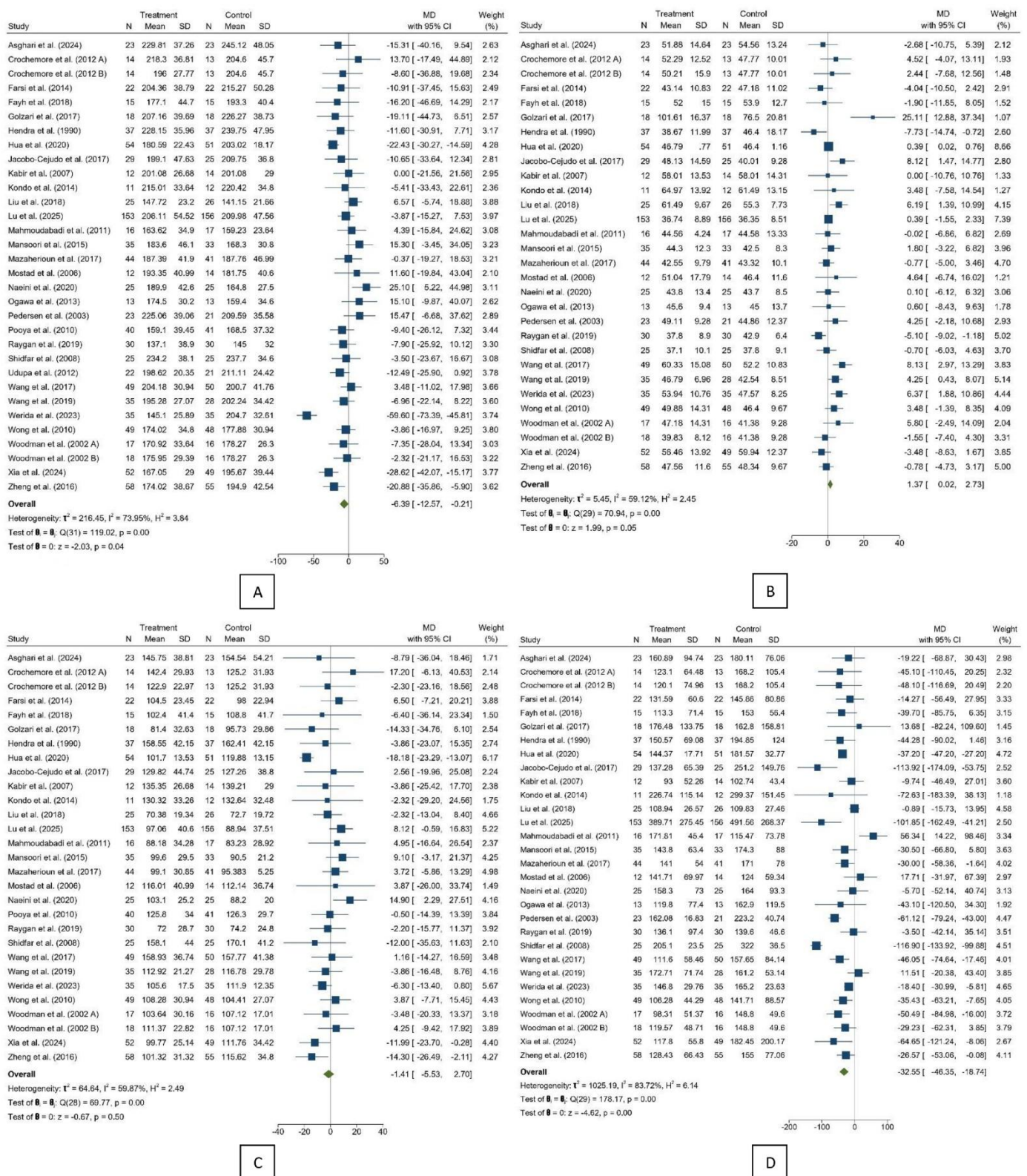


Figure 4. Forest plot of the efficacy of n3-FA on BMI and blood pressure: (A) BMI; (B) SBP; and (C) DBP.

Meanwhile, the meta-analysis evaluating the n3-FA efficacy on lipid profiles showed that n3-FA, compared with placebo, reduced TC by 6.39 mg/dL ($n_{\text{studies}} = 30$; MD = -6.39; 95% CI: -12.57, -0.21; $p = 0.04$), increased HDL by 1.38 mg/dL ($n_{\text{studies}} = 28$; MD = 1.37; 95% CI: 0.02, 2.73; $p < 0.05$), and reduced TG by 32.55 mg/dL ($n_{\text{studies}} = 28$; MD = -32.55; 95% CI: -46.35, -18.74; $p < 0.01$), with moderate, moderate, and substantial heterogeneity observed, respectively (TC: $p < 0.01$; $I^2 = 74\%$; HDL: $p < 0.01$; $I^2 = 59\%$; TG: $p < 0.01$; $I^2 = 84\%$) (**Figure 5A-B, D**). No significant effect was reported on LDL levels ($n_{\text{studies}} = 27$; MD = -1.41; 95% CI: -5.53, 2.70; $p = 0.50$) (**Figure 5C**).



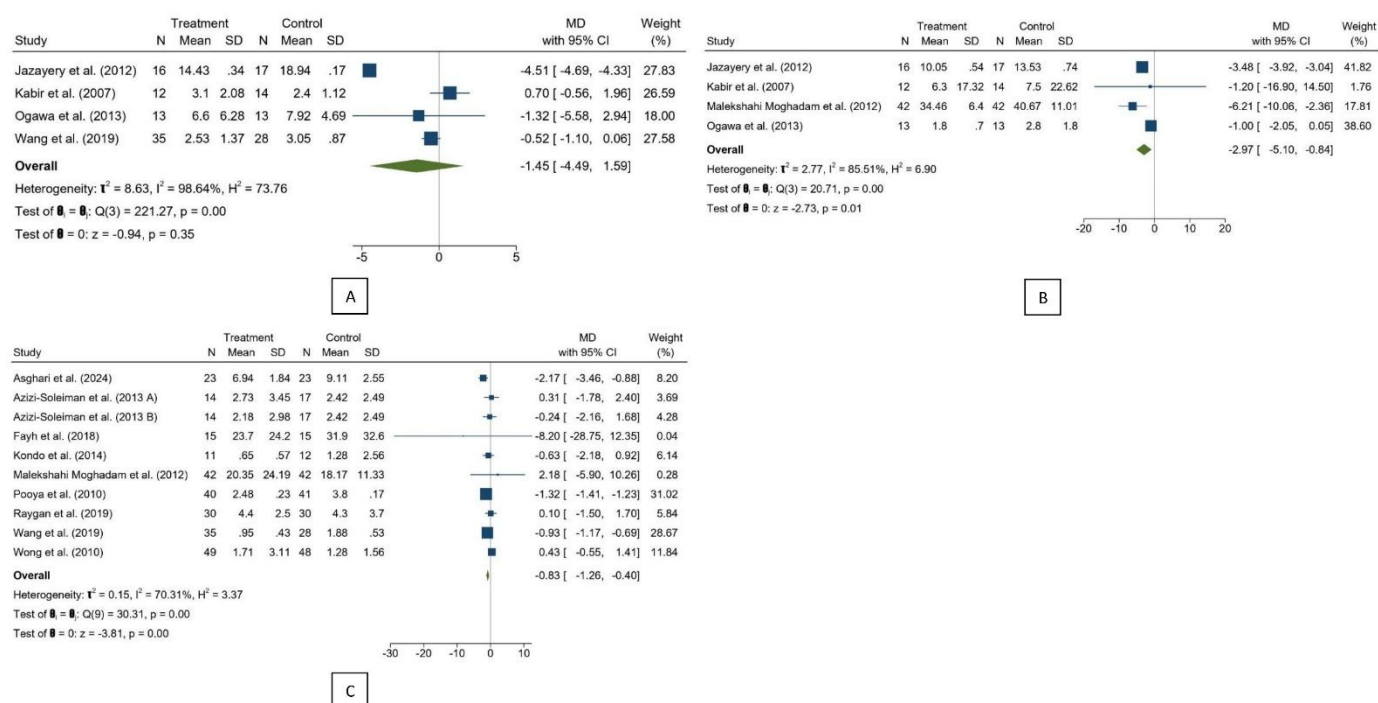


Figure 6. Forest plot of the efficacy of n3-FA on inflammatory markers: (A) IL-6; (B) TNF-α; and (C) CRP.

3.7. Subgroup Analysis

To further explore outcomes with high heterogeneity, subgroup analyses based on EPA and DHA dose (<2,000 vs $\geq 2,000$ mg/day) and supplementation duration (≤ 8 vs > 8 weeks) were performed only on outcomes with substantial heterogeneity and sufficient number of studies for subgrouping (Table 4).

For FBG, although heterogeneity remained high, the effect became significant in studies administering doses of <2,000 mg/day and durations of > 8 weeks. Meanwhile, heterogeneity decreased to moderate, but the effect remained non-significant in studies with supplementation durations of ≤ 8 weeks. For HbA1c, the heterogeneity decreased to moderate, with a consistently significant effect in studies using doses of <2,000 mg/day. In contrast, the effect estimates and heterogeneity for HOMA-IR remained consistent in studies administering doses of <2,000 mg/day and duration of > 8 weeks, but they decreased and became non-significant in studies with duration of ≤ 8 weeks. Overall, for glycemic control variables, doses of <2,000 mg/day and duration of > 8 weeks showed significant results, although heterogeneity remained unstable.

For lipid profiles, heterogeneity decreased to a low level for TC in studies using doses of $\geq 2,000$ mg/day; however, the effect became non-significant. For HDL, the effect became non-significant and heterogeneity remained moderate after subgrouping by either dose or duration. Meanwhile, for LDL, heterogeneity dropped to a low level in studies using doses of $\geq 2,000$ mg/day, but the effect remained non-significant after stratification by either dose or duration. Finally, there were no differences in effect or significance for TG after stratification by dose or duration.

For CRP, stratification by dose and supplementation duration showed that doses of <2,000 mg/day and durations of ≤ 8 weeks produced a significant effect while also reducing heterogeneity. Overall, in addition to dose and supplementation duration, other unmeasured confounding factors in studies may have influenced the overall heterogeneity of the meta-analyses.

Table 4. Subgroup analysis.

Variable	Subgroup	Studies (n)	MD (95% CI)	p-value	Heterogeneity	
					p-value	I ² (%)
FBG (mg/dL)	Overall	33	-2.78 (-7.53, 1.97)	0.25	<0.01	76
	EPA + DHA dosage (mg/day)					
	<2,000	20	-8.42 (-15.12, -1.72)	0.01	<0.01	81
	≥2,000	13	4.66 (-2.08, 11.40)	0.18	<0.01	60
	Supplementation duration (weeks)					
HbA1c (%)	≤8	14	5.45 (-1.42, 12.33)	0.12	0.05	40
	>8	19	-7.16 (-13.38, -0.94)	0.02	<0.01	81
	Overall	27	-0.29 (-0.50, -0.08)	0.01	<0.01	92
	EPA + DHA dosage (mg/day)					
	<2,000	16	-0.51 (-0.71, -0.30)	<0.01	0.01	48
HOMA-IR	≥2,000	11	-0.09 (-0.42, 0.25)	0.61	<0.01	96
	Supplementation duration (weeks)					
	≤8	11	-0.20 (-0.52, 0.13)	0.24	<0.01	77
	>8	16	-0.35 (-0.59, -0.10)	<0.01	<0.01	91
	Overall	16	-0.53 (-0.88, -0.18)	<0.01	<0.01	70
TC (mg/dL)	EPA + DHA dosage (mg/day)					
	<2,000	10	-0.56 (-1.01, -0.12)	0.01	<0.01	74
	≥2,000	6	-0.44 (-1.00, 0.12)	0.12	0.08	50
	Supplementation duration (weeks)					
	≤8	3	0.18 (-0.39, 0.75)	0.54	0.53	0
HDL (mg/dL)	>8	13	-0.65 (-1.01, -0.29)	<0.01	<0.01	69
	Overall	30	-6.39 (-12.57, -0.21)	0.04	<0.01	74
	EPA + DHA dosage (mg/day)					
	<2,000	16	-8.89 (-19.24, 1.45)	0.09	<0.01	82
	≥2,000	14	-3.15 (-7.55, 1.27)	0.16	0.45	0
LDL (mg/dL)	Supplementation duration (weeks)					
	≤8	12	0.24 (-6.77, 7.25)	0.95	0.15	29
	>8	18	-10.50 (-18.74, -2.26)	0.01	<0.01	80
	Overall	28	1.37 (0.02, 2.73)	<0.05	<0.01	59
	EPA + DHA dosage (mg/day)					
TG (mg/dL)	<2,000	15	1.64 (-0.54, 3.83)	0.14	<0.01	65
	≥2,000	13	1.26 (-0.77, 3.28)	0.22	0.01	52
	Supplementation duration (weeks)					
	≤8	11	1.91 (-1.23, 5.05)	0.23	0.01	53
	>8	17	1.26 (-0.28, 2.80)	0.11	<0.01	64
CRP (mg/L)	Overall	27	-1.41 (-5.53, 2.70)	0.50	<0.01	60
	EPA + DHA dosage (mg/day)					
	<2,000	14	-2.66 (-9.15, 3.84)	0.42	<0.01	69
	≥2,000	13	0.99 (-2.60, 4.58)	0.59	0.51	0
	Supplementation duration (weeks)					
TG (mg/dL)	≤8	11	3.15 (-1.67, 7.97)	0.20	0.52	0
	>8	16	-3.46 (8.79, 1.86)	0.20	<0.01	69
	Overall	28	-32.55 (-46.35, -18.74)	<0.01	<0.01	84
	EPA + DHA dosage (mg/day)					
	<2,000	15	-21.43 (-36.20, -6.67)	<0.01	<0.01	63
CRP (mg/L)	≥2,000	13	-42.43 (-66.02, -18.84)	<0.01	<0.01	89
	Supplementation duration (weeks)					
	≤8	11	-28.07 (-47.61, -8.52)	<0.01	<0.01	63
	>8	17	-35.75 (-54.59, -16.91)	<0.01	<0.01	89
	Overall	9	-0.83 (-1.26, -0.40)	<0.01	<0.01	70
TG (mg/dL)	EPA + DHA dosage (mg/day)					
	<2,000	5	-0.85 (-1.53, -0.17)	0.01	0.19	33
	≥2,000	4	-0.51 (-1.73, 0.71)	0.41	<0.01	78
	Supplementation duration (weeks)					
	≤8	4	-1.32 (-1.40, -1.23)	<0.01	0.59	0
CRP (mg/L)	>8	5	-0.53 (-1.30, 0.24)	0.17	0.02	64

3.8. Sensitivity Analysis

Leave-one-out sensitivity analysis demonstrated that the findings for FBG, HbA1c, and HOMA-IR were robust, as evidenced by stable effect estimates (**Supplementary Figure S1A-C**). For BMI, SBP, and DBP (**Supplementary Figure S2A-C**), results also showed stability without substantial changes in the estimated effect. Similarly, for all lipid profile outcomes, exclusion of individual did not materially affect the estimated effect (**Supplementary Figure S3A-D**). Finally, findings for inflammatory markers also showed consistent effect estimates (**Supplementary Figure S4A-C**).

3.9. Publication Bias

Publication bias analysis was conducted by plotting MD against SE, which showed symmetric funnel plots for the FBG, HbA1c, HDL, LDL, and TG outcomes, as well as an asymmetric tendency for the funnel plots of the HOMA-

IR, BMI, TC, and CRP outcomes (**Figure 7A-I**). Formal analysis was then performed to confirm the visual findings, showing that publication bias was not observed for the following outcomes: FBG, HbA1c, HOMA-IR, TC, HDL, LDL, TG, and CRP, as evidenced by Egger's test ($p = 0.37, p = 0.81, p = 0.77, p = 0.10, p = 0.18, p = 0.58, p = 0.82$, and $p = 0.17$, respectively) and Begg's test ($p = 0.64, p = 0.20, p = 0.54, p = 0.64, p = 0.34, p = 0.51, p = 0.48$, and $p = 0.86$, respectively). Statistical findings indicated a possible publication bias for BMI, with a significant result in Egger's test ($p = 0.02$) but not in Begg's test ($p = 0.13$).

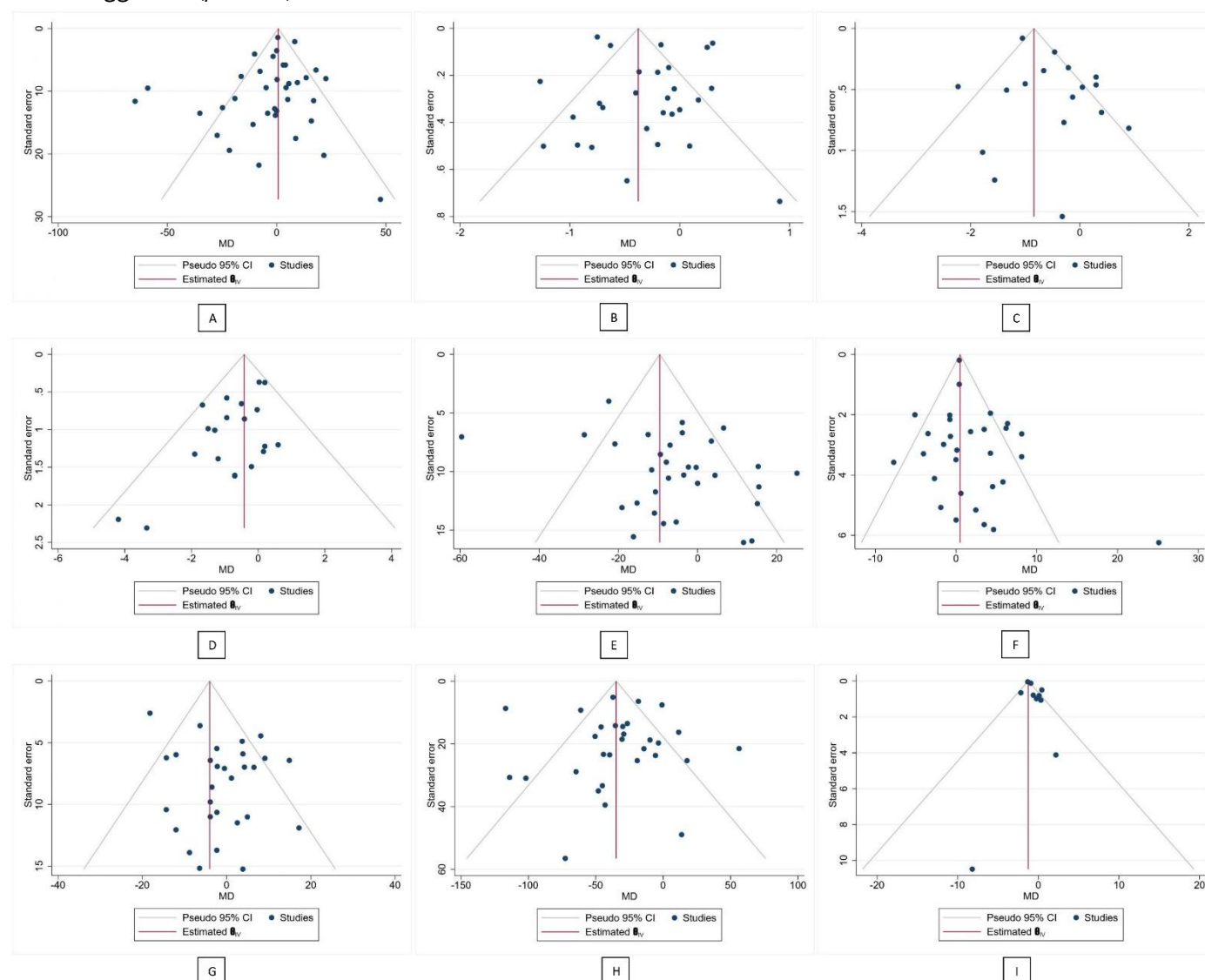


Figure 7. Funnel plots: (A) FBG; (B) HbA1c; (C) HOMA-IR; (D) BMI; (E) TC; (F) HDL; (G) LDL; (H) TG; and (I) CRP.

3.10. Adverse Events and Safety

Thirteen studies (37,42–44,46,50,52,53,56,57,64,67,69) reported information on safety and adverse events and were included in meta-analysis evaluating the incidence ratio of adverse events with n3-FA compared with placebo. One study (38) could not be analyzed because, although it reported adverse events, it did not report the number of cases. The most frequently reported adverse event was gastrointestinal problems.

Random-effects analysis of the thirteen studies demonstrated that adverse events associated with n3-FA compared with placebo were not significant (OR = 0.84; 95% CI: 0.41–1.72; $p = 0.64$) with no heterogeneity ($p = 0.90$; $I^2 = 0\%$) (**Figure 8**). Sensitivity analysis showed robust results, and publication bias was not observed (Data not shown). These findings indicate that n3-FA were well tolerated with a safety profile similar to that of placebo.

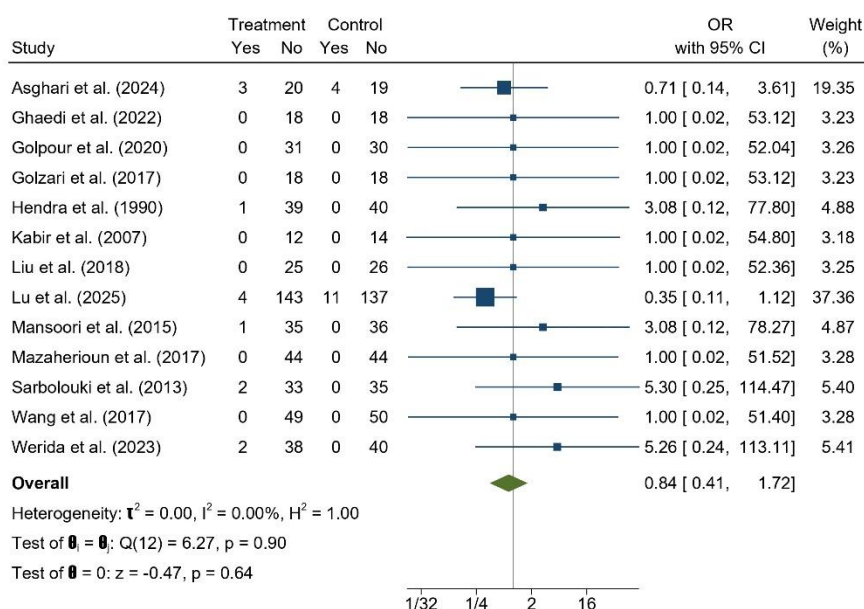


Figure 8. Forest plot of the meta-analysis comparing adverse events between n3-FA and placebo.

3.11. Certainty of Evidence

The assessment using the GRADE approach showed that the evidence for HOMA-IR and adverse events analysis was rated as moderate due to a one-level downgrade in the domains of inconsistency and risk of bias, respectively. The evidence for BMI, SBP, DBP, TC, HDL, and CRP was rated as low due to a two-level downgrade in the risk-of-bias domain for all outcomes and one additional domain. Meanwhile, FBG, HbA1c, LDL, TG, IL-6, and TNF- α were rated as very low because of simultaneous concerns related to risk of bias, inconsistency, and imprecision (**Table 5**). In conclusion, the evidence certainty ranged from moderate to very low, suggesting that the findings should be interpreted cautiously.

Table 5. Summary of findings.

Outcome	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Certainty
FBG	S	V-S	S	N-S	N-S	Very low
HbA1c	S	V-S	N-S	N-S	N-S	Very low
HOMA-IR	N-S	S	N-S	N-S	N-S	Moderate
BMI	S	N-S	N-S	N-S	S	Low
SBP	S	N-S	S	N-S	N/A	Low
DBP	S	N-S	S	N-S	N/A	Low
TC	S	S	N-S	N-S	N-S	Low
HDL	S	S	N-S	N-S	N-S	Low
LDL	S	S	S	N-S	N-S	Very low
TG	S	V-S	N-S	N-S	N-S	Very low
IL-6	S	V-S	V-S	N-S	N/A	Very low
TNF- α	S	V-S	S	N-S	N/A	Very low
CRP	S	S	N-S	N-S	N-S	Low
Adverse events	S	N-S	N-S	N-S	N-S	Moderate

N-S, no serious (no downgrade); S, serious (downgrade [-1]); V-S, very serious (downgrade [-2]); N/A, not assessed.

4. Discussion

This meta-analysis involving 37 RCTs ($n > 2,400$ adult patients with T2DM) revealed that n3-FA significantly improved glycemic control (HbA1c and HOMA-IR), cardiometabolic indices (BMI, TC, HDL, and TG), and inflammatory markers (TNF- α and CRP), but not significantly on FBG, LDL, and IL-6. Although the findings are robust and publication bias was not observed in almost all outcomes, the level of heterogeneity in most outcomes was substantial. Furthermore, the certainty of evidence varies from moderate to very low. Overall, the findings of this meta-analysis should be interpreted with caution.

The finding that n3-FA improved HbA1c but had no significant effect on FBG is consistent with a previous meta-analysis (22), and the observed improvement in HOMA-IR is also in agreement with meta-analysis conducted by Khalili and colleagues (21). However, differences emerged in some specific outcomes. For example, Khalili and colleagues (21) reported significant LDL reduction while our findings did not; additionally, the effects on inflammatory markers were consistent only for CRP, but were less consistent for IL-6 and TNF- α compared with previous meta-analyses (21,22). These differences likely reflect methodological variations across the primary studies or meta-analyses, including the eligibility criteria, whereby previous meta-analyses (21,22) combined plant-based n3-FA with marine-derived EPA/DHA, as well as differences in intervention dose and duration, EPA:DHA composition, formulation, and the baseline metabolic and inflammatory status of the participants. Therefore, we deliberately focused our inclusion criteria on marine- or fish-oil-based n3-FA to reduce variability in intervention composition; this approach improved intervention homogeneity but may also explain the discrepancies in findings compared with the broader scope of previous meta-analyses (21,22). Practically, these differences emphasize the need for cautious interpretation, particularly for findings that remain inconsistent with previous meta-analyses.

The substantial heterogeneity observed in this study necessitated further subgroup analyses. For glycemic control variables (FBG, HbA1c, and HOMA-IR), subgroup analyses showed that n3-FA were effective when administered at doses of <2,000 mg/day and for durations of >8 weeks, although heterogeneity remained high. In contrast, studies using doses of $\geq$ 2,000 mg/day did not provide a significant effect on glycemic control; indeed, the effect on FBG was even nonsignificantly increased. Concerns regarding an increase in FBG following n3-FA supplementation are supported by several lines of evidence, in which methylmercury and polychlorinated biphenyls found in fish oil or seafood may interfere with insulin signaling and lead to increase FBG (15,74). For lipid profile outcomes (TC, HDL, LDL, and TG), stratification by dose or duration failed to explain the substantial heterogeneity. Meanwhile, for the inflammatory marker CRP, dose and duration accounted for the high heterogeneity, where studies with doses of <2,000 mg/day and studies with durations of $\leq$ 8 weeks provided a significant effect with a meaningful reduction in heterogeneity. Therefore, supplementation dose and duration are important factors contributing to the high heterogeneity in this meta-analysis. Furthermore, there were other residual confounding factors that were not explored in this study and may also explain the substantial heterogeneity.

Regarding the safety profile of n3-FA, this study revealed that n3-FA were well tolerated and had a safety profile similar to placebo, as indicated by the pooled analysis showing a non-significant OR and moderate-quality evidence. Gastrointestinal disturbances emerged as the most common adverse effect found in this study, corroborated by a previous meta-analysis that found digestive disturbances and bleeding tendencies to be the predominant side effects, especially at high supplementation doses (75). Therefore, daily n3-FA intake must be monitored for both dosage and duration. This is reinforced by the FDA's recommendation that the daily dose of n3-FA, or EPA plus DHA, should not exceed 3,000 mg/day to prevent adverse side effects (76).

n3-FA affect glycemic control and insulin resistance through several interconnected molecular pathways. EPA, one of the n3-FA, exerts its effects by increasing GLUT4 translocation, which in turn enhances glucose uptake in skeletal muscle cells. In addition, n3-FA improve insulin resistance by enhancing mitochondrial function and β -oxidation, regulating adipocytokine secretion, and inhibiting adipose tissue remodeling (15,77,78). EPA/DHA integration modulates insulin receptor conformation, thereby improving tyrosine phosphorylation of IRS-1 and activating PI3K/Akt pathway, which ultimately leads to increased GLUT4 translocation to the muscle and adipocyte cell membranes (79). Mechanistic review evidence supports that activation of IRS/PI3K/Akt pathway by an agent improves insulin resistance and lowers blood glucose levels (80). This effect is reflected in the findings of this study, which showed a decrease in HOMA-IR. In addition, EPA and DHA improve insulin resistance and increase insulin sensitivity in adipocytes via GPR120/PPAR- γ pathway in macrophages (81). Importantly, the magnitude of these effects depends on the supplementation dose/duration, and baseline metabolic status of the participants as per the findings in this study.

In lipid profiles, patients diagnosed with T2DM often present with hypertriglyceridemia, or elevated TG levels, as well as decreased HDL levels. n3-FA modulate lipid profiles through multiple metabolic pathways, primarily focusing on reducing hepatic triglyceride synthesis and increasing the clearance of TG-rich lipoproteins (82). Molecularly, EPA/DHA suppress hepatic lipogenesis by downregulating SREBP-1c, thereby reducing the synthesis of TG-forming enzymes and the production of VLDL and apolipoprotein B-100 (82–84). In addition, activation of PPAR isoforms, including PPAR- α , PPAR- γ , and PPAR- β/δ , by n3-FA increases fatty acid oxidation and lipoprotein lipase gene expression (85). PPAR- α activation, furthermore, reduces VLDL and TG levels while increasing HDL levels (86).

Given that elevated TG and low HDL levels are associated with cardiovascular risk (87), these molecular mechanisms are consistent with the findings of decreased TG and increased HDL in our meta-analysis. However, the effect on LDL remains controversial; this may be due to variations in dose, EPA-to-DHA ratio across studies, and the participants' baseline lipid profiles.

The anti-inflammatory biological mechanism of n3-FA explains the reduction of TNF- α and CRP through the production of specialized pro-resolving mediators (resolvins, protectins, maresins) that actively promote resolution of inflammation. Evidence indicates that n3-FA reduce systemic inflammation caused by elevated lipid levels in T2DM patients by modulating TLR4 (88). Additionally, n3-FA are known activators of PPAR- γ , which functions to inhibit NF- κ B activation, a key regulator in NLRP3 activation (18). The reduction in NLRP3 activity by n3-FA subsequently leads to reduced CRP production in the liver (89). Other evidence suggests that inhibition of NF- κ B further inhibits the expression of downstream inflammatory factors, including TNF- α , IL-1 β , and IL-6, which correlate with insulin resistance (90,91). Simultaneously, n3-FA have anti-inflammatory effects that serve to reduce chronic inflammation state linked to insulin resistance and cardiometabolic risk. However, the effects on individual inflammatory markers vary due to differences in participants' baseline inflammatory status, the same factor that contributes to the heterogeneity of clinical findings.

The current 2019 ADA nutrition guidelines emphasize that no single diet is suitable for all individuals with T2DM and that medical nutrition therapy should be individualized and integrated into overall DM care, with an emphasis on diets that improve cardiometabolic control, including diets rich in unsaturated fats and regular intake of fatty fish as a source of n3-FA. However, neither the 2019 ADA standards nor the current consensus report evidence explicitly states that available evidence does not support routine n3-FA supplementation for all patients with T2DM (92,93). In this context, this meta-analysis partially aligns with these recommendations by showing that marine-derived n3-FA provide modest but statistically significant benefits on HbA1c, HOMA-IR, BMI, TC, HDL, and the inflammatory markers TNF- α and CRP, and clinically meaningful effects on TG, which are biologically consistent with cardiometabolic benefits. However, the lack of significant effects on FBG, blood pressure, LDL, and IL-6, together with substantial heterogeneity and varying levels of evidence, suggest that these findings are insufficient to justify a broad revision of current dietary recommendations for all patients with T2DM. Rather, the current evidence supports a more nuanced interpretation, whereby foods rich in n3-FA, particularly fatty fish, remain appropriate in individualized DM nutrition therapy, while routine n3-FA supplementation like pharmacological approaches should only be considered selectively and only after confirmation from larger, methodologically rigorous RCTs. In clinical practice, this indicates that the potential benefits of n3-FA are likely most relevant in subgroups of T2DM patients with dyslipidemia or low-grade inflammation, so their use should be positioned as a targeted adjunct intervention, rather than as a universal strategy.

Finally, this study highlights that marine-derived or fish-oil-based n3-FA may have a clinically relevant adjunctive role in selected patients with T2DM, particularly those with adverse cardiometabolic profiles. However, because the level of evidence ranged from moderate to very low and the observed effects were heterogeneous across outcomes, these findings should not be interpreted as support for routine use in all patients with T2DM. Accordingly, well-designed RCTs with larger sample sizes, more rigorous methodologies, and longer intervention and follow-up durations are strongly needed to generate stronger evidence as a basis for clinical recommendations.

This meta-analysis has several strengths. First, the literature search was comprehensive across major databases and citation searching, strictly followed the PRISMA guidelines, and imposed no publication year restrictions, thus minimizing the risk of missing relevant studies. Second, this meta-analysis was more focused by including only studies administering marine-derived or fish-oil-based n3-FA interventions, resulting in a more homogenous intervention profile. Third, this review covered a wide range of clinically relevant outcomes in patients with T2DM, as well as the inclusion of a safety analysis through adverse event meta-analysis provided a more comprehensive benefit-risk evaluation than previous meta-analyses. Fourth, the use of GRADE approach to assess evidence certainty, together with the risk-of-bias evaluation of primary studies, strengthened the interpretation of the findings and their relevance to clinical practice.

Nevertheless, several limitations should also be acknowledged. First, substantial global heterogeneity for several outcomes limited confidence in the pooled estimates and could not be fully explained by dose or duration stratification, requiring cautious interpretation of the findings. Second, variability in participants' baseline characteristics, metabolic status, concomitant therapies, unanalyzed geographical and dietary differences, and variations in n3-FA product composition likely contributed to the heterogeneity and reduced the generalizability of the findings. Third, the methodological quality of the primary studies varied, and adverse events reporting was

often incomplete, raising the possibility of under-reporting of adverse effects and reducing the certainty of evidence. Fourth, most RCTs had short-to-mid durations, so data on long-term effectiveness and safety remain limited, a condition that requires larger-scale RCTs with longer follow-up durations.

5. Conclusions

This meta-analysis concludes that marine-derived n3-FA provide consistent clinical benefits on several cardiometabolic and inflammatory aspects in patients with T2DM, particularly HbA1c, HOMA-IR, BMI, TC, HDL, TG, TNF- α , and CRP. Subgroup analyses suggest that the most consistent glycemic benefits occur with EPA+DHA doses below 2,000 mg/day and supplementation durations longer than 8 weeks, whereas lower-dose regimens may also be favorable for reducing CRP. However, the observed effects should be interpreted cautiously due to the substantial global inter-study heterogeneity and varying certainty of evidence. Therefore, n3-FA can be considered as an adjuvant nutritional strategy in selected patients with T2DM, particularly those with hypertriglyceridemia or low-grade inflammation, but their use must be individualized and should not replace standard T2DM management. To support stronger clinical practice recommendations, large-scale RCTs, structured dose-response studies, and reporting of long-term safety profiles are strongly needed.

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Supplementary Materials: Supplementary Figures (Figure S1-S4).

List of Abbreviations

<i>BMI</i>	Body mass index
<i>CRP</i>	C-reactive protein
<i>DBP</i>	Diastolic blood pressure
<i>DHA</i>	Docosahexaenoic acid
<i>EPA</i>	Eicosapentaenoic acid
<i>FBG</i>	Fasting blood sugar
<i>GLUT4</i>	Glucose transporter-4
<i>GPR120</i>	G-protein-coupled receptor 120
<i>HbA1c</i>	Hemoglobin A1c
<i>HDL</i>	High-density lipoprotein
<i>HOMA-IR</i>	Insulin resistance
<i>IL-6</i>	Interleukin-6
<i>IRS-1</i>	Insulin receptor substrate-1
<i>LDL</i>	Low-density lipoprotein
<i>n3-FA</i>	Omega-3 fatty acids
<i>NF-κB</i>	Nuclear factor- κ B
<i>NLRP3</i>	NOD-like receptor pyrin domain-containing 3
<i>PI3K</i>	Phosphoinositide 3-kinase
<i>PPAR</i>	Peroxisome proliferator-activated receptor
<i>SBP</i>	Systolic blood pressure
<i>SREBP-1c</i>	Sterol regulatory element-binding protein-1c
<i>T2DM</i>	Type 2 diabetes mellitus
<i>TC</i>	Total cholesterol
<i>TG</i>	Triglycerides
<i>TNF-α</i>	Tumor necrosis factor-alpha

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