REVIEW

Comparing the Effects of Docosahexaenoic and Eicosapentaenoic Acids on Inflammation Markers Using Pairwise and Network Meta-Analyses of Randomized Controlled Trials

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ABSTRACT

Recent data from randomized clinical trials (RCTs) suggest that DHA may have stronger anti-inflammatory effects than EPA. This body of evidence has not yet been quantitatively reviewed. The aim of this study was to compare the effect of DHA and EPA on several markers of systemic inflammation by pairwise and network meta-analyses of RCTs. MEDLINE, EMBASE, and The Cochrane Library were searched through to September 2019. We included RCTs of ≥7 d on adults regardless of health status that directly compared the effects of DHA with EPA and RCTs of indirect comparisons, in which the effects of DHA or EPA were compared individually to a control fatty acid. Differences in circulating concentrations of C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and adiponectin were the primary outcome measures. Data were pooled by pairwise and network meta-analysis and expressed as mean differences (MDs) with 95% CIs. Heterogeneity was assessed (Cochran Q statistic) and quantified (I^2 statistic) in the pairwise meta-analysis. Inconsistency and transitivity were evaluated in the network meta-analysis. The certainty of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. Eligibility criteria were met by 5 RCTs (N = 411) for the pairwise meta-analysis and 20 RCTs (N = 1231) for the network meta-analysis. In the pairwise meta-analysis, DHA and EPA had similar effects on plasma CRP [$MD_{DHA\ versus\ EPA}$ = 0.14 mg/L (95% CI: −0.57, 0.85); I^2 = 61%], IL-6 [$MD_{DHA\ versus\ EPA}$ = 0.10 pg/mL (−0.15, 0.34); I^2 = 40%], and TNF-α [$MD_{DHA\ versus\ EPA}$ = −0.10 pg/mL (−0.37, 0.18); I^2 = 40%]. In the network meta-analysis, the effects of DHA and EPA on plasma CRP [$MD_{DHA\ versus\ EPA}$ = −0.33 mg/L (−0.75, 0.10)], IL-6 [$MD_{DHA\ versus\ EPA}$ = 0.09 pg/mL (−0.12, 0.30)], and TNF-α [$MD_{DHA\ versus\ EPA}$ = −0.02 pg/mL (−0.25, 0.20)] were also similar. DHA and EPA had similar effects on plasma adiponectin in the network meta-analysis. Results from pairwise and network meta-analyses suggest that supplementation with either DHA or EPA does not differentially modify systemic markers of subclinical inflammation. *Adv Nutr* 2021;12:128–140.

Keywords: DHA, EPA, omega-3, inflammation, C-reactive protein, interleukin, cardiovascular disease, systematic review, meta-analysis

Introduction

Subclinical or chronic inflammation is now indisputably recognized as a key factor in the development of atherosclerosis and subsequent cardiovascular disease (CVD) (1–3). Chronic inflammation is characterized by elevated blood concentrations of acute-phase proteins and cytokines, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), and by low concentrations of plasma anti-inflammatory markers such as adiponectin (4–6). Systemic inflammation can be attenuated through the intake of specific nutrients and foods (7). Among those, long-chain ω-3 PUFAs (LCn–3PUFAs), mainly EPA and DHA, have raised tremendous interest for their purported anti-inflammatory effects. DHA and EPA are naturally present in most seafood, especially fatty fish, but their cardiometabolic effects have been mainly demonstrated when consumed in high quantity as supplements (7, 8). Fish oil but also krill and algal oils are commonly used in many ω-3 fatty acid supplements. Most randomized controlled trials (RCTs) so far have used a mix of DHA and EPA in various forms and proportions, as DHA and EPA occur concomitantly and naturally in food

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and dietary supplements. A meta-analysis of these RCTs demonstrated the anti-inflammatory effect of LCn–3PUFA supplementation as evidenced by significant reductions in plasma CRP, IL-6, and TNF-α concentrations compared with the control conditions (9). However, several RCTs have tested the hypothesis that individual LCn–3PUFAs are not equally effective in modulating markers of inflammation (10–14). Accordingly, there is increasing evidence from individual trials that DHA and EPA have distinct effects on systemic inflammation, as recently reviewed (15). Specifically, the review indicated that despite greater beneficial effects of DHA compared with EPA on triglycerides, blood pressure, heart rate, and vascular function, the differential effect of EPA and DHA on inflammation markers remained inconclusive. Such data have not yet formed the basis of a systematic review and meta-analysis, which are considered the gold standard of evidence, to inform dietary guidelines. We thus conducted a systematic review and meta-analysis of available RCTs to assess and compare the individual effects of DHA and EPA on surrogate markers of systemic inflammation, namely plasma CRP, IL-6, TNF-α, and adiponectin concentrations. As data from studies having directly compared DHA and EPA are limited, the "network meta-analysis" approach (16, 17) was also used to include both direct and indirect comparisons in the meta-analysis. Thus, the pairwise meta-analysis included RCTs that compared directly the effects of DHA and EPA (direct comparisons) on inflammation, whereas the network meta-analysis included all direct comparison RCTs as well as RCTs that assessed the effects of DHA or EPA individually compared with a control oil or fatty acid (indirect comparisons). To the best of our knowledge, no study has yet compared the independent effect of DHA and EPA on systemic inflammation, using both pairwise and network meta-analysis methodologies. This analysis aimed to answer the following question: do DHA and EPA have similar effects on systemic markers of low-grade inflammation?

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Supplemental Tables 1–10 and Supplemental Figures 1–15 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances.
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Abbreviations used: CRP, C-reactive protein; CVD, cardiovascular disease; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; JELIS, Japan EPA lipid intervention study; LCn–3PUFA, long-chain ω-3 PUFA; MD, mean difference; RCT, randomized controlled trial; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl – Intervention Trial.

Methods

Protocol and registration

The present systematic review and meta-analyses have been conducted according to the Cochrane Handbook for Systematic Reviews of Interventions (18). Results are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and The PRISMA Extension Statement for conducting Network Meta-analyses (19). The protocol was registered at clinicaltrials.gov as NCT03520556 but not with the International Prospective Register of Systematic Reviews (PROSPERO) because the analysis was proposed and undertaken before 1 July, 2018.

Search strategy and data sources

MEDLINE, EMBASE, and The Cochrane Library were searched until 27 September, 2019 using the strategy presented in **Supplementary Table 1**. Manual searches based on references of selected studies and reviews were performed to supplement the electronic search.

Eligibility criteria and study selection

Studies were included in pairwise and/or network meta-analyses if they met all the following criteria: *1*) RCTs that directly compared the effects of DHA to those of EPA, or assessed the effects of DHA or EPA individually compared with a suitable control (i.e., fatty acids other than EPA and DHA as control); *2*) DHA or EPA supplementation with a minimum proportion of 80% for the LCn–3PUFAs; *3*) minimum intervention period of 7 d; *4*) RCTs in adults (aged 19 y and older); *5*) outcomes including plasma concentration of CRP, IL-6, TNF-α, and adiponectin. The following studies were excluded: *1*) RCTs including neonates, children, or adolescents; *2*) RCTs of acute postprandial effects only; *3*) RCTs based on enteral/parenteral nutrition; *4*) co-intervention (e.g., drug, dietary supplement, diet, or exercise) not applied in all intervention arms. Unpublished trials

and literature published in languages other than English or French were not considered.

Two authors (CV, JA) independently screened titles and abstracts of studies retrieved using the search strategy to identify the ones that met the inclusion criteria outlined above. The same authors (CV, JA) independently assessed the full text of preselected studies for eligibility. Disagreements were resolved by consensus and by involvement of another author (BL) if required.

Data extraction

One author (CV) extracted relevant data from included studies. The extracted information was verified by a second author (JA or BL). Relevant data included the following characteristics: name of first author, title, year of publication, journal, RCT design (parallel or crossover; single or double-blind), sample size (randomized, completers; male/female), study duration, washout duration (for crossover only), health status (i.e., healthy, normal-weight/obese, metabolic or other peripheral disease), mean age, mean baseline BMI, mean waist circumference, specification of DHA and EPA supplementation (dose, proportions in capsules, form, source), specification of control or placebo (type of fatty acids, dose), weight loss (yes versus no), primary outcome of the study, outcomes extracted for the present meta-analyses, data analysis (intent-to-treat or per-protocol), funding source, and conflict of interest. Outcome data were also extracted from each study and included mean differences (± SEM) between postintervention values (for pairwise meta-analysis) and mean (± SD) postintervention values (for network meta-analysis). Study authors were contacted to obtain additional information and missing outcome data. Six authors provided additional data (11, 13, 20–23). In the absence of numerical values for outcome measurements or the inability to contact study authors, values were extracted from figures using Plot Digitizer, version 2.6.8 (Free Software Foundation).

Risk of bias assessment

Two authors (CV, BL) independently assessed risk of bias of each study included in this work using the Cochrane Risk of Bias Tool (18). The following categories of bias were assessed: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other bias. Trials were considered at: *1*) high risk of bias if ≥3 out of a maximum of 6 items were rated as "high risk," *2*) low risk of bias if ≥4 out of a maximum of 6 items were rated as "low risk" and a maximum of 1 item rated with a high risk of bias, and *3*) moderate/unclear risk of bias for all other studies (24). Disagreements were resolved by consensus. Risk of bias for network meta-analysis also included assessment of transitivity. To evaluate the assumption of transitivity, we compared the distribution of the potential effect modifiers (BMI, age, study duration, percent male, DHA dose, EPA dose) across the available direct comparisons.

Outcomes

There were 4 prespecified outcomes in the present study: *1*) plasma CRP (mg/L), *2*) plasma IL-6 (pg/mL), *3*) plasma TNF-α (pg/mL), and *4*) plasma adiponectin (mg/L). The pairwise meta-analysis was performed for the first 3 outcomes because only 1 pairwise comparison was available for adiponectin. The network meta-analysis was conducted for the 4 outcomes.

Data synthesis and analysis

We used standard Cochrane methods for pairwise meta-analysis and augmented this evidence using network meta-analysis methods. The latter compare multiple treatments simultaneously in a single analysis by combining direct and indirect evidence within a network of studies. Direct evidence refers to the existing comparison of 2 interventions to each other within a study (e.g., A compared with B). Indirect evidence refers to the evidence obtained through 1 or more common comparators (e.g., in the absence of studies that directly compare A and B, direct evidence of A compared with C, and B compared with C can be used to provide indirect evidence about A compared with B). The combination of direct and indirect evidence is called mixed evidence.

Pairwise meta-analysis.

Data were managed and analyzed with the use of Review Manager (RevMan) version 5.3.2 (The Nordic Cochrane Centre, The Cochrane Collaboration) for the pairwise meta-analysis. The generic inverse variance method with random-effects models was used to synthesize the overall effect estimate of DHA and EPA on plasma CRP, IL-6, and TNF-α. DerSimonian and Laird random-effects models were used even in the absence of statistically significant between-study heterogeneity, as they yield more conservative summary effect estimates in the presence of residual heterogeneity (25, 26). For each outcome, mean differences (MDs) between DHA and EPA were extracted for each pairwise comparison when provided in the publications. If not provided, postintervention values after each treatment (DHA and EPA) in each study were used to calculate MDs between the 2 treatments. MDs were calculated by subtracting means of postintervention values and SEs were calculated from the available data and statistics using published formulas (25). When only medians and IQRs were available, means were estimated from median values using the new method of Luo et al. (27) and SDs were estimated from IQR using the method described by Wan et al. (28). The SEs were then calculated from SD values using Cochrane Formulas (25). Paired analyses were applied to all crossover trials with the use of a conservative correlation coefficient of 0.5 in determining the missing variance data of crossover trials (29). For studies with multiple interventions (e.g., different doses of DHA or EPA) or controls, we did not combine groups but split the "shared" group into 2 or more groups with sample size divided between groups, and included 2 or more comparisons as proposed in the Cochrane Handbook

to overcome unit-of-analysis error (18). The pooled estimates are expressed and presented as MDs with 95% CIs. Interstudy heterogeneity was assessed with the Cochran Q statistic and quantified by the I^2 statistic, where $I^2 \geq 50\%$ at $P < 0.10$ was considered as substantial heterogeneity. Sources of heterogeneity were explored through sensitivity analyses. To determine the particular influence of any single study on the results, each trial comparison was individually removed from the pairwise meta-analysis and the overall effect size and heterogeneity were recalculated. We did not perform a priori subgroup analyses nor investigated publication bias, as there were fewer than 10 direct comparisons available for the analyses of each outcome in the pairwise meta-analysis (25).

Network meta-analysis.

Data for the network meta-analysis were managed and analyzed with the use of STATA/SE version 13 (StataCorp). We performed a frequentist network meta-analysis using a multivariate meta-analysis model and the "network" suite of commands available in STATA (30). For each inflammation outcome, postintervention values after each treatment in each study (DHA versus control and EPA versus control) were extracted and used to calculate MDs between DHA and EPA directly in STATA. Random-effects network meta-analysis was used for plasma CRP, IL-6, and TNF-α. We used the fixed option for adiponectin data, as there was no source of heterogeneity. Network diagrams were performed for each inflammation outcome to show the interactions among the studies included in the network meta-analysis and to illustrate the available direct comparisons between treatments (30). We checked the consistency in the data using both local and global approaches in STATA. We applied the loop-specific and the side-splitting approaches as local methods to evaluate the presence of statistical inconsistency. The loop-specific approach looks at the inconsistency in each closed loop in the network (31) whereas the side-splitting approach detects comparisons for which direct estimates disagree with indirect evidence from the entire network (32). The global approach tests for overall inconsistency from all possible sources in the whole network simultaneously using a design-by-treatment interaction model (33). If inconsistency was suggested, sensitivity analyses were performed to explore the sources of heterogeneity. Publication bias was assessed in the network meta-analysis through generation of comparison-adjusted funnel plots that were visually inspected for asymmetry, but only when 10 trial comparisons or more were available for a specific outcome. Box plots representing the distributions of the potential effect modifiers (transitivity analyses) were obtained using GraphPad Prism version 7.0c for Mac OS X (GraphPad Software).

Grading of the evidence

The certainty of evidence was assessed for each outcome independently by 2 authors (CV, BL) as "very low," "low," "moderate," or "high" using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. Evidence from RCTs received by default a grade of "high" certainty and was then downgraded on the basis of prespecified criteria related to risk of bias (weight of trials shows evidence of serious risk of bias by the Cochrane Risk of Bias Tool), inconsistency (unexplained substantial heterogeneity, $I^2 \geq 50\%$, $P < 0.10$), indirectness (presence of factors that limit the generalizability of the results), imprecision [95% CIs for pooled effect estimates cross a prespecified minimally important difference (MID)], and publication bias (evidence of small-study effects). The GRADE approach was also used to evaluate the certainty of evidence from the network meta-analysis according to the new procedure described by Brignardello-Petersen et al. (34). Briefly, this approach considers rating the certainty of all contributing evidence (direct, indirect, and network) for each pairwise comparison in the network meta-analysis. Intransitivity and incoherence were considered in addition to conventional criteria (risks of bias, inconsistency, imprecision, indirectness, and publication bias).

Results

Search results

The search strategy identified 3354 articles, of which 387 were reviewed in full and 20 were included in the final analysis (**Figure 1**) (10–14, 20–23, 35–45). Only 5 trials compared DHA and EPA directly with data on markers of inflammation as clinical outcomes (10–14). These were included in the pairwise meta-analysis. All 20 trials were included in the network meta-analysis combining the direct and indirect comparisons of DHA and EPA.

Trial characteristics

Characteristics of RCTs included are summarized in **Table 1**. From the 20 RCTs, 17 were parallel-arm trials (10–13, 20–23, 36–42, 44, 45) and 3 had a crossover design (14, 35, 43). Of the 20 RCTs, 10 trials were conducted in North America (USA, Canada) (12–14, 20, 22, 23, 35, 39, 40, 45), 6 in Europe (Spain, UK) (21, 37, 38, 41, 43, 44), 2 in Oceania (Australia) (10, 36), and 2 in Asia (Iran) (11, 42). The duration of the RCTs ranged between 4 and 48 wk. Generally, participants were middle-aged and overweight. The age of study participants included in these studies ranged from 19.3 to 61.5 y. Baseline BMI was between 21.3 and 35 kg/m^2. Eleven RCTs (55%) were conducted in healthy individuals (12, 13, 20, 21, 23, 37, 39–41, 43, 44). There was a relatively equal distribution of men and women across trials. Fourteen RCTs (70%) assessed the effect of DHA on inflammation outcomes (10–14, 20, 22, 23, 35, 37, 38, 42, 43, 45), 11 RCTs (55%) assessed the effect of EPA on inflammation outcomes (10–14, 21, 36, 39–41, 44), and 5 RCTs (25%) reported the effects of both DHA and EPA (10–14). One RCT did not indicate the given dose of DHA (37); for all other RCTs, the median dose was 2000 mg/d for DHA (range: 465–4000 mg/d) and 1869 mg/d for EPA (range 627–3840 mg/d). Of the 14 RCTs on DHA, 5 used DHA from algae (13, 20, 22, 23, 43), 4 from fish oil (10, 14, 42, 45), 1 from enzyme synthesis (38), and the remaining

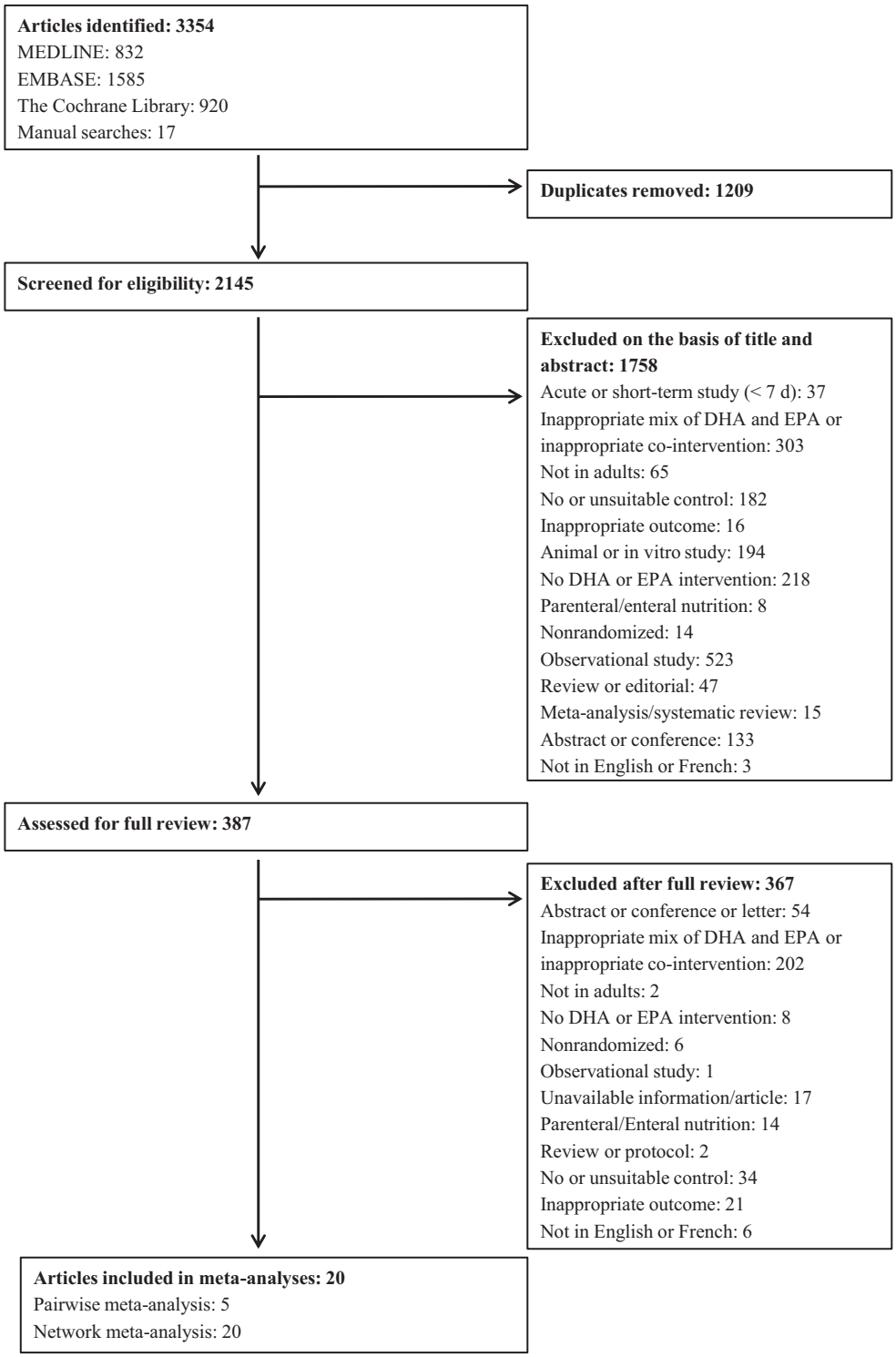

FIGURE 1 Summary of the search and selection process of the studies comparing the effect of DHA and EPA on inflammation markers in adults.

trials did not report the source of DHA. Of the 11 RCTs on EPA, 7 used EPA from fish oil (10, 14, 21, 36, 39, 40, 44), 1 from yeast (13), and the remaining trials did not report the information. Of the 9 RCTs that reported the form of DHA and EPA, 6 used a triglyceride formulation (13, 14, 21, 36, 38, 43), 2 provided the supplements in the form of ethyl esters (10, 41), and 1 used DHA as monoglycerides (45). Olive oil or oleic acid was the most frequently used control in the studies (>50% RCTs). CRP was investigated in 14 RCTs (70%) (10–14, 20, 22, 23, 35, 36, 38, 42–44), IL-6 was investigated

TABLE 1 Characteristics of included randomized controlled trials comparing the effect of DHA and EPA on inflammation markers in adults

First author, year, arms	Design[1]	Duration (weeks)	Health conditions	Participants: *n* randomized (% males)	Drop out (%)	Mean age (y)[2]	Mean BMI (kg/m^2)[2]	Dose (mg/d)	Source and form	Inflammation as primary outcome	Outcomes extracted	Data analysis	Funding source[3]	Country
Allaire, 2016 (14)	Crossover	10 (WO: 9)	Abdominal obesity, low-grade inflammation	Total: 154 (31)	20	M: 57 F: 50	M: 30 F: 29			Yes	CRP, IL-6, TNF-α, adiponectin	Per-protocol	Public	Canada
EPA								2700	FO, TG					
DHA								2700	FO, TG					
Control: corn oil								3000						
Asztalos, 2016 (13)	Parallel	6	Healthy	Total: 121	9					No	CRP, IL-6, TNF-α	ITT	Public-private	USA
EPA low dose				30 (67)[4]	10	52.8	27.4	627	Yeast, TG					
EPA high dose				31 (66)[4]	6	52.2	27.5	1869	Yeast, TG					
DHA				30 (68)[4]	7	52.3	27.0	758	Micro-algae, TG					
Control: olive oil				30 (69)[4]	13	52.2	27.7	2000						
Azizi-Soleiman, 2013 (11)	Parallel	12	T2D	Total: 60	25					Yes	CRP	Per-protocol	None	Iran
EPA				20 (50)[4]	30	51.4	26.9	980	NR					
DHA				20 (50)[4]	30	56.1	27.0	964	NR					
Control: canola oil				20 (47)[4]	15	56.9	28.4							
Baril-Gravel, 2015 (35)	Crossover	4 (WO: 2 to 4)	Abdominal obesity	Total: 151 (57)[4]	24	47.5	29.9			No	CRP, IL-6, adiponectin	Per-protocol	Public-private	Canada
DHA								3500	NR					
Control I: canola														
Control II: oleic acid														
Bradbury, 2017 (36)	Parallel	12	Chronic work stress	Total: 90 (29)	17					No	CRP, IL-6, TNF-α	Per-protocol	Public	Australia
EPA				45 (NR)	16	43.24	25.3	2200	FO, TG					
Control: olive oil				45 (NR)	18	45.38	26.4	950						
Capo, 2014 (37)	Parallel	8	Healthy	Total: 22	32					NR	IL-6, TNF-α	Per-protocol	Public	Spain
DHA				11 (100)	18	20.4	23.5	Unspecified	NR					
Control: olive oil				11 (100)	45	19.3	24.0	Unspecified						
DiLorenzo, 2014 (20)	Parallel	4	Healthy	Total: 50	18	21.8				NR	CRP, IL-6	ITT	Private	USA
DHA				25 (100)	16	NR		2000	Algae, NR					
Control: corn oil				25 (100)	20	NR		2000						
Domingo, 2018 (38)	Parallel	48	HIV, high fasting TG	Total: 39 (90)[4]	NA[5]					No	CRP, IL-6, TNF-α	Per-protocol	Public	Spain
DHA				18 (83)		44	26.2	4000	Enzyme synthesis, TG					
Control: olive oil				21 (95)		45	25.1	7000						
Gray, 2012 (21)	Parallel	6	Healthy	Total: 16	0					NR	IL-6	Per-protocol	Private	UK
EPA				8 (100)	0	24	24.2	1300	FO, TG					
Control: olive oil				8 (100)	0	24	23.5	3000						
Kelley, 2009 (22)	Parallel	13	Hyperlipidemic	Total: 40	15					Yes	CRP, IL-6, TNF-α	Per-protocol	Public	USA
DHA				20 (100)	15	55	27.8	3000	Microalgae, NR					
Control: olive oil				20 (100)	15	53.1	30.6	7500						
Kiecolt-Glaser, 2011 (39)	Parallel	12	Healthy	Total: 68	1					Yes	IL-6, TNF-α	ITT	NR	USA
EPA				34 (59)	NR	23.9	NR	2085	FO, NR					
Control: oil mixture[6]				34 (53)	NR	23.4	NR	NR						

(*Continued*)

TABLE 1 (*Continued*)

First author, year, arms	Design[1]	Duration (weeks)	Health conditions	Participants: *n* randomized (% males)	Drop out (%)	Mean age (y)[2]	Mean BMI (kg/m^2)[2]	Dose (mg/d)	Source and form	Inflammation as primary outcome	Outcomes extracted	Data analysis	Funding source[3]	Country
Kiecolt-Glaser, 2012 (40)	Parallel	16	Healthy, OW	Total: 138	4					Yes	IL-6, TNF-α	Per-protocol	Public	USA
EPA low dose				46 (39)	2	51.1	NR	1042.5	FO, NR					
EPA high dose				46 (37)	4	51.0	NR	2085	FO, NR					
Control: oil mixture[6]				46 (22)	4	51.1	NR	3000						
Mori, 2003 (10)	Parallel	6	T2D	Total: 59	14					NR	CRP, IL-6, TNF-α	Per-protocol	Public	Australia
EPA				(82)[3]	NR	61.2	27.9	3840	FO, EE					
DHA				(72)[3]	NR	60.9	30.6	3680	FO, EE					
Control: olive oil				(75)[3]	NR	61.5	29.9	4000						
Morin, 2018 (45)	Parallel	4.3	Cystic fibrosis	Total: 15 (NR)	27					NR	IL-6	Per-protocol	None	Canada
DHA				NR	NR	32.7	20.1	3200	FO, MAG					
Control: sunflower oil				NR	NR	24.4	20.0	5000						
Neff, 2011 (23)	Parallel	18	Healthy, OW	Total: 49	27					No	CRP, IL-6, TNF-α	Per- protocol	Public-private	USA
DHA				(32)[4]	NR	43	35	2000	Algal oil, NR					
Control: corn-soybean oils				(53)[4]	NR	44	34	5 mL						
Shahbakhti, 2004 (41)	Parallel	12	Healthy	Total: 28 (43)	50	44[7]	NR			NR	IL-6, TNF-α	Per-protocol	Public	UK
EPA				14 (NR)	50	NR	NR	3800	NR, EE					
Control: oleic acid				14 (NR)	50	NR	NR	4000						
Shidfar, 2016 (42)	Parallel	12	Iron deficiency anemia	Total: 76	0					Yes	CRP	Per-protocol	NR	Iran
DHA				38 (0)	0	33.03	21.30	465	FO, NR					
Control: corn oil				38 (0)	0	36.61	22.08	500						
Theobald, 2007 (43)	Crossover	12 (WO: 16)	Healthy	Total: 40 (50)	2.5	M: 51.1 F: 46.2	M: 23.6 F: 24.4			No	CRP, IL-6	Per-protocol	Private	UK
DHA						NR	NR	700	Algae, TG					
Control: olive oil						NR	NR	1500						
Tsunoda, 2015 (12)	Parallel	6	Healthy	Total: 90	9					No	CRP	Per-protocol	Public-private	USA
EPA				30 (87)[4]	10	53.6	27.5	1800	NR					
DHA				30 (72)[4]	13	51.6	27.8	1800	NR					
Control: olive oil				30 (69)[4]	3	49.7	28.1	6000						
Yusof, 2008 (44)	Parallel	8	Healthy	Total: 21	5					NR	CRP, IL-6	Per-protocol	Public	UK
EPA				10 (100)	10	43.7	25.7	1800	FO, NR					
Control: coconut oil				11 (100)	0	44.7	26.5	2600						

[1] All trials were double-blind fashioned except for Capo et al. (37) and DiLorenzo et al. (20) where information was not reported.
[2] Mean age and BMI of subjects who completed the study.
[3] Public funding includes government, university sources, or not-for-profit health agencies; other sources are included in private funding.
[4] In these studies, details on percent male were not provided according to the number of randomized subjects but to the number of subjects who completed the study or were included in the final analysis.
[5] In this trial, 87 participants were randomized and 39 were included in the present inflammatory substudy (here dropout rate is not applicable).
[6] Mix of palm, olive, soy, canola, and coco butter oils.
[7] The median age was reported in this trial.
CRP, C-reactive protein; EE, ethyl ester; F, female; FO, fish oil; ITT, intent-to-treat; MAG, monoglyceride; M, male; NA, not applicable; NR, not reported; OW, overweight; T2D, type 2 diabetes; TG, triglyceride; WO, washout period.

in 17 RCTs (85%) (10, 13, 14, 20–23, 35–41, 43, 44), TNF-α was investigated in 11 RCTs (47%) (10, 13, 14, 22, 23, 36–41), and adiponectin was investigated in 2 RCTs (10%) (14, 35). Subclinical inflammation was specified as the primary outcome in 6 trials (30%) (11, 14, 22, 39, 40, 42). The majority of trials (85%) performed a per-protocol analysis of data; an intent-to-treat analysis of the results was used in only 3 trials (13, 20, 39). Nine RCTs received funding from public agencies (14, 22, 36–41, 44), 3 from private partners (20, 21, 43), 4 from both public and private sources (12, 13, 23, 35), 2 received no funding (11, 45), and the information was not reported for 2 RCTs (39, 42).

Network diagrams

Figure 2 shows the network diagrams for plasma CRP, IL-6, TNF-α, and adiponectin of all available direct comparisons between pairs of interventions (DHA compared with EPA, DHA compared with control, and EPA compared with control) used in the network meta-analysis. The largest number of RCTs assessed the impact of DHA on plasma CRP and IL-6 compared with olive oil as a control ($n = 8$), whereas the same number of RCTs ($n = 5$) compared the effects of EPA and DHA to olive oil on plasma TNF-α. The contribution plots showing the percentage of statistical contribution coming from direct and indirect evidence for each direct comparison in the network for CRP, IL-6, and TNF-α are presented as **Supplementary Figures 1**, **2**, and **3**, respectively. The NMA estimate for the comparison of interest DHA compared with EPA is informed by the direct comparison DHA versus EPA with a contribution of around 40% for CRP and IL-6 compared with 70% for TNF-α.

Risk of bias

Supplementary Figure 4 shows the individual Cochrane risk of bias assessments for all 20 RCTs included in this work. Of the 20 RCTs included in the network meta-analysis, 11 (55%) were judged to be at low risk of bias (12–14, 35, 36, 38–40, 42–44), 9 had a moderate/unclear risk of bias (10, 11, 20–23, 37, 41, 45), and none were classified as being at high risk of bias. Of the 5 RCTs included in the pairwise meta-analysis, 3 trials were judged to be at low risk of bias (12–14) and the others were classified as having a moderate/unclear risk of bias (10, 11).

Supplementary Figures 5 and **6** show the risk of bias proportions for RCTs included specifically in the pairwise meta-analysis and the network meta-analysis, respectively. Among RCTs included in the pairwise meta-analysis, 100% indicated a low risk of bias for blinding selective reporting and other bias, 0% for allocation concealment, 75% for incomplete outcome data, and 50% for random sequence generation (**Supplementary Figure 5**). With regard to the network meta-analysis, 35% of all RCTs indicated a low risk of bias for random-sequence generation, 30% for allocation concealment, 90% for blinding, 55% for incomplete outcome data, 65% for selective reporting, and 100% for "other bias" (**Supplementary Figure 6**). High risks of bias were found for incomplete outcome data and for selective outcome reporting for 2 distinct RCTs (41, 45) (**Supplementary Figure 6**).

Transitivity analyses showed minor differences among studies for subjects' characteristics (i.e., BMI, age, percent male) and RCTs' characteristics (i.e., study duration, DHA dose, EPA dose) (**Supplementary Figure 7**).

Inconsistency

For comparisons in the network meta-analysis, the side-splitting approach suggested no significant inconsistency for plasma CRP, IL-6, and TNF-α (**Supplementary Tables 2**, **3**, and **4**). The loop-specific approach identified 3 loops for CRP, IL-6, and TNF-α without statistical inconsistency (**Supplementary Table 5**). Due to the lack of available data on adiponectin specifically, we were not able to conduct the loop-specific nor the side-splitting approaches for this outcome. The design-by-treatment model showed no significant inconsistency for plasma CRP ($P = 0.79$), IL-6 ($P = 0.93$), TNF-α ($P = 0.85$), and adiponectin ($P = 0.98$).

Inflammation outcomes

Figure 3 summarizes the pooled estimates of plasma CRP, IL-6, TNF-α, and adiponectin for the comparison of DHA compared with EPA from both pairwise and network meta-analyses. The main results of the pairwise meta-analysis are presented as forest plots for CRP, IL-6, and TNF-α in **Supplementary Figures 8**, **9**, and **10**. The main results of the network meta-analysis are presented as interval plots for CRP, IL-6, TNF-α, and adiponectin in **Supplementary Figures 11–14**. Sensitivity analyses were not performed in the network meta-analysis as no inconsistency was observed for all comparisons.

Plasma CRP.

Pairwise meta-analysis of direct comparisons of the effects of DHA and EPA revealed no significant difference on plasma CRP ($MD_{DHA\ versus\ EPA} = 0.14$ mg/L; 95% CI: −0.57, 0.85 mg/L; $P = 0.70$), with evidence of significant heterogeneity ($I^2 = 61\%$, $P_{Heterogeneity} = 0.02$). Removal of Mori et al. 2003 (10) explained all of the heterogeneity [$I^2 = 0\%$, $P_{Heterogeneity} = 0.82$; new $MD_{DHA\ versus\ EPA} = -0.26$ mg/L (95% CI: −0.54, 0.02 mg/L), $P = 0.07$; **Supplementary Table 6**]. Network meta-analysis of all direct and indirect comparisons of DHA and EPA also suggested comparable effects of the 2 modalities on plasma CRP [$MD_{DHA\ versus\ EPA} = -0.33$ mg/L (−0.75, 0.10 mg/L); −12.8%].

Plasma IL-6.

Pairwise meta-analysis of direct comparisons of DHA and EPA showed no significant difference in their effects on plasma IL-6 ($MD_{DHA\ versus\ EPA} = 0.10$ pg/mL; 95% CI: −0.15, 0.34 pg/mL; $P = 0.44$) without evidence of heterogeneity ($I^2 = 40\%$, $P_{Heterogeneity} = 0.17$). Network meta-analysis of all direct and indirect comparisons of DHA and EPA also suggested similar effects on plasma IL-6 [$MD_{DHA\ versus\ EPA} = 0.09$ pg/mL (−0.12, 0.30 pg/mL); +4.6%].

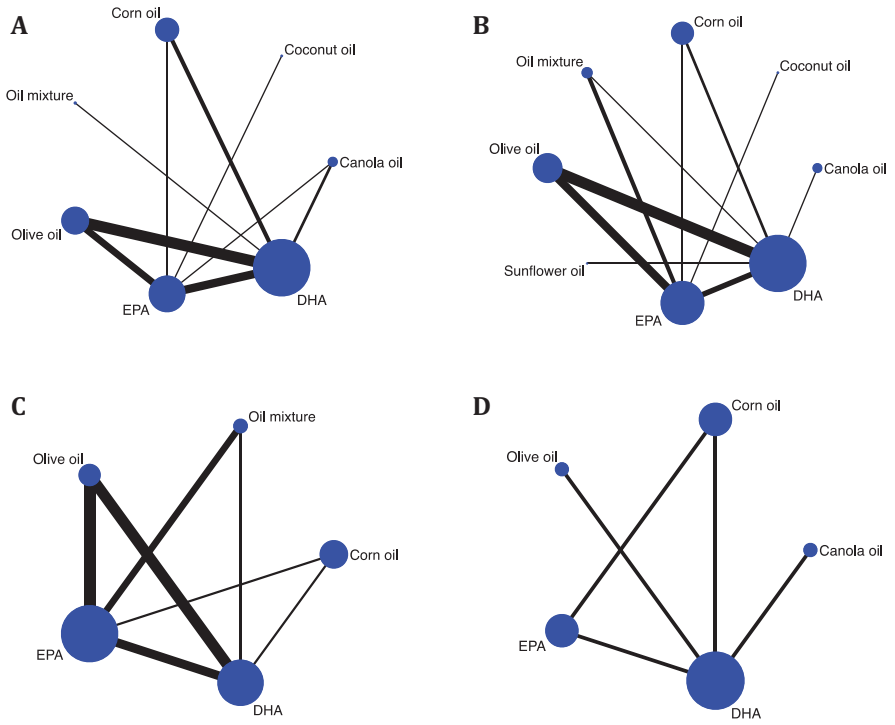

FIGURE 2 Network diagrams from network meta-analysis comparing the effect of DHA and EPA in adults on plasma CRP (Panel A), IL-6 (Panel B), TNF-α (Panel C), and adiponectin (Panel D). The size of the nodes is proportional to the number of participants and the thickness of the lines is proportional to the number of studies available for a particular comparison. CRP: C-reactive protein; oil mixture: mix of palm, olive, soy, canola, and coco butter oils.

Plasma TNF-α.

Pairwise meta-analysis of direct comparisons of the effects of DHA and EPA revealed no significant difference on plasma TNF-α ($MD_{DHA\ versus\ EPA}$ = −0.10 pg/mL; 95% CI: −0.37, 0.18 pg/mL; P = 0.49) without evidence of heterogeneity (I^2 = 40%, $P_{Heterogeneity}$ = 0.17). Similar results were obtained in the network meta-analysis [$MD_{DHA\ versus\ EPA}$ for TNF-α = −0.02 pg/mL (−0.25, 0.20 pg/mL); −0.8%].

			Pairwise meta-analysis						Network meta-analysis
	No. trial		Pooled effect estimates				Heterogeneity		
Outcome	comparisons	N	MD (95% CI)	SMD (95% CI)	SMD (95% CI)	*P*-value	I^2	*P*-value	MD (95% CI)
Proinflammatory									**DHA vs. EPA**
CRP (mg/L)	6	422	0.14 (−0.57, 0.85)	0.16 (−0.64, 0.96)		0.70	61%	0.02	−0.33 (−0.75, 0.10)
IL-6 (pg/mL)	4	396	0.10 (−0.15, 0.34)	0.40 (−0.60, 1.36)		0.44	40%	0.17	0.09 (−0.12, 0.30)
TNF-α (pg/mL)	4	396	−0.10 (−0.37, 0.18)	−0.36 (−1.32, 0.64)		0.49	40%	0.17	−0.02 (−0.25, 0.20)
					−5.0 −2.5 0.0 2.5 5.0				
					Favors DHA Favors EPA				
Anti-inflammatory									
Adiponectin (mg/L)	1	125	0.30 [0.10, 0.50]	2.94 [0.98, 4.90]		0.003	NA	NA	0.29 [-1.08, 1.66]
					−5.0 −2.5 0.0 2.5 5.0				
					Favors EPA Favors DHA				

FIGURE 3 Summary plot of pooled effect estimates from the pairwise and network meta-analyses comparing the effect of DHA and EPA on inflammation outcomes in adults. Pooled effect estimates from the pairwise meta-analysis are expressed as standardized mean differences, represented by diamonds and 95% CIs by the line through the diamond, and were estimated with the use of a generic inverse variance random-effect model. Interstudy heterogeneity was detected with the use of the Cochran's Q statistic and quantified with the use of the I^2 statistic. Mean differences (MDs, 95% CI) for the inflammation outcomes as estimated from the network meta-analysis for the comparison of DHA compared with EPA are also presented. CRP: C-reactive protein; MD, mean difference; SMD, standardized mean difference.

Plasma adiponectin.
The only trial that directly compared the effects of DHA and EPA on plasma adiponectin showed a greater increase with DHA than with EPA ($MD_{DHA\ versus\ EPA} = 0.30$ mg/L; 95% CI: 0.10, 0.50 mg/L; $P = 0.003$). However, DHA and EPA had similar effects on plasma adiponectin [$MD_{DHA\ versus\ EPA} = 0.29$ pg/mL (–1.08, 1.66 mg/L); +4.1%] according to the network meta-analysis.

Small-study effects

Supplementary Figure 15 shows the comparison-adjusted funnel plots including all studies of the network meta-analysis for plasma CRP, IL-6, and TNF-α. There was no visual evidence of funnel-plot asymmetry for CRP and TNF-α (**Supplementary Figure 15**A–C). The funnel plot for IL-6 appears to be slightly asymmetric (**Supplementary Figure 15**B), due mainly to 1 comparison (DHA versus olive oil). Publication bias could not be assessed for adiponectin in the network meta-analysis due to the limited number of RCTs available (<10). Likewise, publication bias was not assessed in the pairwise meta-analysis, as all outcomes had fewer than 10 trial comparisons available for analyses.

GRADE assessment

The certainty of evidence assessment for the pairwise meta-analysis directly comparing the effect of DHA and EPA on markers of systemic inflammation is shown in **Supplementary Table 7**. The certainty of evidence was rated high for IL-6 and TNF-α and moderate for CRP owing to downgrades for serious imprecision. With regard to network meta-analysis, the certainty of network evidence for CRP (**Supplementary Table 8**), IL-6 (**Supplementary Table 9**), and TNF-α (**Supplementary Table 10**) was rated as moderate for most of the pairwise comparisons. Serious imprecision for most of the comparisons drove judgments of moderate quality of evidence. There was no incoherence between direct and indirect evidence for the comparison of interest DHA versus EPA regarding plasma CRP and IL-6. Regarding TNF-α, incoherence was observed for the comparison DHA versus EPA but the direct evidence was of moderate quality and contributed more than the indirect evidence to the network evidence. It was not possible to generate the direct and indirect estimates with the side-splitting approach due to lack of available data. Also, publication bias could not be assessed due to lack of power for assessing funnel plot asymmetry and small-study effects (<10 trial comparisons). Putting aside those concerns, the certainty of evidence was not downgraded with respect to study limitations, indirectness, or inconsistency. The certainty of estimates comparing the effects of DHA and EPA on plasma adiponectin was considered low only due to very serious imprecision.

Discussion

The present work is the first to quantitatively evaluate the differential effect of EPA and DHA on 4 inflammation markers using both pairwise and network meta-analysis methodologies. This work is important because these inflammation-related cardiometabolic risk factors have all been associated etiologically to the risk of CVD. Results suggest that DHA and EPA have similar effects on CRP, IL-6, TNF-α, and adiponectin. Assessment of overall data heterogeneity and quality reveals no major limitations in the interpretation of such results.

The few meta-analyses that have assessed the impact of LCn–3PUFAs in general on markers of inflammation have yielded inconsistent results. Although some meta-analyses of RCTs have shown no effect of LCn–3PUFAs on plasma CRP concentrations (46, 47), others have shown an anti-inflammatory effect of LCn–3PUFA on plasma CRP (9, 48) and IL-6 and TNF-α concentrations (9). As emphasized earlier, most of the RCTs included in these meta-analyses have either used a mix of EPA and DHA in various forms and proportions or have investigated only 1 of the 2 LCn–3PUFAs. The assumption that DHA and EPA trigger different anti-inflammatory responses has been proposed based on data from several in vitro studies (49, 50), but limited clinical evidence supports this claim.

Innes and Calder recently published a systematic review on the differential effects of DHA and EPA on cardiometabolic risk factors (15). Their qualitative analysis of the available data from RCTs revealed inconsistent results regarding the potentially greater anti-inflammatory effects of DHA compared with EPA. Data from these various RCTs were not quantitatively analyzed in this authoritative review. A recent meta-analysis of 20 RCTs was conducted to assess the individual effects of EPA and DHA on blood pressure and inflammatory factors (51). This was, to the best of our knowledge, the first meta-analysis on the topic but issues pertaining to the methodological approach used by the authors need to be addressed. The authors concluded, based on their analysis of the available data, that EPA and DHA have similar effects on CRP concentration, whereas limited evidence on circulating IL-6 and TNF-α did not allow them to draw conclusions. However, they assessed the effects of DHA and of EPA independent of each other and compared summary estimates of the effect of DHA to that of the effect of EPA to assess whether both LCn–3PUFAs have similar or different effects on subclinical inflammation markers. Comparing and drawing inferences about comparative effectiveness from different summary estimates in studies that have not directly compared against each other is of questionable validity and has been strongly discouraged (18). To assess the question of whether EPA and DHA have similar or differential effects on inflammatory factors, it is best to either use studies that have compared these interventions directly, or to use a network meta-analysis approach, through which 2 interventions can be compared indirectly via a common comparator. Here, we were able to

fill this gap by comparing the effect of EPA and DHA on markers of subclinical inflammation using all data available and a rigorous methodological approach. The calculation of summary estimates in our study also took into account data from the control treatment in each RCT, which make the results more rigorous. We stress that the present study does not address whether DHA or EPA have a significant anti-inflammatory effect on their own.

The combined approach of pairwise and network methodologies is a strength of the present study, as are the inclusion of a larger number of studies using the network approach, the inclusion of 4 outcomes (CRP, IL-6, TNF-α, and adiponectin), the risk of bias assessment including transitivity analyses for the network meta-analysis, heterogeneity and inconsistency testing, sensitivity analyses, and judgment of the overall certainty of evidence. Although the evidence from pairwise meta-analysis is limited, the network approach included data from 20 RCTs, thus yielding a much larger sample size and stronger statistical power for the pooled effects being compared. A majority of the trials (11 out of 20) were rated as having a low risk of bias. Relying on RCTs lowered the risk of selection bias due to randomization, and all studies had a double-blind design, thereby decreasing the risk of performance bias. No inconsistency was observed in the network meta-analysis and the only substantial heterogeneity observed for CRP in the pairwise analysis was explained by the removal of 1 study, indicating the overall stability and homogeneity of the results. Accordingly, transitivity analyses did not reveal important effect modifiers, indicating relative stability across RCTs. The certainty of evidence was rated mainly high or moderate in both meta-analyses for plasma CRP, IL-6, and TNF-α. Only a small number of RCTs reported the effect of DHA and EPA on adiponectin concentrations, and results on that outcome need to be analyzed with caution because of the high degree of imprecision. Although our search strategy may have missed studies due to exclusion of those reported in languages other than English or French, this risk is low as we have used a highly rigorous search process as proposed in meta-analysis guidelines. Most of the RCTs included in both meta-analyses did not report information about allocation concealment, which seems to be often confounded with blinding among studies. Despite that, the majority of studies were graded as being at "low risk" of bias. Different doses ($\leq \approx$4g/d) and durations (4 to 48 wk) of EPA and DHA supplementation were used in the RCTs included in the present review. Half of the included RCTs were conducted among healthy individuals whereas the other half included participants with metabolic disorders or health problems. The possibility that dose, study duration, and health conditions of participants may have modified the response of inflammation markers to DHA and EPA cannot be excluded but the limited number of RCTs and participants included in this review did not allow us to conduct rigorous sensitivity analyses based on these factors.

The present work suggests that DHA and EPA have comparable effects on markers of systemic inflammation. From a prevention perspective, EPA and DHA have always been considered to have comparable health benefits and dosing recommendations usually describe a combination of the 2, without differentiation. There is an increasing range of supplements available to help individuals with a typically low fish intake achieve the recommended dietary intake in LCn–3PUFAs. A large proportion of the existing research has thus been conducted using mixed LCn–3PUFAs due to the availability of combined EPA and DHA products. However, the development of separation and purification technologies in recent years has allowed research on the biological effects of purified EPA and DHA. To date, 2 major large intervention trials have been conducted to study the cardioprotective effects of EPA supplements provided as highly purified ethyl esters (52, 53): the Japan EPA lipid intervention study (JELIS) and the Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial (REDUCE-IT). JELIS included 18,645 patients with a plasma cholesterol $\geq$6.5 mmol/L randomly assigned to receive either 1.8 g/d of EPA daily with statin or statin alone for 5 y. REDUCE-IT included 8179 patients on statin therapy randomly assigned to receive daily either 4 g of EPA or placebo (mineral oil) for 5 y. Both studies showed significant 20% to 30% reductions in the risk of major coronary events (52) and in cardiovascular death, heart attacks, and stroke (53). Interestingly, the observed cardiovascular risk reduction with EPA supplementation was not explained by changes in plasma lipid concentrations in both studies, suggesting benefits on other key processes involved in atherogenesis, including inflammation. Future research should examine how supplementing high-risk populations with DHA alone modifies the risk of CVD.

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