The Impact of ω -6 and ω -3 fatty acids on lipoproteins in renal replacement therapy patients: A Network Meta-Analysis of Randomized Clinical Trials

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Abstract

Background Numerous randomized clinical trials (RCTs) and meta-analyses have assessed the effects of supplemental dietary polyunsaturated fatty acids (PUFAs) on levels of low-density lipoproteins (LDLs) and high-density lipoproteins (HDLs), and LDL/HDL ratios in renal replacement therapy patients. However, the results have been ambiguous due to mixed reports of various nutrients used in the intervention group. We performed a network meta-analysis of randomized clinical trials to assess the effects of PUFAs on lipid profiles in renal replacement therapy patients.

Methods RCTs performed prior to September 2020 were gathered from three databases. The means, standard deviations, and the number of cases for each arm were independently extracted by 2 authors for forming a network meta-analysis of LDL and HDL levels, and LDL/HDL ratios in random-effects model.

Results Twenty-seven RCTs (n=1975) were included in this study. The pooled results revealed that the combination of omega-3 fatty acids (n-3) and omega-6 fatty acids (n-6) was significantly lower for the LDL (standardized mean difference [SMD]: -0.95, 95% confidence interval [CI]: -1.87 to -0.13) than the placebo, and the placebo resulted in significantly lower HDL than n-3 (SMD: -0.85, 95% CI: -1.50 to -0.20). There was no evidence of inconsistency or publication bias in the pooled results.

Conclusions Collectively, PUFAs seems to be effective nutrients in controlling lipoprotein among renal replacement therapy patients. To be specific, n-3+n-6 improves LDL, and n-3 improves HDL and LDL/HDL. However, our data provide limited information on specific dosages of PUFAs to guide the clinical treatment of renal replacement therapy patients.

Introduction

Patients with chronic kidney disease and dialysis patients suffer from multiple complications, including anemia, protein loss, uremic bleeding, secondary hyperparathyroidism, and cardiovascular disease. Cardiovascular disease is the most common cause of mortality and morbidity in patients with end-stage renal disease undergoing hemodialysis.[1, 2] The accumulation of cholesterol on the endothelium of blood vessels is the usual cause of atherosclerosis, which can progress to cardiovascular disease. [3] Although lipid-modifying drugs have been prescribed to prevent the development of cardiovascular disease in patients with chronic kidney disease,[4] some studies have shown controversial results on the efficacy of statins in dialysis patients.[5, 6] The benefits of therapeutic strategies other than pharmacological interventions, such as the dietary supplements, should be evaluated for efficacy.

Polyunsaturated fatty acids (PUFAs), one of dietary supplements with more than two double bonds where the first one locates three carbons away from the omega end, have shown little or no effect in preventing cardiovascular disease in the general population,[7] but numerous studies have assessed the effects of PUFAs on lipid profiles in dialysis patients. Randomized clinical trials (RCTs) have yielded controversial effects of PUFAs on the levels of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) in dialysis patients.[8-37] Interestingly, previous meta-analyses of RCTs have shown

that PUFAs have beneficial effects on the treatment of dialysis patients.[38, 39] One meta-analysis supported that omega-3 fatty acids could significantly lower serum triglycerides and LDL-C.[38] The other one synthesis, the largest systematic review and meta-analysis, showed that PUFAs decrease LDL levels and increase HDL levels.[39] However, the study's findings on LDL (I-square=78.3%) and HDL (I-square=91.5%) were highly heterogeneous, most likely due to diversity in interventions. Although the study had attempted to explore sources of heterogeneities by stratifying data according to characteristics, the heterogeneities could not be successfully reduced. In fact, clarifying such interventions improves the quality of the pooled results and provides a better understanding of PUFA effects in dialysis patients.[40] In our experience, different regimens should also be evaluated more precisely. For instance, Vitamin E, a fat-soluble antioxidant, was frequently used either in control group or placebo group in many studies.[9, 41-43] We considered it essential to distinguish the cause of the effects.

Besides, these syntheses usually focused on LDL, HDL, or total cholesterol in the assessment of lipid profiles and cardiovascular disease, but there is evidence indicating that the LDL/HDL ratio is also an important index for predicting cardiovascular disease.[44, 45] An improved meta-analysis study design could provide a more robust conclusion of the effects of PUFAs on lipoprotein levels in dialysis patients. Therefore, the purpose of our study was to clarify whether using PUFAs can improve lipid profiles (LDL, HDL, and LDL/HDL ratio) in dialysis patients through systematic review with network meta-analysis of randomized clinical trials.

Methods

Team members in this advanced review work were nephrologists, dietitian, and an experienced researcher in network meta-analysis (CRD42020150743). Our method of this systematic review followed the Cochrane handbook, and report of this study followed the PRISMA guidance.[46] Data in this study have been published in previous RCTs, and therefore, this work was exempted from institutional review board approval. Based on our study purpose, we formed PICO question:

P: dialysis patients

I: omega-3 fatty acids, omega-6 fatty acids, combination treatments of omega-3 fatty acids or omega-6 fatty acids

C: placebo or not PUFAs treatments

O: LDL, HDL, LDL/HDL ratio

Study selection criteria

According to our PICO, we defined eligibility criteria for evidence selection, and the inclusion criteria as follows: (a) recruiting patients undergoing dialysis; (b) treating patients with omega-3 fatty acids, omega-6 fatty acids, or combination treatments of PUFAs; (c) randomly allocating patients into two or more

groups. This comprehensive review removed studies if: (a) reference was gray literature without details information about trial design, (b) study did not separate dialysis patients from non-dialysis patients when it concurrently recruited both populations, and (c) article did not report LDL, HDL, or LDL/HDL ratio after treatments.

Search strategy and study selection

Our data were mainly from three important biomedical databases including EMBASE, PubMed, and Web of Science. Primary search strategy used relevant terms of dialysis and PUFAs in PubMed. These terms involved not only natural texts but also medical subject headings. Our search applied MeSH relevant terms in PubMed and Emtree in EMBASE. We combined relevant terms of dialysis by using Boolean operator “OR,” and “OR” was also used for combining relevant terms of PUFAs. There was no restriction on language or publication date in this search strategy. Then, we further connected dialysis part and PUFAs part by using Boolean operator “AND.” Then, we adopted the search strategy to EMBASE and Web of Science. Final search was completed in September 2020. Full information about systematic search was in **File S1**.

Two researchers independently selected evidence according to eligibility criteria through two steps. They screened titles and abstracts of those references hit by the systematic search. Then, the researchers excluded ineligible references after full-text review. Our study team met for making final judgement of evidence selection if the two researchers selected evidence differently.

Data extraction and quality assessment

The two researchers also independently extracted data and assessed quality of each trial we selected for our synthesis. They extract details of trial design, location, inclusion year, treatments, numbers of patients, mean age, sex, dialysis period, LDL, HDL, and LDL/HDL ratio at the end of treatment. Our team members extracted mean and standard deviation (SD) because LDL, HDL, and LDL/HDL ratio were usually performed as continuous outcomes. Yet, they calculated SD from standard error (SE) using formula $SE=SD/\sqrt{N}$ if original report only presented SE. When original report only gave interquartile range (IQR), our team members estimated SD according to the formula $IQR/1.35$. If we only found maximum and minimum, our team estimated SD based on Hozo's method.[47]

After data extraction, the two researchers assessed risk of bias in each trial by using the Cochrane Risk of Bias Tool. The assessment evaluated randomization generation, allocation concealment, blinding of participant and personnel, selecting reports, incomplete outcome data, and other source of bias. Our study team had another meeting for making final judgement of quality assessment if the two researchers had any disagreements on the assessment.

Evidence synthesis and statistical analysis

Our study not only synthesized evidence qualitatively, but also appropriately pooled quantitative data through contrast-based network meta-analysis in random-effects model. Because LDL, HDL, LDL/HDL

ratio at the end of treatment were continuous data, our consistency model performed weighted mean difference (WMD) with 95% confidence interval (CI). If original data was in different unites of measurement, we applied standardized mean difference (SMD) to solve the difference in analysis. For instance, those data could be mg/L, mg/dL, ng/L, ng/mL, or pg/mL. Moreover, we tried to clarify the most effective treatment among active treatments, and we calculated surface under the cumulative ranking (SUCRA) for revealing probability of each treatment among the most effective treatments. This method depicts hierarchy of treatment in each outcome through the treatment ranking of probability. Besides, we examined quality of our results in consistency model by detecting inconsistency and publication bias. All analysis we mentioned above were conducted in STATA version 14 for Microsoft Windows.

Results

This study identified 1597 references from Embase (n = 717), PubMed (n = 402), and Web of Science (n = 478). Then, duplicated (n = 433) and irrelevant references (n = 1080) were removed after titles and abstracts screen. Nine systematic reviews, 32 randomized clinical trials without relevant outcomes, and 13 gray literature without detail were excluded from our synthesis. Finally, 30 references from 27 RCTs met the eligibility criteria (**Figure 1**).[8-37]

Characteristics and quality of included studies

The 27 RCTs recruited 1975 dialysis patient from Brazil,[13, 24] Canada,[14] Denmark,[15, 30, 32, 34-36] Egypt,[10] Iran,[9, 16-19, 21, 22, 25-29, 37] Korea,[8, 23] and United States.[11, 12, 31] These trials could be categorized into six treatment strategies including placebo, omega-3 fatty acids, combination of omega-3 fatty acids and omega-6 fatty acids (n-3+n-6), combination of omega-3 fatty acids and vitamin (n-3+VitE), vitamin E, and medium chain triglyceride (MCT). **Table 1** presents relevant information about trial location, inclusion years, treatments, mean age, sex, and dialysis period. **File S2 shows the quality of the included trials.**

Low-density lipoprotein

A total of 16 RCTs with 1050 dialysis patients receiving omega-3 fatty acids, n-3+n-6, n-3+VitE, vitamin E, MCT, and placebo were included in network meta-analysis of LDL (**Figure 2A**).[9, 13-15, 19-23, 25, 26, 30, 32-37] Pooled estimate showed that with placebo as the reference, n-3+n-6 was the only one nutritional supplement reaching significantly lower LDL (SMD: -0.95, 95% CI: -1.87 to -0.13), yet n-3+n-6 did not show significantly lower LDL than omega-3 fatty acids, n-3+VitE, vitamin E, and MCT (**Figure 3**). Our study confirmed this trend in SUCRA analysis, and n-3+n-6 had the best mean rank with the highest SUCRA value (Mean rank = 1.3; SUCRA = 94.1), but mean ranks of the other four nutritional supplements were far away from n-3+n-6 (**File S3**). About quality of pooled estimate for LDL, design-by-treatment interaction model and Egger's test did not evident significant inconsistency (Chi-square = 2.04; $P = 0.916$; **File S4**) and publication bias (*point estimate* = 0.899; $P = 0.457$; **Figure 2B**; **File S5**) in the network meta-analysis.

High-density lipoprotein

Sixteen RCTs with 989 dialysis patients formed a six nodes network meta-analysis for HDL (**Figure 4A**). [9, 13, 15, 19-23, 25, 26, 28, 30, 32-37] Pooled estimate demonstrated that placebo results in significant lower HDL than omega-3 fatty acids (SMD: -0.85, 95% CI: -1.50 to -0.20) and MCT (SMD: -1.62, 95% CI: -3.07 to -0.17). Although n-3+n-6 seemed to lead higher HDL than placebo, it did not reach statistical significance (SMD: 0.72, 95% CI: -0.26 to 1.70; **Figure 3**). SUCRA analysis further manifested that the highest probability rank was MCT (Mean rank = 1.5; SUCRA = 89.3) followed by omega-3 fatty acids (Mean rank = 3; SUCRA = 60.6), vitamin E (Mean rank = 3.4; SUCRA = 52.1), n-3+n-6 (Mean rank = 3.5; SUCRA = 49.5), and n-3+VitE (Mean rank = 3.9; SUCRA=42.5). Placebo had the lowest SUCRA value (Mean rank = 5.7; SUCRA = 6.0; **File S6**). Design-by-treatment interaction model did not detect inconsistency in this pooled estimate (Chi-square = 12.53; $P = 0.051$; **File S7**), and Egger's test did not show significant publication bias (*point estimate* = 0.045; $P = 0.970$) in the network meta-analysis of HDL. (**Figure 4B**; **File S8**).

Low-density lipoprotein to high-density lipoprotein ratio

Available data of LDL/HDL ratio from the included trials formed a four nodes network meta-analysis (omega-3 fatty acids vs n-3+n-6 vs vitamin E vs placebo) though few trials provided the data from 114 cases (**File S9**). [12, 19] Pooled result showed that LDL/HDL ratio in placebo group was significantly higher than in omega-3 fatty acids group (WMD: 2.07, 95% CI: 0.65 to 3.49) and vitamin E group (WMD: 1.93, 95% CI: 0.49 to 3.38). Interestingly, n-3+n-6 only had limited benefit in LDL/HDL ratio with no statistical significance as it was compared to placebo (WMD: -1.23, 95% CI: -3.08 to 0.62; **File S10**). SUCRA analysis also confirmed that that top two probability rank were omega-3 fatty acids (Mean rank = 1.5; SUCRA = 84.8) and vitamin E (Mean rank = 1.8; SUCRA = 72.1), whereas n-3+n-6 (Mean rank = 2.8; SUCRA = 39.6) and placebo (Mean rank = 3.9; SUCRA = 3.5) were the two treatments with lowest probabilities (**File S11**). Because this consistency model included a four arms trial, design-by-treatment interaction model cannot be performed. Loop inconsistency test was used as alternative method for detecting inconsistency in the pooled estimate of LDL/HDL ratio. The test did not find significant inconsistency in the network meta-analysis of LDL/HDL ratio (Chi-square = 0.17, $P = 0.687$; **File S12**), and Egger's test also detected no significant publication bias (*point estimate* = 0.039; $P = 0.958$; **File S13**).

Discussion

Our evidence is the first network meta-analysis investigating the effects of PUFAs on lipid profiles in dialysis patients. This synthesis synthesized 27 randomized clinical trials involving 1975 patients undergoing dialysis and formed a network by omega-3 fatty acids, n-3+n-6, n-3+VitE, vitamin E, MCT, and placebo. We examined three important predictors of cardiovascular disease including LDL, HDL, and HDL/LDL ratio. The networks for LDL and HDL were consisted of the six treatments, and the network for HDL/LDL ratio was consisted of omega-3 fatty acids and n-6, vitamin E, and placebo. Then, we observed PUFAs may benefit on LDL, HDL, and HDL/LDL ratio.

In our study, n-3+n-6 significantly lowered serum LDL level in comparison to placebo. Omega-3 showed relative benefit on serum LDL though the result was not statistically significant. Increase in serum LDL level as well as increase in the proportion of oxidized LDL and small dense LDL particles had contributed to acceleration of atherosclerosis in such patients.[48-51] Basically, previous studies suggested that PUFAs intake can lower serum LDL in general patients, but the studies for dialysis patients were still limited.[52, 53] In a study with animal models, n-3+n-6 significantly lowered serum LDL level in rats.[54] The present meta-analysis further confirmed that PUFAs were the favored energy intake to lower serum LDL, and n-3+n-6 seemed to bear stronger efficacy than n-3. The result was compatible to a previous study showing that PUFAs were favored energy intake to lower serum LDL, compared to saturated fatty acids and carbohydrates.[55] Another issue, previous studies indicated that supplement with omega-3 fatty acids significantly reduced serum LDL.[38, 39] The result was in the same direction to our study even though the result was no statistical significance in our study. Moreover, we considered effects from nutrition supplements will be more vigorous in dialysis patients due to their underlying malnutrition status. With limited data for head-to-head comparison of omega-3 fatty acids versus omega-6 fatty acids groups, further analysis cannot be done in our meta-analysis.

Speaking of HDL, our finding differs from previous meta-analyses, and our meta-analysis claimed that omega-3 fatty acids and MCT were both beneficial for increasing HDL in dialysis patients. Previous meta-analyses took into consideration all the placebo groups equally and came to the results that omega-3 fatty acids had no effects on serum HDL.[38, 39] In contrast, our study separated MCT and omega-6 fatty acids from pure placebo. In fact, we found that RCTs reporting no effect of omega-3 fatty acids on serum HDL had the same problem by applying MCTs in placebo group.[22, 25, 26] On the contrast, RCTs not using MCT as placebo tend to show significant benefit from omega-3 fatty acids on increasing serum HDL, which was also compatible to our study.[15, 19] Actually, previous studies stated that MCT were related to increase serum HDL in general population and animal models, where our meta-analysis further confirmed the benefit for dialysis patient.[56-58]

As we mentioned above, LDL/HDL ratio was proven to be an independent predictor of cardiovascular disease and sudden cardiac death, even stronger than serum LDL or HDL alone.[44, 45] However, few evidence investigating effects of PUFAs on lipids profiles among dialysis patients reported LDL/HDL ratio. Our evidence tried to bridge this knowledge gap, and we found that omega-3 fatty acids and the vitamin E significantly decreased LDL/HDL ratio in comparison to placebo. The claim being reliable, our results may be even more cogent. The result of LDL/HDL ratio was correspondent to the results of analyzing LDL and HDL alone. In discussion of the effect of Vitamin E on LDL/HDL ratio, increasing oxidative stress was accused for dyslipidemia and atherosclerosis in dialyzed patients.[59-61] Previous studies had stated that vitamin E was effective of modifying lipid profiles by reducing oxidative stress, both as oral medication and as dialyzers.[62, 63] In short, we believed that omega-3 fatty acids were capable of lowering LDL/HDL ratio, a strong predictor of cardiovascular diseases. Moreover, vitamin E could lower LDL/HDL ratio in dialyzed patients by reducing oxidative stress as well.

Although some recent meta-analyses studied effects of PUFAs on lipid profile, many outcomes show high heterogeneity.[38, 39] We considered the limitation of these studies lied in not exploring the difference between regimens, especially the regimen used as placebo. In our opinion, the supplements of polyunsaturated fatty acids, vitamin E as well as medium-chained triglycerides are helpful for modifying lipids profiles in patients undergoing dialysis. The role of such supplements are even more important in these particular patients because statins for patient undergoing dialysis may not be as effective as in general populations.[5, 6] Another good meta-analysis in 2019 indicates that omega-3 fatty acids lower cardiovascular mortality though the synthesis does not analyze lipid profile.[64] Our evidence provides a possible explanation to their finding and foster the understanding of effects of PUFAs on cardiovascular outcomes through affecting lipid profile in dialysis patients.

Limitations

Our synthesis has three limitations. Firstly, many dialysis patients have cardiovascular disease, but unfortunately, the trials we synthesized in our study reported baseline cardiovascular disease variously. Our synthesis cannot give a clear suggestion to those with dialysis and different cardiovascular diseases. Secondly, the use of PUFAs is still unclear though we had separated n-3+n-6 and n-3+VitE from n-3. Clarifying combinations of supplements of PUFAs improves the understanding of use of PUFAs, yet our evidence cannot provide guidance with a specific dosage in using PUFAs among dialysis cases. Thirdly, our network meta-analysis of LDL/HDL ratio is based on limited evidence, and thus, the pooled estimate may be under power. In addition, we did not find available data from n-3+VitE. Therefore, we anticipate that future studies present LDL/HDL ratio to manifest whether using PUFAs improve lipid profiles, especially among those patients undergoing dialysis.

Practical Applications

We demonstrate that PUFAs supplements are effective in controlling lipid profiles in dialysis patients. The PUFAs n-3+n-6 decrease levels of LDL, and n-3 fatty acids by itself increase levels of HDL and decreases LDL/HDL ratio. However, our results offer limited information about PUFA dosage for guiding the clinical treatment of dialysis patients. Therefore, we anticipate further studies designing multiple arms will clarify the relationships among PUFA dosages and improved lipoprotein levels and ratios in patients undergoing dialysis.

List Of Abbreviations

RCTs	Randomized clinical trials
PUFAs	Polyunsaturated fatty acids
LDLs	Low-density lipoproteins
HDLs	High-density lipoproteins

n-3	Omega-3 fatty acids
n-6	Omega-6 fatty acids
SMD	Standardized mean difference
CI	Confidence interval
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
SD	Standard deviation
SE	Standard error
IQR	Interquartile range
WMD	Weighted mean difference
SUCRA	Surface under the cumulative ranking
VitE	Vitamin E
MCT	Medium chain triglyceride

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Data described in the manuscript, codebook, and analytic code will be made available upon request pending application and approval.

Competing interests

The authors declare that they have nothing to disclose regarding funding or conflicts of interest with respect to this manuscript.

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Authors' contributions

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Highlights

1. This is the first network meta-analysis about effects of polyunsaturated fatty acids on lipoprotein in dialysis patients.
2. Combination of n-3 and n-6 improves low-density lipoproteins (LDL) in dialysis patients.
3. N-3 improves high-density lipoproteins (HDL) and LDL/HDL ratio in dialysis patients.

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Table

Table 1 Characteristics of the included randomized clinical trials.

Author	Location	Inclusion Year	Treatments	Patients	Mean age	Sex (M/F)	Dialysis Period
An [8]	Korea	2010	1. n-3	23	56.7	12/11	3.42
			2. Placebo	20	58.1	8/12	4.31
Asemi [9]	Iran	2014	1. n-3	30	55.2	20/10	3.6
			2. α T	30	61.2	20/10	3.5
			3. n-3+ α T	30	54.9	20/10	3.4
			4. Placebo	30	59.9	20/10	3.4
Ateya [10]	Egypt	2015	1. n-3	25	14.7	14/11	NR
			2. VitE	24	14.6	13/11	NR
Bowden [11]	USA	NR	1. n-3	44	59.3	25/19	1.83
			2. corn oil	43	60.8	20/23	2.39
Daud [12]	USA	NR	1. n-3	31	59	20/11	3.6
			2. olive oil	32	58	12/20	3.3
de Mattos [13]	Brazil	2012 to 2013	1. n-3+fitE	43	52.7	27/16	5.49
			2. soybean oil+VitE	45	51.3	30/15	3.63
Donnelly [14]	Canada	NR	1. n-3+vitE	16	51	12/4	NR
			2. olive oil	16	51	12/4	NR
Ewers [15]	Denmark	2007	1. n-3	40	64.6	30/10	NR
			2. No supplement	40	64.6	30/10	NR
Gharekhani [16]	Iran	NR	1. n-3	25	56.8	12/13	5
			2. paraffin (placebo)	20	57.2	8/12	6
Jabbari [17]	Iran	NR	1. n-3	57	64.58	42/15	24
			2. Placebo	60	61.05	33/27	12
Kajbaf [18]	Iran	NR	1. n-3	26	57.76	17/9	NR
			2. Placebo	26	58.34	19/7	NR
Khajehdeh [19]	Iran	NR	1. n-3	15	32.7	8/7	2.19
			2. corn oil	15	33.6	8/7	2.46
			3. sesame oil	15	32.3	8/7	2.83
			4. placebo	15	31.1	7/8	2.21
Khalatbari [20]	Malaysia	NR	1. ground flaxseed	15	54	10/5	2.58
			2. NR	15	54.5	6/9	2.83
Khorsroshahi [21]	Iran	NR	1. n-3	44	51.5	32/12	NR
			2. soft gel pill	44	48.6	31/13	NR
Kooshki [22]	Iran	NR	1. n-3	17	50	10/7	1.75
			2. Placebo	17	50	11/6	2.3
Lee [23]	Korea	2012	1. n-3	8	60	2/6	NR
			2. Olive oil	7	64.4	3/4	NR
Lemos [24]	Brazil	NR	1. flaxseed oil+ α T	70	55.7	39/31	2.4
			2. mineral oil+ α T	75	58.3	46/29	2.9
Mirfatahi [25]	Iran	2014 to 2015	1. flaxseed oil	17	68	12/5	4.4
			2. MCT	17	59	10/7	4.6
Moeinzadeh [27]	Iran	NR	1. n-3	26	57.76	17/9	NR
			2. Placebo	26	58.34	19/7	NR
Naini [28]	Iran	2012	1. n-3	45	57.7	24/21	NR
			2. Placebo	45	59.3	27/18	NR
Omrani [29]	Iran	2013 to 2014	1. n-3	29	55	16/13	NR
			2. VitE	29	56	19/10	NR
Rantanen [30]	Denmark	2014 to 2016	1. n-3	56	64.2	37/19	1
			2. olive oil	56	60.5	37/19	2.2
Saifullah	USA	2006	1. n-3+VitE	15	58	11/4	NR

[31]			2. Placebo+VitE	8	57	7/1	NR
Sorensen	Denmark	NR	1. n-3	81	66	53/28	3
[32]			2. olive oil	80	68	51/29	2.17
<hr/>							
	Svensson	Denmark	NR	1. n-3	28	60	16/12 NR
[35]			2. olive oil	30	58	23/7	NR
Svensson	Denmark	2002 to	1. n-3	103	66	69/34	3.7
[36]		2003	2. olive oil	103	68	64/39	3.7
Taziki	Iran	NR	1. n-3	15	47	5/10	3
[37]			2. no intervention	18	59.5	6/12	3.5
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NR, no report; VitE, vitamin E; α T, alpha-tocopherol; n-3, omega-3 fatty acids; n-6, omega-6 fatty acids; MCT, medium chain triglyceride.

Figures

Figure 1

Flowchart of the systematic review and meta-analysis. HDL, high-density lipoprotein; LDL, low-density lipoprotein; PUFA, polyunsaturated fatty acid; RCT, randomized controlled trial.

Figure 2

(A) Network plots of low-density lipoprotein low and (B) funnel plot of low-density lipoprotein. CI, confidence interval; MCT, medium chain triglyceride; n-3, omega-3 fatty acids; n-6, omega-6 fatty acids; SUCRA, surface under the cumulative ranking; VitE, vitamin E.

LDL

Compared to n-3

	Mean with 95% CI
Placebo	0.13 (-0.36,0.62)
Vitamin E	-0.03 (-0.58,0.52)
n-3+Vitamin E	-0.17 (-1.34,1.01)
Medium chain triglyceride	0.27 (-0.86,1.41)
n-3+n-6	-0.83 (-1.68,0.02)

Compared to Placebo

Vitamin E	-0.16 (-0.83,0.51)
n-3+Vitamin E	-0.29 (-1.49,0.91)
Medium chain triglyceride	0.14 (-1.03,1.32)
n-3+n-6	-0.95 (-1.78,-0.13)

Compared to Vitamin E

n-3+Vitamin E	-0.13 (-1.34,1.08)
Medium chain triglyceride	0.31 (-0.93,1.54)
n-3+n-6	-0.79 (-1.73,0.15)

Compared to n-3+Vitamin E

Medium chain triglyceride	0.44 (-1.18,2.05)
n-3+n-6	-0.66 (-2.07,0.74)

Compared to Medium chain triglyceride

n-3+n-6	-1.10 (-2.24,0.04)
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HDL

Compared to n-3

Placebo	-0.85 (-1.50,-0.20)
Vitamin E	-0.10 (-0.79,0.60)
n-3+Vitamin E	-0.25 (-1.34,0.84)
Medium chain triglyceride	0.77 (-0.63,2.17)
n-3+n-6	-0.14 (-1.18,0.91)

Compared to Placebo

Vitamin E	0.75 (-0.15,1.65)
n-3+Vitamin E	0.60 (-0.51,1.71)
Medium chain triglyceride	1.62 (0.17,3.07)
n-3+n-6	0.72 (-0.26,1.70)

Compared to Vitamin E

n-3+Vitamin E	-0.15 (-1.36,1.06)
Medium chain triglyceride	0.87 (-0.68,2.41)
n-3+n-6	-0.04 (-1.26,1.19)

Compared to n-3+Vitamin E

Medium chain triglyceride	1.02 (-0.68,2.71)
n-3+n-6	0.11 (-1.20,1.43)

Compared to Medium chain triglyceride

n-3+n-6	-0.90 (-2.31,0.51)
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-3 -2 -1 0 1 2 3

Figure 3

Forest plots of head-to-head comparison for low-density lipoprotein and high-density lipoprotein. CI, confidence interval; n-3, omega-3 fatty acids; n-6, omega-6 fatty acids; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Figure 4

(A) Network plots of high-density lipoprotein and (B) funnel plot of high-density lipoprotein. CI, confidence interval; MCT, medium chain triglyceride; n-3, omega-3 fatty acids; n-6, omega-6 fatty acids; SUCRA, surface under the cumulative ranking; VitE, vitamin E.

Supplementary Files

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