Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 1649–1656

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

Effect of omega-3 fatty acid plus vitamin E Co-Supplementation on lipid profile: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 15 February 2019
Accepted 12 March 2019

Keywords:
Omega-3
Fatty acids
vitamin E
Lipid profile
Dyslipidemia

ABSTRACT

Background: Dyslipidemia is linked to chronic inflammation, which in return leads to a set of chronic disorders. Omega-3 fatty acids have been reported to reduce inflammation. Furthermore, Vitamin E is a fat-soluble vitamin which has antioxidant and anti-inflammatory effects. Vitamin E and omega-3 fatty acids co-supplementations may be more effective than the single supplementation in control dyslipidemia. Therefore, we designed and conducted the current systematic review and meta-analysis to investigate the effect of co-supplementation of vitamin E and omega-3 fatty acids on the lipid profile.
Methods: A comprehensive search for studies published between January 1990 and July 2018 was performed. The initial search extracted 3015 potentially relevant articles. After studying these publications, 9 RCTs were potentially eligible and retrieved in full text.
Results: The meta-analysis indicate that on total cholesterol, HDL, LDL and triglyceride individually did not show any significant difference between intervention and control groups, but vitamin E an omega-3 fatty acids co-supplementations significantly reduce VLDL levels.
Conclusions: Based on the available evidence, omega-3 fatty acid and vitamin E co-supplementation can reduce VLDL, although its effect on other lipid profile parameters requires more well-designed studies.

1. Introduction

Dyslipidemia is a morbidity consisting of increased triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC), as well as diminished levels of high-density lipoprotein cholesterol (HDL-C) [1]. Several primary and secondary causes such as genetics and lifestyle including dietary habits, physical inactivity and also obesity have been recognized for this disorder so far [2]. The incidence of dyslipidemia changes by age, and is usually higher in men than women [3]. Poor control of dyslipidemia is linked to chronic inflammation [4] which in return leads to a set of disorders such as type 2 diabetes mellitus (T2DM) and chronic kidney disease as well as cardiovascular diseases [3,5]. Thus, proper control of dyslipidemia is an important part of medical care in subjects with high risk of CVD.

Both pharmacological and life-style interventions can be considered to control dyslipidemia. Multiple strategies in diet therapy have been launched to ameliorate hyperlipidemia, such as the inclusion of omega-3 fatty acids in the diet [6]. Many studies have shown that omega 3 fatty acids include beneficial properties in preventing CVD [7]. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been reported to downregulate the expression of inflammatory related genes through suppression of the NF-kB signaling pathway by inhibiting IkB phosphorylation [8]. They also improve the lipid profile by increasing HDL [9] and decreasing LDL and TG [10,11].

Abbreviations: TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus; EPA, Eicosapentaenoic acid; DHA, docosahexaenoic acid; CVD, Cardiovascular disease; PUFA, polyunsaturated fatty acids; MD, Mean Difference; IU, International Unit.

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https://doi.org/10.1016/j.dsx.2019.03.018
1871-4021/

Furthermore, Vitamin E is a fat-soluble vitamin which has antioxidant and anti-inflammatory effects. Vitamin E decreases lipid peroxidation in vitro and in vivo by breaking chain propagation [12]. Evidences show that vitamin E suppresses atherogene development via influencing endothelial and smooth muscle cells of the arteries [13,14]. In addition, supplementation with vitamin E ameliorates LDL resistance to oxidation [15].

On the other hand, since polyunsaturated long chain fatty acids (PUFAs) are sensitive to oxidation, the combination of omega-3 fatty acids and antioxidants have earlier been used in previous evidences. It seems that antioxidants inhibit the oxidative stress that may be induced by omega-3 fatty acids. Thus, their co-supplementations may be more effective than the single supplementation [16]. There are several documents that have investigated the effect of vitamin E and omega-3 fatty acid co-supplementation on various metabolic parameters [17–20]. However, the effect of this combination on the lipid profile has not yet been summarized in a systematic review and meta-analysis study. Therefore, we designed and conducted the current systematic review and meta-analysis to investigate the effect of co-supplementation of vitamin E and omega-3 fatty acids on the lipid profile.

2. Materials and methods

We followed the Cochrane Collaboration guidelines for the design, implementation, analysis and reporting of this systematic review and meta-analysis.

2.1. Inclusion and exclusion criteria

Trials included in this systematic review had to meet the following three criteria: (1) placebo controlled with a parallel design, (2) trials that compared lipid profile indices among subjects who were supplemented with a combination of omega-3 FAs plus vitamin E compared to placebo, (3) studies that provided sufficient data on lipid profile indices at baseline and at the end of the intervention to determine the differences in means (MD) with 95% confidence intervals (95% CI). Studies excluded if: (1) they had an observational design (cross-sectional, case-control, cohort); (2) they had a quasi-experimental design (non-randomized or uncontrolled); (3) They were book sections, letter to editor, abstracts without adequate data or reviews.

2.2. Literature search

For identifying eligible trials for this systematic review and meta-analysis, we systematically searched the following electronic databases up to 20th May 2018: Medline, Embase, Scopus, Web of Science and Cochrane Library. We also checked the citation and reference lists of identified articles to find additional pertinent studies. Also gray literature databases and clinical trials registration databases for unpublished studies were searched. We used Mesh terms to search in Medline and index heading in other databases. Search keywords include; Lipids OR Lipid Profile AND Fatty Acids, Omega-3 OR n-3 Fatty Acids OR n-3 Polyunsaturated Fatty Acid AND Vitamin E OR Tocopherols OR alpha Tocopherol OR beta-Tocopherol OR gamma-Tocopherol. Search details are available in **Appendix s1**.

2.3. Data extraction and risk of bias assessment

The titles and abstracts of all retrieved publication were scrutinized by two independent reviewers (M.M and J.H) for eligibility. Full texts of the remaining articles were assessed to reach a final decision on inclusion or exclusion. Disagreements between two reviewers were settled by discussion or third senior reviewer (M.S). Two independent reviewers used a predefined, standardized, electronic data extraction form to extract relevant information from the eligible studies as following: (1) author's name; (2) year of publication; (3) study location; (4) study size; (5) study design; (6) geographical location; (7) vitamin E and omega3 FAs dosage, (8) duration of intervention. Two independent reviewers (M.S and J.H) assessed the methodological quality of the included trials using the Cochrane Handbook for Systematic Reviews of Interventions.

2.4. Statistical analyses

In this study, the effect size (ES) to which treatment improved lipid profile indices was defined as the mean difference. Pooled estimates of the effect of vitamin E and omega3 FAs combination on lipid profile indices, using ES, were obtained using a random effects model. Between-study heterogeneity was examined using the I^2 measure of inconsistency and chi^2 test of heterogeneity. All analyses were conducted using Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014.

3. Results

3.1. Literature search and characteristics of included studies

The electronic search identified 3015 unique publication by searching 5 bibliographic (242 from PubMed, 1369 from Embase, 439 from Scopus, 1414 from Web of Science, 67 from Cochrane Library) and gray literature databases. After the initial screening, based on titles and abstracts, 2979 publications were excluded and 36 remained for full text evaluation. Following detailed assessments, 9 unique trials met the inclusion criteria and were included in the meta-analysis. Fig. 1 shows the process of study selection. Main characteristics of the included studies are summarized in Table 1. Trials were conducted in Iran (eight trials) and Brazil (one trial) and were published between 2014 and 2017.The daily dose of vitamin E was 400 IU in all trials, and the durations of intervention ranged from 6 to 13 weeks. The sample size ranged from 56 to 120 participants. The trials included samples from the healthy women (N = 1), Women with gestational diabetes (N = 1), women with type 2 diabetes (N = 1), women with polycystic ovary syndrome (N = 1), hemodialysis patients (N = 1), Women with fibrocystic breast disease (N = 1), patients with Parkinson's disease (N = 1) and patients with cardiovascular disease (N = 2). Two studies (22.22%) adopted unclear random allocation, while the remaining described adequate methods of random sequence generation. We judged four trials as having an unclear risk of bias because they did not explain an obvious method of allocation concealment. Blinding of participants and personnel (performance bias) was judged to be unclear for four trials, but the majority of trials assessed to be at low risk of blinding of outcome assessment (detection bias) (7 trials). The main reason for high risk of bias was incomplete outcome data (attrition bias). Three trials were judged to be at high risk for attrition bias while the remaining (four trials) used an appropriate method for the analysis approach. All trials were judged to be at low risk of bias for reporting bias and other biases.

3.2. The effects of supplementation with combination of omega-3 FAs plus vitamin E on serum levels of LDL

Fig. 2 shows a forest plot of omega-3 FAs plus vitamin E on serum LDL levels. In four studies, the LDL level decreased significantly ($P < 0.05$) Table 1. However, the pooled effect of the combination on eight trials with 427 participants (214 cases and 213

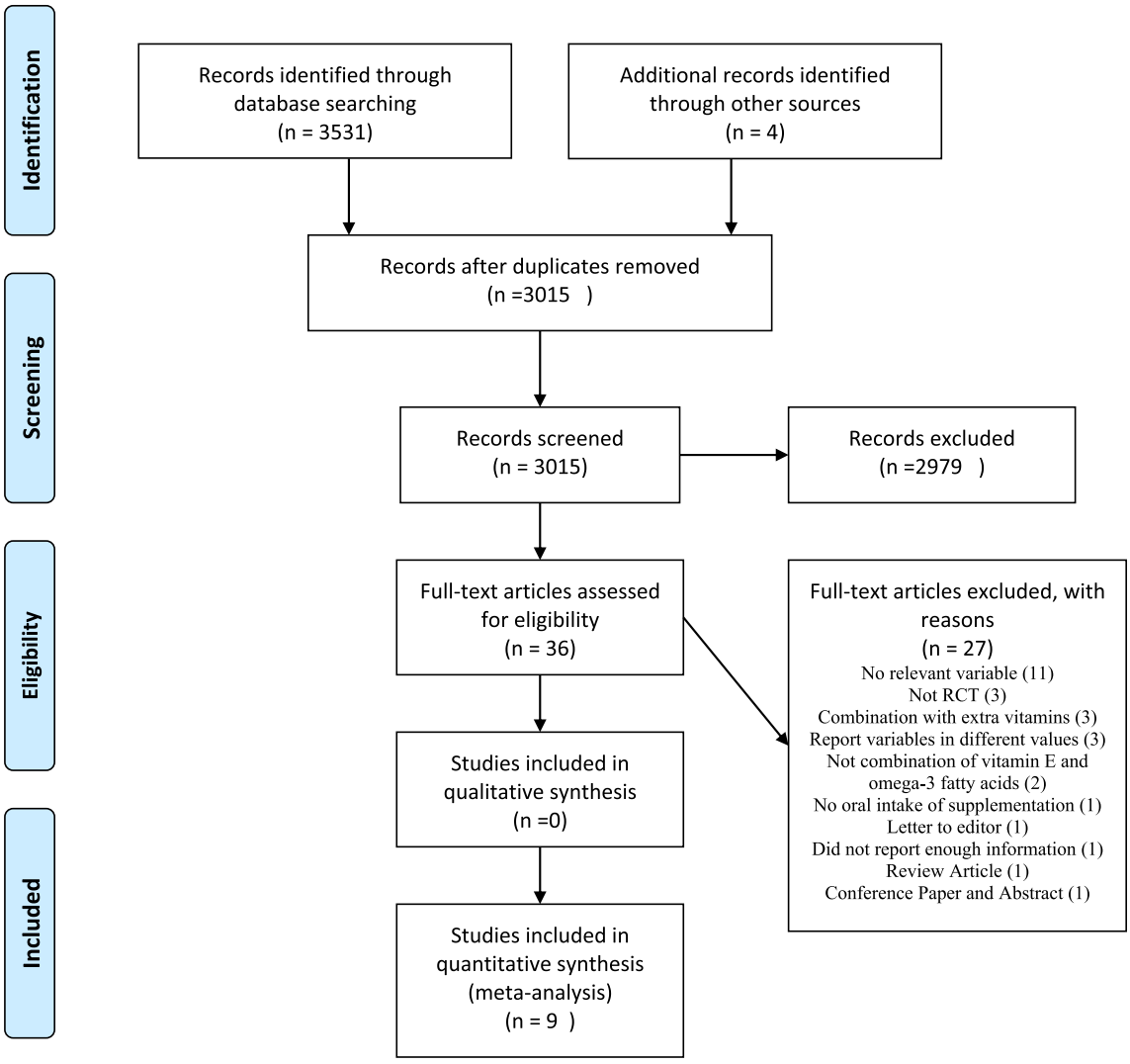

Fig. 1. PRISMA 2009 Flow Diagram of study selection.

controls) showed no significant difference between the intervention versus placebo groups, MD = −3.97 mg/dL (95% CI [−13.04, 5.09], P = 0.39); see Fig. 2. There was considerable statistically significant heterogeneity between studies (P < 0.001, I^2 = 82%). Egger's test for publication bias was not significant (Egger's regression intercept: 7.82, 95%CI: 29.04 to 13.40, P = 0.40). Meta-regression of trials found that, the duration of intervention had no effect on heterogeneity between studies (Linear regression coefficient = −0.11 (95% CI = −0.33 to 0.10), P = 0.25). In a subgroup analysis, no significant difference was observed in the subset of trials administering Omega-3 Fatty Acids with plant origin (SMD: 0.09, 95% CI: −0.91 to 0.73, P = 0.83), and trials with animal origin (SMD: 0.26, 95% CI: 0.55 to 0.03, P = 0.08) (Fig. 2).

3.3. The effects of supplementation with combination of omega-3 FAs plus vitamin E on serum levels of HDL

There were seven randomized controlled trials in which serum levels of HDL was compared between combination of omega-3 FAs plus vitamin E group and placebo involving 381 participants (192 cases and 189 controls). The intervention increased HDL levels in only two trials significantly (P < 0.05)and the serum levels of HDL were identical between combination of omega-3 FAs plus vitamin E versus placebo groups among the 7 trials (MD: 1.15 mg/dL, 95% CI: −0.83 to 3.13, P = 0.26) with noticeable inter-study heterogeneity (I^2 = 75%, P < 0.001) (Fig. 3). There was no evidence of publication bias found by the Egger test (Egger's regression intercept: 6.84, 95%CI: 24.47 to 10.78, P = 0.36). The duration of intervention had no effect on heterogeneity between studies (Linear regression coefficient = −0.01 (95% CI = −0.23 to 0.21), P = 0.91). In a subgroup analysis, no significant difference was observed in the subset of trials administering Omega-3 Fatty Acids with plant origin (SMD: 0.34, 95% CI: −0.20 to 0.88, P = 0.22), and trials with animal origin (SMD: 0.11, 95% CI: 0.52 to 0.30, P = 0.08) (Fig. 3).

3.4. The effects of supplementation with combination of omega-3 FAs plus vitamin E on serum levels of VLDL

We retrieved five trials in which the serum levels of VLDL were compared between combination of omega-3 FAs plus vitamin E group and placebo. The VLDL level declined significantly in three trials compared to the control group (P < 0.05) Table 1 and the overall MD on 5 trials consisting of 304 participants (152 cases and 152 controls), showed significant lower levels in the intervention group compared to the placebo group (MD = − 2.96 mg/dL, 95% CI = −5.84 to −0.09, P = 0.04, Fig. 4). There was no evidence of

Table 1
Main characteristics of included studies.

Study	Country	Subjects	Sample size	Vitamin E Dosage	n-3 fatty acids Dosage				Duration (w)	Gender	Age				Main outcome[¥,*]
											Placebo		Intervention		
					Weight (mg)	EPA (mg)	DHA (mg)	ALA (mg)			Mean	SD	Mean	SD	
Alves Luzia et al, 2015 [21]	Brazil	Healthy women	74	400 IU	1000	540	360	-	13	F	54.0	8.0	50.0	7.0	↓TC, ↓LDL, ↔HDL, ↔TG
Asemi et al, 2015 [20]	Iran	Hemodialysis patients	120	400 IU	1250	600	300	-	12	M/F	59.9	15.7	54.9	14.3	↔TC, ↔LDL, ↔HDL, ↔TG, ↔ VLDL
Mahmoodi et al, 2014 [19]	Iran	Women with T2D	75	400 IU	1800	NR	NR	NR	12	F	53.83	0.46	54	0.45	↓TC, ↓LDL
Mirhashemi et al, 2017 [18]	Iran	FBD patients	56	400 IU	1000	-	-	400	12	F	47.6	5.8	45.3	7.2	↓TG, ↓VLDL, ↑HDL
Rahmani et al, 2017 [22]	Iran	PCOS Patients	68	400 IU	1000	-	-	400	12	F	26.6	5.6	24.9	5.5	↓TG, ↓VLDL, ↓TC, ↓LDL, ↔HDL
Ramezani et al, 2015 [23]	Iran	CAD Patients	67	400 IU	4000	720	480	-	8	M	58.5	1.33	56.3	1.62	↔TG, ↔TC, ↔LDL, ↔HDL
Saboori et al, 2016 [24]	Iran	CAD Patients	60	400 IU	4000	720	480	-	8	M	-	-	-	-	↔TC, ↔LDL, ↔HDL, ↓TG
Taghizadeh et al, 2016 [17]	Iran	GDM	60	400 IU	1000	-	-	400	6	F	29.4	4.4	28.6	6.3	↔TC, ↓LDL, ↑HDL, ↓TG, ↓VLDL
Taghizadeh et al, 2017 [25]	Iran	PD patients	60	400 IU	1000	NR	NR	NR	12	M/F	66	10.4	63.9	8.9	↔TC, ↔LDL, ↔HDL, ↔TG, ↔VLDL

[*] ↓ This symbol is a sign of decreasing variables in the intervention group, ↑ This symbol is a sign of increasing variables in the intervention group, ↔ This sign indicates that there is no difference between the two groups, NR: not reported, IU: International Unit, M: male, F: female
[¥] PCOS: polycystic ovary syndrome, GDM: gestational diabetes, T2D: type 2 diabetes, FBD: fibrocystic breast disease, PD: Parkinson's disease, CAD: cardiovascular disease, EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid, ALA: alpha-linoleic acid, TG: Triglyceride, TC: Total Cholesterol, VLDL: Very Low Density Lipoprotein, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein.

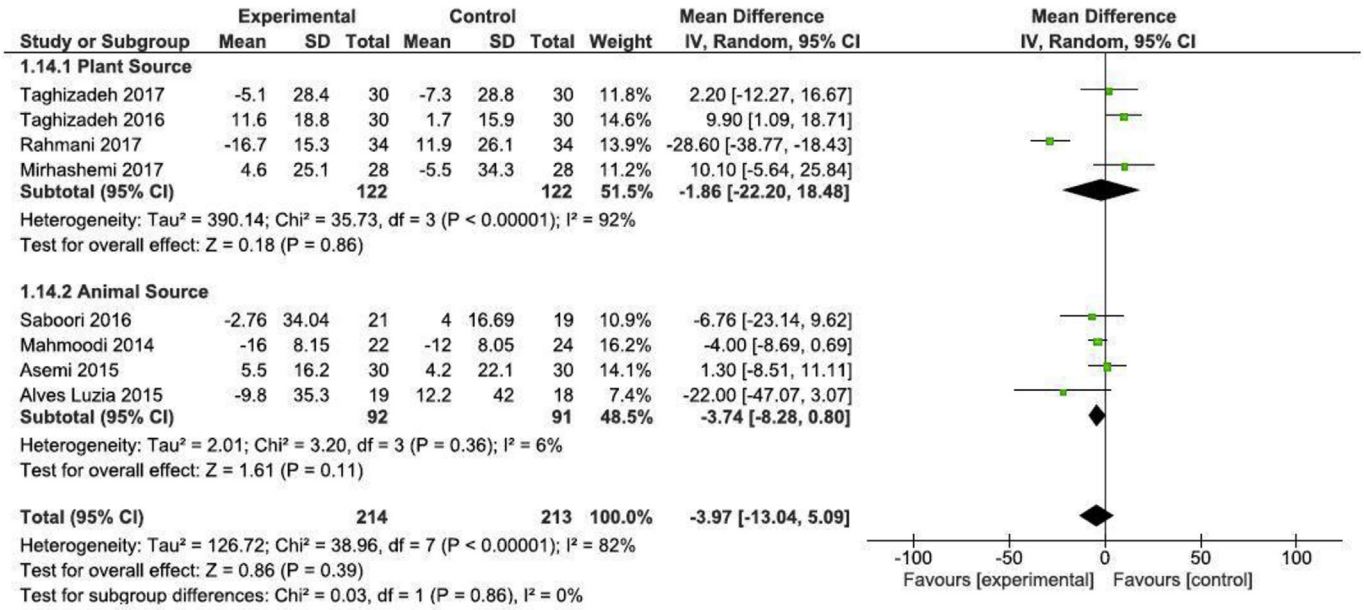

Fig. 2. forest plot of omega-3 FAs plus vitamin E on serum LDL levels.

publication bias for this meta-analysis (Egger's regression intercept: 60.91, 95%CI: 180.45 to 58.63, P = 0.20). Noticeable heterogeneity was also observed (P = 0.003; I^2 = 75%). Meta-regression analysis showed that duration of intervention (Linear regression coefficient = 0.02 (95% CI = −0.34 to 0.40), P = 0.83) did not affect the heterogeneity of the studies. In a subgroup analysis, no significant effect was observed in the subset of trials administering Omega-3 Fatty Acids with animal origin (SMD: 0.11, 95% CI: −0.40 to 0.61, P = 0.68), but a significant decrease of serum VLDL was found in the subset of trials administering Omega-3 Fatty Acids with plant origin (SMD: 0.61, 95% CI: 0.87 to −0.35, P< 0.001) (Fig. 4).

3.5. The effects of supplementation with combination of omega-3 FAs plus vitamin E on serum levels of TG

Among the eight trials which evaluated the effect of combination of Omega 3 plus vitamin E on serum triglyceride, four studies showed a significant declining trend (P < 0.05) Table 1. Fig. 5 shows the forest plots of the pooled estimates of the mentioned intervention (192 cases and 189 controls). In the current meta-analysis, no significant difference was noted in serum levels of TG (MD = −11.30 mg/dL, 95% CI: 23.00 to 0.40, P = 0.06) between the intervention and control groups. Substantial between study heterogeneity was noted (I^2 = 75%, P< 0.001). There was no evidence of

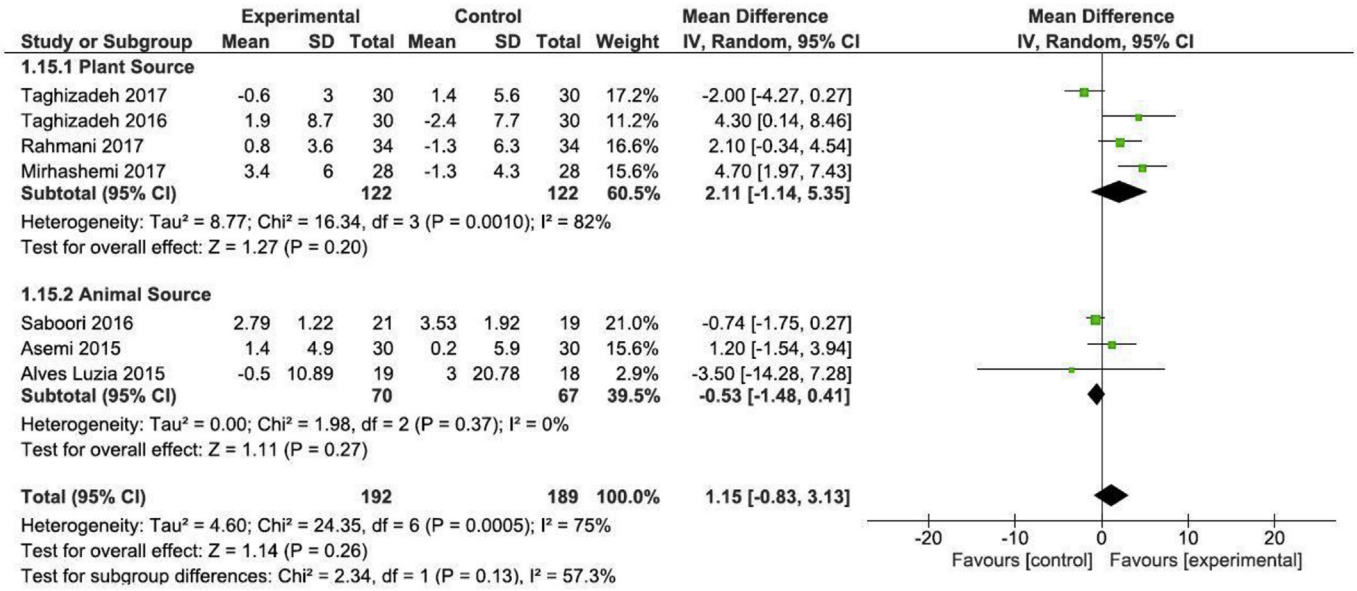

Fig. 3. forest plot of omega-3 FAs plus vitamin E on serum HDL levels.

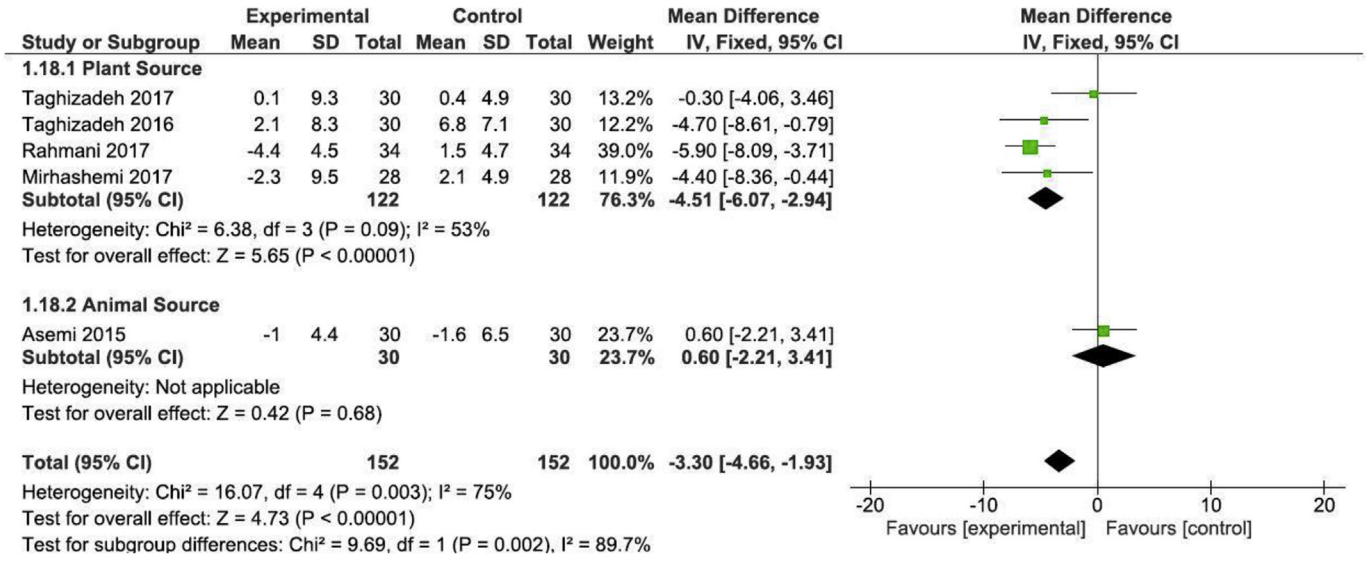

Fig. 4. forest plot of omega-3 FAs plus vitamin E on serum VLDL levelsA.

publication bias (Egger's regression intercept: 9.71, 95%CI: 28.79 to 9.36, P = 0.24). The duration of intervention had no effect on heterogeneity between studies (Linear regression coefficient = −0.04 (95% CI = −0.31 to 0.22), P = 0.66). In a subgroup analysis, no significant difference was observed in the subset of trials administering Omega-3 Fatty Acids with plant origin (SMD: 0.40, 95% CI: −1.08 to 0.28, P = 0.25), and trials with animal origin (SMD: 0.47, 95% CI: 1.25 to 0.30, P = 0.23) (Fig. 5).

3.6. The effects of supplementation with combination of omega-3 FAs plus vitamin E on serum levels of TC

Eight RCTs reported TC level (214 cases and 213 controls) in which three of them showed a significant reduction (P < 0.05) (Table 1). The random effects model showed no significant difference in serum levels of TC (MD = −6.11 mg/dL, 95% CI: 15.30 to 3.09, P = 0.19) between the combination of omega-3 FAs plus vitamin E and control groups. There was considerable statistically significant heterogeneity between studies (P < 0.001, I^2 = 81%). Egger's test for publication bias was not significant (Egger's regression intercept: 10.28, 95%CI: 23.52 to 2.96, P = 0.10). Meta-regression of trials found that, the duration of intervention had no effect on heterogeneity between studies (Linear regression coefficient = −0.10 (95% CI = −0.36 to 0.15), P = 0.36). In a subgroup analysis, no significant difference was observed in the subset of trials administering Omega-3 Fatty Acids with plant origin (SMD: 0.15, 95% CI: −0.77 to 0.48, P = 0.65), and trials with animal origin (SMD: 0.50, 95% CI: 1.19 to 0.19, P = 0.16) (Fig. 6).

4. Discussion

In the present systematic review and meta-analysis, we

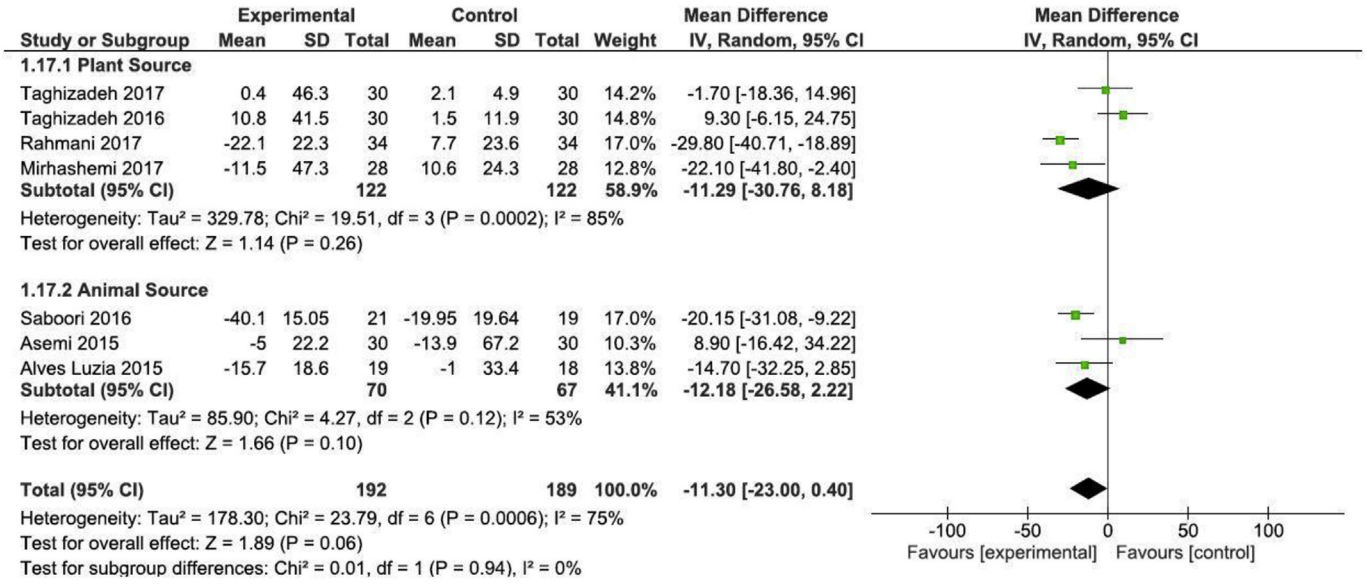

Fig. 5. forest plot of omega-3 FAs plus vitamin E on serum TG levels.

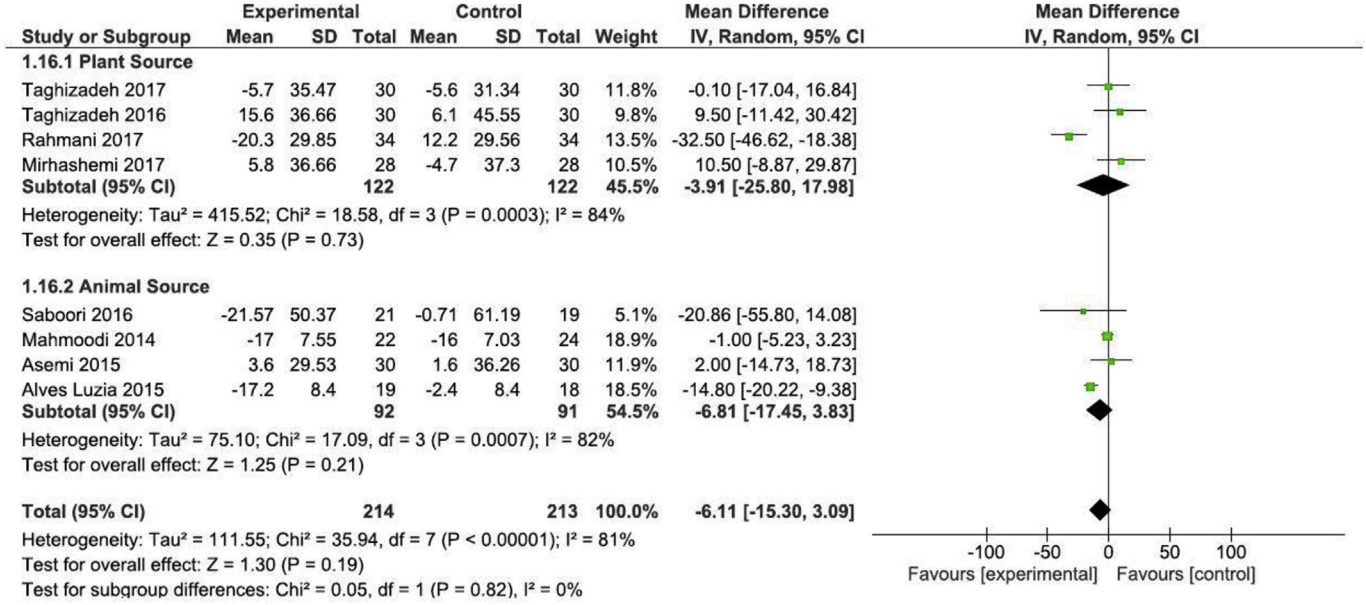

Fig. 6. forest plot of omega-3 FAs plus vitamin E on serum TC levels.

examined the effects of omega 3 fatty acids and vitamin E co-supplementation on the lipid profile. We finally included nine articles and analyzed the lipid profile parameters. To the best of our knowledge, this is the first systematic review and meta-analysis to evaluate the outcomes of vitamin E and omega-3 fatty acids co-supplementation on the lipid profile. We found that omega-3 and vitamin E co-supplementation has no statistically significant effects on levels of TC, TG, LDL, and HDL. We also found that vitamin E and omega-3 can significantly decrease VLDL levels, but due to high study heterogeneity ($I^2 = 75\%$), the results should be interpreted with caution. Previous systematic reviews have evaluated the effect of Omega3 fatty acids individually. Balk et al. in a systematic review and meta-analysis showed that fish oil supplementation alone results in a significant triglyceride reduction, HDL and LDL elevation, and no effect on total cholesterol [9]. A systematic review showed that fish oil supplementation on diabetic patients effectively decreased triglyceride, elevated LDL-C, but had no significant effect on total cholesterol and HDL-C [26].

Since plant and animal sources of omega-3 fatty acids have different biological effects and their sensitivity to oxidation is also different [27], we divided the sources of omega-3 fatty acids into two groups of animal sources and plant sources in order to perform a subgroup analysis. However, due to the close prognosis of omega-3 doses used in our included studies, we did not succeed in subgroup analyzing for omega-3 dosage. In terms of vitamin E, all included studies in this systematic review used the same dose of vitamin E (400 IU/d), so we were unable to imply further profound analysis.

Eight of nine included studies evaluated the LDL levels in serum after co-supplementation with omega-3 fatty acids and vitamin E,

and there was no significant change in LDL levels). Also, subgroup analysis of omega-3 fatty acid sources did not show a significant difference in the LDL levels. The great heterogeneity ($I^2 = 82\%$) of included studies may have affected this result. However, the results of our study coincide with previous studies on supplementation of omega-3 fatty acids on LDL, a systematic review and meta-analysis showed that fish oil supplementation worsens LDL-C [9]. Other studies have also shown that omega-3 supplementation may either be ineffective or elevate LDL levels [28,29]. Previous studies indicate that omega-3 fatty acids increase the conversion of VLDL to LDL [30] which is dose dependent [31]. In addition, studies have shown that solely fish oil supplementation increases oxidative stress, which could be due to the effect of fish oil on the reduction of antioxidant enzyme expression [32]. On the other hand, vitamin E has been shown to be the most potent antioxidant in reducing atherosclerotic lesions induced by oxidized LDL [33]. Whereas a combination of fish oil and vitamin E could have the potency to reduce oxidized LDL-C and reduce the cholesterol profile [21]. Overall, the present meta-analysis showed a neutral effect of the combination of Omega 3 and vitamin E which indicates a preventive effect for cholesterol elevation.

The overall pooled effect showed that co-supplementation of omega-3 fatty acids and vitamin E has no significant effect on HDL compared to placebo. The subgroup analysis showed that the source of fatty acids did not affect HDL levels. Our results were inconsistence to Wei et al. research, in which they showed that DHA significantly increases the HDL level, while EPA does not have such an effect [28]. This inconsistency between our results and Wei et al. study could be due to the difference in the baseline values of HDL. This eight RCTs showed no significant difference in serum levels of TC Subgroup analysis of omega-3 fatty acids, also showed no significant difference in TC levels. Previous meta-analysis of human trials, also concluded that omega 3 fatty acids alone have no clinical effects on TC levels [34]. Cohort studies have also found that supplementation of omega-3 fatty acids alone or in combination with vitamin E did not affect TC [35].

In the present meta-analysis, serum levels of TG reduced in four studies after supplementation with omega-3 fatty acid and vitamin E compared to placebo, even though this reduction was not statistically significant according to the meta-analysis. This effect was not significant either when subgroup analysis was perfumed for the omega-3 source. Previous studies have shown that supplementation with omega-3 fatty acids can reduce triglyceride levels [36]. Although there was no significant reduction in triglyceride levels in our study, considering a significant decrease in VLDL, it seems that omega-3 and vitamin E co-supplementation reduce triglyceride levels more efficiently compared to cholesterol. Furthermore, according to previous studies triglyceride reduction by Omega 3 supplementation is dose dependent and it also relies on the baseline values of triglyceride [9] which could have affected the results of the current meta-analysis.

This results of the meta-analysis showed that the VLDL significantly declined in participants treated with combination of omega-3 FAs plus vitamin E compared with placebo The subgroup analysis showed that plant sources of omega-3 fatty acids in combination with vitamin E have a more significant effect on VLDL levels, while the combination of animal sources with vitamin E did not show this influence. Our results are inconsistent with previous studies on the effect of omega-3 on reducing VLDL levels [37,38]. A meta-analysis showed a consistent decrease in VLDL production rate following supplementation with omega-3 [39]. Suggested mechanisms indicate that the decrease of hepatic VLDL and TG production, maybe due to the catabolism of VLDL to LDL, via enhanced binding of omega 3 fatty acid-enriched VLDL to lipoprotein lipase [40]. Omega-3 fatty acid intervention reduces the TG level by both lowering the secretion of hepatic TG as VLDL, and by increasing the rate of TG removal from the circulation [41,42]. In addition, studies have shown that omega-3 fatty acid supplementation reduces Apo CIII [43,44]. Apo CIII plays an important role in the hypertriglyceridemia pathogenesis, especially for suppressing the action of LPL, thus slowing TG clearance [45]. Apo CIII also interacts with the attachment of TG-rich lipoproteins with hepatic Apo B/E receptors, reducing the removal speed of these particles from the circulation.

Our systematic review and meta-analysis was based on a comprehensive database search, and it is thus very unlikely that related studies were overlooked. The included trials were limited number of studies, therefore the outcomes should be declared with caution. A limitation of the present systematic review and meta-analysis was the relatively homogenous ethnicity/race profile of the included study participants. Eight of 9 studies were performed in Iran, which may limit the external validity of these outcomes to other populations [46].Most of the included studies in this meta-analysis were evaluated as good quality. Risk of selection, performance, detection and reporting bias was low in the majority of studies. However 3 studies in the final outcome report have an attrition bias.

5. Conclusion

In summary, the outcomes of this systematic review and meta-analysis showed that omega-3 fatty acids and vitamin E co-supplementation decrease VLDL. However, omega-3 and vitamin E co-supplement had no significant effect on TC, TG, LDL and HDL. Based on the available evidence, further well-designed and larger trials are needed to clarify efficiency of omega-3 fatty acid and vitamin E co-supplementation in the improvement of the lipid profile parameters.

Conflicts of interest

All authors declare that they have no competing interests.

Contributions

J.H contributed to the study design, data analysis, and interpretation; and drafted and edited the manuscript. M.S. contributed to the statistical analysis and edited the manuscript. M.A. contributed to the data collection and edited the manuscript. A.A. and M.R. are contributed to performing search and data collection. M.M. contributed to edited manuscript and preparing the final article version.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.03.018.

Funding

None.

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