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Safety and tolerability of prescription omega-3 fatty acids: a systematic review and meta-analysis of randomized controlled trials

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Safety and tolerability of prescription omega-3 fatty acids: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background

Omega-3 fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] are widely recommended for health promotion. Over the last decade, prescription omega-3 fatty acid products (RxOME3FAs) have been approved for medical indications. Nonetheless, there

¹ Drs. Cheng-Ho Chang and Ping-Tao Tseng contributed equally as the first author.

is no comprehensive analysis of safety and tolerability of RxOME3FAs so far.

Methods

A systematic review of randomized controlled trials (RCTs) was carried out based on searches in six electronic databases. The studies involving marketed RxOME3FA products were included, and adverse-effect data were extracted for meta-analysis. Subgroup analysis and meta-regression were conducted to explore the sources of potential heterogeneity.

Results

Among the 21 included RCTs (total 24,460 participants; 12,750 from RxOME3FA treatment cohort and 11,710 from control cohort), there was no definite evidence of any RxOME3FA-emerging serious adverse event. Compared with the control group, RxOME3FAs were associated with more treatment-related dysgeusia (fishy taste; $p = 0.011$) and skin abnormalities (eruption, itching, exanthema, or eczema; $p < 0.001$). Besides, RxOME3FAs had mild adverse effects upon some non-lipid laboratory measurements [elevated fasting blood sugar ($p = 0.005$); elevated alanine transaminase ($p = 0.022$); elevated blood urea nitrogen ($p = 0.047$); decreased hemoglobin ($p = 0.002$); decreased hematocrit ($p = 0.009$)]. Subgroup analysis revealed that EPA/DHA combination products were associated with more treatment-related gastrointestinal adverse events [eructation (belching; $p = 0.010$); nausea ($p = 0.044$)] and low-density lipoprotein cholesterol elevation ($p = 0.009$; difference in means = 4.106 mg/dL).

Conclusion

RxOME3FAs are generally safe and well tolerated but not free of adverse effects.

Post-marketing surveillance and observational studies are still necessary to identify long-term adverse effects and to confirm the safety and tolerability profiles of RxOME3FAs.

Keywords:

omega-3 fatty acid; prescription; adverse effect; adverse event; safety; tolerability

1. Introduction

Omega-3 fatty acids (OME3FAs), especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are essential nutrients for humans and are promising nutraceuticals [1]. There has been much evidence showing their benefits for not only various physical conditions[2-9] but also several mental disorders [10-16]. Nowadays, the supplementation with OME3FAs or fish oil products has become increasingly popular worldwide. However, dietary supplements are usually loosely regulated as compared to prescription drugs. Supplements do not have to meet strict government regulatory standards on purity, quality, efficacy, and safety as pharmaceutical agents do. As a result, fish oil dietary supplements on the market may contain uncertain concentrations of OME3FAs and possibly saturated fat or other contaminants [17, 18].

Over the last decade, prescription omega-3 fatty acids (RxOME3FAs) have been available in many countries. Oral RxOME3FAs are indicated as an adjuvant therapy in adult patients for secondary prevention of post-myocardial infarction and the treatment of hypertriglyceridemia in European countries and for the treatment of hypertriglyceridemia (serum triglyceride levels ≥ 500 mg/dL) in the US [19].

RxOM3FAs appear to have favorable safety and tolerability profiles [20, 21]. Unlike

other triglyceride-lowering therapies, such as niacin or fenofibrate, RxOM3FAs have not been associated with risk of rhabdomyolysis when taken alone or in combination with statins [22]. However, according to the Micromedex® database, there are still some safety concerns, especially regarding hypersensitivity (e.g., “use with caution in patients with known hypersensitivity to fish and/or shellfish”), the risk of bleeding, elevated low-density lipoprotein (LDL) cholesterol, increased alanine transaminase (ALT) or aspartate transaminase (AST), and the risk of recurrent atrial fibrillation/flutter [23]. Concurrent use of RxOM3FAs and anticoagulants or antiplatelet agents may increase the risk of bleeding [23]. On the other hand, recent evidence suggests that the bleeding risk is more modest than originally hypothesized [24, 25] and there is also evidence against the association between OME3FAs and atrial fibrillation/flutter [26].

There are two subgroups of RxOME3FA preparations available on the worldwide market: EPA/DHA combinations and EPA-only products [21]. In the US, most of the approved RxOME3FA products are EPA/DHA combinations, including Lovaza® (“omega-3-acid ethyl ester”), Omtryg® (“omega-3-acid ethyl ester A”), and Epanova® (“omega-3-carboxylic acid”). The EPA-only product, Vascepa® (“icosapent ethyl”), is the only single-compound formulation in the US [20]. In other countries, there are some other RxOME3FA products, such as Omacor® (“omega-3-acid ethyl ester 90”), Lotriga® (“omega-3-acid ethyl ester”), and Epadel® (“ethyl icosapentate”). In Japan, Epadel is approved for the treatment of hyperlipidemia as well as for alleviation of ulcer, pain, and cold feeling associated with arteriosclerosis obliterans [27]. (see Supplementary Table S1 for the overview of RxOME3FA products).

Based on the prescribing information on RxOME3FAs, it has been suggested that these two subgroups may have different adverse-effect profiles [20, 27]. For the combination products, gastrointestinal complaints, e.g., eructation, dyspepsia, and taste perversion, are the most

commonly reported adverse events (AEs) (incidence >3% and greater than placebo). For EPA-only products, arthralgia is the only adverse event (AE) occurring at an incidence >2% and more frequently than placebo [20, 27]. Warnings about LDL elevation have been mentioned in the labeling of DHA-containing products but not EPA-only preparations [23].

Given these uncertainties and controversies, the aim of this systematic review and meta-analysis was to comprehensively assess the literature on randomized controlled trials (RCTs) to investigate the potential for AEs and laboratory abnormalities associated with marketed RxOME3FAs. In addition, the differences between EPA/DHA combinations and EPA-only products were explored as well.

2. Methods

2.1 Protocol

The present study followed the guidelines of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [28]. The current meta-analysis fulfilled the certification requirements of the Institutional Review Board of the Kaohsiung Veterans General Hospital (approval # VGHKS17-EM10-01).

2.2 Literature search and screening

To focus our search results on marketed RxOME3FAs, we used the following search string: “omega-3-acid ethyl ester” OR “omega-3-acid ethyl ester 90” OR “omega-3-acid ethyl ester A” OR “omega-3-carboxylic acid” OR “icosapent ethyl” OR “ethyl icosapentate” OR

“lovaza” OR “omacor” OR “lotriga” OR “epanova” OR “omtryg” OR “vascepa” OR “epadel” without specific limit on the languages . The above search terms covered major generic and brand names of RxOME3FAs not only in the US but also in Asian and European countries [29].

To identify eligible studies, we searched databases for studies available by September 17, 2017 (electronic databases PubMed, EMBASE, ProQuest, ScienceDirect, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov). In addition, to expand the list of potential eligible references, we performed manual searches for references found in relevant articles and package inserts.

The titles and abstracts of studies retrieved by the search strategy were screened by two review authors (CH Chang and NY Chen) to determine whether the studies were potentially eligible for inclusion in this meta-analysis. In case of disagreement on eligibility, we reached an agreement through consensus.

2.3 Study selection and quality appraisal

All the studies included in this analysis had to meet the following inclusion criteria: (1) RCTs that compared the adverse effect of RxOME3FAs versus controls, either in the form of a placebo, other medication, or “no treatment”; (2) human subjects in the trials. To include as many eligible studies as possible, we did not set a limit on the diseases in articles and we did not set a limit on the languages. Studies that were apparently noneligible were excluded in case of exclusion criteria: (1) review articles, (2) animal studies, (3) non-RCT trials, (4) topics not related to the adverse effects of marketed RxOME3FA products, and (5) dietary supplements. We used the Jadad scale to evaluate the quality of each included study [30].

2.4 Data extraction and correspondence with the authors

Using a predetermined list of data forms of interest, two review authors (CH Chang and NY Chen) independently evaluated the selected studies for review. The data extraction form included a description of the types of participants, the type, dose, and duration of marketed RxOME3FAs, as well as AEs, serious adverse events (SAEs), and laboratory measurements for each of the reviewed studies. When needed, an email addressed to the corresponding author was sent requesting unpublished data. In the present study, we examined the safety and tolerability profiles of RxOME3FAs through the systematic review and meta-analysis of SAEs (safety), AEs (tolerability) and laboratory measurements (safety and tolerability). SAEs were defined as AEs that resulted in death, a life-threatening condition, inpatient hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or a condition that requires further intervention to prevent one of the consequences mentioned above [31].

2.5 Methods of meta-analysis

In the present study, the meta-analytic procedures consisted of two parts: (a) analysis of dichotomous outcomes: differences in treatment-related AEs, and (b) analysis of continuous outcomes: differences in treatment-related laboratory findings.

Due to anticipated heterogeneity, all the effect measures were synthesized using a random-effects model rather than a fixed-effects meta-analysis because random-effects modeling is more stringent in terms of inclusion of among-study variance [32]. Under the

preliminary assumption that the units of measurement of target laboratory data are heterogeneous among the recruited studies, we chose Hedges' g and 95% confidence intervals (CIs) to combine the effect sizes for continuous items, according to the manual of the Comprehensive Meta-Analysis ver. 3 software. Hedges' g greater than 0 indicated a significantly worse effect of RxOME3FAs. In the case of the same units for measuring target continuous laboratory variables, we also used differences in means as effect sizes, which can be defined as "values after RxOME3FAs treatment minus values before RxOME3FAs treatment." For dichotomous outcomes, the summary of effect sizes was defined as the odds ratio (OR). An OR greater than 1 indicated significantly more AEs of RxOME3FAs.

The meta-analytic procedures were performed in the Comprehensive Meta-Analysis software, version 3 (CMA ver. 3.0; Biostat, Englewood, NJ). A two-tailed p value of less than 0.05 was assumed to indicate statistical significance.

2.6 Heterogeneity, publication bias, and sensitivity test

The heterogeneity test had been investigated using Q statistics and the corresponding p values [33]. The I^2 statistics indicated the proportion of variation among the recruited studies [34]. Two steps of investigation of potential publication bias had been applied. At first, if there had been fewer than 10 datasets, we applied the funnel plot to investigate publication bias [35]; on the other hand, in the case of ≥ 10 datasets, we chose Egger's regression to investigate it [36]. When there was evidence of publication bias, we performed Duval and Tweedie's trim-and-fill test to adjust the effect sizes for potential publication bias [37]. Furthermore, to evaluate the potential confounding effect of any outlier within the included studies, we conducted a sensitivity test by the one-study removal method, which has been widely used in meta-analyses, to detect the potential outliers. In brief, we removed one study

at a time and reanalyzed the results of meta-analysis to see if there was any change in the results of the meta-analysis. If the results of the meta-analysis changed, then, that study might be the outlier or had a larger sample size [38].

2.7 Meta-regression and subgroup analysis

To investigate potential sources of heterogeneity, meta-regression was carried out by the unrestricted maximum likelihood method in case of at least five datasets. Furthermore, to find the differences between EPA/DHA combinations and EPA-only products, a subgroup analysis was performed when at least three articles were included [39].

3. Results

3.1 Systematic review and the selection process

The full search strategy is illustrated in Figure 1. We examined the full text of the remaining 49 articles, and 26 of them were found to be ineligible because there was no report of adverse effects and the articles did not meet the inclusion criteria for the meta-analysis. Among the remaining 23 articles, two studies were excluded because we could not extract specific adverse-effect data from the articles or obtain the unpublished data from the corresponding authors [40, 41]. Thus, the remaining 21 articles were included in the present meta-analysis [42-62]. The characteristics of the included studies are described in Table 1.

3.2 Description and quality assessment of the included studies

The included studies originated from the United States ($n = 13$), the United Kingdom ($n = 2$), the Netherlands ($n = 1$), Norway ($n = 1$), Japan ($n = 3$), and Taiwan ($n = 1$). All the trials were published between 1997 and 2017. The total number of participants in all reviewed studies was 24,460 (12,750 from RxOME3FA treatment cohort and 11,710 from control cohort) with a reported mean age of 54.642 years. The duration of trials ranged from 6 to 96 weeks.

Among the 21 included RCTs, four used EPA-only products, and the other 17 studies involved EPA/DHA combinations. Sixteen of them were RxOM3FA-alone, and the other five were add-on-statin studies [47-51]. In terms of the characteristics of recruited subjects, there were 15 studies for dyslipidemia, three studies on cardiovascular diseases, one study on postmenopausal healthy women, one study on type 2 diabetes mellitus, and one study on Huntington disease.

3.3 Methodological quality of the included studies

The details of methodological quality assessment of the included studies are provided in Table 1. Across the included studies, the mean Jadad score was 3.71 with a standard deviation (SD) of 1.10.

3.4 Review of the SAEs

Among the 21 included studies, there were some reports of SAEs, not only in the

RxOME3FA-treated arm but also in the control arm [43, 46-48, 50, 52, 54, 56, 57, 59, 60, 62]. None was considered by the investigators to be associated with RxOME3FAs. Only an incident of myelofibrosis in a patient receiving Lotriga (TAK-085; 2 g/day) was regarded as having a possible relation with the study drug by the authors [56].

3.5 Main results of the meta-analysis of the prevalence rates of AEs (dichotomous items)

Among the included studies, the prevalence rates of AEs were successfully extracted from 20. The detailed results on the meta-analysis of prevalence rates of AEs among the participants taking RxOME3FAs and the rates among controls are listed in Table 2A. In brief, there were significantly higher prevalence rates only for “dysgeusia” (OR = 4.229, 95% CI = 1.399 to 12.780, $p = 0.011$) and “skin rash” (OR = 2.461, 95% CI = 1.869 to 3.242, $p < 0.001$) among participants taking RxOME3FAs than among the controls.

3.5.1 Sensitivity test

The main results of the meta-analysis did not change after removal of any one of the included studies except for the situations listed below. The significant result of meta-analysis of the prevalence rate of skin rash changed to “insignificant” after removal of the dataset of Yokoyama et al. (2007) [48]. The insignificant result in meta-analysis of the prevalence rate of constipation changed to “significant” after removal of the dataset of Kowey et al. (2010) [52]. The insignificant result from the meta-analysis of prevalence rates of myalgia changed to “significant” after removal of the dataset of Holman et al. (2009)[49] or removal of the dataset on 4000 mg/day OME3FAs (Tatsuno et al., 2013) [57]. The significant results from

the meta-analysis of the prevalence rate of dysgeusia changed to insignificant after removal of the dataset of Heydari et al. (2016) [60].

3.5.2 Meta-regression

The main results of meta-regression are listed in Supplement Table S2A.

3.5.3 Subgroup analysis

We performed subgroup analysis and the results are listed in Table 3A.

If we focused on those trials with EPA/DHA combination products, then there was a significantly higher prevalence rate of eructation and nausea among the participants taking combination products than among controls. As for EPA-only products, there was no significant finding. Meta-analysis was performed on arthralgia and showed no significant differences between the participants taking EPA-only products and controls.

3.6 Main results on laboratory adverse effects on lipid profiles (continuous items)

Among the included studies, lipid profiles were successfully extracted from 11. The detailed results of meta-analysis of adverse effects on laboratory measurements among the participants taking RxOME3FAs and among controls are listed in Table 2B.

In brief, there was harmful effect on low-density lipoprotein (LDL; $k = 13$, Hedges' $g = 0.208$, 95% CI = 0.052 to 0.364, $p = 0.009$; difference in means = 4.106 mg/dL, 95% CI = 1.349 to 6.863), but beneficial effect on non-high-density lipoprotein (non-HDL) ($k = 7$, Hedges' $g = -0.214$, 95% CI = -0.382 to -0.045, $p = 0.013$; difference in means = -5.317 mg/dL, 95% CI = -9.521 to -1.112), total cholesterol (T-Cho; $k = 12$, Hedges' $g = -0.136$, 95% CI = -0.264 to -0.007, $p = 0.039$; difference in means = -3.792 mg/dL, 95% CI = -7.715 to 0.130), triglyceride (TG; $k = 11$, Hedges' $g = -0.474$, 95% CI = -0.693 to -0.255, $p < 0.001$; difference in means = -39.692 mg/dL, 95% CI = -61.164 to 18.220), and very low-density lipoprotein (VLDL; $k = 5$, Hedges' $g = -0.499$, 95% CI = -0.856 to -0.143, $p = 0.006$; difference in means = -7.048 mg/dL, 95% CI = -13.190 to -0.905) among the participants taking RxOME3FAs in comparison with controls.

3.6.1 Sensitivity test

The main results of meta-analysis did not change after removal of any one of the included studies except for the situation listed below. Only the significant result of meta-analysis of differences in adverse effects on non-HDL and T-Cho changed to “insignificant” after removal of some included datasets; this phenomenon might be due to the smaller sample sizes after removal of those datasets.

3.6.2 Meta-regression

The main results of meta-regression are listed in Supplement Table S2B.

3.6.3 Subgroup analysis

We carried out subgroup analysis and the results are listed in Table 3B.

In brief, most of the results of subgroup analysis did not change for some combination products. Nevertheless, we did not perform subgroup analysis on some EPA-only products because there were fewer than three datasets.

3.7 Main results on laboratory adverse effects on non-lipid profiles (continuous items)

Among the included studies, non-lipid laboratory measurements were successfully extracted from 5. The detailed results are listed in Table 2B. In brief, there were significantly worse effects on fasting blood sugar (Fasting sugar or AC sugar; $k = 8$, Hedges' $g = 0.121$, 95% CI = 0.036 to 0.206, $p = 0.005$; difference in means = 3.750 mg/dL, 95% CI = 0.921 to 6.579), alanine transaminase (ALT; $k = 8$, Hedges' $g = 0.099$, 95% CI = 0.014 to 0.184, $p = 0.022$; difference in means = 1.856 U/L, 95% CI = 0.270 to 3.443), blood urea nitrogen (BUN; $k = 5$, Hedges' $g = 0.132$, 95% CI = 0.002 to 0.263, $p = 0.047$; difference in means = 0.595 mg/dL, 95% CI = -0.221 to 1.411), hemoglobin (Hb; $k = 6$, Hedges' $g = 0.204$, 95% CI = 0.075 to 0.334, $p = 0.002$; difference in means = -0.280 g/dL, 95% CI = 0.095 to 0.464), and hematocrit (Hct; $k = 6$, Hedges' $g = 0.173$, 95% CI = 0.043 to 0.302, $p = 0.009$; difference in means = -0.639%, 95% CI = 0.152 to 1.127) without significant heterogeneity ($Q = 1.810$, $df = 5$, $I^2 < 0.001\%$, $p = 0.875$) among participants taking RxOM3FAs relative to controls.

In contrast, there were beneficial effects on alkaline phosphatase (ALP; $k = 5$, Hedges' $g = -0.206$, 95% CI = -0.335 to -0.076, $p = 0.002$; difference in means = -4.169 U/L, 95% CI =

-7.260 to -1.077) and platelets (Plt; $k = 6$, Hedges' $g = -0.170$, 95% CI = -0.299 to -0.041, $p = 0.010$; difference in means = $9.167 \times 1000/\mu\text{L}$, 95% CI = -16.215 to -2.120) among the participants taking RxOM3FAs than among the controls.

3.7.1 Sensitivity test

The main results of meta-analysis did not change after removal of any one of the included studies except for the situation listed below. Only the significant result of meta-analysis of differences in adverse effects on ALP, ALT, BUN, and Plt changed to “insignificant” after removal of some of the included datasets; this phenomenon might be due to a smaller sample size after removal of those datasets.

3.7.2 Meta-regression

The main results of meta-regression are listed in Supplement Table S2B.

3.7.3 Subgroup analysis

The main results are listed in Table 3B. If we focused on the trials with EPA/DHA combination products, then there was a significantly worse effect on Creatine kinase (CK) among the participants taking combination products than among controls. Nonetheless, the significance of the adverse effects on fasting blood sugar and ALT changed to insignificance in the subgroup analysis of combination products. In addition, because there were fewer than three datasets, the subgroup analysis was not performed on EPA-only products.

4. Discussion

To our knowledge, this is the first systematic review and meta-analysis of the safety and tolerability of RxOME3FAs. To avoid inclusion of studies involving dietary supplements, we focused on specific generic and brand names rather than common terms like EPA, DHA, or omega-3 fatty acids. The comprehensive search strategy in the six electronic databases enabled more specific identification and synthesis of all available and eligible studies so far.

Among the included studies (duration from 6 to 96 weeks), either RxOM3FA-alone or add-on-statin studies, there was no report of definitely RxOME3FA-related SAE.

Concerning non-serious adverse effects, our findings comprised three parts: (1) treatment-related AEs; (2) treatment-related adverse effects on lipid profiles; (3) treatment-related adverse effects on non-lipid profiles.

4.1 Treatment-related AEs

To enhance the comparability and comprehensibility of terminology, we classified AEs based on the Medical Dictionary for Regulatory Activities (MedDRA) with some minor modifications [63, 64].

The main findings are that “dysgeusia” and (skin) “rash” are more prevalent among patients taking RxOME3FAs than among controls.

“Dysgeusia” is a MedDRA-preferred term, which means a “fishy taste” or “taste alteration” in the context of RxOME3FA treatment. This makes sense considering that most of the RxOME3FA products are made from fish oil extracted from fatty fishes. We classified this adverse effect into “gastrointestinal disorders” because the fishy taste is most likely due to gastrointestinal regurgitation without neurological mechanisms involved. Subgroup analysis of combination products revealed a higher prevalence rate of eructation (belching) and nausea in comparison with the controls. This finding is in line with the product labeling saying that the combination RxOME3FAs may cause gastrointestinal AEs. The other main finding, “rash,” is also a MedDRA-preferred term, and was statistically significant because of the (outlier) dataset of Yokoyama et al. (2007) [48] (relative weight 90.44%, see Figure 3A). Nonetheless, Yokoyama *et al.* did not use MedDRA terminology and reported “skin abnormalities” including heterogeneous conditions of not only eruption and exanthema but also itching and eczema [48]. Therefore, it is difficult to clarify the nature and underlying mechanism of this finding.

Meta-analysis was also performed on “arthralgia” and yielded a nonsignificant result for RxOME3FAs overall (Table 2A) and for EPA-only products in subgroup analysis (Table 3A). According to the package insert of Vascepa (icosapent ethyl), arthralgia is the only AE occurring at an incidence >2.0% and more frequently than placebo, but in the present meta-analysis, the data from Yokoyama et al. (2007) [48] may have diminished this relation (Figure 3B). In this add-on-statin trial, patients in the control arm had more adverse events of “pain” (joint pain, lumbar pain, muscle pain) as compared with the EPA arm (2.0% versus 1.6%).

4.2 Treatment-related adverse effects on lipid profiles

The meta-analytic results on lipid profiles revealed a significantly beneficial effect of RxOME3FAs on TG, non-HDL, T-Cho, and VLDL. Among these findings, the effect on TG was the most robust, which is reasonable considering the official indication of RxOME3FAs.

In terms of adverse effects, RxOME3FAs had small but significant harmful effect upon LDL (Hedges' $g = 0.208$, 95% CI = 0.052 to 0.364, $p = 0.009$; difference in means = 4.106 mg/dL, 95% CI = 1.349 to 6.863). It is our understanding that statins may reduce LDL by as much as 20% to 60% [65] and may mask the effect of RxOME3FAs on LDL in the present study. The meta-analytic result can become more significant after removal of the add-on-statin study (Davidson et al. 2007) [47] (Hedges' $g = 0.239$, 95% CI = 0.065 to 0.413, $p = 0.007$; difference in means = 4.563, 95% CI = 1.627 to 7.499). The included datasets here were exclusively from trials involving combination products. On the contrary, the original studies on EPA-only preparations revealed no significant LDL differences as compared with the control groups [48, 54, 55].

The different effects of EPA and DHA on lipid profiles were explored in a recent meta-analysis of RCTs, which showed that although EPA and DHA both reduce TG levels, they have divergent effects on LDL and HDL [66]. It is proposed that DHA-containing formulations are associated with more significant increases in LDL and HDL than EPA-only therapies are [67]. Further research is needed to elucidate the significance and mechanisms underlying these differences.

4.3 Treatment-related adverse effects on non-lipid profiles

The meta-analytic results on non-lipid laboratory tests (Table 2B) showed that RxOME3FAs may have an adverse effect on Fasting sugar (Hedges' $g = 0.121$, 95% CI = 0.036 to 0.206, $p = 0.005$), ALT (Hedges' $g = 0.099$, 95% CI = 0.014 to 0.184, $p = 0.022$), BUN (Hedges' $g = 0.132$, 95% CI = 0.002 to 0.263, $p = 0.047$), Hb (Hedges' $g = 0.204$, 95% CI = 0.075 to 0.334, $p = 0.002$), or Hct (Hedges' $g = 0.173$, 95% CI = 0.043 to 0.302, $p = 0.009$). The mean differences were all relatively small and may have little or no clinical importance (i.e., difference in means were Fasting sugar = 3.750, ALT = 1.856, BUN = 0.595, Hb = -0.280, and Hct = -0.639). In fact, among the original studies, there were few reports of treatment-related non-lipid laboratory abnormalities, except for some reports of mild elevation of liver enzymes[47-49, 53]. Further clinical trials and observational studies are needed to clarify and confirm these findings, especially in the general population and patients with other comorbidities.

4.4 Limitations

There are several limitations of the present meta-analysis. First, because the underlying diseases might potentially affect the side effect profiles, the generalizability of our findings may be limited by the disease groups in our included RCTs (mostly for patients with metabolic or cardiovascular diseases). The safety and tolerability profiles may be different in other populations such as the general population, or patients with other comorbidities. Second, although we have contacted all the authors regarding unpublished data, there was still a lack of extractable and analyzable data for many target outcomes of interest, especially in subgroup analyses. Regarding concerns about the risk of bleeding and recurrent atrial fibrillation/flutter, these cannot be addressed by the present study owing to the lack of adequate data, either binary or continuous, for the meta-analysis. The safety of concurrent use

of RxOME3FAs and anticoagulants or antiplatelet agents is also beyond the scope of the present study. Third, there was a significant publication bias among our findings, including the results on dysgeusia, rash, arthralgia, and LDL. Although we performed an adjustment for the publication bias (see Table 2A & 2B), this adjustment may still leave some potential bias in our findings. Fourth, as the limitation of meta-analysis, we could not directly adjust the potential confounding factors during the analytic procedure, such as mean dosage of RxOME3FAs. To overcome this limitation, we arranged meta-regression to investigate the potential correlation between effect sizes and mean dosage of RxOME3FAs (Supplement table S2A and S2B). Overall, we did not observe significant correlations between RxOME3FAs dosage and effect sizes of any clinical variables.

There is considerable debate as to the relative merits of using RCT data as opposed to observational data in systematic reviews of adverse effects. In theory, well-conducted RCTs yield unbiased estimates of treatment and adverse effects. In reality, RCTs are usually designed and powered to explore efficacy and involve a relatively small number of participants who have been selected for the research purposes [68]. As a meta-analysis of RCTs, the current study may not be able to identify rare or long-term adverse effects and cannot replace observational studies, especially post-marketing surveillance.

5. Conclusion

RxOME3FAs are generally safe and well tolerated but not free of adverse effects. The present study showed that these products are associated with some non-serious adverse events and mild laboratory abnormalities. Post-marketing surveillance and observational studies are necessary to identify rare, long-term adverse effects and to refine and confirm the safety and tolerability profiles of RxOME3FAs.

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Declaration of interest

There are no financial or other relationships that might lead to a conflict of interest for all authors.

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Figure captions:

Figure 1. Flowchart of the selection strategy and inclusion/exclusion criteria for the present meta-analysis.

Figure 2. Forest plots showing the pooled effect sizes [odds ratio (OR) in panel A and Hedges' g in panel B] and 95% confidence intervals (CIs) comparing patients treated and not treated with RxOME3FAs. (A): RxOME3FAs were associated with significantly greater prevalence rates of dysgeusia ($p = 0.011$) and skin rash ($p < 0.001$). (B): RxOME3FAs were associated with significantly more adverse effects upon Fasting sugar ($p = 0.005$), ALT ($p = 0.022$), BUN ($p = 0.047$), Hb ($p = 0.002$), Hct ($p = 0.009$), and LDL ($p = 0.009$). In contrast, RxOME3FAs were also associated with significantly more beneficial effects upon ALP ($p = 0.002$), Plt ($p = 0.010$), VLDL ($p = 0.006$), TG ($p < 0.001$), T-Cho ($p = 0.039$), and non-HDL ($p = 0.013$).

Figure 3. Forest plots showing the effect sizes [odds ratio (OR) in panels A and B and Hedges' g in panel C] and 95% confidence intervals (CIs) from individual studies and pooled results of the included studies. (A): individual studies and pooled results of dysgeusia ($p = 0.011$) and skin rash ($p < 0.001$). (B): individual studies and pooled results of arthralgia in the subgroup analyses of EPA/DHA combination products ($p = 0.768$) and EPA-only products ($p = 0.329$). (C): individual studies and pooled results of LDL in the subgroup analysis of EPA/DHA combination products ($p = 0.009$; difference in means = 4.106 mg/dL).

Table 1: Characteristics of the included studies

Author, year	Country	Population	Study design	Comparison	Subjects	Mean age (mean±SD)	Duration (weeks)	Total Jaded score	Extracted data*
Harris, 1997	USA	Dyslipidemia patient	DB-RC T	Omacor 4 g/day Corn oil	22 20	46.0±11.0 45.0±9.0	16.0	3	(2), (3)
Borthwick, 1998	UK	Dyslipidemia patient	DB-RC T	Omacor 4 g/day Corn oil	29 26	54.1±9.2 52.8±9.2	22.0	3	(1), (2)
Johansen, 1999	Norway	PTCA patient	DB-RC T	Omacor 4 g/day Corn oil	196 192	60.3±9.3 59.1±9.3	24.0	3	(1), (2)
van Dam, 2001	Netherlands	Dyslipidemia patient	DB-RC T	Omacor 4 g/d Gemfibrozil	45 44	49.7 50.1	12.0	4	(1)
Puri, 2005	UK	HD patient	DB-RC T	Vascepa 2g/d Placebo	67 68	50.0±9.3 49.0±9.0	48.0	5	(1)
Davidson, 2007	USA	Dyslipidemia patient	DB-RC T	Simvastatin + Lovaza 4 g/day Simvastatin + vegetable oil capsules	122 132	60.3±10.1 59.3±10.8	8.0	4	(1), (2)
Yokoyama, 2007	Japan	Dyslipidemia patient	SB-RC T	EPADEL 1.8 g/day + statin Statin	9326 9319	61.0±8.0 61.0±9.0	260.9	3	(1)

				Simvastati					
				n + Lovaza		60.3±10.			(1)
				4 g/day		1			
Maki, 2008	USA	Dyslipide	DB-RC	39					
		mia	T	39		59.3±10.	6.0	2	
		patient				8			
				n +					
				vegetable					
				oils					
				Atorvastat					
				in +					(1)
				omacor 2					
				g/d					
				Omacor 2	200	63.0			
Holman,	USA	Type 2 DM	DB-RC	197		64.0			
2009		patient	T	201		64.0	16.0	5	
				Atorvastat	202	65.0			
				in + olive					
				oil 2 g/d					
				Olive oil +					
				olive oil					
				Lovaza 4					
				g/d +					(1)
				simvastati					
Maki, 2009	USA	Dyslipide	DB-RC	17					
		mia	T	17		60.1±2.7	12.0	2	
		patient							
				Placebo +					
				simvastati					
				n					
				Lovaza 4		59.8±13.			
Kowey,	USA	sPAF	DB-RC	332		4			(1)
2010		patient	T	331		61.2±12.	24.0	5	
				Corn oil		3			
				Lovaza 4					
				g/d	19	56.4±2.7	6.0	3	(1), (2)
Maki, 2011	USA	Dyslipide	DB-RC	19					
		mia	T	19					
		patient							
				Corn oil					
				Vascepa 4	233	61.1±10.			
Ballantyne,	USA	Dyslipide	DB-RC	236		3	12.0	4	(1), (3)
2012		mia	T						

Jacobson, 2012	USA	Dyslipide mia patient	DB-RC T	patient	Vascepa 2	233	61.8±9.4			
					g/d		61.1±10.			
					Placebo		3			
					Vascepa 4		51.9±10.			(1), (3)
					g/d	77	3			
					Vascepa	76	53.4±9.3	12.0	3	
					2g/d	76	53.4±8.3			
					Placebo					
					TAK-085 2		53.9±10.			
					g/d		8			(1), (2)
Tatsuno, 2013 (ORD)	Japan	Dyslipide mia patient	DB-RC T			206				
					TAK-085 4	210	55.0±10.	12.0	5	
					g/d		5			
					EPA-E 1.8	195	55.6±10.			
					g/d		5			
					TAK-085 2		56.0±11.			(1)
Tatsuno, 2013 (ORL)	Japan	Dyslipide mia patient	SB-RC T			165				
					TAK-085 4	171	55.9±10.	52.0	2	
					g/d		1			
					EPA-E 1.8	167	55.8±10.			
					g/d		3			
de Ferranti, 2014	USA	Dyslipide mia patient	DB-RC T		Lovaza 4					
					g/d	12	13.3±2.4	24.0	5	(2)
					Corn oil	12	14.7±2.7			
					Epanova 2		51.1±9.8			(1), (2),
					g/d	100	51.2±8.8			
					Epanova 3	101	52.9±10.	12.0	5	(3)
Kastelein, 2014	USA	Dyslipide mia patient	DB-RC T		g/d	99	9			
					Epanova 4	99	50.8±10.			
					g/d		6			
					Corn oil					
							60.0±10.			
					Lovaza 4	180	0			(1), (2)
Heydari,20 16	USA	AMI patient	DB-RC T		g/d	178	58.0±10.	24.0	4	
					Corn oil		0			

Sandhu, 2016	USA	PM healthy women	SB-RC T	Lovaza	4							
				g/d								(1), (2)
				Lovaza	4	54	56.6±6.9					
				g/d	+	53	57.9±5.1	96.0	3			
Su, 2017	Taiwan	Dyslipide mia patient	DB-RC T	raloxifene		53	57.1±5.9					
				No treatment								
				Omacor	2		54.7±9.2					(1), (2),
				g/d		82	53.7±11.					
				Omacor	4	84	0	8.0	5			
				g/d		87	54.4±10.					(3)
				Olive oil			7					

Extracted data*:(1) adverse events; (2) lipid profiles; (3) non-lipid laboratory measurements

number of studies*: (1) =19; (2) =11; (3) =5

Abbreviations: AMI: acute myocardial infarction; DHA, docosahexaenoic acid; DM: diabetes mellitus; EPA, eicosapentaenoic acid; HD: Huntington disease; ORD: omega-3 fatty acids randomized double-blind study; ORL: omega-3 fatty acids randomized long-term study; PTCA: percutaneous transluminal coronary angioplasty; PM: post-menopausal; RCT: randomized controlled trial; DB-RCT: double-blind randomized controlled trial; SB-RCT: single-blind randomized controlled trial; RxOM3FAs, prescription omega 3 fatty acids; sPAF: symptomatic paroxysmal atrial fibrillation; UK: the United Kingdom; USA: the United States of America.

Table 2A: Meta-analysis of treatment-related adverse events

Treatment-related adverse events		Meta-analysis result				Heterogeneity				Publication bias		
SOC	Adverse events	Data	OR	95% CIs	p	Q value	df	I ² (%)	p	Significance	Adj. ES	95% CIs
Gastrointestinal Disorders	Abdominal pain	3	0.671	0.230 to 1.95	0.464	0.625	2	<0.001	0.732	Sig.	0.990	0.422 to 2.3

			3								24	
			0.63								0.15	
Constipation	3	3.2	8 to	0.15	2.53	2	21.1	0.2	Sig.	1.0	7 to	
		98	17.0	5	7		54	81		03	6.4	
			64								28	
			0.88									
Diarrhea	17	1.2	0 to	0.23	18.8	1	15.0	0.2	n/s	--	--	
		14	1.67	8	33	6	43	77				
			4									
			1.39								1.55	
Dysgeusia	5	4.2	9 to	0.01	0.11	4	<0.0	0.9	Sig.	4.4	6 to	
		29	12.7	1	7		01	98		28	12.6	
			80								01	
			0.59								0.48	
Dyspepsia	6	1.5	9 to	0.35	1.78	5	<0.0	0.8	Sig.	1.1	7 to	
		70	4.1	9	9		01	78		72	2.8	
			11								23	
			0.57									
Eructation	6	1.8	1 to	0.30	7.55	5	33.8	0.1	n/s	--	--	
		29	5.8	9	7		37	82				
			57									
			0.52								0.42	
Gastroesoph	6	1.2	7 to	0.60	4.29	5	<0.0	0.5	Sig.	0.9	7 to	
ageal reflux		57	3.0	6	3		01	08		58	2.1	
			00								45	
			0.80									
Nausea	13	1.2	4 to	0.30	13.3	1	10.2	0.3	n/s	--	--	
		68	2.0	7	72	2	58	43				
			02									
			0.35								0.53	
abdominal	4	1.3	9 to	0.64	1.82	3	<0.0	0.6	Sig.	1.8	9 to	
pain, upper		70	5.2	5	8		01	09		54	6.3	
			22								82	
			0.60									
Vomiting	4	2.2	7 to	0.22	1.92	3	<0.0	0.5	n/s	--	--	
		55	8.3	4	2		01	89				
			71									
General	Fatigue	3	3.6	0.58	0.16	0.07	2	<0.0	0.9	n/s	--	--

Disorders		13	4 to	7	2	01	65						
and			22.										
Administrati			338										
on Site													
Conditions													
			0.66									0.44	
	Arthralgia	8	1.2 7 to	0.52 9.50	7	26.3 0.2		Sig.		0.8 2 to			
			17 2.22	2 5		54 18				63 1.6			
Musculoske			3									85	
letal and			0.41										
Connective	Back pain	8	0.6 8 to	0.13 2.92	7	<0.0 0.8		n/s		-- --			
Tissue			84 1.12	2 2		01 92							
Disorders			1										
			0.66									0.66	
	Myalgia	8	0.8 3 to	0.06 4.14	7	<0.0 0.7		Sig.		0.8 8 to			
			18 1.0	0 5		01 63				23 1.0			
			08									15	
			0.49									0.48	
	Bronchitis	4	0.9 8 to	0.86 0.76	3	<0.0 0.8		Sig.		0.8 3 to			
			44 1.79	1 76		01 57				79 1.6			
			3									01	
			0.45									0.29	
	Gastroenterit	4	1.0 4 to	0.85 2.81	3	<0.0 0.4		Sig.		0.7 8 to			
is			83 2.5	7 7		01 21				88 2.0			
			83									86	
Infections			0.66									0.59	
and	Influenza	6	1.2 8 to	0.44 3.22	5	<0.0 0.6		Sig.		1.1 6 to			
Infestations			99 2.5	1 4		01 65				25 2.1			
			28									26	
			0.65										
	Nasopharyng	11	0.9 8 to	0.77 16.0	1	37.5 0.0		n/s		-- --			
	itis		48 1.3	6 21	0	82 99							
			67										
			0.47									0.55	
	Pharyngitis	5	0.7 9 to	0.22 2.87	4	<0.0 0.5		Sig.		0.8 5 to			
			56 1.1	9 7		01 79				52 1.3			
			93									08	
	Upper	8	1.0 0.70	0.91 5.89	7	<0.0 0.5		Sig.		1.0 0.72			

Injury, poisoning and procedural complications	respiratory tract infection		20	6 to 1.4	6	6	01	52		45	6 to 1.5
				73							06
				0.32							
	Contusion	3	0.7	4 to 1.8	0.56	1.57	2	<0.001	0.4	n/s	--
Nervous System Disorders				44							
				0.52							0.42
	Headache	7	1.2	1 to 3.16	0.58	5.92	6	<0.001	0.4	Sig.	1.0
				3							2 to 2.66
Skin and subcutaneous disorders				1.86							1
				1.86							1.84
	Rash	7	2.4	9 to 3.2	<0.001	3.44	6	<0.001	0.7	Sig.	2.4
				42							6 to 3.1
Cardiovascular disorders				0.20							70
				0.20							
	Hypertension	3	0.7	9 to 2.6	0.65	0.92	2	<0.001	0.6	n/s	--
				67							--

Abbreviation: adj. ES: Adjusted effect size; CI: confidence interval; n/s: not significant; OR: odds ratio; Sig.: significant

SOC: System Organ Class

Table 2B: Meta-analysis of treatment-related laboratory effects

		Meta-analysis result				Heterogeneity				Publication bias		
		Data	Hedge's g	95% CIs	p	Q value	df	I ² (%)	p	Significance	Adj. ES	95% CIs
Lipid profiles				-0.20								
	HDL	15	-0.077	4 to 0.04	0.232	23.80	1	41.17	0.048	n/s	--	--
				9		0	4	6				
	LDL	13	0.208	0.05 to 2	0.009	28.79	1	58.32	0.004	Sig.	0.03	-0.14

				0.36								2 t
				4								o
												0.2
												11
												-0.
				-0.38								39
Non-HDL	7	-0.214	2 to	0.013	12.25	6	51.03	0.057	Sig.	-0.22	1 t	
			-0.0		3		4			7	o -	
			45									0.0
												63
				-0.26								
T-Cho	12	-0.136	4 to	0.039	18.82	1	41.57	0.064	n/s	--	--	
			-0.0		6	1	1					
			07									
				-0.69								
TG	11	-0.474	3 to	<0.00	47.20	1	78.81	<0.00	n/s	--	--	
			-0.2	1	3	0	5	1				
			55									
				-0.85								
VLDL	5	-0.499	6 to	0.006	26.18	4	84.72	<0.00	n/s	--	--	
			-0.1		0		1	1				
			43									
				0.03								
AC sugar	8	0.121	6 to	0.005	2.258	7	<0.00	0.944	n/s	--	--	
			0.20				1					
			6									
				-0.11								
HbA1c	3	0.103	1 to	0.345	0.849	2	<0.00	0.654	n/s	--	--	
			0.31				1					
Non-lipid profiles			8									
				-0.14								-0.
												12
Uric acid	3	0.052	9 to	0.610	0.453	2	<0.00	0.797	Sig.	0.06	2 t	
			0.2				1			8	o	
			54									0.2
												59
				-0.31			38.10					
Albumin	3	-0.105	2 to	0.317	3.231	2	7	0.199	n/s	--	--	

Parameter	Group	Mean	SD	Min	Max	n	p-value	Significance	Mean Difference	95% CI
ALP	5	-0.206	0.002	3.897	4	<0.001	0.420	Sig.	-0.23	1 t
ALT	8	0.099	0.022	1.701	7	<0.001	0.975	n/s	--	--
Apo-B	3	-0.058	0.554	4.816	2	58.46	0.090	n/s	--	--
AST	8	0.040	0.352	3.719	7	<0.001	0.811	Sig.	0.06	0 t
Bicarbona te	3	-0.154	0.064	0.617	2	<0.001	0.734	n/s	--	--
BUN	5	0.132	0.047	4.060	4	1.488	0.398	n/s	--	--
Ca	3	0.081	0.329	1.892	2	<0.001	0.388	n/s	--	--
CK	5	0.050	0.547	10.93	4	63.42	0.027	Sig.	-0.06	25

Parameter	Group	n	Mean	SD	t	p	Significance	95% CI
Cl	Control	5	0.001	0.130	0.992	0.371	4	<0.001
	Experimental	5	0.001	0.130	0.992	0.371	4	<0.001
Cre	Control	8	0.024	0.108	0.585	5.948	7	<0.001
	Experimental	8	0.024	0.108	0.585	5.948	7	<0.001
K	Control	5	-0.036	0.154	0.712	8.471	4	52.78
	Experimental	5	-0.036	0.154	0.712	8.471	4	52.78
Na	Control	5	0.037	0.167	0.573	3.749	4	<0.001
	Experimental	5	0.037	0.167	0.573	3.749	4	<0.001
P	Control	3	0.000	0.162	1.000	<0.001	2	<0.001
	Experimental	3	0.000	0.162	1.000	<0.001	2	<0.001
T-Bil	Control	5	-0.062	0.168	0.349	1.803	4	<0.001
	Experimental	5	-0.062	0.168	0.349	1.803	4	<0.001
Total protein	Control	5	0.050	0.196	0.506	5.112	4	21.75
	Experimental	5	0.050	0.196	0.506	5.112	4	21.75

			0.07									
Hb	6	0.204	5 to 0.33 4	0.002	2.921	5	<0.00 1	0.712	n/s	--	--	
												0.0
			0.04									06
Hct	6	0.173	3 to 0.3 02	0.009	1.810	5	<0.00 1	0.875	Sig.	0.11 6	to 0.	
												22
												6
												-0.
			-0.29									33
Plt	6	-0.170	9 to -0.0 41	0.010	4.278	5	<0.00 1	0.510	Sig.	-0.21 5	1 t o -	
												0.1
												00
			-0.11									
WBC	5	0.014	8 to 0.1 47	0.833	0.461	4	<0.00 1	0.977	n/s	--	--	

Abbreviation: adj. ES: Adjusted effect size; CI: confidence interval; n/s: not significant; Sig.: significant

Table 3A: Subgroup analysis of treatment-related adverse events

Treatment-related adverse events		Meta-analysis result							
		Data	Odds ratio	95% CI	p	Data	Odds ratio	95% CI	p
SOC	Adverse events	Combination products (EPA+DHA)				EPA-only products			
Gastrointestinal Disorders	Abdominal pain	3	0.671	0.230 to 1.953	0.464	n/d	n/d	n/d	n/d
	Constipation	3	3.298	0.638 to 17.064	0.155	n/d	n/d	n/d	n/d
	Diarrhea	12	1.408	0.940 to 2.109	0.096	5	0.932	0.557 to 1.561	0.789
	Dysgeusia	5	4.229	1.399 to 12.780	0.011	n/d	n/d	n/d	n/d
	Dyspepsia	6	1.570	0.599 to	0.359	n/d	n/d	n/d	n/d

				4.111					
	Eructation	4	4.247	1.411 to 12.779	0.010	n/d	n/d	n/d	n/d
	Gastroesophageal reflux	6	1.257	0.527 to 3.000	0.606	n/d	n/d	n/d	n/d
	Nausea	9	1.730	1.014 to 2.950	0.044	4	0.732	0.375 to 1.430	0.361
	Upper abdominal pain	4	1.370	0.359 to 5.222	0.645	n/d	n/d	n/d	n/d
	Vomit	4	2.255	0.607 to 8.371	0.224	n/d	n/d	n/d	n/d
General									
Disorders and Administration	Fatigue	3	3.613	0.584 to 22.338	0.167	n/d	n/d	n/d	n/d
Site Conditions									
Musculoskeletal	Arthralgia	5	1.137	0.483 to 2.678	0.768	3	2.238	0.443 to 11.295	0.329
and Connective Tissue	Back pain	8	0.684	0.418 to 1.121	0.132	n/d	n/d	n/d	n/d
Disorders	Myalgia	7	1.033	0.535 to 1.993	0.924	n/d	n/d	n/d	n/d
	Bronchitis	4	0.944	0.498 to 1.793	0.861	n/d	n/d	n/d	n/d
	Gastroenteritis	4	1.083	0.454 to 2.583	0.857	n/d	n/d	n/d	n/d
Infections and	Influenza	5	1.148	0.496 to 2.656	0.747	n/d	n/d	n/d	n/d
Infestations	Nasopharyngitis	8	1.078	0.727 to 1.598	0.710	3	0.589	0.284 to 1.222	0.155
	Pharyngitis	5	0.756	0.479 to 1.193	0.229	n/d	n/d	n/d	n/d
	Upper respiratory tract infection	8	1.020	0.706 to 1.473	0.916	n/d	n/d	n/d	n/d
Injury, poisoning and procedural complications	Contusion	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d
Nervous System	Headache	7	1.283	0.521 to	0.588	n/d	n/d	n/d	n/d

Disorders				3.163					
Skin and									
subcutaneous	Skin rash	6	2.248	0.922 to 5.482	0.075	n/d	n/d	n/d	n/d
tissue disorders									
Cardiovascular	Hypertension	3	0.747	0.209 to 2.667	0.653	n/d	n/d	n/d	n/d
disorders									

Abbreviation: CI: confidence interval; n/d: not done

Table 3B: Subgroup analysis of treatment-related laboratory effects

Treatment-related laboratory effects		Meta-analysis result							
		Data	Hedges'	95% CI	<i>p</i>	Data	Hedges'	95% CI	<i>p</i>
			<i>g</i>				<i>g</i>		
			Combination products (EPA+DHA)				EPA-only products		
Lipid profiles	HDL	15	-0.077	-0.204 to 0.049	0.232	n/d	n/d	n/d	n/d
	LDL	13	0.208	0.052 to 0.364	0.009	n/d	n/d	n/d	n/d
	Non-HDL	7	-0.214	-0.382 to -0.045	0.013	n/d	n/d	n/d	n/d
	T-Cho	12	-0.136	-0.264 to -0.007	0.039	n/d	n/d	n/d	n/d
	TG	11	-0.474	-0.693 to -0.255	<0.001	n/d	n/d	n/d	n/d
	VLDL	5	-0.499	-0.856 to -0.143	0.006	n/d	n/d	n/d	n/d
	AC sugar	6	0.123	-0.003 to 0.249	0.057	n/d	n/d	n/d	n/d
Non-lipid profiles	HbA1c	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d
	Uric acid	3	0.052	-0.149 to 0.254	0.610	n/d	n/d	n/d	n/d
	Albumin	3	-0.105	-0.312 to 0.101	0.317	n/d	n/d	n/d	n/d
	ALP	5	-0.206	-0.335 to -0.076	0.002	n/d	n/d	n/d	n/d
	ALT	6	0.104	-0.022 to 0.231	0.105	n/d	n/d	n/d	n/d
	Apo-B	3	-0.058	-0.249 to	0.554	n/d	n/d	n/d	n/d

			0.134					
AST	6	-0.016	-0.142 to 0.110	0.803	n/d	n/d	n/d	n/d
Bicarbonate	3	-0.154	-0.316 to 0.009	0.064	n/d	n/d	n/d	n/d
BUN	5	0.132	0.002 to 0. 263	0.047	n/d	n/d	n/d	n/d
Ca	3	0.081	-0.082 to 0.243	0.329	n/d	n/d	n/d	n/d
CK	3	0.200	0.037 to 0. 362	0.016	n/d	n/d	n/d	n/d
Cl	5	0.001	-0.129 to 0.130	0.992	n/d	n/d	n/d	n/d
Cre	6	0.083	-0.043 to 0.209	0.197	n/d	n/d	n/d	n/d
K	5	-0.036	-0.226 to 0.154	0.712	n/d	n/d	n/d	n/d
Na	5	0.037	-0.092 to 0.167	0.573	n/d	n/d	n/d	n/d
P	3	0.000	-0.162 to 0.162	1.000	n/d	n/d	n/d	n/d
T-Bil	5	-0.062	-0.191 to 0.068	0.349	n/d	n/d	n/d	n/d
Total protein	5	0.050	-0.097 to 0.196	0.506	n/d	n/d	n/d	n/d
Hb	6	0.204	0.075 to 0.334	0.002	n/d	n/d	n/d	n/d
Hct	6	0.173	0.043 to 0. 302	0.009	n/d	n/d	n/d	n/d
Plt	6	-0.170	-0.299 to - 0.041	0.010	n/d	n/d	n/d	n/d
WBC	5	0.014	-0.118 to 0.147	0.833	n/d	n/d	n/d	n/d

Abbreviation: CI: confidence interval; n/d: not done

Highlights

- Among the 21 included RCTs, there was no definite evidence of any

RxOME3FA-emerging serious adverse event.

- RxOME3FAs were associated with more treatment-related dysgeusia (fishy taste) and skin abnormalities (eruption, itching, exanthema, or eczema). Besides, RxOME3FAs had mild adverse effects upon some non-lipid laboratory measurements.
- EPA/DHA combination products were associated with more treatment-related gastrointestinal adverse events [eructation (belching); nausea] and mild elevation of low-density lipoprotein cholesterol.

A

B

A

B

** : the trial with add-on statin, ESs change to Hedges' *g*=0.239, 95%CI=0.065 to 0.413, *p*=0.007 after removal of Davidson MH (2007)

C