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ORIGINAL ARTICLE

Does omega-3 fatty acids supplementation affect circulating leptin levels? A systematic review and meta-analysis on randomized controlled clinical trials

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Summary

Background Omega-3 fatty acids have attracted researchers for their effect on circulatory hormone-like peptides affecting weight control.

Objective Our objective was to conduct a systematic review and meta-analysis on randomized controlled trials (RCTs) assessed the effects of omega-3 supplementation on serum leptin concentration and to find the possible sources of heterogeneity in their results.

Methods We searched PubMed/Medline, Google Scholar, Ovid, SCOPUS and ISI web of science up to April 2014. RCTs conducted among human adults, examined the effect of omega-3 fatty acid supplements on serum leptin concentrations as an outcome variable were included. The mean difference and standard deviation (SD) of changes in serum leptin levels were used as effect size for the meta-analysis. Summary mean estimates with their corresponding SDs were derived using random effects model.

Results Totally 14 RCTs were eligible to be included in the systematic review, and the meta-analysis was performed on 13 articles. Our analysis showed that omega-3 supplementation significantly reduces leptin levels (mean difference (MD) = −1·71 ng/ml 95% confidence interval (CI): −3·17 to −0·24, $P = 0·022$). Subgroup analysis based on BMI status showed that the omega-3 supplementation reduces leptin when used for nonobese subjects (MD = −3·60 ng/ml; 95% CI −6·23 to −0·90; $P = 0·011$); however, this was not true for obese participants (MD = −0·86 ng/ml; 95% CI: −2·63 to −0·90; $P = 0·296$). Subgroup analysis based on omega-3 source also showed that omega-3 from marine sources may significantly reduce leptin levels (MD = −1·73 ng/ml; 95% CI −3·25 to −0·2; $P = 0·026$), but plant sources do not significantly affect serum leptin levels (MD = −1·48 ng/ml; 95% CI −6·78 to 3·23; $P = 0·585$). Our results were highly sensitive to one study.

Conclusions Omega-3 supplementation might moderately decrease circulatory leptin levels only among nonobese adults. RCTs with longer follow-up period, using higher doses for obese adults and exploring the effect in different genders, are needed to replicate our results.

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Introduction

Adipose tissue is supposed to be an endocrine organ because of its ability to secrete bioactive peptides and adipokines including interleukin-6 (IL-6), monocyte chemotactic protein-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1), retinol binding protein 4 (RBP4), tumour necrosis factor-alpha (TNFα), visfatin, apelin, adiponectin and leptin[1] which are shown to play multiple endocrine roles. Among adipokines secreted by adipose tissue, human leptin has recently attracted scientists because of its various hormonal functions.[2] It is shown that leptin affects long-term energy balance regulation and suppresses food intake, thus may induce weight loss.[3] Furthermore, it is proposed that leptin may impress circulatory system, surfactant activity of lungs, fertility, brain and also bones.[1] Leptin is primarily manufactured in the adipocytes settled in white adipose tissue; furthermore, it may also be produced by other organs like brown adipose tissue, ovaries, placenta, skeletal muscles, stomach, bone marrow, pituitary glands, liver and mammary epithelial cells.[4]

Dietary factors like overfeeding might result in an increase in leptin expression and its blood concentrations in healthy human subjects.[4] On the other hand, fasting has been shown to decrease plasma leptin concentrations[5] much greater than the change in

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adipose mass, indicating that the fat mass changes are not exclusively responsible for the decrease in circulating leptin concentrations.[6] The meal composition may also affect leptin levels.[7] It is proposed that dietary fat like omega-3 fatty acids may directly influence leptin gene expression by interacting transcription factors or indirectly through affecting fatty acid oxidation, synthesis or storage, although data about such an effect are conflicting.[8] Studies which tried to assess the effect of omega-3 supplementation on circulating leptin levels have led to inconsistent results. Some studies have shown a reducing effect[9–11], while the majority of published clinical trials could not show a significant association.[12–14]

To the best of our knowledge, no systematic review and meta-analysis are published trying to assess the effect of omega-3 consumption on circulatory leptin levels. As the published data about such an association are conflicting, we tried to conduct a systematic review to summarize the data from randomized controlled clinical trials (RCTs) conducted in human adults exploring the effect of omega-3 supplementation on serum leptin levels and if possible to perform a meta-analysis to quantify the effect.

Materials and methods

Literature search

PubMed/Medline, Google Scholar, Ovid, SCOPUS and ISI web of science were searched up to April 2014 using the following keywords including MeSH and non-MeSH terms: 'Fatty Acids, Omega-3', 'Eicosapentaenoic Acid', 'Docosahexaenoic Acids', 'Fatty Acids, Omega-3', 'Eicosapentaenoic Acid', 'Docosahexaenoic Acid', 'n-3 PUFA', 'n-3 Fatty Acids', 'Fatty Acids, n-3', 'n 3 Fatty Acids', 'n-3 Polyunsaturated Fatty Acid', 'n 3 Polyunsaturated Fatty Acid', 'alpha-Linolenic Acid', 'omega 3' and 'n-3' in combination with 'Adipokines', 'leptin' and 'adipocytokines'. Moreover, the reference lists from related retrieved articles were checked to search for further relevant studies. Titles and abstracts were separately screened by two authors (MH and RG) to find potentially relevant trials for the full review. Any discrepancies were resolved discussing with ASA.

Inclusion criteria

Studies were included in the meta-analysis if they met all of the following criteria: (i) were randomized controlled trial (RCT) in design; (ii) conducted in human adults; (iii) intervened using omega-3 fatty acid supplements [fish oil, pure eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) or alpha-linolenic acid (ALA)]; (iv) assessed serum leptin concentrations as an outcome variable; (v) no other food or supplement was used in intervention or control group.

Exclusion criteria

Among remaining studies, those trials with at least one of the following criteria were excluded: (i) the outcomes had not been clearly stated; (ii) studies without clear inclusion and exclusion criteria; (iii) subjects were treated using food or food groups instead of omega-3 fatty acid supplements.

Quality assessment

We used the quantitative 5-point Jadad score to assess the quality of the included trials based on randomization, allocation concealment, blinding, follow-up completeness and the use of intention-to-treat analysis. One point score was assigned for each item. Therefore, the possible score would be between 0 (lowest quality) and 5 (highest quality).[15]

Data extraction

We extracted data on publication (the last name of the first author, year and country of population), number of individuals in intervention and control groups, follow-up period, age, gender, mean and standard deviation (SD) of change in serum leptin levels. Five studies[12,13,16–18] presented the mean with standard error (SE), and we calculated SD from SE and number of participants in each group. One of our studies did not report after intervention period mean and SD for leptin levels in control group, and we obtained these data by contacting authors.[11] Another study performed by Patel *et al.*[19] had reported median and interquartile range (IQR) for serum leptin levels, and we calculated means and SDs using a formula proposed by Hozo *et al.*[20] We calculated correlation coefficient with using two articles that reported the change in mean and its corresponding SD for leptin levels[10,14] and used them to calculate the mean changes and their corresponding SDs for other studies.[9,11–13,16–19,21–23] A study performed by Vargas *et al.*[16] compared the effects of both marine and plant originated omega-3 fatty acids supplementation with placebo in their study; therefore, we extracted two effect sizes from this study and included them as two separate studies in meta-analysis.

Statistical analysis

The mean differences and their corresponding SDs of changes in serum leptin levels between intervention and control groups were used as effect size for the meta-analysis. Summary mean differences with their corresponding SDs were derived using random effects model,[24] which incorporates between study variability. Subgroup analysis was performed to check for the sources of between studies heterogeneity. Statistical assessment of heterogeneity between studies was assessed incorporating Cochran's Q test and I-squared.[25] Sensitivity analysis was used to explore the extent to which meta-analysis results might depend on a study or a group of studies. Publication bias was tested by visual inspection of funnel plots. In these funnel plots, the difference in mean changes were displayed against their standard errors (SEs) as a measure of the precision for studies. Statistical assessment of the asymmetry in funnel plot was performed using Egger's regression asymmetry test and Begg's adjusted rank correlation test.[26] Statistical analyses were carried out by the use of

STATA, version 11.2 (StataCorp, College Station, TX, USA). *P*-values < 0·05 were considered statistically significant.

Results

Our search retrieved 613 articles; after removing duplicates, 127 articles were remained. After screening titles/abstracts, 22 related articles were carefully assessed for the eligibility.[3,9–14,16–19,21–23,27–34] After taking exclusion criteria into account, fourteen RCTs were remained to be included in the current systematic review.[9–14,16–19,21–23] However, meta-analysis was performed on 13 studies because there was one newly published paper that we couldn't access to its full text[34] (Table 1). The study selection process is illustrated in Fig. 1.

The characteristics and main outcomes of 14 RCTs included in our systematic review and meta-analysis are presented in Table 1. The studies included 915 adults aged 18–85 year in their studies and their intervention period ranged between 3 and 24 weeks. Omega-3 supplementation dose ranged between 170 mg/day and 7·7 g/day. In general, four studies[9–11,22] showed that omega-3 supplementation significantly reduces circulatory leptin levels, while other studies could not show a significant effect.

Our meta-analysis on 13 eligible studies revealed that the omega-3 supplementation can significantly reduce serum leptin levels (mean difference (MD) = −1·71 ng/ml 95% confidence interval (CI): −3·17 to −0·24, $P = 0·022$) (Fig. 2). There was no evidence of heterogeneity between studies' results [Cochrane Q test, $P = 0·894$, I^2 (I-squared) = 0·0%]. Although heterogeneity was not found, we categorized studies based on subjects' body mass index (BMI) status (overweight or obese/normal) and omega-3 source (marine/plant source) because studies were different according their subjects' weight status and the source of supplemented omega-3 fatty acids. Subgroup analysis based on BMI status showed that omega-3 can significantly reduce leptin when used in nonobese subjects (MD = −3·60 ng/ml; 95% CI −6·23 to −0·96; $P = 0·011$), whereas the overall effect for studies in obese subjects was also reducing but not significant (MD = −0·86 ng/ml; 95% CI: −2·63 to −0·90; $P = 0·296$) (Fig. 2). Subgroup analysis based on omega-3 source showed that marine sources of omega-3 fatty acids can significantly reduce leptin levels (MD = −1·73 ng/ml; 95% CI −3·25 to −0·2; $P = 0·026$); however, omega-3 from plant sources might not significantly affect serum leptin levels (MD = −1·48 ng/ml; 95% CI −6·78 to 3·23; $P = 0·585$) (Fig. 3). Meta-regression could not show any association between omega-3 dose used for supplementation and the effect size seen by studies ($P = 0·209$).

Sensitivity analysis showed that removing a study performed by Mostowik *et al.*[9] can considerably change the effect of omega-3 on serum leptin to nonsignificant (MD = −1·12, 95% CI: −2·75 to 0·51). Several RCTs had lower study quality as assessed by the Jadad scale. However, omega-3 supplementation on leptin was not significantly different in trials with high or low study quality scores. Thus, study quality might not have a systematic influence on our findings. Although a slight asymmetry was seen in Begg's funnel plot, there was no evidence of publication bias using asymmetry tests (Egger's test, $P = 0·874$; Begg's test, $P = 0·584$) (Fig. 4).

Discussion

In the present systematic review and meta-analysis, we found that omega-3 supplementation might significantly reduce leptin concentration when compared with placebo. We also found that marine sources of omega-3 are more effective than their plant sources. Furthermore, omega-3 supplementation could not reduce leptin concentration in obese subjects. To the best of our knowledge, this is the first systematic review and meta-analysis trying to assess the effect of omega-3 supplementation on circulating leptin levels. Our result confirms the reducing effect of high omega-3 foods consumption on leptin levels proposed by previous narrative reviews. For example, Moreno-Aliaga *et al.*[35] in their review concluded that the inclusion of either lean or fatty fish or fish oil capsules in the diet as in energy-restricted diet may lead to weight loss, which may come with a decrease in leptin levels. Gray *et al.*[36] also in a narrative review proposed that omega-3 supplementation may decrease the circulating leptin levels in nonobese subjects and conversely increases leptin levels in obese subjects. Although our results confirm the conclusion made by Gray *et al.*[36] for nonobese participants, we could not show the reducing effect of omega-3 supplementation on leptin levels among obese participants. In the current study, we tried to systematically search for all published studies with broad search terms across multiple databases and also contacted authors for clarification and additional data, which minimized the potential publication bias and misclassification. We tried to include papers with highest quality in the current systematic review and meta-analysis; because, we limited our analysis to randomized, placebo-controlled trials most of which were double-blinded. We tried to include studies that used omega-3 fatty acids supplements and excluded studies in which other food or supplements were used for intervention.

New evidences have shown that high plasma leptin level has inflammatory effects on circulatory system which might lead to cardiovascular diseases development;[37] on the other hand, a limited number of studies have reported that high leptin concentrations might cause insulin resistance.[38]

Omega-3 supplementation has been shown to improve low-grade inflammation in adipose tissue associated with obesity;[39] moreover, the ability of n-3 PUFA to regulate adipokine gene expression and secretion has been observed in low-grade inflammation human subjects.[40] People with obesity have high-grade inflammation in comparison with overweight people;[39] therefore, they might need higher doses of omega-3 supplementation than nonobese people, and this may explain why we could not find a significant effect of omega-3 supplementation on circulatory leptin levels in the obese.

In vitro studies with EPA and DHA have reported that the ability of these fatty acids to stimulate leptin mRNA expression and leptin secretion in a dose-dependent manner in primary rat adipocytes.[41] However, little is still understood about the mechanisms underlying this stimulatory action. Insulin has been

Table 1. Randomized controlled trial studies included in the systematic review and meta-analysis

First Author (year), country	Subjects and gender	Age	Study design	Duration (week)	Intervention	Control	Subjects	Jadad score	Results
Krebs JD (2006), U.K.[22]	F*:116	44·7 ± 13·2†	Double-blinded RCT	24 week	EPA:1·3 g/day DHA:2·9 g/day with energy reduction diet	Energy reduction diet and 2·8 g/day ALA and 1·4 g/day oleic acid	Overweight women with insulin-resistant women	2	Serum leptin significantly decreased
MostowikM(2013), Poland[9]	F:12, M:36	62·9 ± 9·15	Double-blinded RCT	4 week	EPA:460 mg/day DHA:380 mg/day	Soy bean oil	Patient with stable coronary heart disease	3	Serum leptin decreased significantly
Guebre-Egziabher F (2013), France[12]	F:6 M:6	50·5 ± 10·8	RCT	10 week	Group A: 1·8 gr/day EPA Group B: 3·8 gr/day EPA		Nondialysed patients with stage chronic kidney disease	2	Serum leptin did not change significantly
Stirban A (2013) Germany[34]	F/M:34	NA§	Double-blind, placebo-controlled randomized, crossover study	6 week	Group A: 2 gr/day EPA and DHA Group B: Olive oil		Subjects with type 2 diabetes mellitus	NA	Serum leptin did not change significantly
Munro I (2013), Australia[14]	M:11 F:22	41·11 ± 11·27	Double-blinded RCT	12 week	DHA: 1·6 g/day EPA:0·42 g/day and diet with energy reduction diet	Energy reduction diet and mono saturated fatty acid 6 g/day	Obese healthy adult	2	Serum leptin did not change significantly
Ramel A (2009), Iceland[10]	F/M:278	20–402‡	RCT	8 week	Energy reduction diet with EPA and DHA; 1·3 g/d	Energy reduction diet and 6 placebo capsules/day	Overweight and obese	2	Serum leptin decreased significantly
Vargas (2011), U.S.A.[16]	F:62	29 ± 6·5	Double-blinded RCT	6 week	Group A: fish oil:3·6 g/day group B:ALA: 3·7 g/day	Placebo soybean oil:6 capsules/day (each capsule:200 mg oleic acid, 429 mg LA, 57 mg ALA)	Women with polycystic ovary syndrome	2	Serum leptin decrease in two groups but not significantly
Taylor C.G (2010), Canada[17]	M:17 F:17	52·4 ± 7·8	RCT	12 week	ALA: 7·7 g/day	Diet like intervention group without ALA	Patient with Well-Controlled Type 2 diabetes	1	Serum leptin did not change significantly
Spencer M (2013), U.S.A.[13]	M:11 F:22	53·3 ± 8·2	Double-blinded RCT	12 week	Fish oil: 4 g/day	Corn oil 4 g/day	Nondiabetic subjects with at least three features of the metabolic	2	Serum leptin decreased but not significantly
SatohN(2009), Japan[18]	F:53 M:39	51·7 ± 14·3	Single-blinded RCT	12 week	EPA:1·8 g/day with weight reduction diet	Weight loss diet	Obese subjects with metabolic syndromes	3	Serum leptin decreased but not significantly
Kabir M (2007), Italy[21]	F:27	55 ± 3·7	Double-blinded RCT	8 week	EPA: 1·8 g/d DHA: 0·7 g/d	3 g/day paraffin oil	Women with type 2 diabetes without hypertriglyceridaemia	2	Serum leptin increased but not significantly

(continued)

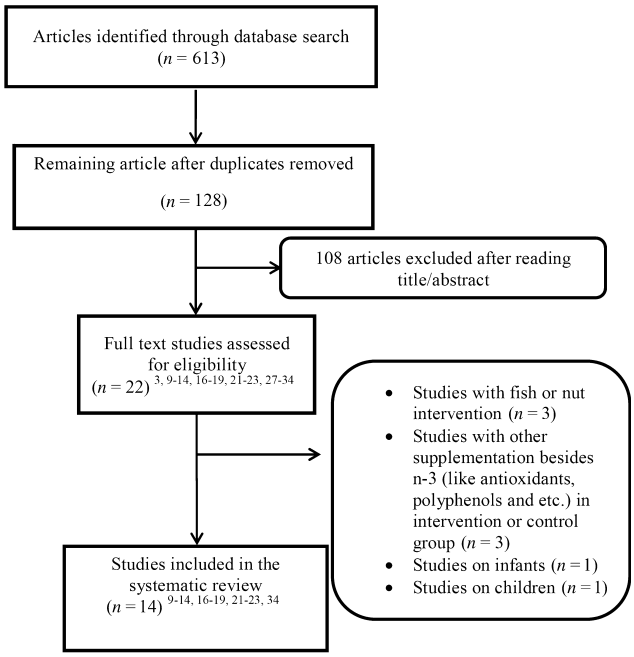

Fig. 1 Study selection process.

described as a major determinant of leptin production, and it is shown that omega-3 supplementation can reduce insulin levels which may describe the decreases in leptin levels.[42] Several *in vivo* studies in rats and mice have also reported that long-term intake of diets high in omega-3 fatty acids result in significant decreases in plasma leptin, which might be secondary to decreases observed in white adipose tissue mass.[43] Eicosanoids that are synthesized from EPA and DHA are very effective in gene expression and fat mass reduction.[5]

We found that marine source omega-3 significantly decreases leptin levels while this situation was not right for plant source omega-3. The majority of included studies had used fish oil for supplementation; Fish oils are not only the source of omega-3 fatty acids but they also provide vitamins E and D. Therefore, it is possible that these factors have led to significant effect of omega-3 from marine sources on serum leptin levels.[44,45] In our meta-analysis, there were two articles which assessed the effect of plant source omega-3 on human subjects.[16,17] Vargas *et al.*[16] and Taylor *et al.*[17] conducted their studies on subjects with insulin resistance and showed no significant reduction in leptin levels. New evidences have represented that insulin resistance may be associated with depressed desaturase enzyme activity,[46]; therefore, these patients can't transform ALA to EPA and DHA, and this may explain why these studies could not show the beneficial effect of omega-3 supplementation on leptin levels.

It must kept in mind that our sensitivity analysis showed that removing a study performed by Mostowik *et al.*[9] considerably change the effect of omega-3 on serum leptin to nonsignificant. In this study, Mostowik *et al.*[9] had used moderate dose of marine source omega-3 (1000 mg/day) for 4 weeks in subjects with low-grade inflammation because they excluded every subjects with sever obesity and inflammatory disease, and all patients

Table 1. (Continued)

First Author (year), country	Subjects and gender	Age	Study design	Duration (week)	Intervention	Control	Subjects	Jadad score	Results
MicallefM. A (2008), Australia[11]	F:33 M:27	55·4 ± 7·7	Double-blinded RCT	3 week	Tuna fish oil: 4 g/day	4 g/day sunola oil	Patient with hyperlipidaemia	1	Serum leptin significantly decreased
Patel JV(2006), UK[19]	M:35	65·3 ± 7·6	RCT	12 week	Omega 3 supplement: 1 g/day	Usual care	Post-MI men	2	Leptin decreased but not significantly
Olza J (2010), Spain[23]	F:37 M:10	75	RCT	24 week	Enteral formula containing EPA: 75 mg/l and DHA: 35 mg/l	Enteral feeding without omega-3	Old patients with total enteral nutrition	2	Leptin increased but not significantly

*F, female; M, male.
†Mean ± standard deviation (SD).
‡Range.
§NA, not available.

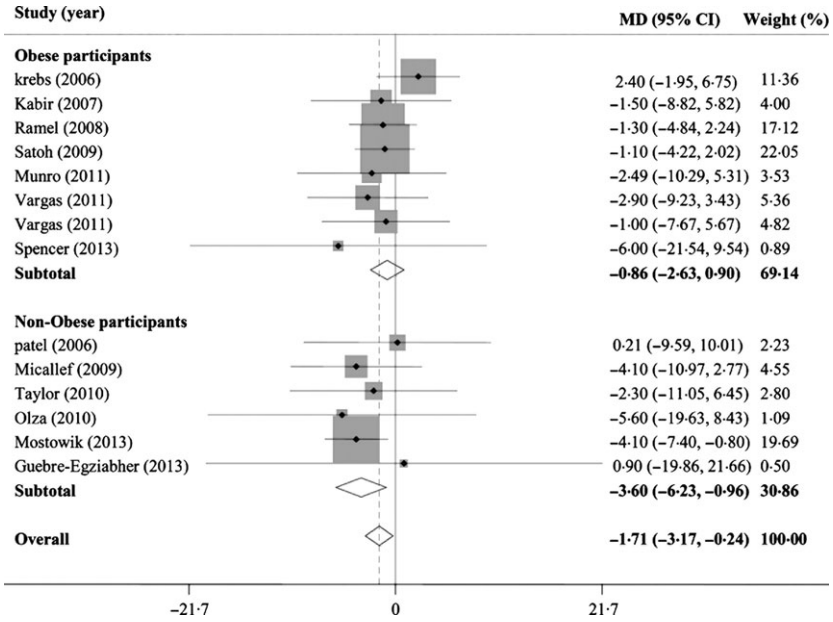

Fig. 2 Forest plot showing the effect of omega-3 supplementation on serum leptin concentrations based on body mass index status using random effects model.

were asked to increase their oily fish consumption. Without the study performed by Mostowik *et al.*,[9] we could not see any effect of omega-3 supplementation on leptin levels both among obese and nonobese participants. Therefore, the interpretation of our results must be performed with caution.

There are several limitations that must be considered while interpreting our results. The duration of follow-up for studies was short. There was only one investigation which followed the participants for more than 12 weeks.[22] The different effect of omega-3 supplementation on leptin levels among males and females might also be interesting. We could not find any study, exploring the effect of omega-3 supplementation among different genders; therefore, the difference between genders about the magnitude of omega-3 supplementation could not be addressed in the current analysis. We also could not include a study performed by Stirban *et al.*[34] which was newly become visible in PubMed in the current meta-analysis. The study concluded that omega-3 fatty acids might not reduce serum leptin after 6 weeks intervention in subjects with type 2 diabetes mellitus.

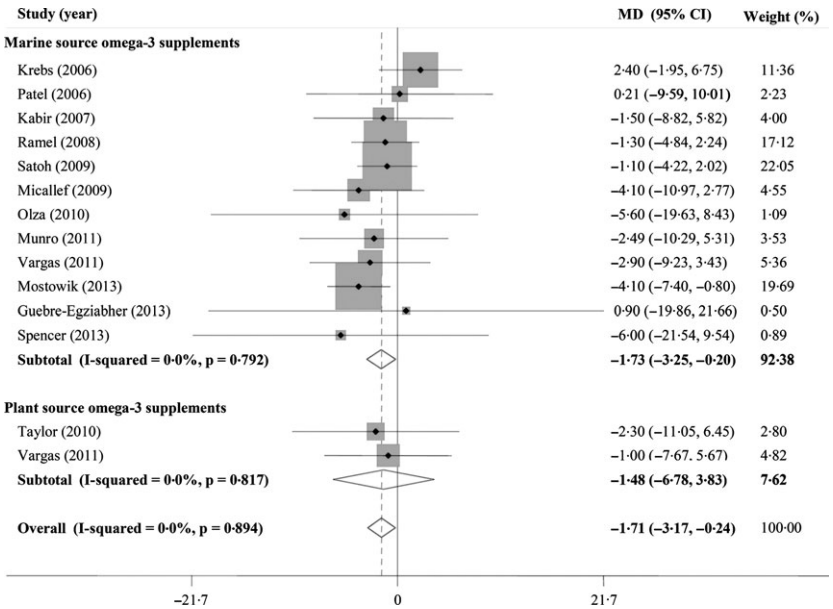

Fig. 3 Forest plot representing the effect of omega-3 supplementation on serum leptin concentrations based on omega-3 source using random effects model.

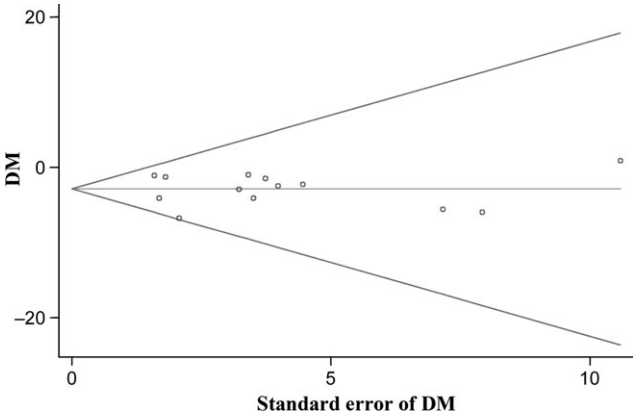

Fig. 4 Begg's funnel plot (with pseudo 95% confidence interval) in mean difference (MD) *vs* standard errors (SEs) of mean differences for studies that reported the effect of omega-3 on serum leptin concentration.

In conclusion, the current systematic review and meta-analysis on randomized, placebo-controlled clinical trials found that omega-3 supplementation particularly from marine sources moderately decreases circulating leptin levels only among non-obese participants. This result is highly sensitive to a specific study, and more RCTs with longer follow-up period, using higher doses for intervention and exploring the effect in different genders, are needed.

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Author's contribution

A.S.A. and M.H.: contributed to the conception, design, statistical analyses, data interpretation and manuscript drafting. A.S.A.: contributed to the data analysis. All authors approved the final draft of manuscript.

Conflict of interest

The authors declare no conflict of interest.

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