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# Is Omega-3 Supplementation Changes the Body Weight, Fat Mass, and Fat-Free Mass? A Systematic Review and Meta-Analysis of Rcts

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## 1. Abstract

**1.1. Background:** Current evidence showed omega-3s reduced the weight, although some studies demonstrate weight gain, so this meta-analysis estimates the effect of omega-3s in the weight changes.

**1.2. Methods:** Online databases including Cochrane, Medline, Embase, and Central Register of Controlled Trials were searched up to 30 July 2020, and it registered on PROSPERO (CRD42017064110). Our search resulted in 377 articles; we analyzed 11 studies. RCTs assessing the effects of omega-3 supplements on body composition and collected data on weight changes, FM, and FFM, included in the study. This meta-analysis was performed using means and SD were calculated in random-effects models based on the results of the Q-test. A sensitivity analysis evaluated the stability of the results, and publication bias was assessed by funnel and Egger's plots.

**1.3. Results:** The total sample size in the studies was 314 participants; the duration was 6 to 24-weeks, and age was between 10 to 75y. 10 studies (13 comparison groups) investigated. Weight losses by 0.19 kg (95%CI=-0.53 to 0.14, p<0.001); FM reduces by 0.18 kg (95%CI=-0.42 to 0.05, p<0.001); but FFM increased by 0.27 (95%CI=0.06 to 0.48, p<0.001). For heterogeneity, the criterion of significance was I2> 75%. The level of statistical significance was set at 0.05. Subgrouping suggested differences between the duration, dose, age, and sex of participants for weight loss or other outcomes.

**1.4. Conclusion:** Evidence suggests that omega-3 reduced weight simultaneously with FM. The effects of omega-3s on changes in FFM are contradictory. Further studies about the duration, dose, and type were recommended.

## 2. Introduction

Obesity is a disorder of the body metabolism. The prevalence of obesity is increasing among adults and children around the world. About 2 billion people are overweight and one-third of them are patients with obesity [1, 2], so it is reasonable to describe obesity as a public health problem that impairs the health and quality of life both in children and adults. This increasing trend causes excess mortality, morbidity, and substantial economic cost. Comorbidities of obesity are another worldwide issue that could make the problem of obesity more difficult. Type 2 diabetes and dyslipidemia are examples of obesity-related comorbidities that globally increased. Besides, these comorbidities attributed to increased body fatness and body weight. From the past decades, studies show the amount of fat mass is a key factor in treating, preventing, and delaying the onset of obesity [3, 4].

Many studies showed nutrients have a direct effect on body composition [5-7]. As body fat percentage is a marker of obesity, measurement of the effect of nutrients on fat mass could be effective. One of these nutrients is omega-3 fatty acids. Polyunsaturated fatty acids (PUFA) include omega-3, omega-6, and omega-9 fats [8-10]. Omega-3s are essential nutrients for humans, that include alpha linoleic acid (ALA; 18:3), eicosapentaenoic acid (EPA; 20:5), and

docosahexaenoic acid (DHA; 22–6). ALA found in seeds, nuts, flaxseed, and canola oil. Whereas the main source of EPA and DHA is marine foods, in particular fatty fishes like sardine and mackerel, the human body can synthesize EPA and DHA from ALA, but its efficiency is low, with reported rates of less than 15%, so these essential fatty acids should be obtained from the diet or through supplementation [11-16]. It is recommended that adults intake 500 mg per day of EPA and DHA by consuming 2 servings of fish per week. The adequate Intakes (AIs) for omega-3s are 1.1 to 1.6 g per day for adults [17]. Although fish consumption increased in recent decades, DHA and EPA intake from foods contributes a very small amount to total daily omega-3 intake (about 40 mg in children and teens and 90 mg in adults) [18]. So, the American Heart Association recommends supplementation for adults not eating enough oily fish [8]. Because of this low intake, this supplement should be considered more seriously than before.

Although studies with animals have shown that dietary intake of omega-3 in obese animals may reduce body weight, body fat accumulation, and particularly visceral fat, the effectiveness of supplementation with omega-3 as an adjunct to weight loss in humans is less certain [6, 19, 20]. Otherwise, confounding factors change the effect of omega-3 on body weight. First of all, EPA and DHA play different roles in the body, their involvement in different tissues, and is beneficial in different doses [21, 22], whether and how EPA and DHA initiate their effects on obesity concerning dosage and proportion are still unclear. On the other hand, the response to omega-3 supplements in healthy populations differs from patients and these supplements in health and disease situations could cause different results. For example, in patients with pancreatic cancer, omega-3 supplementation resulted in 1 kg weight gain at three weeks and 2 kg at seven weeks, and approximately 95% of the weight gain was lean body mass [23], but for healthy men, omega-3s may increase RMR that could consume fat storage in the body and result in weight loss [5, 24-26]. Besides, omega-3 raises fasting glucose and interrupts insulin signaling [27] that related to resistance to weight loss [28, 29].

Researches showed omega-3 through different mechanisms affect body weight [20]. Although results are conflicting, some of the evidence that supports these mechanisms are: 1) high concentration of omega-3 in RBC membrane phospholipids could decrease the risk of obesity, 2) the omega-6 to omega-3 ratio plays an important role in increasing the of obesity prevalence, 3) low dietary intake of omega-3 is associated with increased fat accumulation in body tissues such as liver, 4) consumption of omega-3 increase in HDL that decrease obesity, 5) in young healthy men, omega-3 particularly EPA and DHA may increase RMR during rest and exercise in healthy adults, and substrate oxidation to favor a greater usage of fat [5, 20, 22, 24-26, 30-38].

There is controversy about the weight loss potential of omega-3 in human studies. Some studies suggest omega-3 is more effective in preventing weight gain rather than assisting weight loss and it should be noted that different amounts of omega-3 supplementation and the relative proportions of EPA to DHA could affect changes in weight. It was suggested that the effect of omega-3 on weight reduction, if any, is likely to be small, with gradual changes over time. Although it has been suggested that omega-3 may reduce body fat in humans by increasing fat oxidation and energy expenditure studies with humans have provided conflicting results [6]. Furthermore, the baseline amount of fat in the body affects the response to omega-3 supplementation. In this context, trials with human participants demonstrate when compared to healthy-weight individuals, females and/or males with obesity have lower concentrations of omega-3 [39].

Based on these data, we propose that omega-3 fatty acids as supplements could help reduced weight and which components of the body are most affected by this weight reduction. Until now, to our knowledge, no systematic review or meta-analysis has investigated the effects of omega-3 supplementation on weight, BMI, fat mass, and LBM changes. We aimed to systematically review the effects of omega-3s on weight changes as an outcome of obesity and comorbidities. We were also interested in how effects changed by the type, dose, and duration of omega-3 and were to emphasis on classifying the interventions conducted to omega-3 supplementation based on randomized trial approaches and to review the literature. Given the discrepancy in these methodological aspects, the results would be interpreted differently in each of the previously mentioned studies. Therefore, we conducted this meta-analysis to provide an update on the therapeutic effect of omega-3 supplementation.

## 2.1. The Objectives of This Study Were

To assess the effects of increased intake of omega-3 supplements for weight reduction, adiposity, and body fat. The primary review question was, 'Do omega-3 supplementation (EPA, DHA) alter body weight?'

Secondary questions include the following. If omega-3 supplementation reduces weight:

* does weight reduction depend on the dose of EPA or DHA taken per day?

* do effects differ between men and women who take supplemental omega-3 sources?

* dose weight reduction happens stronger with longer trial duration?

## 3. Methods and Materials

### 3.1. Criteria for Considering Studies for This Review

The studies were limited to randomized clinical controlled trials (RCTs) evaluating the effects of interventions of omega-3 supplementation on body weight and its composition and compare high

er with lower dosage omega-3 supplementation and assessed our primary outcomes. Animal experiments were not included. Also, duration or type of omega-3 (EPA and DHA), were not important.

Studies included diet advice to promote omega-3 intake, and diet versus placebo was excluded. Characteristic of the studies showed in (Table 1).

**Table 1:** Cochrane Risk of Bias

| Citation | Sequence generation | Allocation concealment | Blinding of participants, personnel and outcome assessors | Incomplete outcome data | Selective outcome reporting | Other sources of bias |
|---|---|---|---|---|---|---|
| Helen M. Parker JSC. 2019. | H | L | H | U | L | U |
| L. Pacifico EB. 2015. | L | L | L | U | L | L |
| Noreen EE and S. 2010. | L | L | U | L | L | L |
| Irene A. Munro and Manohar L. Garg. 2012. | L | L | L | L | L | L |
| Mortazavi A and N. 2018. | L | N/A | L | L | L | L |
| Mansoori A and S. 2015. | L | L | H | L | L | L |
| Huerta AE and N-C. 2013. | L | L | L | L | L | L |
| Gunnarsdottir I and T. 2008. | L | L | U | L | L | L |
| Shirin Jafari Salim1 SA. 2017. | H | L | N/A | L | L | L |
| Samantha L. Logan LLS. 2015. | L | L | H | N/A | L | L |
| Roma Krzymi?ska-Siemaszko NC. 2015. | L | L | L | L | L | L |
| % | 81.81 | 90.9 | 45.45 | 72.72 | 100.0 | 90.9 |

'Low', or 'High' risk of bias, or can express 'Some concerns' [1]

1. Higgins, J.P., et al., Assessing risk of bias in a randomized trial. Cochrane Handbook for Systematic Reviews of Interventions, 2019: p. 205-228.

Studies in men and/or women at any risk of disease (with or without existing disease) were eligible, including healthy individuals, athletes, cancer, cardiovascular disease, diabetes mellitus, and obesity. Including these populations allows us to understand the role of omega-3 supplement in both Health and disease conditions (primary and secondary prevention). Participants were adults (aged between 11 to 74.97 years old). We excluded participants who were pregnant. No one of the participants involved in designing the study question, objects, determining the outcome measures. Also, none of them advised us on writing the conclusions or comments on the charts, figures, and tables, but we do have plans to disseminate the results of the research to any relevant communities.

Those trials were included in our review that designed to investigate the effect of various doses and types, and ingredients of omega-3 supplements, including EPA, and DHA on changes in body weight, fat mass, and fat-free mass. We also included the trials that compared therapeutic interventions with either placebo or control. The intervention must have been dietary supplementation in oil or capsule form. We excluded studies using excluding enteral and parenteral formulas.

The primary measured outcomes were limited to changes in body weight, weight gain, and weight loss. We analyzed weight as measured by a technician or self-reported. A combined spectrum of weight considered. One of our secondary outcomes had to be measured fat mass, and fat-free mass. The review included studies if any of their participants experienced or were assessed for any primary or secondary outcome. The tools used to measure the outcomes included any weight scale, bioelectric analysis (BIA), dual-energy X-ray absorptiometry (DXA), and bod pod. We chose

studies for this review that had assessed at least one primary review outcome.

### 3.2. Search Methods for Identification of Studies

This article has been reported by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [40]. This systematic review is registered on PROSPERO (CRD42017064110). We conducted a systematic bibliographic search for studies that examined the relation of omega-3 supplementation and weight. Methods for the set of this review were based on Cochrane. Two independent reviewers performed a systematic search in the selected online electronic databases including Cochrane, PubMed (Medline), Ovid version of Embase, Central Register of Controlled Trials, and the WHO International Clinical Trials Registry Platform. The search was conducted from the earliest publication date through 30 July 2020. We did not apply any date limits to newly added terms. The following key terms were used: (weight OR weight gain OR weight loss OR body composition OR fat mass OR fat-free mass) AND (omega-3 OR EPA OR DHA) mesh. Moreover, the terms intervention, experiment, randomized clinical trial, clinical controlled trial, blind, placebo was searched. A Grey literature search was done on google scholar. We also searched the references of selected studies and earlier meta-analyses to identify additional potential studies for inclusion in our analysis.

### 3.3. Data Collection and Analysis

For Selection of studies, we combined the search results for this review and two others, MS and AM, de-duplicating and assessing them at the same time. After remove the duplicates, by two independent, trained reviewers, relevant studies selected and screened for inclusion. The selection was made based on the screening of

titles and abstracts. Then, full-texts of the remaining articles were assessed independently by pairs of authors and the final list of studies was determined by discussion, including minor differences being resolved with another author. We rejected titles and abstracts on the initial screen only if the reviewer could determine from the title and abstract that the article was not a report of a randomized controlled trial; did not address omega-3 intake. We rejected studies only when it was certain that no primary or secondary outcome events occurred, and none of the secondary outcome risk factors were measured. When we could not reject a title/abstract with certainty, we obtained the full text of the article for further evaluation. Eligible interventions could be supplementation (taken orally as oil or capsules), but dietary advice, diet provided, or food interventions not included. The minimum duration of supplementation was not important.

Data extraction and management: We extracted data concerning participants, interventions, and outcomes, as described above in the selection criteria section. We extracted data from supplementation RCTs. We extracted continuous data and also the latest point available in fixed-term trials, but in studies where participants were followed up for varying durations (aside from dropouts), we extracted the participants' data from the first time point following the mean trial duration. For primary and secondary outcomes, we extracted numbers of participants experiencing an outcome and total numbers of participants randomized. For continuous outcomes, we extracted the number of participants assessed, means, and standard deviations of the final readings in each treatment arm; we calculated standard deviations from other variance data where appropriate. The reviewers carefully examined all documents and extracted the relevant data to obtain the proper and relevant information on the authors, publication year, the country where the trials were conducted, characteristics of participants (age and health status), study design, sample size, intervention and control groups, type of intervention, duration of supplementation, the applied measurement tools, scales, and outcomes. In the case of disagreement, the research team discussed and interchanged the viewpoints to reach an agreement. The data extracted from each selected RCT included only the primary outcome was extracted when multiple endpoints were reported.

Assessment of risk of bias in included studies: Study inclusion, data extraction, and assessment of the risk of bias were conducted independently in duplicate. We assessed the Cochrane risk of bias tool domains, as well as assessing risk from compliance problems and attention bias, specific to our set of reviews. Accordingly, each domain was assessed as having a low, unclear, or high risk of bias [41], We considered trials to be at low summary risk of bias if we judged randomization, allocation concealment, and the blinding of participants, personnel, and outcome assessors to be adequate (we considered all other trials to be at moderate or high risk of bias).

### 3.4. Measures of Treatment Effect a Data Synthesis, Unit of Analysis Issues

Two researchers combined treatment-control differences in outcomes across studies. Continuous data were extracted as means and SDs. Effect sizes were calculated based on the mean changes in scores of the treatment and placebo groups and their reported standard deviations (SDs). Mean change from baseline of weight measurements was calculated for the treatment and control groups, and the standardized mean difference (SMD) was computed as the measure of effect. All the studies had provided quantitative data and the weighted mean difference with 95% CI. The MD divided by the study's standard deviation that used to create an index for standardized MD to comparable across the studies. STATA software [ver.16] (Stata Corp, College Station, Texas 77845 USA) was used for analysis.

### 3.5. Trim and Fill

The missing data was deal with: "Meta trim fill" in STATA software that performs the nonparametric "trim-and-fill" method to account for publication bias in meta-analysis. The command estimates the number of studies potentially missing from a meta-analysis because of publication bias, imputes these studies, and computes the overall effect-size estimate using the observed and imputed studies [42].

We sought trial registry entries and study protocols to help us assess which studies measured each outcome. Where trials appeared to have collected but did not report data. We prioritizing our efforts on larger studies that would tend to provide more information to the review. Where it was clear that data existed but could not be located to use within the review, we noted this and assessed the potential effect of this missing data on effect sizes narratively.

Assessment of heterogeneity: Heterogeneity was assessed applying I squared (I2) statistical method, and the criterion of significance was I2> 75%. The chi-square test for heterogeneity was performed to determine whether the distribution of the results was compatible with the assumption that inter-trial differences were attributable to chance variation alone. The level of statistical significance was set at 0.05, a priori.

Subgroup analysis and investigation of heterogeneity and Sensitivity analysis: Where change scores were not reported outcome, pre- and post-intervention values were used to calculate the change score, and SDs were estimated as prescribed by the Cochrane Handbook for Systematic Reviews of Intervention. To correct for small sample bias, the standardized mean effect for the RCTs was calculated. Effect sizes across studies were summarized for each domain using random-effects modeling. Random-effects models assume that the studies are drawn from unequal populations and therefore account for the variation in the underlying effects in the estimates of uncertainty. Random-effects models were appropri-

ate, as heterogeneity was expected because of differences among studies in the assessment tools used to measure weight.

Subgroup analysis for gender, dose, and duration by removing the most influential study followed by removing the next influential study was performed to reduce heterogeneity and to test the robustness of the results, respectively [7, 22, 33, 43-46]. The chi-square test was included in the forest plots. Funnel plots for each outcome were also prepared and evaluated to assess potential publication bias. The risk of publication and small study biases were evaluated using funnel plots. All analyses were performed using STATA version 16 (StataCorp, College Station, TX, USA).

## 4. Results

Up to 30 July 2020, we identified 2349 publications. After filter RCTs 392 remain and just 377 were human studies, within which 4 papers were duplicates and therefore were excluded. An additional 3 studies were obtained by cross-referencing. After the initial screening for the titles and abstracts, 218 were excluded. The remaining was 152 articles were considered for the retrieval of the full texts. After assessing the full-texts of these articles, 27 studies were assessed for eligibility and quality. No articles were excluded due to the languages used, all of 11 were in English and have available full-text. Consequently, 11 articles remained for the final meta-analysis and systematic review. The study selection flow chart demonstrates in (Figure1).

The risk of bias was assessed for all studies. The Sequence generation risks of bias (due to the lack of information in the method of randomization, n=2) and allocation concealment (due to the lack of information in allocation concealment, n=1) were low. The risks of bias for the included studies were high in terms of the Blinding of participants, personnel, and outcome assessors (n=6). Risk of bias due to Incomplete outcome data for (n=3), due to Selective outcome reporting (n=0), and other sources of bias (n=2) were observed. Cochrane risk of bias showed in (Table 2).
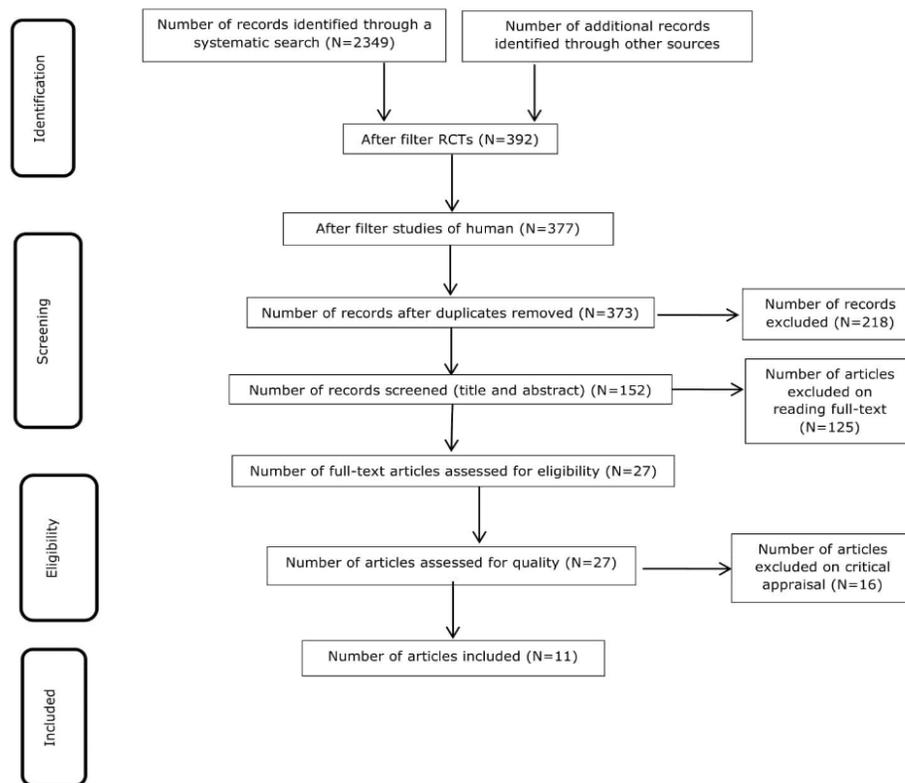


**Figure 1:** Flowchart for the selection of included trials. RCT: randomized clinical trial.

**Table 2:** Characteristics of the included trials.

| First author, publication year, [ref. no.] | Study design | Country | Number of Participants | | Age (y) | Criteria | | Daily dose (g/day) Experiment ingredients | | placebo | Duration (months) | gender |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Treatment | Control | | Inclusion | Exclusion | EPA | DHA | | | |
| Noreen,2010 | RCT | USA | 22 | 22 | 34 | Healthy and active adults (18-55y) | intake fatty fish at least 3 times a month, or were supplementing their diet with omega-3s, or had metabolic or endocrine disorder | 1600 | 800 | Safflower Oil | 6 | m/f |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pacifico,2015 | RCT | Italy | 14 | 16 | 11 | age < 18 y BMI > 85th percentile, NAFLD | Smoking, and history of DM, renal disease, TPN, alcohol intake, use of hepatotoxic medications, and previous use of omega-3 | 0 | 250 | linoleic acid | 24 | m |
| Parker*,2019 | RCT | Australia | 25 | 25 | 33.6 | non-smokers 18 to 60y BMI: 25.0-29.9; WC: >94 cm | obesity, dyslipidemia, DM, hypertriglyceridemia, renal disease, liver disease, were taking lipid-lowering medication, taking supplements containing omega-3 within the previous 6 months, regular alcohol intake | 588 | 412 | olive oil | 6 | m |
| Parker*,2019 | " | " | " | " | " | " | | " | " | " | 12 | m |
| Jafari,2017 | RCT | Iran | 21 | 21 | 55 | 45–65 y , CAD BMI: ≥25 | DM, cancer, myopathies, smoking taking warfarin, multivitamins, and omega-3 fatty acids or fish oil supplements | 720 | 480 | paraffin | 8 | m |
| Gunnarsdottir, 2008 | RCT | Iceland, Spain, Ireland | 80 | 80 | 31 | BMI: 27.5–32.5, age 20–40 y; WC >94 and >80 | weight change due to weight-loss diet within 3 months before the start of the study, use of pmega-3 supplements, calcium or vitamin-D, DM, HT, hyperlipidemia and pregnancy or lactation | 633 | 430 | sunflower oil capsules, no seafood | 8 | m/f |
| Mansoori*,2015 | RCT | Iran | 24 | 22 | 55.8 | DM, PPARγ Pro12Ala polymorphism | traveling abroad, poor compliance, digestive issues, detection of colon cancer | 400 | 1450 | paraffin | 8 | m/f |
| Mansoori*,2015 | " | " | " | " | " | " | " | 400 | 1450 | monounsaturated oil | 8 | m/f |
| Munro*.2012 | RCT | Australia | 18 | 14 | 40.5 | 18 – 60y, BMI: 30-40, university campus students | DM, a chronic inflammatory condition, already following an energy-restricted diet, allergic to fish, taking fish oil capsules or consuming two or more oily fish meals per week were excluded from the study, pregnant or lactating | 420 | 1620 | monounsaturated oil | 44 | m/f |
| Munro*.2012 | " | " | " | " | " | " | " | 420 | 1620 | " | 14 | m/f |
| Logan,2015 | RCT | Canada | 12 | 12 | 66 | 60–76 yr, score >25/30 on the Mini Mental State Exam, consumed one meal or less of fish/wk | Decline to participate | 2000 | 1000 | olive oil | 12 | m/f |
| Krzymińska-Siemaszko,2015 | RCT | Poland | 30 | 20 | 74.97 | low muscle mass | intake of any steroids, anti-platelet, anti-thrombotic drugs, omega-3 supplements during the 3 months | 660 | 440 | vitamin E | 12 | m/f |

*Abbreviations: CAD: Coronary artery disease; NAFLD: Non-alcoholic fatty liver disease; m/f: Male/female; DM: diabetes melituse; TPN: total parenteral nutrition; BMI: body mass index; WC: waist circumference; HT: hypertension;

[1]Trials that have performed measurements at two points in time have been considered as two separate comparisons.

Effects of interventions are summarized here, and a fuller account of results (supplementary text) with additional tables, forest plots and funnel plots, and details of all sensitivity analyses and subgroups, can be found in the supplementary materials.

The effect of the omega-3 supplement on weight change: 10 studies (13 comparison groups) randomized controlled trials that measured at least one of our primary outcomes, with a total of 314 participants, investigated the effects of omega-3 on the weight changes as compared to control groups. Meta-analyses, sensitivity analyses, funnel plots, and subgrouping of data suggest that omega-3 supplementation probably affects weight loss SMD was -0.19 (95% CI= -0.53 to 0.14, p < 0.0001), indicating evidence for the efficacy of the interventions. However, heterogeneity existed between the studies, I2= 74.2% (p < 0.0001). We assessed 10 randomized controlled trials as being at a low summary risk of bias (Figure 2).

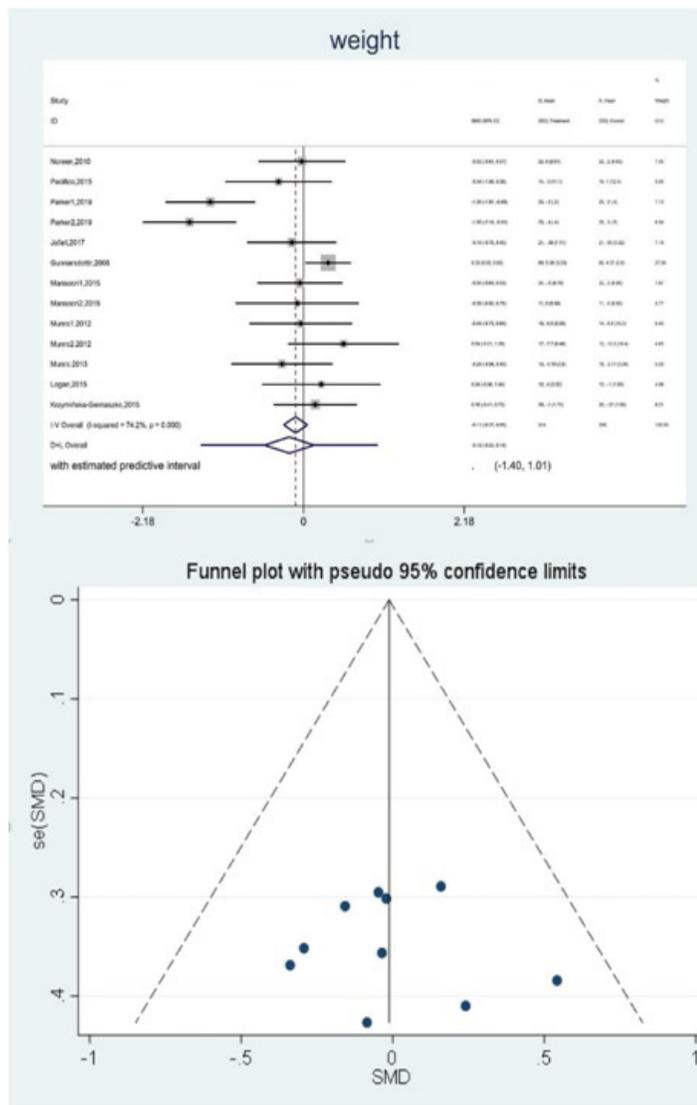The effect of the omega-3 supplement on fat mass: 6 studies (8 comparison groups), with a total of 151 participants, investigated the effects of omega-3 on the fat mass as compared to control groups. This is confirmed by no effect on fat mass (SMD= -0.18, 95% CI= -0.42 to 0.05, p < 0.0001), indicating an evidence for the efficacy of the interventions. However, heterogeneity existed between the studies, I2= 0.0% (p= 0.986). We included 6 randomized controlled trials that measured at least one of our primary outcomes (Figure 3).

The effect of the omega-3 supplement on fat-free mass: 8 studies (10 comparison groups), with a total of 194 participants, investigated the effects of omega-3 on the fat-free mass as compared to control groups. The pooled SMD was 0.27 (0.06, 0.48) (95% CI= 0.06 to 0.48, p < 0.001), indicating an evidence for the efficacy of the interventions. However, heterogeneity existed between the studies, I2= 63.6% (p < 0.003) (Figure 4).



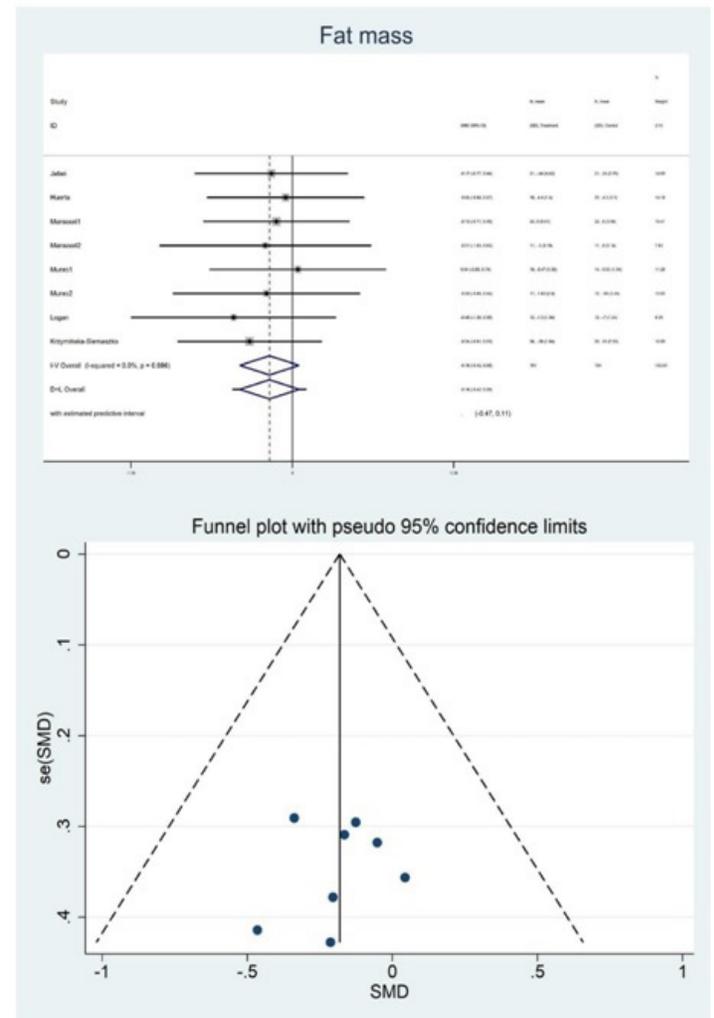**Figure 2:** The effect of the omega-3 supplement on weight change



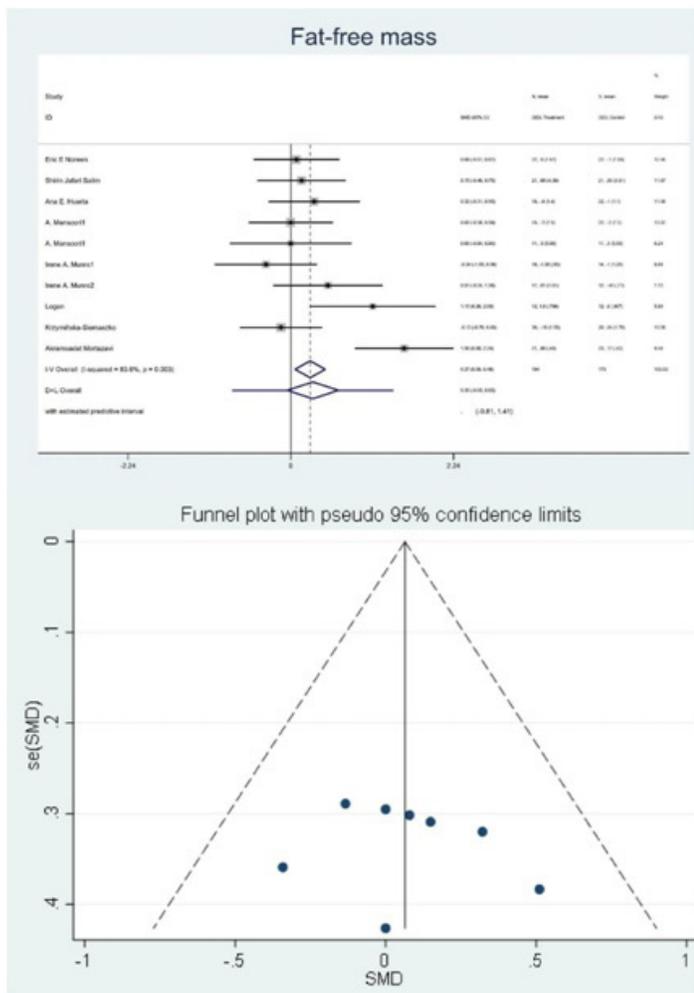**Figure 3:** The effect of the omega3 supplement on fat mass

**Figure 4:** The effect of the omega-3 supplement on fat-free mass

### 4.1. Subgroup Analysis

We sub grouped data based on dose, trial duration, age, sex. Subgrouping results need to be interpreted with caution.

### 4.2. Subgrouping by Dose

The dose of EPA did not statistically significant differences between some outcomes. In the study of Munro 2012, weight increased by 420 mg of EPA for 14 months (SMD= 0.05, 95% CI= -0.42, 0.52; 2 trials with 50 participants; I-squared = 24.5%, p = 0.266), same these results happened for DHA. The effects on fat mass and fat-free mass did not vary by the EPA or DHA dose changed (supplementary tables A).

### 4.3. Subgrouping by Duration

We looked for effects of duration to determine the main effect of omega-3 in short or long trials. In 12 months' weight decreased by 0.37 kg (95% CI= -1.20, 0.46, I-squared = 84.0%, p = 0.000, 4 trials, 82 participants). Fat mass decreased by 0.16 kg (95% CI= -0.53, 0.22, I-squared = 0.0%, p = 0.986, 2 trials: 56 participants). For fat-free mass the overall effect of duration of omega-3 supplementation is 0.06 (-0.16, 0.29), (I-squared = 0.0%, p = 0.791), 6

trials, 161 participants (supplementary tables B).

### 4.4. Subgrouping by Sex

Weight in trials that include male/ female or female is 0.15 kg increased (95% CI= -0.04, 0.34; 7 trials, 229 participants), but in studies by male participants 0.83 kg weight reduction was accrued (95% CI= -1.51, -0.16; 3 trials, 85 participants). In male/female trials fat mass 0.18 kg (95% CI= -0.47, 0.12, Subtotal (I-squared = 0.0%, p = 0.947); 3 trials, 100 participants) decreased but in males this effect was not obvious. For fat-free mass was not change in male/female subgroup (SMD= 0.00, 95% CI= -0.26, 0.27), subtotal (I-squared = 0.0%, p = 0.706); 3 trials, 122 participants).

### 4.5. Subgrouping by Age

For determining the effect of age on weight change due to omega-3 supplementation, Subgrouping by of under 40 years vs. over 40 years was done. In under 40 years' weight decreased by 0.60 kg (95% CI= -1.55, 0.35), subtotal (I-squared = 92.6%, p = 0.000); 3 trials, 152 participants. For over 40 years, weight increased by 0.07 (95% CI= -0.19, 0.32), subtotal (I-squared = 0.0%, p = 0.846), 5 trials, 133 participants). Fat mass just in over 40 years decreased SMD= -0.20, 95% CI= -0.46, 0.05, subtotal (I-squared = 0.0%, p = 0.978); 5 trials, 133 participants, but change not seen in under 40 years' fat mass. Also, fat-free mass just in over 40 years increased SMD= 0.34, 95% CI -0.11, 0.79, subtotal (I-squared = 0.0%, p = 0.978); 6 trials, 145 participants, but change not seen in under 40 years' fat mass.

### 5. Discussion

The total sample size in the studies was 314 participants. The minimum sample size of comparison groups was found to be 11 and the maximum was 24 [44]. The duration of the interventions ranged from 6 to 24 weeks. All the participants were at the age of 10 to 75 years. 10 studies (13 comparison groups) investigated the effects of omega-3 supplementation on weight. In the case of weight loss, there has been a fair test of the treatment (Omega-3 supplementation) against placebo under experimental conditions that found small evidence of beneficial. Weight losses by 0.19 kg (95% CI= -0.53 to 0.14, p < 0.0001); fat mass reduces by 0.18 kg (95% CI= -0.42 to 0.05, p < 0.0001); but fat-free mass increased by 0.27 (95% CI= 0.06 to 0.48, p < 0.001). Sub-grouping suggested differences between the duration of trials, dose of the supplement, age, and sex of participants for weight reduction or other outcomes. Supplementation with omega-3 is sensible and appropriate to promote health due to weight loss. In overall completeness and applicability of evidence, and quality of the evidence, the level of heterogeneity in our results was 75%.

As the potential biases in the review process, a major confounder in the comparison of omega-3 supplements with placebo in trials is the fact that the number of the previous resources of omega-3 in the body was not determined. As the basal resource of omega-3

especially in adipose tissue, affects the application of omega3 in the body, and daily intake of omega-3 from food has huge differences, so there is a high risk of bias for uncontrolled factors which are known to be substantial for this indication. Publication bias occurred in the evidence for more publication with effective results and can cause misleading in the estimate of the treatment effects, which makes it difficult to determine the efficacy of omega-3 supplementation. However, the small sample size may affect the bias.

Agreements and disagreements with other studies or reviews: Today, with the spread of obesity around the world, weight loss approaches are receiving increasing attention. Because weight is an available measure of obesity, weight changes can indicate changes in obesity in public health. Recent studies demonstrate nutrients, such as omega-3 fatty acids supplements, cause change the weight. The mechanism by which omega-3 decrease fat mass or increase fat-free mass is due to the effect of omega-3 on the expression of genes and changes in the number of neurotransmitters in the brain [47, 48]. Therefore, in combination with genetic factors, insufficient levels of EPA or DHA could lead to metabolic dysfunction and obesity. The effect of omega-3 is due to alter body composition especially the decrease in fat mass or increase in fat-free mass. Of course, studies in this area are contradictory [8, 19, 24, 33]. There is a considerable variety of data available on body composition and omega-3 fatty acids in different populations. Different results may be due to the effect of confounding factors. Some of these factors are the dose of supplements, and duration of the trial, sex, and age of the participants.

Recent studies demonstrate omega-3 interventions were effective in losing weight [25, 33, 44, 46, 49, 50]. Although, two studies demonstrate weight gain [43, 45]. Trials have shown that omega-3s affect weight changes by altering body composition. Almost all previous studies have shown that fat mass decreases with omega-3 supplementation [7, 22, 44, 45, 50, 51]. Our results showed that the rate of reduction of fat mass is small (0.18 kg), although, in some of these studies, fat-free mass increases simultaneously [7, 25, 50] other studies showed a decrease in fat-free mass [22, 44, 45]. Therefore, the interpretation of omega-3 weight loss should be interpreted by considering each of the components of reduced weight.

The gender of participant's effect on the response to supplementation. As omega-3 fatty acids are associated with fat mass, and the amount of fat mass is higher in females, trials with male participants have weight reduction after omega-3 supplementation [33, 46, 51], whereas male/female or female trials had slight weight gain, and fat mass slightly decreased in this sub-group [25, 43, 44]. Besides, fat-free mass doesn't alter in any sex sub-groups.

The older a person gets, the fat mass increased and a fat-free mass decreased. In all the trials, with any age, omega-3 reduced weight

Except Gunnarsdottir et al. and Huerta et al. with the mean age of (31 and 38 years) [43, 45], but the result of meta-analysis reveals mild weight loss accrued in response to omega-3s in over 40 years old, whereas the results were reversed in the group over 40 years.

The American Heart Association and the European Society for Cardiology recommend an intake of 1 gr per day EPA and DHA to prevent cardiovascular disease and comorbidities such as obesity, thus indicating that consuming omega-3 fatty acids could help reduced fat storage in the body. Our study demonstrates a dose of EPA, in 420 mg per day could very mild decreased weight, but not other outcomes. Clinical evidence shows an improvement in weight loss with the use of 250-2040 mg of omega-3 per day [33, 44, 46, 49, 50]. Although these studies are very beneficial two studies showed 700 mg omega-3 caused weight gain [43, 45], future studies should distinguish the effects of different doses of omega-3s on weight.

Based on our knowledge, to date, we have no trial to investigate the relationship between duration of omega-3 supplementation and weight changes. The result of subgrouping demonstrated just in 12 months of supplementation, omega-3 decreased weight and its components, but the results are not robust.

One of the Limitations is none of the trials reviewed in our research did consider the tools for evaluation of fat mass and fat-free mass. Assessment of body composition with BIA, DXA, and other tools makes small differences, which can have a negative effect on summarizing the results [52]. Another limitation found was data of included trials analyses without considering the omega-3 intake from foods. Also, this meta-analysis did not consider the genetic, physical activity, ethnic, and environmental risk factors that are effective in shaping the composition of the body, Because of the limited sample size.

## 6. Conclusions

Based on our findings, supplementation with omega-3 could alter the body composition; decreased weight, decreased fat mass, and increased fat-free mass. Sub-group analysis of omega-3 supplementation revealed age, duration, dose, and sex as effective remedies for improvement of weight loss. Thus, further investigations are recommended in this regard.

This study showed that omega-3 fatty acids were effective for individuals with obesity; however, the benefits of omega-3 were more significant in males, under the age of 40, in 12 months of supplementation with 420 gr of EPA.

In the future studies assessment, the effect of omega-3 supplementation on fat distribution in the body, such as visceral or subcutaneous fat suggested, and assess the effect of plant omega-3s which are converted to DHA and EPA in the body. It is also recommended to evaluate the effect of very high doses and different durations

of omega-3s on altering the body composition. The combination of omega-3 with other obesity-related nutrients (especially vitamin D and E, Q10) was recommended.

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