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Meta-analysis

The effect of long chain omega-3 polyunsaturated fatty acids on muscle mass and function in sarcopenia: A scoping systematic review and meta-analysis

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SUMMARY

Background & aims: Sarcopenia is characterized by the progressive loss of skeletal muscle mass and function, which reduces mobility and quality of life. Risk factors for sarcopenia include advanced age, physical inactivity, obesity, and chronic diseases such as cancer or rheumatoid arthritis. Omega-3 long chain polyunsaturated fatty acids (LC PUFAs) might be associated with a reduction in risk of sarcopenia due to their anti-inflammatory effects.

Methods: We conducted a systematic review and meta-analysis to quantify the effects of omega-3 LC PUFAs on muscle mass, volume and function parameters. The National Library of Medicine's MEDLINE/PubMed database was searched on 9th October 2020 for randomized controlled trials that used omega-3 LC PUFAs as an intervention with muscle-related endpoints. A snowballing search to identify additional studies was completed on 23rd April 2021. The meta-analysis was conducted using meta-essentials worksheet 3. Bias was assessed using the Jadad scale.

Results: 123 studies were identified with the systematic searches. Most studies were performed in disease populations, such as cancer or chronic obstructive pulmonary disease (COPD), or in healthy individuals after a fatiguing exercise bout. The endpoints lean body mass, skeletal muscle mass, mid-arm muscle circumference, handgrip strength, quadriceps maximal voluntary capacity (MVC), and 1-repetition maximum chest press were selected for meta-analysis based on the number of available studies; thus 66 studies were included in the quantitative synthesis. Using a random effects model and 2-tailed p-value, there was a significant relationship in favor of omega-3 LC PUFA supplementation for lean body mass (effect size 0.27, 95%CI 0.04 to 0.51), skeletal muscle mass (effect size 0.31, 95%CI 0.01 to 0.60) and quadriceps MVC (effect size 0.47, 95%CI 0.02 to 0.93).

Conclusion: The results indicate that there is a positive effect of omega-3 LC PUFA supplementation on overall body muscle mass and strength. Small study size and heterogeneity limit the applicability of these findings for sarcopenia prevention. Larger trials in populations at risk of sarcopenia would strengthen the evidence base.

1. Introduction

Muscle mass and function are essential to good health and quality of life. A number of conditions can result in loss of muscle and its quality and function, including sarcopenia, cachexia, and muscle disuse atrophy. Sarcopenia has been defined as "a

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progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality" [1]. Sarcopenia is considered primarily a disease of aging and is characterized by the progressive loss of skeletal muscle mass and function. Secondary sarcopenia can be classified according to causes related to inactivity, disease or malnutrition [2]. Inactivity from extended bed rest, a sedentary lifestyle, or zero gravity causes a rapid decline in muscle mass and quality, and a loss of muscle function. Diseases that are associated with sarcopenia have a strong inflammatory component and include cancer and its treatment, chronic obstructive pulmonary disease (COPD), heart failure and type 2 diabetes mellitus [3].

Sarcopenia is associated with a decline in functional capacity of the muscle, which leads to physical disability, lower quality of life, and an increased risk of death [4]. Patients with sarcopenia cause significantly higher healthcare costs related to longer hospital stays and a greater need for residential living facilities [5,6]. Events such as falls are more likely in patients with sarcopenia, who frequently also have immune system dysfunctions and hence have an increased risk for infection especially after surgery [7]. Sarcopenia ultimately increases healthcare expenditure across different care settings [8].

The latest working group operational definition of sarcopenia from 2019 primarily uses low muscle strength to identify probable sarcopenia, and low muscle quantity or quality is required for a diagnosis [1]. The new criteria mark a shift from prior definitions of sarcopenia with low skeletal muscle mass and a measure of muscle function (for example, walking speed) or additionally muscle strength, particularly handgrip strength being used for diagnosis [4]. Due to technological limitations in measuring muscle quantity and quality, muscle strength was now considered a more reliable indicator of sarcopenia [1].

Studies in community-dwelling older adults show sarcopenia prevalence is approximately 10% [9–11]. Hospitalized and institutionalized older adults have an even higher prevalence of sarcopenia [12–14]. Comprehensive studies show that sarcopenia prevalence increases with age and can vary by sex. For example, in a nutritional survey conducted in the US of 4984 adults aged over 60 years, sarcopenia prevalence was lower in males than females, with a significantly higher prevalence in those aged over 80 years compared to younger age groups [15]. Assessment of general sarcopenia prevalence in free-living or patient populations is hampered by the sarcopenia definition and measurement instrument used, which can estimate widely variable prevalence within the same population [16].

While the precise mechanisms whereby progressive muscle loss occurs are not yet fully understood, it is believed to be a multifactorial process with a range of causes. Five main factors are believed to be involved in the development of sarcopenia [17]:

1. Neuromuscular degeneration
2. Changes in muscle protein turnover
3. Changes in hormone levels and sensitivity
4. Chronic inflammation and oxidative stress
5. Behavior and lifestyle factors

Neuromuscular degeneration involves related processes of muscle fiber atrophy, a decrease in the number of alpha-motor neurons, the replacement of muscle by fibrous connective tissue, and the infiltration of muscle tissue with adipocytes [17,18]. Skeletal muscle undergoes repeated cycles of denervation and enervation during adult life. Structural changes to the neuromuscular junction lead to enervation failure and the gradual increase in permanently denervated muscle fibers [19,20]. Preferential atrophy of fast-twitch (type II) muscle fibers due to aging is thought to be primarily responsible for a loss of function and strength [21].

The balance between muscle protein synthesis and degradation affects overall turnover. While this allows adaptation to changes in nutrition, metabolism and physical activity, poor homeostasis, which results from a reduction in protein synthesis and a shift towards proteolysis, is believed to contribute to muscle loss in aging [21]. Both increased muscle protein degradation and a blunted anabolic response to stimuli such as hyperinsulinemia are thought to contribute to sarcopenia [17].

Insulin-like growth factor 1 (IGF-1) is, besides insulin, the main anabolic signaling molecule. Muscle hypertrophy and protein synthesis is stimulated by the binding of IGF-1 and insulin to their receptors in the muscle cell membrane, activating the phosphatidylinositide 3-kinases (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway, initiating the anabolic process. Muscle protein synthesis can also be stimulated via activation of mTOR complex 1 by amino acids. In addition, insulin has a direct effect on muscle cells, stimulating their growth as well as the uptake of glucose. Myocytes become less sensitive to the anabolic effects of insulin as they age [21]. Exercise is another strong stimulant for muscle protein synthesis, acting through multiple pathways including the mTOR pathway, as reviewed elsewhere [22].

Muscle wasting diseases are linked to inflammation. It is assumed that chronic, low-grade inflammation tends to increase due to aging, while chronic or serious disease and their treatments can cause an inflammatory cascade. Elevated concentrations of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor-necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β) link inflammation to change that occurs in aging [7]. For example, IL-6 and TNF-α contribute to a reduced effect of insulin on protein synthesis by interfering with the insulin signaling cascade [23].

Both nutrition and physical activity impact sarcopenia by regulating muscle (protein) turnover, singularly and together [24]. Short or extended periods of inactivity or low food, especially protein, intake will encourage muscle atrophy, while adequate nutrient intakes in conjunction with physical activity will stimulate increases in muscle mass [17]. Thus a central role for exercise in preventing sarcopenia and muscle senescence is suggested [7]. Protein and amino acid intake during a meal will promote an anabolic response to improve or maintain muscle mass [25]. Protein intake recommendations for elderly individuals vary but are generally considered to be higher than for younger individuals [25]. Both, protein intake and exercise also affect the sensitivity of cells to insulin, and are linked directly and indirectly to inflammation. For example, the transient increase in reactive oxidative species from exercise causes an adaptive anti-inflammatory response that has a net effect of reducing chronic inflammation [26]. Exercise also assists in creating an energy deficit that could indirectly reduce chronic inflammation through a reduction in body adipose tissue mass [26].

1.1. Omega-3 LC PUFA and effects on mechanisms of sarcopenia

The main bioactive omega-3 LC PUFAs are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA are present in seafood and in the oil extracted from seafood ("fish oil"), as well as in krill oil and some algal oils [27]. EPA and DHA can also be bio-synthesised from alpha-linolenic acid (ALA) which is found in many foods of plant origin, but this conversion process is considered to be poor in humans [28]. The main sources of EPA and DHA in the diet include fish and seafood, fortified foods, and dietary supplements. For patients with sarcopenia, fish oils can be incorporated into oral nutrition supplements and enteral feeds. Once consumed, EPA and DHA are

incorporated into cell membranes, including inflammatory immune cells [29–31] and the sarcolemma of skeletal muscle fibers [32,33]. This incorporation is linked to their biological activity in the regulation of inflammation [29–31]. EPA and DHA reduce the production of inflammatory eicosanoids (prostaglandins, thromboxanes, leukotrienes) from the omega-6 PUFA arachidonic acid [34] and act as substrates for production of alternative chemical mediators that down-regulate (resolve) inflammation (resolvins, protectins, maresins) [35–37]. Through these, and other membrane-mediated events, EPA and DHA alter both intracellular and intercellular signals. Within cells this leads to altered patterns of inflammatory gene expression and protein production [29–31]. The net result is decreased production of inflammatory cytokines, chemokines, adhesion molecules, proteases and enzymes related to inflammation [29–31]. The anti-inflammatory and inflammation resolving effects of EPA and DHA are relevant to both prevention and treatment of muscle wasting [33].

The aim of this systematic review was to identify the effects of omega-3 LC PUFAs on endpoints related to muscle mass and muscle function (described in Table 1).

2. Materials & methods

2.1. Data sources and searching strategy

The National Library of Medicine's MEDLINE/PubMed database was searched for primary research articles reporting clinical trials or potentially relevant observational studies reporting relationships between omega-3 LC PUFA supplementation and a measure of muscle strength, function, volume, fatigue or quality. The search terms were “omega-3 and muscle”. As this was an exploratory review, search filters were not applied. The search was conducted on 9th October 2020. The searching strategy was not registered as it was a scoping systematic review, which are recommended not to be registered [46]. Articles were assessed for inclusion based on being a clinical study performed using an omega-3 supplement, and including a muscle-related endpoint, and the decision recorded in a Microsoft Excel spreadsheet. The initial screening was performed by JB. After screening abstracts of potentially relevant articles, the full-text was accessed for inclusion into the meta-analysis. A snowballing search of the reference lists of included articles was conducted to identify further articles that may have been missed in the MEDLINE/PubMed search [47]. The snowballing search was conducted by JB, BT and IW, and the results logged in a Microsoft Excel spreadsheet. The snowballing search was completed on 23rd April 2021.

2.2. Data extraction and quality assessment

The Jadad scale was used to assess study quality at the individual study level [48]. A five-point score was assigned to each study based on blinding, randomization, and reporting of dropouts. Studies that had a score of 4 or 5 had a low risk of bias, whereas those with scores of 3 or less were considered to be at high risk of bias. Study meta-data included number of participants, intervention type, dose, control type, study population information (adult/elderly, healthy/diseased), and intervention length. Potentially relevant endpoints fell under the following topics: muscle fatigue, muscle volume, muscle strength, muscle quality, and inflammation marker (see Supplemental Table 2 for the list of endpoints extracted). At this stage, the categories muscle fatigue and muscle quality were taken out of the analysis because the low number of studies and diverse endpoints precluded meta-analysis. Inflammation markers were also removed as they could not be adequately included as an explanatory variable in the meta-analysis at the study level. Information extracted related to the endpoints included the number of subjects in each intervention group, the change in parameter from baseline for all intervention groups, or mean difference, and standard deviation.

Table 1
Clinical endpoints related to muscle mass and muscle function.

Lean body mass
Lean body mass (LBM), also called fat free mass, is the difference between total body weight and body fat weight. It provides only an approximate estimate of muscle mass because the weight of organs and bone is also included in this measure. LBM is measured using dual-energy x-ray absorptiometry (DEXA), magnetic resonance imaging (MRI) or bioelectrical impedance analysis (BIA).
Skeletal muscle mass
Skeletal muscle mass (SMM) is a more sensitive indicator of body functional muscle mass than lean body mass. International definitions of sarcopenia relate to a loss of SMM [24]. SMM is measured using DEXA, MRI, computed tomography (CT) or BIA, with MRI and CT being the gold standards because they can measure muscle tissue more accurately than other techniques [17]. However, DEXA has become more popular in the last decade through its ease of use, lower cost and radiation exposure, and wider availability [38].
Mid-Arm Muscle Circumference
Mid-arm muscle circumference (MAMC) is a measure of somatic protein reserves, and therefore estimates the quantity of fat and muscle mass in the body [39,40]. The measure is based on several assumptions for its reliability. It is assumed that the circumference of the upper arm is representative for the rest of the body; however unequal fat distribution throughout the body may affect the measure's predictability. Conditions that cause swelling in the upper body such as oedema affect the measurement, as does immobility. The measurement is simple to perform using a tape measure.
Handgrip strength
A useful functional marker of muscle function is handgrip strength, which predicts the ability to perform everyday activities. Handgrip strength peaks around the age of 40 years and thereafter declines, and is a good predictor of age-related functional outcomes [41]. A dynamometer measures static force exerted by the hand, and a standardized protocol is available to position subjects for repeated measures [41]. Handgrip strength is considered to be a robust measure, even with different assessors or dynamometers. The measurement device is portable and low-cost, and it can be implemented in large studies and surveys.
Quadriceps Maximal Voluntary Capacity
Various strength tests are available that estimate the functional capacity of skeletal muscle. Gait, balance and mobility require adequate lower limb strength, which can be measured using the quadriceps maximal voluntary capacity (MVC). Quadriceps MVC appears to decline at a greater rate than handgrip strength across the spectrum of aging [42]. A strength testing chair is used for the test, which can be applied to measure both knee extensors and flexors, although the quadriceps are responsible for knee extension.
1-Repetition Maximum Chest Press
The 1-repetition maximum (1RM) chest press is a measure of the strength of the chest muscles [43]. It is defined as the maximum weight a subject can press with one repetition using a barbell lying in a supine position on a horizontal bench. While the predictive value of the measurement has not been investigated often in regards to sarcopenia, it is considered to be a gold standard measurement of muscle strength [44]. Strength training programs can be tailored to individuals' strength as a percentage of the 1RM chest press, which is important for exercise in older adults [45].

2.3. Data synthesis and statistical analysis

Based on the number of studies obtained for each endpoint, a meta-analysis was conducted for LBM, SMM, mid-arm muscle circumference, handgrip strength, quadriceps MVC and 1RM chest press using the Meta Essentials worksheet 3 for continuous data, which allows for the use of raw data (means, standard deviations and sample size) or for tests of differences to be used [49]. We used the change in parameters between the final measurement and baseline. For studies that included a fatiguing exercise bout or had planned surgery as part of the study design, we included data comparing the parameter change after supplementation between baseline and before the event to avoid the effect of acute inflammation on the parameter in question. For all analyses, standardized mean differences are reported. We used the random effects model, two-sided p-value and Hedge's g measure of effect size to give a more conservative estimate for the meta-analysis. Analyses were performed to determine the effect of healthy/disease subgroups and adult/elderly sub-groups, and dose. Publication bias in the meta-analysis was assessed by visually inspecting the funnel plot and heterogeneity with the I^2 statistic. When the funnel plot indicated that certain studies were outliers, their effect was investigated by removing them from the meta-analysis to determine the effect on the outcome as a sensitivity analysis.

3. Results

We identified 1933 abstracts, of which 1823 were excluded, leaving 110 articles for potential inclusion. 18 articles were excluded after assessment of the full text (9 observational studies, 8 with non-relevant endpoints, one non-English article). From the 92 included articles, a snowball search was conducted, which identified a further 31 articles. These 123 articles underwent a bias assessment. Four articles were found to report sub-studies of studies already included. Thus, 119 articles were included in the qualitative assessment. After studies with endpoints in the categories muscle fatigue, muscle quality and inflammation were removed, 66 articles were selected for quantitative synthesis (meta-analysis) and are listed in Supplemental Table 1. The results of the article selection process are presented in a PRISMA flow chart (Fig. 1).

3.1. Lean body mass

We found 35 articles reporting the results of intervention studies with omega-3 LC PUFAs and lean body mass (measured in kg). 8 studies were excluded: one study did not have a control group without omega-3 LC PUFAs [50], four did not report LBM at both baseline and end of the intervention [51–54], one reported LBM in g/kg body weight [55], one did not include a measure of variability [56], and one reported change as a beta-coefficient [57]. One study reported results separately for males and females [58], and another included two different omega-3 LC PUFA doses [59] and results were therefore analyzed along these strata in the meta-analysis. Thus, 29 comparisons were included in total. Studies were conducted in both healthy and diseased groups, most commonly patients with cancer. Reported dosing ranged from 600 to 4000 mg per day EPA plus DHA. One study used high dose ALA as the intervention [58], and in one study omega-3 LC PUFAs were part of a multi-ingredient supplement that included whey protein, creatine, calcium and vitamin D [60]. Another study compared two doses containing a different ratio of omega-3 LC PUFAs; therefore, the dose reported in Table 2 is the difference between the low and high dose of omega-3 LC PUFAs [61]. A cluster of studies used an oral nutritional supplement including 2200 mg EPA [62–66]; this supplement also includes DHA (785 or 1100 mg depending upon the region) but this is often not specified [67]. In total, 2101 subjects were included in the meta-analysis. Due to the relatively large number of participants, no study contributed more than 4% to the overall results. Results were derived from studies at both low and high risk of bias (Table 2).

The Forest plot summarizing the results of the meta-analysis of omega-3 LC PUFAs on LBM is presented in Fig. 2. There was a significant increase in lean body mass with omega-3 LC PUFAs (mean difference: 0.27, 95% CI: 0.04 to 0.051, $p = 0.018$). The sub-group analysis on healthy or patient populations also showed a significant increase in LBM in healthy subjects (mean difference: 0.28, 95% CI: 0.07 to 0.48) but not for disease groups (mainly cancer patients), which showed a non-significant effect of similar magnitude (mean difference: 0.27, 95% CI: −0.05 to 0.60). There was no significant effect of omega-3 LC PUFA dose and excluding the study that used the ALA intervention did not affect the results. Based on the funnel plot and publication bias tests, there was moderate heterogeneity ($I^2 = 89\%$, $p < 0.001$), and asymmetry was not particularly evident (Egger regression $P = 0.07$).

3.2. Skeletal muscle mass

We found 9 articles reporting the results of intervention studies with omega-3 LC PUFAs on skeletal muscle mass (SMM). We excluded one study for not including a control group [86], so the final analysis included 8 studies with data on 406 subjects (Table 3). Most studies were performed in populations such as patients with COPD, cancer or morbid obesity. All studies used supplements containing both EPA and DHA. The studies were all small, recruiting between 14 and 38 subjects per treatment arm. Five studies had a low risk of bias.

The Forest plot summarizing the random-effects meta-analysis of omega-3 LC PUFAs on SMM is presented as Fig. 3. There was a significant increase in SMM in the omega-3 LC PUFA intervention group compared to control (mean difference 0.31, 95% CI 0.01 to 0.60, $p = 0.013$). Due to the small number of studies, dose and subgroup analyses were not performed. The I^2 value of 36% indicated moderate heterogeneity. No publication bias was evident from the funnel plot or Egger's regression ($p = 0.6$).

3.3. Mid-arm muscle circumference

We found 11 articles reporting the results of intervention studies with omega-3 LC PUFAs on mid-arm muscle circumference (MAMC) as an outcome measure. One study was excluded because MAMC was not compared between treatment groups [92], one because results were not reported as absolute values [93], and one because post-intervention MAMC was not reported. The 8 included studies were performed in healthy adults and in diseased populations (various cancer patients and maintenance dialysis), and 355 subjects were included overall (Table 4). The small number of studies meant that we did not perform a subgroup analysis nor investigate the effect of dose on the study outcomes.

The Forest plot summarizing the random-effects meta-analysis of omega-3 LC PUFAs on MAMC is presented in Fig. 4. There was a positive, non-significant relationship found between omega-3 LC PUFA supplementation and MAMC (effect size 0.30, 95% CI -0.23 to 0.83). There was substantial heterogeneity ($I^2 = 77.6\%$, $p < 0.001$) and the Egger regression statistic was non-significant ($p = 0.58$), indicating that the data were not asymmetric. Only two studies were at low risk of bias for this analysis.

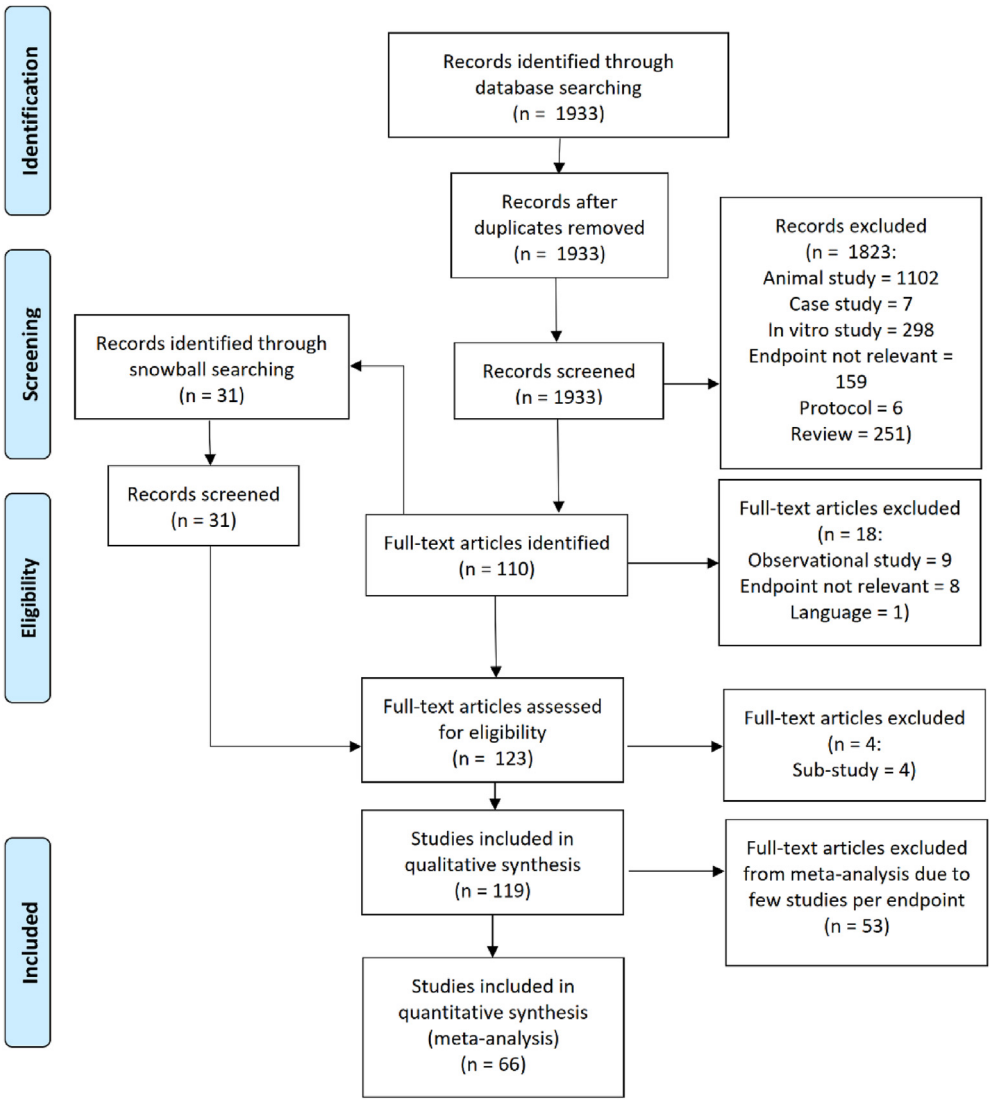

Fig. 1. PRISMA flow diagram of study inclusion.

3.4. Handgrip strength

We found 14 articles reporting the results of intervention studies with omega-3 LC PUFAs on handgrip strength. One study did not report the results of the handgrip strength test except that there was no significant difference between treatment groups [68], and another was excluded as both treatment arms included the same dose of omega-3 LC PUFAs [50]. The 12 included studies used for the meta-analysis are listed in Table 5, reporting results from 1437 participants overall. Studies were performed in healthy subjects and diseased populations, and studies included a similar number of subjects with the exception of the study reported by Rolland with 800 subjects randomized to either omega-3 LC PUFAs or placebo [100]. This study used a 2×2 factorial design for which a comparison was available only for the omega-3 LC PUFA versus placebo groups and not for the combinations with the multidomain intervention. The total dose of omega-3 LC PUFAs was relatively high (1000–3400 mg/d) for most studies. Three studies had a high risk of bias.

The Forest plot summarizing the random-effects meta-analysis of omega-3 LC PUFAs on handgrip strength is presented in Fig. 5. There was no statistically significant relationship found between omega-3 LC PUFA supplementation and handgrip strength (effect size: 0.91, 95% CI: −1.13 to 2.96, $p = 0.326$). The results did not appreciably change when healthy/diseased or adult/elderly subgroups were separately analyzed. Two studies were outliers on the funnel plot [102,105]. When these two studies were excluded, meta-analysis favored a significant effect of omega-3 LC PUFAs on handgrip strength (mean effect size: 0.83, 95% CI 0.19 to 1.47, $p = 0.003$). There was considerable heterogeneity ($I^2 = 97\%$, $p < 0.001$), although asymmetry was not found (Egger regression $p = 0.65$).

3.5. Quadriceps maximal voluntary capacity

We identified studies that measured quadriceps maximal voluntary capacity (MVC) or knee extensor MVC; as several measured MVC after a fatiguing exercise bout, we only used endpoints taken from before the exercise bout (post-supplementation) compared with baseline (pre-supplementation). We found 11 articles reporting the results of intervention studies with omega-3 LC PUFAs with endpoints that included quadriceps or knee extensor MVC; one study was excluded as there was no comparison of pre-supplementation and post-supplementation values [107]. The 10

Table 2
Included studies reporting on lean body mass (LBM).

Study first author & year	Intervention: Change in LBM, mean (SE)	Control: Change in LBM, mean (SE)	Difference: Intervention-control	Weighting in the meta-analysis	Subgroup studied	Reported omega-3 PUFA dose (/day)	Bias risk	Ref.
Calder 2018	0.07 (0.14)	−0.03 (0.15)	–	3.47%	COPD	2000 mg EPA + DHA	Low	[68]
Cornish 2018	0.5 (6.2)	0.7 (5.9)	–	3.16%	Healthy	1980 mg EPA, 990 mg DHA	Low	[69]
Cornish 2009 (male)	1.2 (7.1)	0.4 (7.2)	–	3.16%	Healthy	14,000 (ALA)	Low	[58]
Cornish 2009 (female)	0.7 (5)	0.4 (5)	–	3.30%	Healthy	14,000 (ALA)	Low	
Couet 1997	0.2 (0.66)	−0.24 (0.46)	–	2.61%	Healthy	1100 mg EPA, 700 mg DHA	High	[70]
Damiot 2019	−0.3 (1.6)	−0.3 (1.6)	–	3.07%	Healthy	1100 mg EPA, 1000 mg DHA	High	[71]
de Luis 2005	−1.0 (8.7)	0.8 (8.2)	–	3.76%	Head and neck cancer	720 mg EPA[a]	High	[61]
Fearon 2003	0.54 (0.3)	0.24 (0.4)	–	3.99%	Cancer cachexia	2200 mg EPA, 960 mg DHA	Low	[72]
Fearon 2006 - high dose	–	–	0.1 (0.61)	4.07%	Cancer cachexia	4000 mg EPA	Low	[59]
Fearon 2006 - low dose	–	–	−0.9 (0.61)	4.04%	Cancer cachexia	2000 mg EPA	Low	
Haidari 2019	0.40 (0.4)	−1.10 (0.9)	–	3.21%	Colorectal cancer	108 mg EPA, 500 mg DHA, 52 mg other	Low	[73]
Hanai 2018	1.00 (8.0)	0.20 (7.0)	–	3.30%	Head and neck cancer	2112 mg EPA*	High	[62]
Hayward 2016	1.133 (2)	0.38 (1)	–	3.22%	Healthy	540 mg EPA, 360 mg DHA	High	[74]
Healy 2017	2 (18)	3.1 (18)	–	4.00%	Esophageal cancer	2200 mg EPA preoperatively, 2300 mg EPA post-operatively*	Low	[63]
Hossain 2020	–	–	704 (893)	3.67%	Colorectal cancer	3000 mg EPA	Low	[75]
Jannas-Vela 2020	−0.5 (3.7)	−0.7 (3.9)	–	3.13%	Healthy	2000 mg EPA, 1000 mg DHA	Low	[76]
Krzymińska-Siemaszko 2015	−0.17 (6.9)	0.04 (7.5)	–	3.38%	Healthy	660 mg EPA, 440 mg DHA + 200 mg other omega-3 fatty acids	High	[77]
Logan 2015	1.6 (1.3)	0.6 (1.5)	–	3.15%	Disease	2000 mg EPA, 1000 mg DHA	High	[78]
Moses 2004	0.3 (0.5)	0.6 (0.8)	–	3.13%	Cancer cachexia	2200 mg EPA*	Low	[64]
Noreen 2010	0.5 (0.5)	−0.1 (1.2)	–	3.53%	Healthy	1600 mg EPA, 800 mg DHA	Low	[79]
Ogasawara 2018	1.8 (6.5)	0.5 (6.9)	–	3.56%	COPD	1100 mg EPA*	Low	[80]
Paixao 2017	−0.50 (4.5)	−0.10 (6.8)	–	3.46%	Breast cancer	940 mg EPA, 780 mg DHA	Low	[81]
Philpott 2019	−1.4 (0.4)	−1.2 (0.4)	–	3.04%	Healthy	~2000 mg EPA, ~2000 mg DHA	High	[82]
Ryan 2009	0.3 (3.7)	−1.9 (3.7)	–	3.62%	Esophageal cancer	2200 mg EPA*	Low	[65]
Sanchez-Lara 2014	1.6 (5)	−2 (6)	–	3.83%	Lung cancer	Two servings of Prosure*	High	[66]
Shirai 2017	2.3 (7.1)	0.5 (8.2)	–	3.88%	Healthy	1100 mg EPA, 500 mg DHA*	High	[83]
Snijders 2018	1.2 (1.4)	−0.3 (2.1)	–	3.21%	Healthy	700 mg EPA, 450 mg DHA	High	[60]
Solís-Martínez 2018	−0.20 (3.8)	−1.30 (3.6)	–	3.71%	COPD	2000 mg EPA	High	[84]
Sugawara 2010	2.40 (3.9)	−0.30 (2.0)	–	3.32%	Lung cancer	2940	High	[85]

[a] (difference with low omega-3 group). *This study used a branded Oral Nutrition Supplement known to contain 440 mg DHA in addition to 990 mg EPA per serving [67].

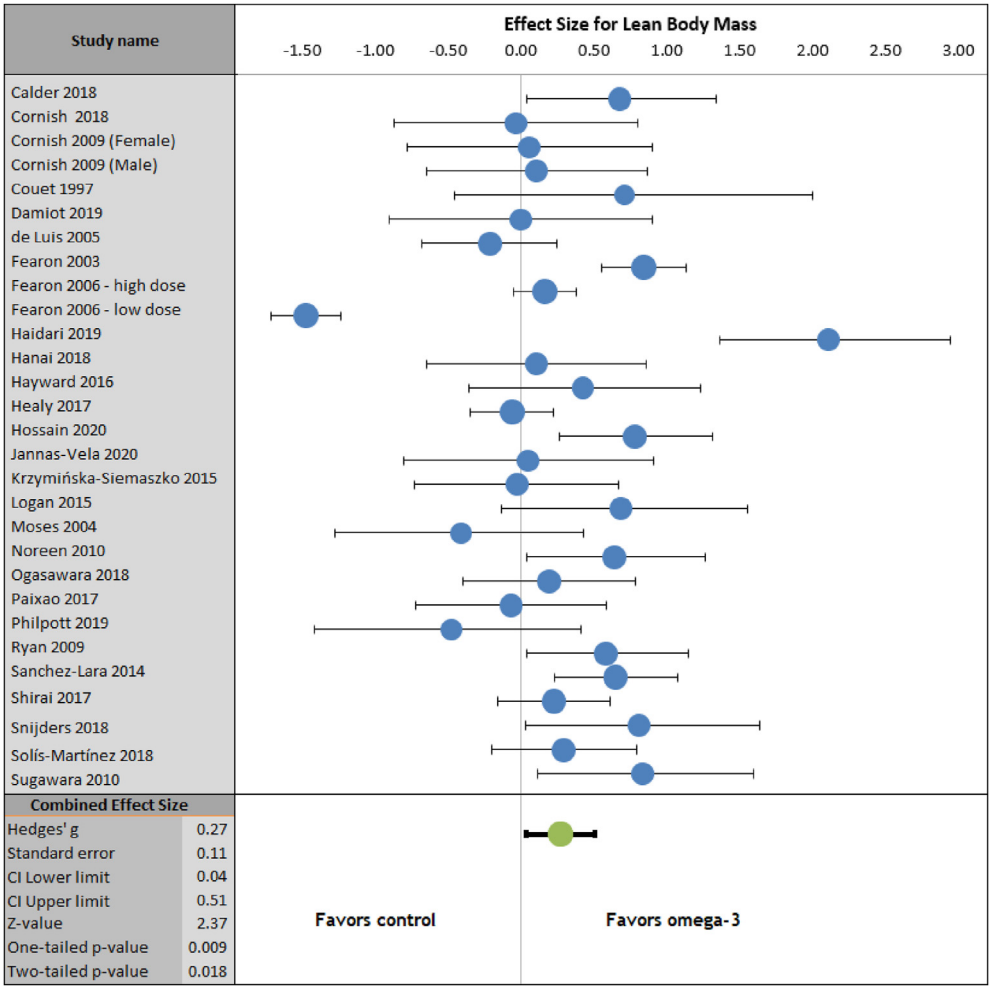

Fig. 2. Forest plot of random-effects meta-analysis on effect of omega-3 LC PUFA supplementation on lean body mass.

Table 3
Included studies reporting skeletal muscle mass (SMM).

Study first author and year	Intervention: Change in SMM, mean (SE)	Control: Change in SMM, mean (SE)	Weighting in the meta-analysis	Subgroup studied	Reported omega-3 PUFA dose (mg/day)	Bias risk	Ref.
Akita 2019	−0.2 (5.3)	−0.8 (5.8)	14.5%	Disease	Two servings of Prosure[a]	High	[87]
Aredes 2019	−3.44 (7.5)	−3.16 (6.3)	11.1%	Disease	2000 mg EPA, 450 mg DHA	Low	[88]
Bakker 2019	0.6 (3.72)	−3 (3.11)	12.6%	Disease	1680 mg EPA, 380 mg DHA	High	[89]
Calder 2018	0.02 (0.05)	−0.1 (0.5)	11.0%	Disease	2000 mg DHA + EPA	Low	[68]
Dad'ová 2020	0.2 (3.7)	0 (5.4)	13.8%	Healthy	125 mg EPA, 105 mg DHA	Low	[90]
Krzymińska-Siemaszko 2015	0.08 (1.0)	0.06 (1.0)	9.58%	Healthy	660 mg EPA, 440 mg DHA + 200 mg other omega-3 fatty acids	High	[83]
Ogasawara 2018	0.2 (1.0)	−0.3 (1.5)	11.8%	Disease	1100 mg EPA[a]	Low	[80]
van de Bool 2017	0.6 (0.6)	0.3 (0.6)	15.6%	Disease	500 mg EPA, 237 mg DHA	Low	[91]

[a] This study used a branded Oral Nutrition Supplement known to contain 440 mg DHA in addition to 990 mg EPA per serving [67].

included studies used for the meta-analysis are listed in Table 6, reporting results for 329 participants overall. The studies were all performed in either healthy subjects or patients with COPD, and covered a wide range of doses from 102 mg to 5000 mg omega-3 LC PUFAs per day. One study compared three different doses with placebo [108]. The weighting of each study in the meta-analysis was similar because most were small with 10–20 subjects per treatment arm. Two studies had a high risk of bias. Due to the low number of included studies, we did not perform analyses using subgroups.

The Forest plot summarizing the results of the meta-analysis of omega-3 LC PUFAs on quadriceps MVC is presented in Fig. 6. There was a statistically significant increase in quadriceps/knee MVC with omega-3 LC PUFAs (mean difference 0.47, 95% CI 0.02 to 0.93, $p = 0.022$). No significant omega-3 LC PUFA dose effect was found, although the number of studies was small. There was significant heterogeneity ($I^2 = 67.5\%$, $p < 0.001$). The Egger regression statistic indicated that asymmetry may be present ($p = 0.09$). When the article from Rodacki and co-workers [115], identified as an outlier in the funnel plot, was excluded, the Hedge's g for the meta-

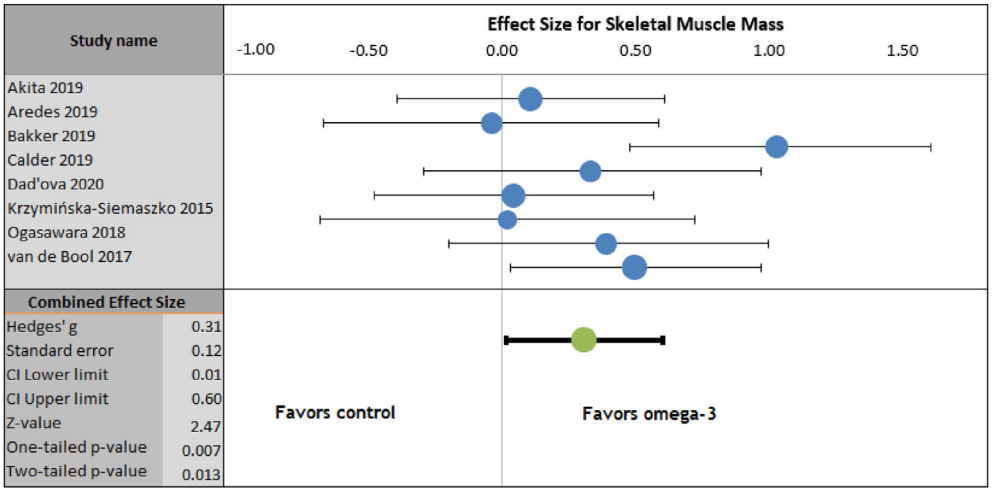

Fig. 3. Forest plot of random-effects meta-analysis on effect of omega-3 LC PUFA supplementation on skeletal muscle mass.

Table 4
Included studies of mid-arm muscle circumference (MAMC).

Study first author and year	Intervention: Change in MAMC, mean (SE)	Control: Change in MAMC, mean (SE)	Weighting in the meta-analysis	Subgroup studied	Reported omega-3 PUFA dose (/day)	Bias risk	Ref.
Chagas 2017	0.60 (3.7)	−0.10 (2.3)	10.9%	Leukemia/lymphoma	367 mg EPA, 243 mg DHA	High	[94]
Corder 2016	0.4 (1.1)	0.5 (1.5)	11.7%	Healthy	3000 mg DHA	Low	[95]
De Luis 2005	0.3 (3.9)	0.3 (3.1)	14.3%	Head and neck cancer	720 mg EPA (difference with low omega-3 group)	High	[61]
Feijó 2019	−0.3 (0.87)	−0.7 (1.0)	14.3%	Gastric cancer	3200 mg EPA + DHA[a]	High	[96]
Fietkau 2013	0.39 (0.67)	−0.83 (0.73)	13.4%	Head and neck cancer	2000 mg EPA, 850 mg DHA	Low	[97]
Gharekhani 2014	1.5 (4.2)	1.1 (2.1)	13.2%	Maintenance dialysis	1080 mg EPA, 720 mg DHA	High	[98]
Jouris 2011	0.3 (1.0)	0.6 (1.1)	11.0%	Healthy	2000 mg EPA, 1000 mg DHA	High	[98]
Tsuchiya 2019	0.45 (1.5)	0.34 (1.7)	11.3%	Healthy	600 mg EPA and 260 mg DHA	High	[99]

[a] This study used a branded Oral Nutrition Supplement known to contain 440 mg DHA in addition to 990 mg EPA per serving [67].

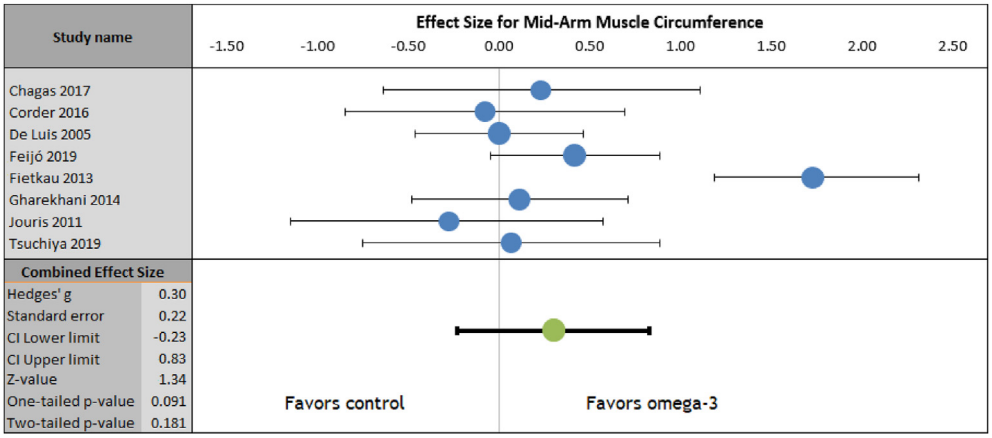

Fig. 4. Forest plot of random-effects meta-analysis on effect of omega-3 LC PUFA supplementation on mid-arm muscle circumference.

analysis decreased to 0.27 (95% CI 0 to 0.53) and remained statistically significant (p = 0.025).

3.6. 1-Repetition maximum chest press

We found 5 articles reporting the results of intervention studies with omega-3 LC PUFAs on 1-repeat maximum (1RM) chest press results. For two studies, the 1RM chest press results were only reported as part of a composite score and not individually; therefore the results were not included in the meta-analysis [60,104]. One study reported results separately for men and women [58]; this study used flaxseed oil (a source of ALA) as an intervention. The included studies are listed in Table 7. The small number of studies meant that we did not perform a sub-group analysis nor investigate the effect of dose on the study outcomes.

The Forest plot summarizing the results of the meta-analysis of omega-3 LC PUFA supplementation on 1RM chest press is presented in Fig. 7. A negative, non-significant effect of omega-3 LC

Table 5
Included studies of hand grip strength.

Study first author and year	Intervention: Change in handgrip strength, mean (SE)	Control: Change in handgrip strength, mean (SE)	Difference: Intervention - control	Weighting in the meta-analysis	Subgroup studied	Reported omega-3 PUFA dose (mg/day)	Bias risk	Ref.
Berbert 2005	51 (53)	6 (34)	–	8.61%	Rheumatoid arthritis	1800 mg EPA, 1200 mg DHA	High	[101]
Dad'ova 2020	1 (2)	0.9 (2.3)	–	8.78%	Healthy	125 mg EPA, 105 mg DHA	Low	[90]
Fietkau 2013	−1.57 (0.96)	−2.72 (0.99)	–	8.89%	Head, neck and esophageal cancer	2000 mg EPA, 850 mg DHA	Low	[97]
Hossain 2020	–	–	0.1 (2.4)	8.80%	Colorectal cancer	3000 mg EPA	Low	[75]
Hutchins-Wiese 2013	−6.1 (2.8)	2.8 (1.0)	–	8.55%	Healthy	1200 mg EPA + DHA	Low	[102]
Krzymińska-Siemaszko 2015	−0.17 (7.2)	0.84 (7.6)	–	8.60%	Healthy	660 mg EPA, 440 mg DHA + 200 mg other omega-3 fatty acids	High	[83]
Logan 2015	1.6 (3.1)	−0.3 (2.4)	–	8.44%	Healthy	2000 mg EPA, 1000 mg DHA	High	[77]
Nilsson 2020	3 (2.3)	2.3 (1.6)	–	8.59%	Healthy	1510 mg EPA, 950 mg DHA	Low	[103]
Rolland 2019 (only placebo and omega-3 subjects included)	−3.5 (−0.35)	−3.9 (−0.34)	–	9.03%	Healthy	225 mg EPA, 800 mg DHA	Low	[100]
Smith 2015	1 (0.4)	0.5 (0.2)	–	8.36%	Healthy, elderly	1860 mg EPA, 1500 mg DHA	Low	[104]
van der Meij 2012	–	–	1.8 (0.15)	5.04%	Lung cancer	2020 mg EPA, 920 mg DHA[a]	Low	[105]
Wu 2015	–	–	2.3 (0.74)	8.31%	Heart failure	6500 mg fish oil	Low	[106]

[a] This study used a branded Oral Nutrition Supplement known to contain 440 mg DHA in addition to 990 mg EPA per serving [67].

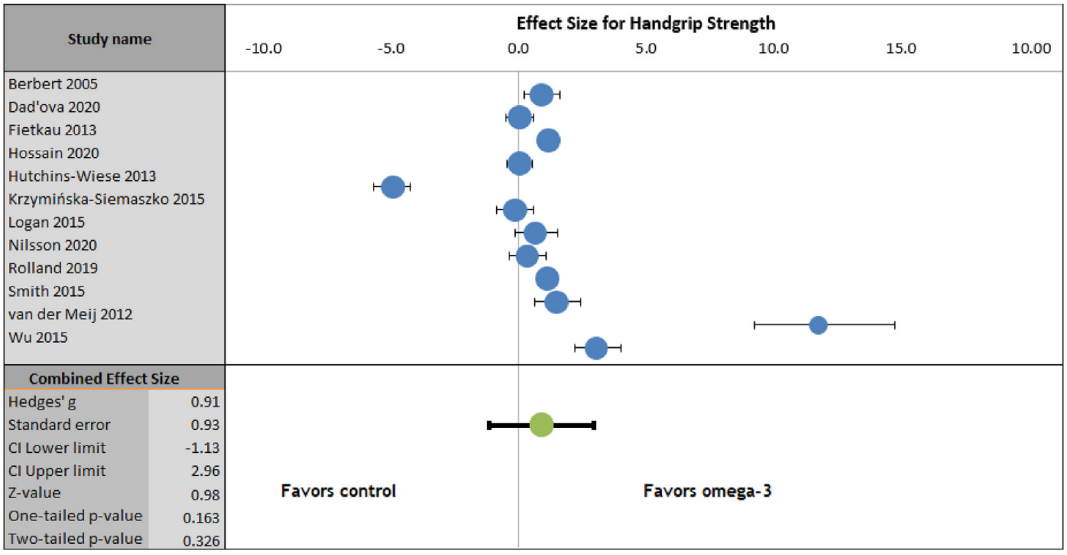

Fig. 5. Forest plot of random-effects meta-analysis on effect of LC omega-3 PUFA supplementation on handgrip strength.

PUFAs was seen on 1RM maximum chest press measurements (effect size −0.29, 95% CI -1.76 to 1.18). Substantial heterogeneity was present (I^2 = 78.2%, p < 0.001) but there was no evidence of asymmetry (Egger regression p = 0.8), with the results of Hayward et al., 2016 [74] producing an outlier in the funnel plot.

4. Discussion

We found that lean body mass, skeletal muscle mass and quadriceps MVC all increased after omega-3 LC PUFA supplementation. These results indicate that omega-3 LC PUFAs could be useful in increasing skeletal muscle mass or strength, particularly in populations at risk of sarcopenia. The quadriceps is required for locomotion and may be more susceptible to wasting in the elderly [42]. A reduction in muscle mass would parallel decreases in muscle strength of the quadriceps. Hence the effects of omega-3 LC PUFAs on muscle mass and quadriceps MVC are likely to be linked. Most trials used EPA and DHA and the trial that used a high intake of ALA [58] did not see effects on any outcome.

Although it might be anticipated that there would be a dose response effect of increased intake of omega-3 LC PUFAs, we did not find evidence for such dose effect on these outcomes. This may suggest that the threshold for an effect is reached by many studies, although it is more likely that the lack of a clear dose response effect reflects the heterogeneity between studies, the small number of studies reporting on any particular outcome, their varying duration, and the variations in relative amounts of EPA and DHA used particularly in the low-to-medium dose range. Many people do not meet omega-3 LC PUFA intake recommendations [116], and have low red blood cell omega-3 LC PUFA levels [117]. The doses

Table 6
Included studies of quadriceps maximal voluntary capacity (MVC).

Study first author and year	Intervention: Change in quadriceps/knee MVC, mean (SE)	Control: Change in quadriceps/knee MVC, mean (SE)	Weighting in the meta-analysis	Subgroup studied	Reported omega-3 PUFA dose (mg/day)	Bias risk	Ref.
Broekhuizen 2005	9 (21)	12 (24)	10.9%	COPD	400 mg STA, 760 mg GLA, 1200 mg ALA, 700 mg EPA, 340 mg DHA	Low	[109]
Hingley 2017	−4 (17)	−22 (19)	8.2%	Healthy	140 mg EPA, 560 mg DHA	High	[110]
Lewis 2015	27 (158)	6 (131)	8.9%	Healthy	375 mg EPA, 230 mg DPA, 510 mg DHA	Low	[111]
McGlory 2019	−33 (34)	−69 (35)	7.4%	Healthy	2970 mg EPA, 2030 mg DHA	Low	[112]
Mickleborough 2015	9.3 (19.7)	6.7 (20.9)	9.1%	Healthy	58 mg EPA, 44 mg DHA	Low	[113]
Nilsson 2020	9 (9.7)	7.9 (12.7)	9.1%	Healthy	1510 mg EPA, 950 mg DHA	Low	[103]
Ramos-Campo 2020	2.74 (13)	0.57 (16)	8.9%	Healthy	240 mg EPA, 2100 mg DHA	Low	[114]
Rodacki 2014	35.5 (7)	17 (7)	7.0%	Healthy	400 mg EPA, 300 mg DHA	High	[115]
Sugawara 2010	5 (1.4)	−0.6 (9.8)	8.8%	COPD	1200 mg PUFAs	High	[85]
VanDusseldorp 2020[a]	2G: −8.33 (63) 4G: −16.0 (52) 6G: 0.54 (68)	−19.5 (69)	2G: 7.21% 4G: 7.22% 6G: 7.19%	Healthy	2G: 800 mg EPA, 600 mg DHA 4G: 1600 mg EPA, 1200 mg DHA 6G: 2400 mg EPA, 1800 mg DHA	Low	[108]

[a] Three doses are reported for this study, 2G used 2 g fish oil, 4G used 4 g fish oil, 6G used 6 g fish oil.

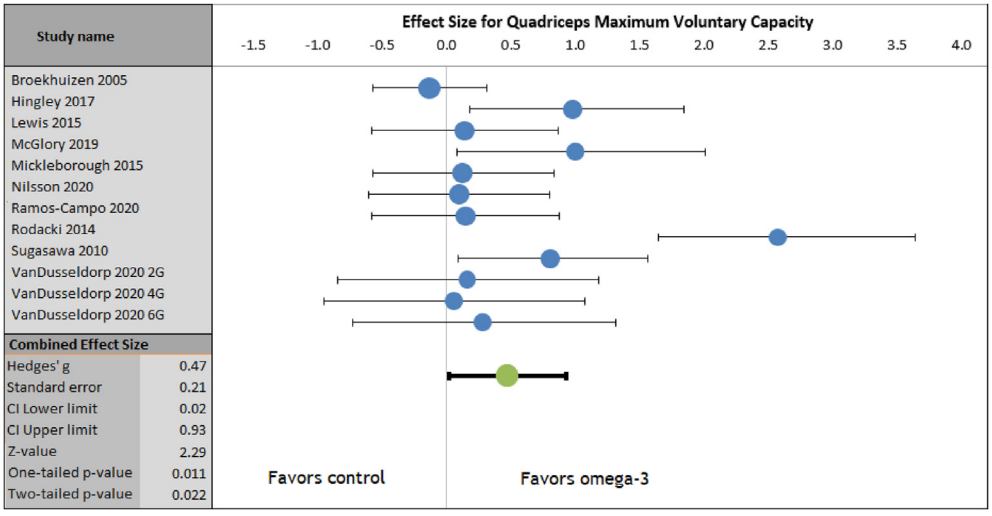

Fig. 6. Forest plot of random-effects meta-analysis on effect of omega-3 LC PUFA supplementation on quadriceps maximal voluntary contraction.

Table 7
Included studies of 1-repetition maximum (1RM) chest press.

Study first author and year	Intervention: Change in 1RM chest press, mean (SE)	Control: Change in 1RM chest press, mean (SE)	Weighting in the meta-analysis	Reported omega-3 PUFA dose (/day)	Bias risk	Ref.
Cornish 2018	15.8	15.4	25.1%	1980 mg EPA, 990 mg DHA	Low	[69]
Cornish 2009 (male)	23.5	20.8	25.8%	14,000 mg ALA	Low	[58]
Cornish 2009 (female)	14.6	15.4	25.1%			
Hayward 2016	3.33	3.80	24.1%	540 mg EPA, 360 mg DHA	High	[74]

used in most studies were generally much higher than amounts recommended for cardiovascular disease prevention; however, the lack of clear dose effect may indicate that a low-dose supplement is sufficient to improve lean body mass. Future trials should carefully assess the effect of different doses of omega-3 LC PUFAs in appropriately designed studies of ample sample size.

The meta-analyses did not identify an effect of omega-3 LC PUFAs on MAMC, handgrip strength, or 1RM chest press. The low number of subjects and studies hampered the ability to draw definitive conclusions about the effect of these relationships.

A systematic review and meta-analysis by Abdelhamid et al. published in 2019 on RCTs supplementing omega-3 or omega-6 PUFAs for at least 26 weeks did not find an effect of omega-3 LC PUFAs on muscle mass and functional outcomes such as handgrip strength [118]. Our finding of a lack of effect on handgrip strength agrees with this earlier analysis, but our finding of an effect on muscle mass differs. Nevertheless, once two outliers were removed, we found a positive effect for handgrip strength as well. The Abdelhamid meta-analysis included a much smaller number of studies for each endpoint than ours due to the inclusion requirement of a 26-week intervention, and the number of studies that met the inclusion criteria was low. We did not exclude studies according to length of supplementation, and therefore we were able to include a larger number of studies for each endpoint, increasing statistical power to find a significant association if one exists.

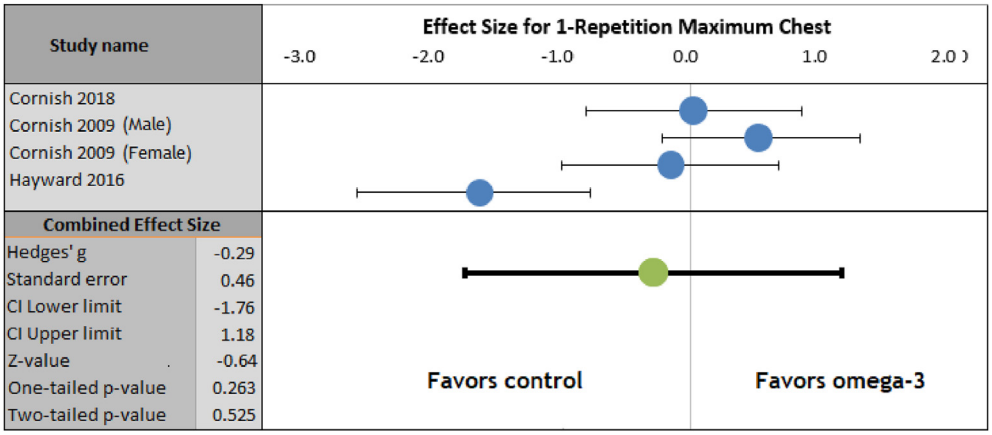

Fig. 7. Forest plot of random-effects meta-analysis on effect of omega-3 LC *PUFA supplementation* ation on 1-repetition maximum chest press.

With higher intakes, EPA and DHA increase in plasma over the course of days to weeks [119,120], reaching a new steady state fairly quickly. Incorporation into white and red blood cells takes longer and a new steady state is not reached for many weeks to months [120]. It is known that EPA and DHA are incorporated into skeletal muscle cells over a period of weeks [32,33]. Furthermore, the augmentation of muscle protein synthesis during a hyperaminoacidemic-hyperinsulinemic clamp found by Smith et al. occurred after 8 weeks of combined EPA and DHA supplementation [32,121], suggesting an anticipated shorter time frame for effects of supplemental omega-3 LC PUFAs. Therefore, it is plausible that significant effects of omega-3 LC PUFAs could be seen with a shorter supplementation time than 26 weeks, the threshold used in the previous meta-analysis. All but six studies in our analysis supplemented for more than 2 weeks, and median study supplementation duration was 56 days.

Another meta-analysis using studies performed in elderly subjects identified that omega-3 LC PUFA supplements increased muscle mass, whereas grip strength was not affected [122]. Our findings using a broader set of studies, including different patient groups, agree with these earlier findings in the elderly. Also, Huang et al. [122] did not find an effect of omega-3 LC PUFAs on 1RM leg strength and we did not find an effect on 1RM chest press. On the other hand, we found an improvement in quadriceps MVC; this seems to contrast with the lack of effect on 1RM leg strength, since these are both strength measurements in the same area of the body. Due to our broader inclusion criteria, we included more studies in our meta-analysis: we used data from 10 studies, compared to Huang et al. with 3 studies for this endpoint [122]. Including data from a larger number of studies may have allowed a significant effect to be seen for this parameter.

Our research has some limitations. Firstly, we conducted a meta-analysis based on published mean values. A more sensitive approach is to obtain individual subject data. This would also allow for the effect of inflammation markers or other potential confounders such as subject age, body weight or nutritional status on the muscle parameters to be taken into account. Secondly, as this was a scoping review, we wanted to include a wide range of studies to identify potential associations across different muscle-related endpoints. This meant that we did not restrict studies based on number of subjects, patient populations, type of supplement used, dose, muscle fatigue or disuse procedures, or duration of supplementation, all of which may affect outcomes. As we excluded few studies and attempted to include as many datapoints as possible, our results are less likely to be affected by selection or publication bias. On the other hand, the broad inclusion criteria may introduce greater variability and a lower likelihood of finding a significant result due to heterogeneity in study design and patient populations. Indeed, the Egger's regression statistic indicated that heterogeneity was significant for several outcomes.

The link between omega-3 LC PUFA supplementation and increases in muscle mass and strength is supported by mechanistic evidence [123]. Hyperinsulinemic clamp studies in adults of different age groups found an increase in muscle protein synthesis in the hyperglycemic state after supplementation with a combination of EPA and DHA given as ethyl esters [32,121], pointing to a stimulation of muscle protein anabolism by omega-3 LC PUFAs.

Even though we found that omega-3 LC PUFA supplementation could increase muscle mass and strength, the majority of studies were small and heterogeneity was high. There were also few studies conducted in sarcopenic patients, our population of interest, therefore the sample size would be too small. The bias assessment also indicated that many studies were at risk of bias due to a lack of blinding or randomization, or had deficits in reporting these study design elements. More conclusive results could be drawn from larger studies with rigorous control of sources of bias. Dosing ranges used across the studies were also large and an incorporation of different dosing levels into study design could also be beneficial, as discussed earlier. The use of standard procedures to assess outcomes would allow the results from different studies to be compared.

In summary, our scoping meta-analysis found that omega-3 LC PUFA supplementation had a positive effect on lean body mass, skeletal muscle mass and quadriceps MVC. These results could have implications for sarcopenia prevention. Further research will help to determine whether omega-3 LC PUFAs could improve functional outcomes in muscle-wasting disorders such as sarcopenia and cancer cachexia.

5. Conclusion

This scoping review and meta-analysis shows that omega-3 LC PUFA supplementation was associated with improvements in muscle mass and function, namely lean body mass, skeletal muscle mass and quadriceps MVC. However, the heterogeneity present in the studies and a wide range of doses used limit the applicability of the findings to sarcopenia prevention. Further research conducted in free-living elderly populations that investigate functional endpoints and mechanisms of action would advance the evidence base.

Declaration of competing interest

PCC acts as an advisor/consultant to DSM Nutritional Products, BASF AS, Cargill, Smartfish, Fresenius-Kabi, Nutrileads, Bayer Consumer Care and GSK Consumer Healthcare. BT and IW are employed by DSM Nutritional Products. JKB is a consultant for DSM Nutritional Products.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2021.10.011.

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Author contributions

Julia K. Bird: data curation, formal analysis, visualization, Roles/Writing - original draft. Philip C. Calder: Conceptualization, Writing - review & editing. Barbara Troesch: Conceptualization, Writing - review & editing, Project administration. Ines Warnke: Conceptualization, Writing - review & editing.

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