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Effects of n-3 EPA and DHA supplementation on fat free mass and physical performance in elderly. A systematic review and meta-analysis of randomized clinical trial

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ABSTRACT

The most studied n-3 polyunsaturated fatty acids (n-3 PUFAs) are eicosapentaenoic acid (EPA; 20:5n−3) and docosahexaenoic acid (DHA; 22:6n−3), and their intake seem to have a positive effect on skeletal muscle. This systematic review and meta-analysis aims to investigate the effect of n-3 EPA and DHA supplementation on fat free mass, and on different indexes of physical performance in the elderly. Eligible studies included RCT studies that investigated EPA and DHA intervention. Random-effects models have been used in order to estimate pooled effect sizes, the mean differences, and 95 % CIs. Findings from 14 studies (n = 2220 participants) lasting from 6 to 144 weeks have been summarized in this article. The meta-analyzed mean differences for random effects showed that daily n-3 EPA + DHA supplementation (from 0.7 g to 3.36 g) decreases the time of Time Up and Go (TUG) test of −0.28 s (CI 95 %−0.43, −0.13;). No statistically significant effects on physical performance indicators, such as 4-meter Walking Test, Chair Rise Test and Handgrip Strength, have been found. The fat free mass follows an improvement trend of +0.30 kg (CI 95 % -0.39, 0.99) but not statistically significant. N-3 EPA + DHA supplementation could be a promising strategy in order to enhance muscle quality and prevent or treat frailty.

1. Introduction

Aging is characterized by a decline of muscle mass, documented by decreased muscle strength and/or physical performance deterioration. Muscle weakness could be debilitating for the functional independence of elderly individuals, with increased risk of falls and disability (Krzymińska-Siemaszko et al., 2015). The muscle mass preservation and function is critical for the adverse outcomes prevention, such as physical frailty, mobility disability, and loss of independence in older adults (Smith et al., 2015).

The age-related muscle mass decline is due to many different factors, including hormonal changes, oxidative damage, chronic inflammation, neurodegenerative changes, drugs taken or the status of diseases. Even a lifestyle characterized by low physical activity, lack of mobility and an unbalanced diet, with inadequate amounts of calories and protein, that could contribute to muscle mass loss (Krzymińska-Siemaszko et al., 2015).

Diet and nutritional supplementation may represent a strategy to achieve maintenance of muscle mass (Rondanelli et al., 2015). In particular, the role of n-3 polyunsaturated fatty acids (n-3 PUFAs) for improving muscle mass and physical performance parameters was deeply investigated. N-3 PUFAs are a class of long chain fatty acids; Eicosapentaenoic acid (EPA; 20:5n–3) and docosahexaenoic acid (DHA; 22:6n–3) have been the most studied n-3 polyunsaturated fatty acids (PUFAs) and can be found in mostly fatty fish. Current recommendations for EPA and DHA intake for general health vary from country to country

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but are typically recommend from 250 to 500 mg/day as a combination of both fatty acids.

An adequate intake from foods in n-3 PUFAs (1.6 g/day and 1.1 g/day for men and women, respectively) resulted in a better total-body skeletal muscle mass (SMM) in 111 patients receiving standard haemodialysis treatment; on the contrary, a higher dietary ratio of n-6/n-3 PUFAs seemed to be associated with a reduced muscle mass (Wong et al., 2015). A recent review showed that fish consumption could be considered as "functional food" for elderly with sarcopenia. People should consume at least three servings weekly in order to have a minimum intake of 4–4.59 g daily of n-3 PUFAs (Rondanelli et al., 2020).

The positive effect of EPA and DHA intake on skeletal muscle was widely described by several researchers, conducted either in vitro (Jeromson et al., 2018; Kamolrat and Gray, 2013), in murine models (Kamolrat et al., 2013; You et al., 2010) or in humans (McGlory et al., 2019; Smith et al., 2015, 2011). The results from recent studies demonstrate that dietary supplementation with fish oil-derived n-3 PUFAs stimulates muscle protein synthesis and improves muscle mass and function in sedentary older adults, by mediating cell signaling and inflammation-related oxidative damage (Cruz-Jentoft et al., 2020; Gray and Mittendorfer, 2018).

Thus, there is a growing evidence that n-3 PUFAs have anabolic effects on skeletal muscle metabolism (Robinson et al., 2018). According to Di Girolamo et al., the anabolic effect of n-3 PUFAs seem to be independent from their anti-inflammatory properties (Di Girolamo et al., 2014). This action is at least partially mediated via increased activation of mTOR-p70s6k (mammalian target of rapamycin/ribosomal protein kinase S6) signaling pathways, influencing skeletal muscle mass, in particular when combined to mechanical stimulation (Smith et al., 2011).

The intake of EPA and DHA as dietary supplements appears to be a promising, safe and low-cost strategy in the prevention and management of sarcopenia, especially when combined with healthy dietary patterns and anabolic stimulus by physical activity (Di Girolamo et al., 2014; Dupont et al., 2019; Robinson et al., 2018).

Given this background, this systematic review and meta-analysis of randomized clinical trials aims to assess the effects in elderly individuals of n-3 EPA + DHAs supplementation on fat free mass and on functional parameters such as Time Up and Go (TUG) test, 4-meter Walking test, Chair Rise Time test and handgrip test.

2. Methods

The present systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (Moher et al., 2009).

It was performed through the following steps:

- formulation of the review question: "n-3 PUFAs supplementation and fat free mass or muscle mass and function";
- definition of participants: elderly women and men;
- search strategy for the identification of relevant intervention studies that included the effect of n-3 PUFAs supplementation;
- analysis of the data through the systematic review and meta-analysis;

2.1. Eligibility criteria

Potentially eligible studies were English written and reported EPA and DHA treatments in adult and elderly subjects. The search was not restricted for year of study publication or for the duration of follow-up of treatment. Supplementation was administered both in healthy subjects and in those with diagnosed diseases.

Eligible studies for inclusion in the systematic review were intervention studies in humans, targeting older adults. Eligible studies for meta-analysis were required to report baseline and follow-up values, the mean change (Δ-change) and relative standard deviation from baseline, and/or the mean difference among intervention groups vs. control group concerning body composition (fat free mass) and physical performance tests (TUG test, 4-meter Walking test, Chair Rise Time test and handgrip test).

Studies in which n-3 EPA + DHA supplementation were combined with other supplements, such as leucine, creatine, vitamin D, whey protein and/or calcium, were excluded.

2.2. Information sources and data items

To identify the studies that were eligible for this meta-analysis, we conducted a computerized search of clinical trials from (2010 to September 2020); in Ovid-MEDLINE EMBASE Web of Science. To minimize publication bias, the references cited in the text of the selected articles were also included in the search.

2.3. Search

We carried out an electronic search using primarily Medline, Google Scholar, Scopus, and the Science Citation Index databases, for studies published after September 2010, without any language restriction. The search was carried out as follows: "n-3 PUFAs" OR "omega-3" OR "EPA" OR "DHA" AND "muscle mass" OR "fat free mass" OR "sarcopenia" AND "elderly".

2.4. Study selection

After literature search and filter applications (humans; clinical trials), the eligible studies were selected through full-text revision. The selected studies were included in the systematic review; if applicable, the studies were included in the meta-analysis.

2.5. Data collection process

The data were extracted in duplicate from all reports and independently recorded on a piloted form by 2 authors. The reviewers were not blind to authorship. The following data were extracted from each study: (1) patient characteristics (ie, mean age, country, and inclusion and exclusion criteria); (2) intervention characteristics (ie, daily treatment dose and administration time); (3) control characteristics (ie, placebo

type, daily dose, and administration time); and (4) outcome measures. Differences among reviewers related to data extraction were resolved by discussion, and a consensus was reached.

2.6. Risk of bias in individual studies

The risk of bias of each study was assessed using the Cochrane Collaboration Risk of Bias tool (Higgins et al., 2011) and considering as factors contributing to the study quality the generation of the allocation sequence, the allocation concealment, the blinding of outcome data, the presence of incomplete data and the selective reporting. These factors were classified as low risk of bias, high risk of bias, or unclear risk of bias. Studies with a low risk of bias for at least three items were held as good; studies with a low risk of bias for at least two items were considered as fair, and studies with a low risk for no item or only for one item were regarded as poor.

2.7. Summary measures

The outcomes considered were fat free mass and functional parameters such as Time Up and Go (TUG) test, 4-meter Walking test, Chair Rise Time test and handgrip test. The outcomes were expressed as mean values.

2.8. Risk of bias across studies

The studies selected were critically appraised using "risk of bias" based on the study design. According to the recommendations outlined in the Cochrane Handbook, the following criteria were included (Cumpston et al., 2019): "random sequence generation," "allocation concealment," "blinding of participants," "incomplete outcome data," "selective outcome reporting," and "other bias." We assigned a judgment related to the risk of bias by answering a prespecified question about the adequacy of the study in relation to the entry, such that a judgment of "low" indicated a low risk of bias, "high" indicated a high risk of bias, and "unclear" indicated an unclear or unknown risk of bias. Two authors independently assessed bias, and any disagreement or misunderstanding was resolved by discussion until a consensus was reached

3. Results

3.1. Studies characteristics

The literature search retrieved 365 articles through the database search and, after filter applications (humans; clinical trials), 29 papers were selected through full-text revision. 15 studies were excluded. The 14 remaining studies were selected for the current systematic review. Of these 14, 7 studies were included in a meta-analysis. Fig. 1 shows the study selection procedure.

Studies included (Table 1) were all randomized clinical trials (RCT). Intervention period lasted from a minimum of 6 weeks to a maximum of 144 weeks. The 14 studies included a total of 2220 subjects both women and men. 10 studies (Da Boit et al., 2017; Dasarathy et al., 2015; Deger et al., 2016; Gharekhani et al., 2014; Krzymińska-Siemaszko et al., 2015; Murphy et al., 2011; Rolland et al., 2019; Smith et al., 2015, 2011; Wang et al., 2017) considered a cohort of men and women (2062 subjects); 3 studies (Logan and Spriet, 2015; Rodacki et al., 2012; Tardivo et al., 2015) considered a cohort of only women (117 subjects) and one study considered only men for a total of 23 subjects (Cornish et al., 2018).

4 studies (Cornish et al., 2018; Rodacki et al., 2012; Smith et al., 2015, 2011) involved healthy older subjects (total of 132 subjects); three studies (Krzymińska-Siemaszko et al., 2015; Logan and Spriet, 2015; Rolland et al., 2019) considered community-dwelling elderly individuals (1753 subjects); other studies considered patients undergoing hemodialysis (65 subjects) (Deger et al., 2016; Gharekhani et al., 2014), postmenopausal woman with metabolic syndrome (MetS) (63 subjects) (Tardivo et al., 2015), type 2 diabetic patients with abdominal obesity (99 subjects) (Wang et al., 2017) or with nonalcoholic steatohepatitis (NASH) (Dasarathy et al., 2015), patients with non-small cell lung cancer (NSCLC) who were naive to chemotherapy (40 subjects) (Murphy

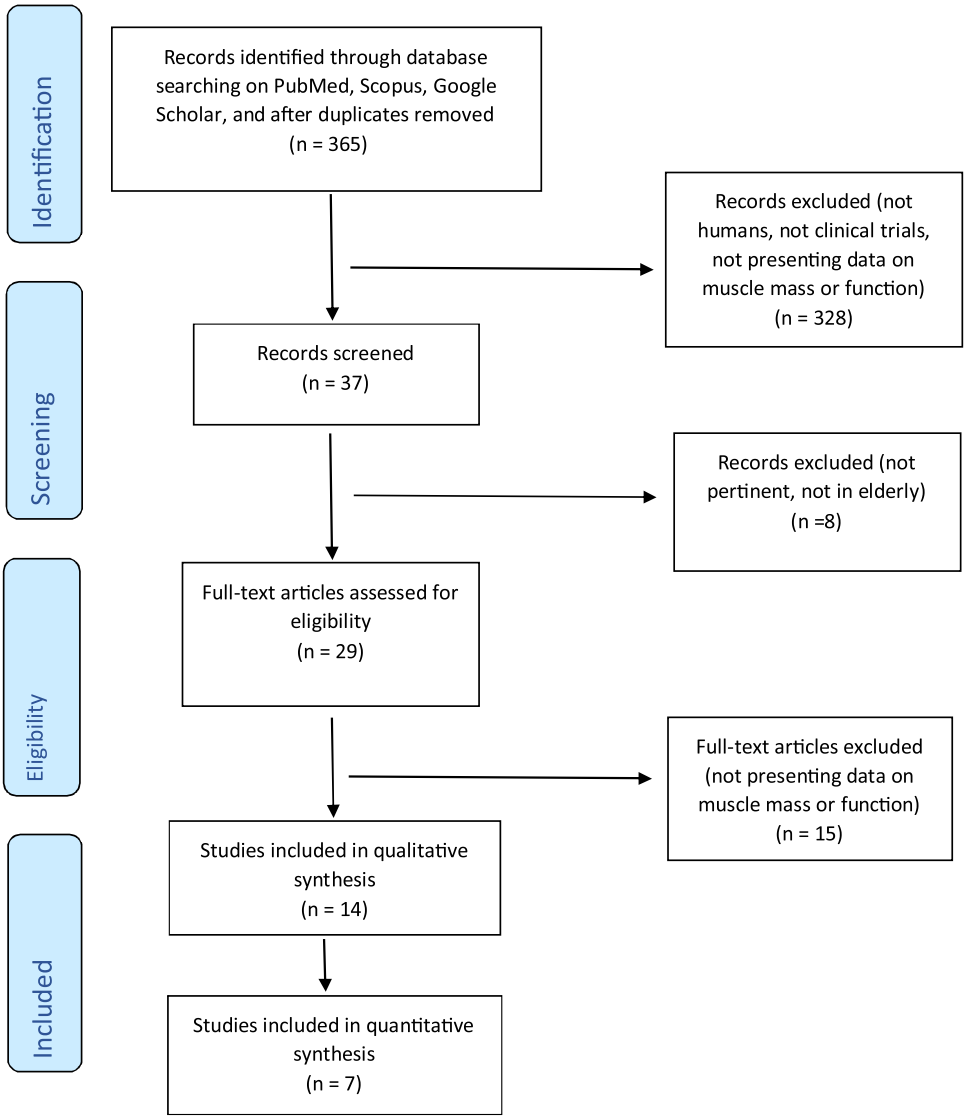

Fig. 1. Flow diagram.

Table 1
Studies included in the systematic review.

First author, year	Study design	Setting	Total daily amount of n-3 PUFAs	Intervention: Number of subjects (M, F;); type of intervention; Age (mean ± ds) BMI (mean ± ds)	Parallel treatments: Number of subjects (M, F); type of treatments; Age (mean ± ds) BMI (mean ± ds)	Duration of the intervention	Outcomes of interest	Results about body composition / physical performance
(Cornish et al., 2018)	RCT	Older men aged ≥ 65 y old	3 g n-3 PUFAs (1.98 g EPA, 0.99 g DHA)	N = 11 (11 M;) n-3 PUFAs + resistance training 3 times/week; Age: 71.4 ± 6.2 BMI: 27.5 ± 4.2	N = 12 (12 M) 3 g of a n- 3-6-9 PUFAs blend + resistance training3 times/week; Age: 70.9 ± 5.0 BMI: 27.7 ± 3.5	12 weeks	Muscle mass, muscle strength and functional ability	Decrease of percent body fat, increase of lean tissue mass, chest press and leg press strength, improvement of timed-up-and-go and 6-minute walk distance due to resistance exercise. n-3 didn't enhance these parameters.
(Da Boit et al., 2017)	RCT	Healthy older adults	3 g n-3 PUFAs (2.1 g EPA, 0.6 g DHA)	N = 27 (14 M, 13 F) n-3 PUFAs + resistance exercise training twice weekly; Age: 69.8 ± 4.0 for male; 70.5 ± 3.9 for female BMI: 25.1 ± 5.3 for male; 25.9 ± 4.9 for female	N = 23 (13 M, 10 F) 3 g safflower oil + resistance exercise training twice weekly; Age: 71.5 ± 5.1 for male; 70.9 ± 2.6 for female BMI: 24.7 ± 2.6 for male; 25.8 ± 4.6 for female	18 weeks	Muscle mass and function; sex difference	Men: similar increase in muscle quality in the intervention and placebo groups. Women: greater increase in the intervention group
(Dasarathy et al., 2015)	Prospective, double-blind RCT	Diabetic adults with nonalcoholic steatohepatitis (NASH)	3.6 g n-3 PUFAs (2.16 g EPA and 1.44 g DHA)	N = 18 (6 M, 12 F) n-3 PUFAs; Age: 51.5 ± 6.9 BMI: 34.8 ± 4.6	N = 19 (2 M, 17 F) corn oil; Age: 49.8 ± 12.1 BMI: 35.7 ± 7.0	48 weeks	Body composition	There was no significant change in body weight or in any of the measures of body composition in either of the groups during the course of the study
(Deger et al., 2016)	Double-blind RCT	hemodialysis (HD) patients with systemic inflammation	2.9 g n-3 PUFAs (1.93 g EPA, 0.96 g DHA)	N = 11 (9 M, 2 F) n-3 PUFAs; Age: 53.0 ± 9.0 BMI: 28.0 ± 7.0	N = 9 (8 F, 1 M) Placebo (not specified); Age: 53.0 ± 13.0 BMI: 35.0 ± 9.0	12 weeks	Change in forearm muscle protein breakdown	Attenuation of forearm muscle protein breakdown but did not influence skeletal muscle protein synthesis, skeletal muscle net protein balance or any component of the whole-body protein balance.
(Gharekhani et al., 2014)	Single-blind RCT	HD treatment for at least 3 months	1.8 g n-3 PUFAs (1080 mg EPA, 720 mg DHA)	N = 25 (13 M, 12 F) n-3 PUFAs; Age: 56.8 ± 13.1 BMI: 23.8 ± 3.82	N = 20 (12 M, 8 F) Paraffin oil; Age: 57.2 ± 15.2 BMI: 23.3 ± 3.24	16 weeks	Mid-arm muscle circumference, dry body weight (after HD treatment), and BMI	Supplementation did not produce significant changes in nutrition indices, including BMI, dry body weight, MAC.
(Krzymińska-Siemaszko et al., 2015)	RCT	community-dwelling elderly aged ≥60 y old, with decreased muscle mass or at risk of low muscle mass	1.3 g n-3 PUFAs (660 mg EPA, 440 mg DHA +200 mg other n-3 PUFAs fatty acids)	N = 30 (11 M, 19 F) n-3 PUFAs; Age: 75.0 ± 8.23 BMI: 23.4 ± 3.14	N = 20 (4 M, 6 F) 1 drop of vitamin E solution (11 mg); Age: 74.9 ± 7.49 BMI: 22.9 ± 3.39	12 weeks	Body composition, muscle strength and physical performance	No statistically significant differences in the analysed components of body composition, in muscle strength nor in physical performance (4-meter Walking Test and Go test) in any group.
(Logan and Spriet, 2015)	RCT	healthy, community-	3 g n-3 PUFAs (2	N = 12 (12 F) n-3 PUFAs;	N = 12 (12 F) 3 g olive oil;	12 weeks	Body composition,	Significantly increase of lean body mass

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Table 1 (*continued*)

First author, year	Study design	Setting	Total daily amount of n-3 PUFAs	Intervention: Number of subjects (M, F;); type of intervention; Age (mean ± ds) BMI (mean ± ds)	Parallel treatments: Number of subjects (M, F); type of treatments; Age (mean ± ds) BMI (mean ± ds)	Duration of the intervention	Outcomes of interest	Results about body composition / physical performance
		dwelling older women aged 60−76 years old	g EPA, 1 g DHA)	Age: 66.0 ± 1.0	BMI: 26.3 ± 1.0		strength and physical function	and physical function (decreasing Timed Get Up and Go Test).
(Murphy et al., 2011)	Open-label study with control group	patients with nonsmall cell lung cancer (NSCLC) naïve to chemotherapy	2.2 g n-3 PUFAs (EPA)	BMI: 27.9 ± 1.3 69 % of patients in the FO group maintained or gained muscle compared with 29 % of patients in the SOC group. Four patients in the SOC group became sarcopenic over the course of chemotherapy whereas no patients in the FO group became sarcopenic.	N = 16 (9 M, 7 F) n-3 PUFA; Age: 63.0 ± 2.1	N = 24 (12 M, 12 F) Standar of care (SOC) Age: 64.0 ± 1.8	6 weeks	Body composition against SOC during chemotherapy
BMI: 26.2 ± 1.1	BMI: 27.3 ± 1.2							
(Rodacki et al., 2012)	RCT	Healthy older women	0.7 g n-3 PUFAs (0.4 g EPA and 0.3 g DHA)	Group 1 (n = 15): 2 g/die Fish oil + 90 days of strength training. Group 2 (n = 15):fish oil 60 days before strength training; Age: 63.8 ± 1.4 for Group 1; 63.3 ± 2.0 for Group 2 BMI: 27.7 ± 1.3 for Group 1; 25.7 ± 1.1 for Group 2	Group 3 (N = 15): strength training; Age: 64.9 ± 1.0 BMI: 25.4 ± 1.6	90 or 150 days	Muscle strength and functional capacity	FO supplementation along with strength training improved the response of the neuromuscular system. However, supplementation with FO for an additional period pretraining did not cause any additional effects.
(Rolland et al., 2019)	RCT	non-demented, older, and community-dwelling, older people aged ≥ 70 y old	1.025 g n-3 PUFAs (800 mg DHA, 225 mg EPA)	Group 1 (N = 422): n-3 PUFAs Group 2 (N = 417): n-3 PUFAs + the multidomain intervention; Age: 65.7 ± 4.7 for Group 1; 75.5 ± 4.5 for Group 2 BMI: 26.3 ± 4.1 for Group 1; 26.2 ± 4.3 for Group 2	Group 3 (N = 420): placebo + the multidomain intervention; Group 4 (N = 420): placebo alone; Age: 75.1 ± 4.2 for Group 3; 75.1 ± 4.4 for Group 4BMI: 26.0 ± 4.0 for Group 3; 26.0 ± 3.9 for Group 4	144 weeks	Muscle strength (chair stand test, handgrip), walking speed (performed on a 4-mcourse) and balance tests	No significant differences at 3-year follow-up were observed in the repeated chair stand test score and handgrip test between any of the three intervention groups and the placebo group.
(Smith et al., 2011)	RCT	Healthy older adults aged ≥65 y-old	3.36 g n-3 PUFAs (1.86 g	N = 8 (5 M, 3 F) n-3 PUFAs; Age: 71.0 ± 1.0	N = 7 (5 M, 2 F) Corn oil; Age: 71.0 ± 2.0	8 weeks	Rate of muscle protein synthesis and the anabolic	Supplementation increases muscle anabolic signalling

(*continued on next page*)

Table 1 (*continued*)

First author, year	Study design	Setting	Total daily amount of n-3 PUFAs	Intervention: Number of subjects (M, F;); type of intervention; Age (mean ± ds) BMI (mean ± ds)	Parallel treatments: Number of subjects (M, F); type of treatments; Age (mean ± ds) BMI (mean ± ds)	Duration of the intervention	Outcomes of interest	Results about body composition / physical performance
			EPA, 1.5 g DHA)	BMI: 25.6 ± 1.0	BMI: 25.7 ± 1.7		signalling cascade	activity and the insulin/amino acid–mediated increase in muscle protein synthesis
(Smith et al., 2015)	Double-blind RCT	Healthy 60−85-y-old men and women	3.36 g n-3 PUFAs (1.86 g EPA, 1.5 g DHA)	N = 29 (10 M, 19 F) n-3 PUFAs; Age: 68.0 ± 5.0 BMI: 26.1 ± 4.1	N = 20 (5 M, 10 F) Corn oil; Age: 69.0 ± 7.0 BMI: 25.3 ± 4.2	24 weeks	Thigh muscle volume, handgrip strength, one repetition maximum (1-RM) muscle strength, body fat mass	n–3 PUFA therapy increased thigh muscle volume, and 1-RM muscle strength, but didn't affect body weight, total-body fat mass, or the intermuscular fat content
(Tardivo et al., 2015)	Prospective RCT	Postmenopausal woman with metabolic syndrome (aged 45−70 y-old	0.9 g n-3 PUFAs (0.54 g EPA, 0.36 g DHA)	N = 33 (33 F) Diet + n-3 PUFAs; Age: 55.1 ± 6.6 BMI: 32.8 ± 4.7	N = 30 (30 F) Diet alone; Age: 55.0 ± 7.3 BMI: 32.0 ± 4.6	24 weeks	Body composition, muscle mass (%)	Significant reduction in BMI and waist circumference in both groups without significant changes in body fat or muscle mass.
(Wang et al., 2017)	Double-blind RCT	type 2 diabetic patients with abdominal obesity	2.4 g n-3 PUFAs (1.34 g EPA and 1.07 g DHA)	N = 49 (15 M, 34 F) n-3 PUFAs; Age: 64.6 ± 5.5 BMI: 25.4 ± 2.6	N = 50 (20 M, 30 F) Corn oil; Age: 66.3 ± 5.1 BMI: 25.9 ± 2.8	24 weeks	Body composition	No significantly changes in body composition during the intervention

et al., 2011).

The intervention group was settled up to consume n-3 PUFAs capsules, from 0.7 g to 3.36 g daily. The control group received placebo identical-looking pills, containing mainly corn or olive oil. Mean of age was 65.53 ± 5.0 and 65.90 ± 6.22 years for intervention and placebo group, respectively; mean of body mass index (BMI) was 26.97 ± 3.44 kg/m^2 and 27.19 ± 3.64 kg/m^2 for intervention group and placebo group, respectively.

3.2. Effects of n-3 EPA and DHA supplementation on fat free mass

A dosage of n-3 EPA + DHA from 1 g to 3 g, provided as fish oil capsules, was considered in various studies. Cornish et al. showed the effectiveness of 3.0 g/die of EPA + DHA (1.98 g of EPA and 0.99 g of DHA) supplementation, combined with progressive resistance training to improve body composition, in healthy older men (aged ≥ 65 years old). The results of this study revealed a body fat decreased from 31.9 % to 31.1 %), as lean tissue mass increased from 55.5–56.1 kg. Another study (Da Boit et al., 2017) evaluated the gender effects of 3 g/die of n-3 PUFAs supplementation on resistance exercise training for increasing in muscle mass in healthy older men and women, showing no differences between groups. (Da Boit et al., 2017).

In the study of Smith et al. (Smith et al., 2011), a daily dose of 3.36 g of EPA + DHA fatty acid supplementation (1.86 g EPA, 1.5 g DHA), for 8 weeks, showed an increase of muscle anabolic signalling activity and an insulin/amino acid–mediated increase in muscle protein synthesis above basal, postabsorptive values in healthy older adults aged ≥ 65 years old (Smith et al., 2011). The same dosage did not significantly affect body weight, total-body fat mass, or the intermuscular fat content, but increased thigh muscle volume (Smith et al., 2015).

A lower dosage of 2.4 g/die n-3 PUFAs (1.34 g EPA and 1.07 g DHA), was administered by Wang et al. to type 2 diabetic patients with abdominal obesity without affect body composition during the intervention (Wang et al., 2017).

A dosage of 2.2 g/die of n-3 PUFAs (EPA) was chosen by Murphy et al. to examine the effect of nutritional intervention with fish oil on weight and body composition against standard of care (SOC) during the course of chemotherapy in patients with non-small cell lung cancer showing maintenance of weight, muscle mass, and muscle quality compared with patients receiving SOC. 69 % of patients receiving FO maintained or gained weight (0–6.7 kg) during chemotherapy, while in the SOC group, only 29 % of patients maintained or gained weight (0–4.6 kg) (Murphy et al., 2011).

Krzymińska-Siemaszko et al. conducted a study in community-dwelling elderly individuals (aged ≥ 60 years old), with decreased muscle mass or at risk of low muscle mass. The intervention group was administered two capsules daily containing 660 mg EPA, 440 mg DHA +200 mg other n-3 PUFAs +10 mg of vitamin E during or immediately after meals, for a total daily amount of 1.3 g of n-3 PUFA, for 12 weeks. Using this dosage, no statistically significant differences were observed in the analysed components of body composition in the intervention or placebo group (Krzymińska-Siemaszko et al., 2015).

2 studies (Deger et al., 2016; Gharekhani et al., 2014) were conducted in patients undergoing hemodialysis (HD) with supplementation of 1080 mg EPA and 720 mg DHA for 16 weeks. The results showed not-significant changes in nutrition indices, including BMI, dry body weight, and mid-arm muscle circumference (MAC) (Gharekhani et al., 2014).

On a second study, a higher dose of 1.93 g EPA, 0.96 g DHA, administered for 12 weeks, was associated with attenuation of forearm muscle protein breakdown in patients with systemic inflammation, but did not influence skeletal muscle protein synthesis, skeletal muscle net protein balance. or any component of the whole-body protein balance (Deger et al., 2016).

A smaller dosage of 540 mg EPA, 360 mg DHA was investigated by Tardivo et al. (Tardivo et al., 2015) in postmenopausal women with metabolic syndrome (MetS), aged 45−70 years old. Supplementation showed a significant reduction in BMI and waist circumference in both groups without significant changes in body fat or muscle mass (Tardivo et al., 2015).

3.3. Effects of n-3 PUFAs supplementation on physical performance

In the study of Cornish et al. (Cornish et al., 2018), subjects treated with n-3 PUFAs improved chest press and leg press strength (increase from 50.5–60.1 kg and from 110.1–150.4 kg, respectively) and timed-up-and-go test (decrease from 6.13 to 5.73 s). However, these improvements in physical performance, similar to those on body composition, were to be attributed to progressive resistance training and not to n-3 PUFAs supplementation exclusively (Cornish et al., 2018).

The study by Da Boit et al. showed that in women who received 2.7 g/die of n-3 PUFAs (2.1 g EPA and 0.6 g DHA) for 18 weeks, the maximal isometric torque was greater (34.3 % ± 17.8 %) than in the placebo group (15.8 % ± 10.6 %) (Da Boit et al., 2017). According to Smith et al., 24 weeks of 3.36 g/die n-3 PUFAs (1.86 g EPA, 1.5 g DHA) supplementation increased thigh muscle volume and one repetition maximum muscle strength (Smith et al., 2015).

In the study of Krzymińska-Siemaszko et al. (Krzymińska-Siemaszko et al., 2015), the administration of daily amounts of 1.3 g of n-3 PUFA, for 12 weeks in community-dwelling elderly individuals with decreased muscle mass or at risk of low muscle mass, didn't produce a statistically-significant improvement in muscle strength nor in physical performance (4-meter Walking Test and Go test) (Krzymińska-Siemaszko et al., 2015). Accordingly, even Rolland et al. (Rolland et al., 2019) observed no significant differences in muscle strength and physical performance, using a similar low dose of supplementation in non-demented, community-dwelling, older people (aged ≥ 70 years old). In particular, 1.025 g/die n-3 PUFAs (800 mg DHA, 225 mg EPA), combined or not with multi-domain intervention (group sessions integrating advice for physical activity, nutrition, cognitive training, and preventive consultations), was administered for 36 months. No significant differences were observed at 3-year follow-up in the repeated chair stand test score and handgrip test between any of the intervention groups and the placebo group (Rolland et al., 2019).

On the contrary, an improvement of physical function (decreasing Timed Get Up and Go Test) was observed by Logan and Spriet (Logan and Spriet, 2015) in a study conducted in healthy, community-dwelling older (aged 60−76 years old) administered with 3 g/die of n-3 PUFAs (2 g EPA, 1 g DHA), for 12 weeks. Even the study of Rodacki et al. (Rodacki et al., 2012) demonstrated that the inclusion of a daily dose of 0.4 g EPA and 0.3 g DHA supplementation in a program of strength training improved muscle strength and functional capacity in elderly women, more than exercise training alone.

3.4. Meta-analyzed data

The meta-analyzed MD (mean differences for random effects) showed a not statistically significant increase in fat free mass (0.30 kg; CI 95 %: -0.39 to 0.99; p = 0.40) (Fig. 2). The forest plot included a total of 233 subjects (120 in the intervention group and 113 in the control group). The heterogeneity chi square test is not statistically significant (P = 0.60), and it showed that there is no variation in study outcomes.

Concerning physical performance parameters, the meta-analyzed MD showed a statistically significant improvement in TUG test (-0.28 s; CI 95 %: -0.43 to -0.13; p = 0.0003) (Fig. 3). The forest plot included a total of 92 subjects (49 in the intervention group and 42 in the control group). The heterogeneity chi square test is not statistically significant at the level of P = 0.63 and it showed that there is no variation in study outcomes.

Regarding others physical performance parameters, the meta-analyzed MD showed a not statistically significant improvement in TUG test (-0.06 s; CI 95 %: −0.20 to 0.08; p = 0.40) (Fig. 4). The forest plot included a total of 940 subjects (476 in the intervention group and 464 in the control group). The heterogeneity chi square test is not statistically significant (P = 0.77) and it showed that there is no variation in study outcomes.

Furthermore, the meta-analyzed MD showed a not statistically significant improvement in Chair Rise Time test (-0.17 s; CI 95 %: −0.97 to 0.63; p = 0.67) (Fig. 5). The forest plot included a total of 890 subjects (447 in the intervention group and 443 in the control group). The heterogeneity chi square test is not statistically significant (P = 0.62) and it showed that there is no variation in study outcomes.

Finally, concerning strength, the meta-analyzed MD showed a not statistically significant decrease in handgrip test (-0.04 kg; CI 95 %: −1.31 to 1.24; p = 0.96) (Fig. 6). The forest plot included a total of 915 subjects (464 in the intervention group and 451 in the control group). The heterogeneity chi square test is p < 0.05 and it showed that there is variation in study outcomes.

3.5. Analysis of publication bias

There was no evidence of publication bias across the randomized controlled trials included in this review as showed by Egger and in Table 2.

4. Discussion

This review showed that supplementation, from 6 to 144 weeks of n-3 PUFAs, with a daily dose ranging from 0.7 g to 3.36 g, improved TUG test in a population of middle-aged and elderly adults.

The results concerning the physical performance (4-meter Walking test and Chair Rise Time test), strength (handgrip) test and body composition (fat free mass) were not statistically significant.

The lack of significant improvements in the other investigated variables was probably due to the limited number of studies considered. In addition, the study population was not homogeneous and patients had no diagnosis of sarcopenia.

Similar to the current findings, a recent review that assessed the efficacy of increasing dietary n-3 PUFAs, n-6 PUFAs or mixed total PUFAs on musculoskeletal outcomes and functional status, in adults aged 40 years or older, found no significant modification on fat free (skeletal) muscle mass (Abdelhamid et al., 2019). Conversely, according to

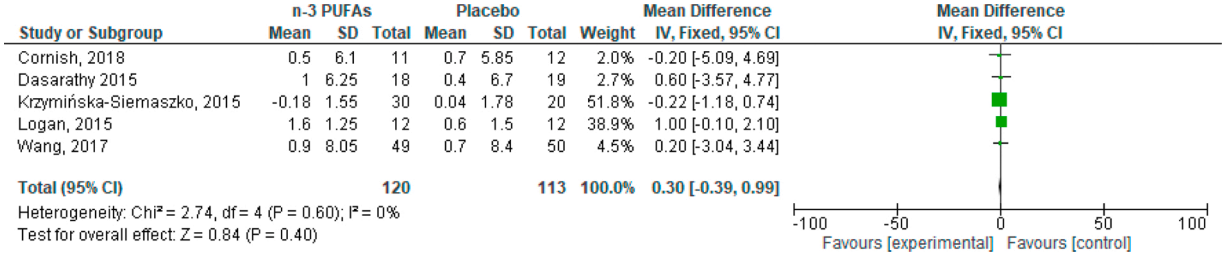

Fig. 2. Forest plot for randomized controlled trials of n-3 EPA + DHA supplementation on fat free mass (kg) subgroup meta-analysis (n = 223).

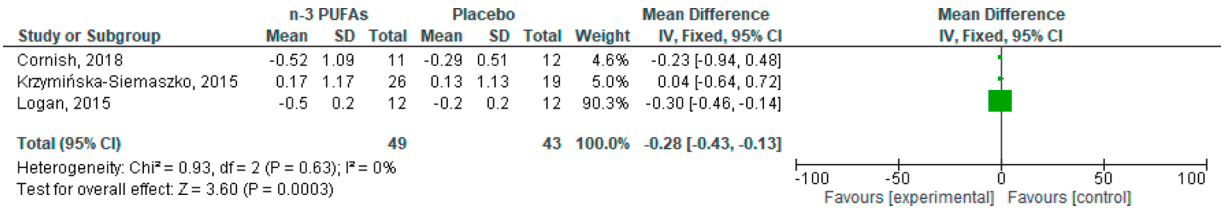

Fig. 3. Forest plot for randomized controlled trials of n-3 EPA + DHA supplementation on Time Up and Go test (s) subgroup meta-analysis (n = 92).

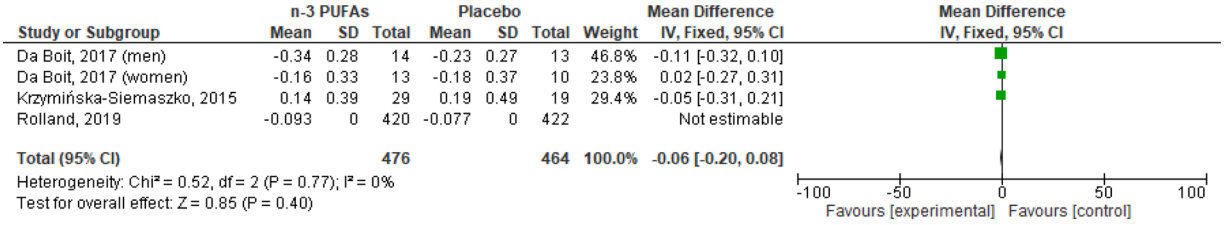

Fig. 4. Forest plots for randomized controlled trials of n-3 EPA + DHA supplementation on 4-meter Walking test (s) subgroup meta-analysis (n = 940).

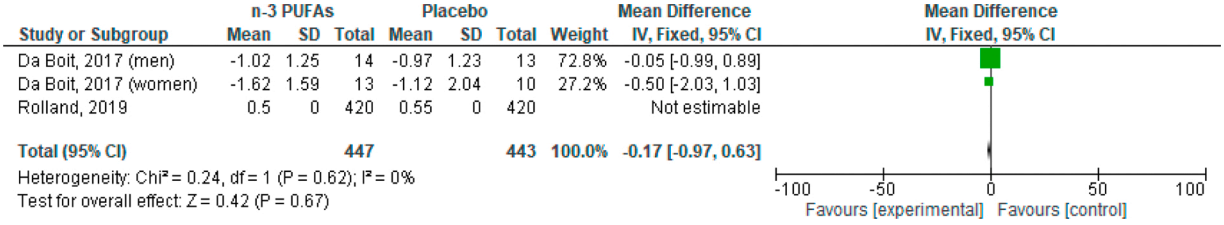

Fig. 5. Forest plot for randomized controlled trials of n-3 EPA + DHA supplementation on Chair Rise Time test (s) subgroup meta-analysis (n = 890).

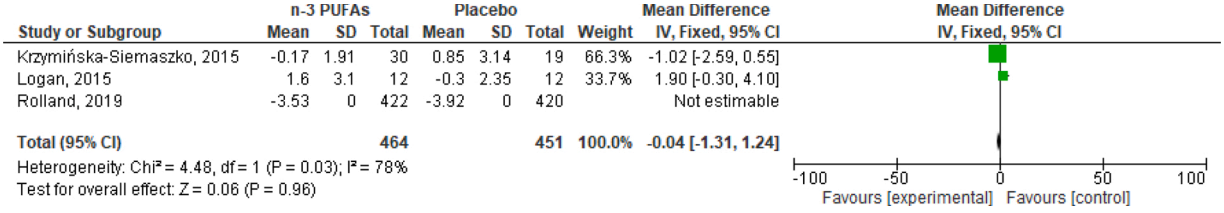

Fig. 6. Forest plot for randomized controlled trials of n-3 EPA + DHA supplementation on Handgrip test (s) subgroup meta-analysis (n = 915).

Table 2
Risk of bias for studies included in the meta-analysis according to the Cochrane Risk of Bias Tool[a].

First author, year	Random-sequence generation	Allocation concealment	Participant-personnel blinding	Outcome-assessment blinding	Incomplete outcome data	Selective reporting	Other bias
Cornish et al., 2018	Fair	Fair	Fair	Unclear	Unclear	Fair	Fair
Da Boit et al., 2017	Fair	Fair	Fair	Unclear	Unclear	Fair	Fair
Dasarathy et al., 2015	Fair	Fair	Fair	Unclear	Unclear	Fair	Fair
Krzymińska-Siemaszko et al., 2015	Fair	Fair	Fair	Unclear	Unclear	Fair	Fair
Logan and Spriet, 2015	Fair	Fair	Fair	Unclear	Unclear	Fair	Fair
Rolland et al., 2019	Fair	Fair	Fair	Unclear	Unclear	Fair	Fair
Wang et al. (2017)	Fair	Fair	Fair	Unclear	Unclear	Fair	Fair

[a] Bias designations by study criteria are indicated by 7 domains with categories including low risk if negative aspects of the study design were not likely to influence the study findings, high risk if the study design was likely to influence the study findings, or unclear risk if high or low risk could not be assigned because of a lack of evidence.

another recent review by Tessier et al., supplementation of EPA + DHA doses of around 3 g/die had a positive impact on physical performance, muscle strength, and muscle mass in older adults, and this minimal amount may be required for beneficial effects when provided alone, i.e., not combined with other nutrients (Tessier and Chevalier, 2018).

The exact mechanism of the anabolic action of n-3 PUFAs on skeletal muscle is still debated. However, the literature describes some hypothetic mechanisms: reduction in pro-inflammatory cytokines (anti-inflammatory effects), the stimulation of muscle protein synthesis via the mTOR-p70S6k signaling pathway activation, improvement of insulin sensitivity, and diminution of mitochondrial reactive oxygen species emission (Dupont et al., 2019).

Another point of interest regards the daily dose of n-3 PUFAs supplementation. In fact, the proper dose n-3 PUFAs may represent a useful therapeutic strategy to overcome anabolic resistance for treating sarcopenia (Stella et al., 2018). In the elderly, high doses of n-3 PUFAs equal/higher than 1650 mg daily resulted in increased muscle mass, function, and whole body energetics (Logan and Spriet, 2015; Smith et al., 2015). In a recent review, it was observed that dosages ranging from 2 to 5 g/die for a minimum of four weeks resulted in improvements in anabolic signaling efficience and muscle strength outcomes (Tachtsis et al., 2018).

Another important concern is that many studies included in the current review considered EPA and DHA supplementation concurrent with physical activity, mainly resistance exercise training, so it's not clear what the positive effect on muscle mass was due to (Cornish et al., 2018; Da Boit et al., 2017; McDonald et al., 2014; Rodacki et al., 2012). In fact, in addition to diet and supplementation, it's well known that physical exercise has a positive effect on the individual components of sarcopenia, such as muscle strength (Peterson et al., 2010), muscle quality and quantity (Tsuzuku et al., 2018) and physical performance (Jadczak et al., 2018).

Some studies (Cornish et al., 2018; Da Boit et al., 2017; Rodacki et al., 2012; Rolland et al., 2019) included in the current review considered physical training along with n-3 PUFAs supplementation, both in intervention and placebo groups. In these cases, the authors observed that n-3 PUFAs did not improve the parameters investigated, such as body composition evaluation and physical performance tests.

It is important to note the doses of n-3 supplementation and the times and the types of physical activity performed were different in these studies.

Furthermore, an investigation by Strandberg et al., conducted in healthy active older women, has revealed that the gain in skeletal muscle mass occurs only when resistance training is combined with a healthy diet, in particular when n-6/n-3 PUFAs ratio was <2 (Strandberg et al., 2015).

Despite the fact that results from considered studies are contrasting, it will be important to assess the proper dose of n-3 EPA + DHA that could potentially be used as therapeutic strategy to overcome anabolic resistance and to combat muscle weakness in elderly.

The strength of this meta-analysis is represented, firstly, by the homogeneity between the studies considered for each variable, according to Chi^2 Heterogeneity test, except for the handgrip test subgroup meta-analysis. Secondly, there is no evidence of publication bias across the randomized controlled trials included in the meta-analysis according to the Cochrane Risk of Bias Tool.

The main limitation of the present investigation is represented by the heterogenicity of the method, and tools used for body composition evaluation, in the considered studies. In fact, in the meta-analyzed data of fat free mass, three studies (Krzymińska-Siemaszko et al., 2015; Logan and Spriet, 2015; Wang et al., 2017) used bioelectrical impedance analysis and one study (Cornish et al., 2018) used dual-energy x-ray absorptiometry (DXA).

Studies about the effects of EPA and DHA supplementation in humans are limited. Further investigations and high quality RCTs are needed to better investigate the n-3 PUFAs supplementation effects on body composition, in particular on fat free mass, and physical performance in the elderly, especially in those presenting low muscle mass or at risk of sarcopenia. Despite the positive role of physical activity on fat free mass being well recognized, the relationship between n-3 PUFAs supplementation and muscle mass and function is still not clear, especially when dietary supplementation is combined with resistance training, as suggested by the results of some studies (Cornish et al., 2018; Da Boit et al., 2017; Rodacki et al., 2012; Rolland et al., 2019).

In conclusion, this systematic review and meta-analysis found a significant improvement in TUG test, so n-3 EPA + DHA supplementation could be a promising strategy in order to enhance muscle quality and to prevent and treat sarcopenia, even if further research considering n-3 EPA + DHA supplementation in association with physical activity is needed to better understand the potential of n-3 PUFAs to prevent muscle loss in the elderly.

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Declaration of Competing Interest

The authors declare no conflicts of interests.

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