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ORIGINAL RESEARCH

The Relationship Between Omega-3, Omega-6 and Total Polyunsaturated Fat and Musculoskeletal Health and Functional Status in Adults: A Systematic Review and Meta-analysis of RCTs

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Abstract

We conducted a systematic review and meta-analysis to assess the effects of increasing dietary omega-3, omega-6 and mixed polyunsaturated fatty acids (PUFA) on musculoskeletal health, functional status, sarcopenia and risk of fractures. We searched Medline, Embase, The Cochrane library, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) databases for Randomised Controlled Trials (RCTs) of adults evaluating the effects of higher versus lower oral omega-3, omega-6 or mixed PUFA for ≥ 6 months on musculoskeletal and functional outcomes. We included 28 RCTs (7288 participants, 31 comparisons), 23 reported effects of omega-3, one of omega-6 and four of mixed total PUFA. Participants and doses were heterogeneous. Six omega-3 trials were judged at low summary risk of bias. We found low-quality evidence that increasing omega-3 increased lumbar spine BMD by 2.6% (0.03 g/cm^2, 95% CI −0.02 to 0.07, 463 participants). There was also the suggestion of an increase in femoral neck BMD (of 4.1%), but the evidence was of very low quality. There may be little or no effect of omega-3 on functional outcomes and bone mass; effects on other outcomes were unclear. Only one study reported on effects of omega-6 with very limited data. Increasing total PUFA had little or no effect on BMD or indices of fat-free (skeletal) muscle mass (low-quality evidence); no data were available on fractures, BMD or functional status and data on bone turnover markers were limited. Trials assessing effects of increasing omega-3, omega-6 and total PUFA on functional status, bone and skeletal muscle strength are limited with data lacking or of low quality. Whilst there is an indication that omega-3 may improve BMD, high-quality RCTs are needed to confirm this and effects on other musculoskeletal outcomes.

Keywords Fatty acids omega-3 · Musculoskeletal physiological phenomena · Bone density · Muscle strength · Fatty acids omega-6 · Fatty acids unsaturated · Meta-analysis · Randomised controlled trial · Aged · Alpha-linolenic acid · Docosahexaenoic acids · Eicosapentaenoic acid

Introduction

Decline in musculoskeletal health presents a significant risk to functional ability for older individuals, with concomitant reduction in quality of life, greater demand on health and social care services and higher risk of mortality. Sarcopenia (loss of skeletal muscle mass and strength), loss of bone mass and structural integrity (osteopenia or osteoporosis) are common in later life and are partially inter-dependent [1, 2], with each contributing to increased frailty, physical disability, risk of falls and fractures [3, 4]. Loss of bone mass starts in adults around 30 to 40 years of age and women in the post-menopausal decade experience a particularly high rate of decline. Men also experience progressive, albeit smaller, loss of bone mass [5]. Loss of skeletal muscle mass and

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function and the development of sarcopenia follow similar trajectories to bone [6]. Together sarcopenia and fractures have high prevalence and economic burden [7, 8]. This is predicted to increase so that by 2045, 13% to 22% of those aged > 65 years in Europe will be sarcopenic [9], and 20% of women and 5% of men aged > 50 years will have osteoporosis. Currently, approximately half of women and a fifth of men over the age of 60 years will experience an osteoporotic fracture [7]. As the number of individuals aged ≥ 60 is expected to double worldwide by 2050 [10] development and implementation of effective strategies to reduce the global burden of musculoskeletal decline is critical to avoid unsustainable demands on future health and social care systems. Dietary intervention to reduce or delay musculoskeletal decline may represent a relatively easily achievable component of such strategies, and thus it is of particular public health importance to further our understanding of how nutritional factors contribute to musculoskeletal health during ageing.

Dietary fat is important to normal muscle structure and function. Fatty acids act as a key substrate for ATP production and thus provide a major energy source during aerobic exercise [11], as well as being key structural components of the sarcolemma (muscle cell membrane). Several mechanisms have been proposed for omega-3 and omega-6 polyunsaturated fatty acids (PUFA) in musculoskeletal health [12–14]. These include PUFA-induced maintenance of antioxidant-oxidant balance, preventing the oxidative stress that can lead to skeletal muscle atrophy; omega-6-induced activation of transcription factor peroxisome proliferator activator receptor gamma (PPARγ), which inhibits osteoblast growth, negatively affecting bone remodelling [15]; omega-3 effects on increasing calcium absorption, by modulating calcium-ATPase when levels are low [16]; PUFAs promoting osteoblastic differentiation through increased production of IGF-1 and parathyroid hormone and omega-3 FAs causing downregulation of chemicals involved in osteoclastic growth [13, 17].

Overall, omega-3 is suggested to exhibit protective effects on bone and muscle whilst omega-6 is thought to have pro-inflammatory effects with detrimental consequences to musculoskeletal health. Thus, a higher omega-3: omega-6 ratio is proposed as beneficial. This is supported by studies showing populations with high omega-3: omega-6 ratios, such as the Japanese or Inuit, have lower rates of osteoporosis than populations with lower omega-3: omega-6 dietary ratios [18].

Previous systematic reviews evaluating the effects of omega-3, omega-6 or total PUFA on skeletal muscle and bone health, sarcopenia or fracture risk have been limited to specific PUFAs (usually omega-3) [19–22], specific population subgroups (e.g. post-menopausal women) [19] or specific outcomes (e.g. bone markers or osteoporosis) [23] and most did not meta-analyse. Effects of total PUFA have not been investigated recently [24]. There is thus a need for a comprehensive review of omega-3, omega-6 and mixed PUFAs on bone and skeletal muscle health or functional status, in order to inform public health nutritional policy for musculoskeletal health in older individuals. We therefore undertook this systematic review to assess effects of increasing dietary omega-3, omega-6 or mixed total PUFA on key musculoskeletal outcomes and functional status in adults aged 40 years or older.

Methods

We conducted the review following methods recommended by The Cochrane Handbook and reported the process and results in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [25, 26]. This review was part of a set of reviews evaluating the effects of PUFAs on various health outcomes [27–34]; detailed methods are reported elsewhere [35]. The methods reported below are those specific to this review.

Selection Criteria

We included randomised controlled trials (RCTs) that compared higher versus lower omega-3, omega-6 or mixed PUFA (i.e. providing both omega-3 and omega-6), over a period of at least 24 weeks. We included studies reported as full text, trials registry entries and conference abstracts. Participants included healthy adults and those at risk of or diagnosed with sarcopenia and/or osteopenia, aged ≥ 40 years (where ≥ 90% of participants were aged ≥ 40 years or where data could be separated out for those aged ≥ 40). Studies of pregnant women or acutely ill patients were excluded. Participants with non-acute co-morbidities were included except where the co-morbidity was likely to affect fatty acid absorption or musculoskeletal outcomes (e.g. coeliac disease, cystic fibrosis, systemic lupus erythematosus, rheumatoid arthritis, ulcerative colitis and Crohn's Disease).

Interventions had to aim to increase or decrease omega-3, omega-6 and/or total PUFA intakes, or achieve ≥ 10% increase or decrease from baseline. Interventions could include dietary supplementation (oils, capsules, enriched foods or naturally rich food sources given by mouth), or provided diet or dietary advice. Multifactorial interventions (with exercise, smoking cessation, medications or other dietary aims) were excluded unless the effect of change in PUFA could be separated out from other interventions. The control group had to have lower PUFA intake (including usual diet; no advice; no supplementation; placebo or an intervention aiming at lowering PUFA intake). Primary outcomes included:

- *For bone* fracture incidence, any measure of BMD, e.g. bone mineral density (BMD), bone mineral content (BMC) or total bone mass.
- *For muscle* sarcopenia or dynapenia (age-associated loss of muscle strength) incidence, skeletal muscle mass.
- *For functional status* mobility scores or other validated functional status measures, e.g. Barthel Index or Activities of Daily Living (ADL).

Secondary outcomes included direct measures of muscle strength or physical performance (e.g. grip strength, gait speed), fracture risk score, osteoporosis or osteopenia incidence and bone turnover markers. A study was eligible for inclusion if it assessed any primary or secondary outcome.

Search Methods for Identification of Studies

We identified studies using complex and extensive search strategies and duplicate assessment as described elsewhere [35], creating a database of trials that randomised participants to increased omega-3, omega-6 or total PUFA compared to lower omega-3, omega-6 or total PUFA and assessed effects over at least 24 weeks. From the database, studies were chosen for this review that had assessed any primary or secondary outcome (even when not fully reported). Reference lists of all included primary studies and relevant systematic reviews were hand-searched for additional references.

Data Collection and Assessment of Risk of Bias

Two reviewers independently assessed inclusion, extracted data (characteristics, methods and results data) and assessed risk of bias. Risk of bias was assessed using the Cochrane Risk of Bias tool [36]. A trial was considered to be at low summary risk of bias where randomisation, allocation concealment, blinding of participants and personnel and blinding of outcome assessors were all judged adequate [35]. We tried to contact authors where inclusion could not be ascertained, where outcomes were measured but not reported or not reported in a usable format.

Data Synthesis

Our primary analyses assessed effects of total PUFA, omega-6, omega-3 on our primary outcomes. Treatment versus control differences in outcomes were combined across studies where appropriate using relative risks (RR) or mean differences (MD) in random-effects meta-analysis (using Review Manager Version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The random-effects model was used since dietary interventions are heterogeneous. Change from baseline was preferred; however, we used end data where change data were not reported or reported with no variance. Where different scales measured the same outcome we ensured all scales worked in the same direction (inverting where necessary), before combining data using standardised mean differences (SMD). For SMDs, 0.2 represented little or no effect, 0.5 a moderate effect and 0.8 a large effect. Where a representative study at low summary risk of bias was included in the meta-analysis, we translated the pooled SMD back into the scale used in that trial to help understand effect sizes.

Subgroup analyses were planned to explore the effects of the long-chain omega 3 (LCn-3) EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid), their precursor alpha linoleic acid (ALA), omega-6 and mixed PUFA intake on primary outcomes where at least ten RCTs reported a single comparison. Planned subgroup analyses included gender, baseline risk of osteoporosis/skeletal muscle loss (general population; those at higher risk, e.g. post-menopausal women, early menopause, 65+, family history; those with osteopenia/sarcopenia; those with diagnosed osteoporosis), intervention type, trial duration, baseline LCn-3, ALA, omega-6 or total PUFA intake [35]. Sensitivity analyses were carried out to assess the effects of methodological rigour (including only studies with a low summary risk of bias), study size and fixed effects meta-analysis. Funnel plots were planned to explore potential reporting biases for the primary outcomes where we included ≥ 10 studies in single meta-analyses.

The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework was used to assess strength of evidence across studies for primary outcomes. Outcome data were interpreted as usual for this set of reviews [35]. RR < 0.92 or > 1.08 was considered an effect, whilst change from baseline of $\geq 5\%$ was required for continuous measures except for cumulative measures such as BMD and adiposity (where a change of $\geq 2\%$ was required). This 2% change compares with changes of 0.4% annual decrease in BMD in older adults and the 5% decrease with 3% annual decreases in grip strength in older adults [37].

Results

Study flow from 37,810 titles and abstracts generated by electronic searches through to our database of 363 RCTs of at least 6 months duration comparing higher with lower omega-3, omega-6 and/or total PUFA intake has been detailed previously [35]. Of the 363 RCTs in the database 28 RCTs (7288 participants, 31 comparisons) met our inclusion criteria, of which 25 RCTs (27 comparisons) contributed to meta-analyses (see Fig. 1 for the flow diagram). Characteristics of these 28 included studies are summarised in Table 1, full details are in the database [35]. Fourteen included RCTs

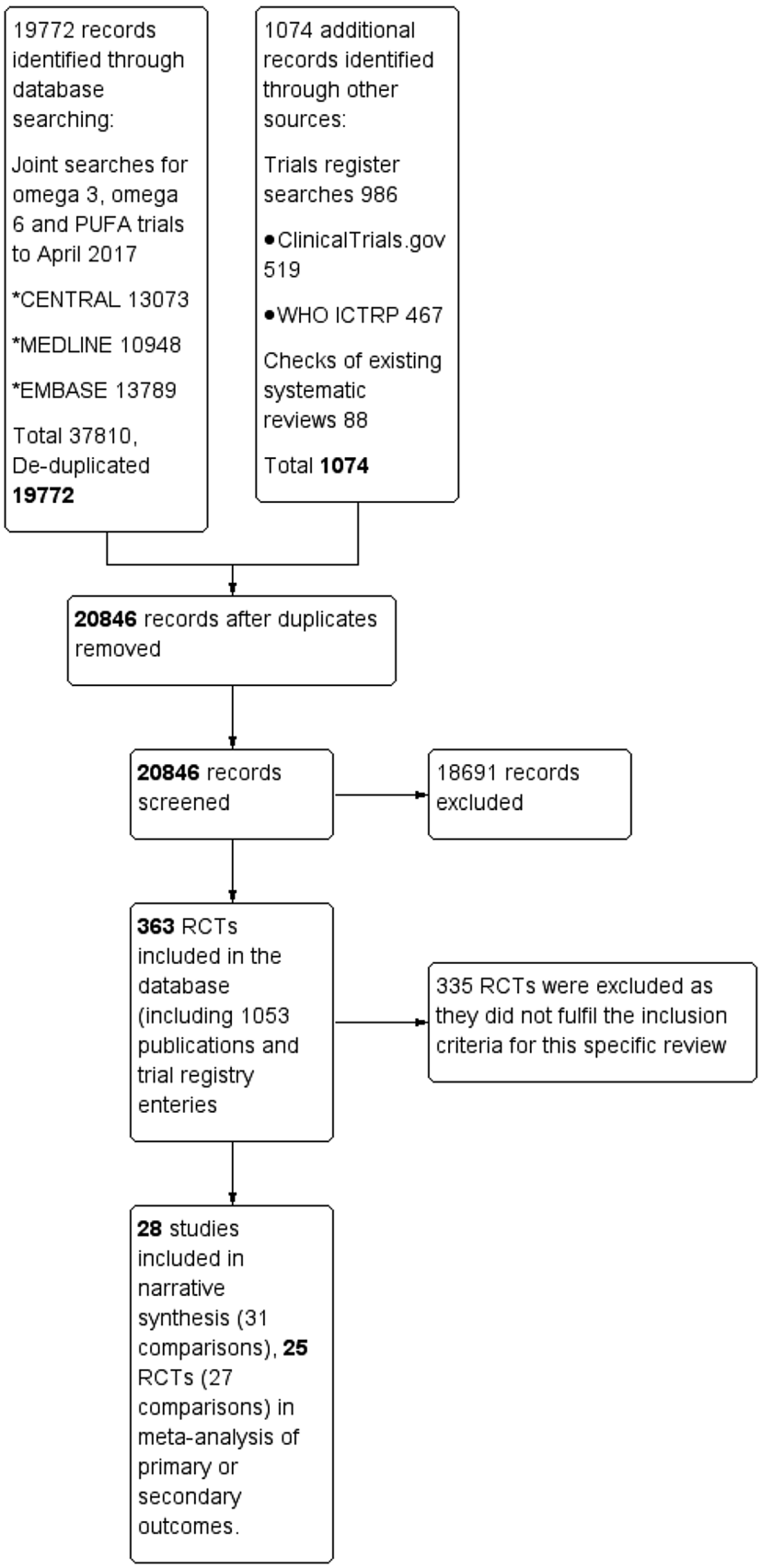

Fig. 1 Study flow diagram

Table 1 Characteristics of included studies

Study/location	Participants	N (I/C)	Intervention/duration	Outcome measures	Summary risk of bias
Omega-3 intervention studies:					
Baxheinrich 2012/Germany [39]	Metabolic syndrome patients. Mean age (sd): 52.3 (10.6) int., 50.3 (9.8) control	95 (47/48)	Rapeseed oil and margarine (3.5 g/d ALA) versus olive oil/6 months	Primary: lean mass %	Moderate/high
Clark 2016/UK [68]	Adults with DM or impaired glucose. Mean age (sd): 61.8 (NR) int., 58.1 (NR) control	33 (16/17)	FO capsules (3.9 g EPA + DHA) versus maize oil/9 months	Primary: Lean mass % and kg	Moderate/high
Dasarathy 2015/USA [60]	NASH patients with DM. Mean age (sd): 51.5 (6.9) int., 49.8 (12.1) control	37 (18/19)	FO capsules (5.8 g EPA + DHA) versus corn oil/11 months	Primary: Lean mass, bone mass	Moderate/high
Dodin 2005/Canada [40]	Healthy menopausal women. Mean age (sd): 54.0 (4.0) int., 55.4 (4.5) control	199 (101/98)	Flaxseed (9.1 g/d ALA) versus wheat germ/12 months	Primary: BMD	Moderate/high
EPOCH 2011/Australia [69]	Healthy older adults with no cognitive impairment. Mean age NR, but 65–90 recruited	391 (195/196)	FO capsules (2.3 g EPA + DHA) versus olive oil/18 months	Primary: Yale Physical Activity Survey (not reported)	Moderate/high
FOSTAR 2016/Australia [70]	Adults with knee osteoarthritis. Mean age (sd): 60.8 (10) int., 61.1 (10) control	202 (101/101)	FO supplement (4.5 g/d EPA + DHA) versus sunola + fish (0.45 g EPA + DHA)/2 years	Primary: BMD, WOMAC function score	Low
Gruenwald 2009/Germany [58]	People with moderate-to-severe hip/knee osteoarthritis. Age, mean (sd) yrs: control 62.4 (8), intervention 62.2 (7.7)	177 (90/87)	FO capsules (600 mg/d EPA + DHA) ± glucosamine sulphate/6 months	Primary: WOMAC function score	Low
Hutchins-Wiese 2013/USA [41, 42]	Older post-menopausal women. Age, mean (sd) yrs: control 75 (7), intervention 75 (6)	126 (85/41)	FO capsules (1.2 g/d EPA + DHA) versus olive oil/26 weeks	Primary: Fracture incidence Secondary: walking speed, repeated chair rises, hand grip, OC, BAP, NTX, PTH	Moderate/high
MAPT 2017/France and Monaco [55]	Elderly adults ≥ 70 years with memory complaint but no dementia Mean age (sd): 75·6(4·7) and 74.4 (4.4)int., 75·1 (4·3) and 75 (4.1)control	1680** (840/840)	Omega-3 (1.025 g/d EPA + DHA) versus paraffin oil (± multidomain intervention)/3 years	Primary: Short physical performance battery (SPPB), Fried frailty criteria (gait speed)	Low
MEMO 2008/Netherlands [71]	Independently living people aged ≥ 65 Mean age (sd), years: 69.9 (3.4) int high dose, 70.1 (3.7) control	202 (96/106)*	Omega-3 (1.8 g/d EPA + DHA) versus high oleic acid sunflower oil/6 months	Primary: WHOQOL-BREF (Physical health domain 7–35)	Moderate/high
Norouzi 2014/Iran [72]	Patients with chronic traumatic spinal cord injury. Mean age (sd): 51.15 (13.43) int., 54.12 (11.76) control	110 (55/55)	Omega-3 (1 g/d EPA + DHA) versus unclear placebo/14 months	Primary: FIM + FAM (locomotion subscale)	Moderate/high

Table 1 (continued)

Study/location	Participants	N (I/C)	Intervention/duration	Outcome measures	Summary risk of bias
NutriStroke 2009/Italy [73]	Stroke survivors in a rehab unit. Mean age (sd): 61.3 (13.6) n3, 66.3 (11.4) n3 + antiox int., 68.4 (12.6) placebo, 65.1 (12.8) antiox-control	72** (38/34)	FO capsules (0.5 g/d EPA + DHA) versus unclear placebo (± antioxidants)/12 months	Primary: Rivermead Mobility Index (RMI)	Moderate/high
OMEGA AD 2006/Sweden [74]	People with mild-to-moderate Alzheimer's disease. Mean age (sd): 72.6 (9.0) int., 72.9 (8.6) control.	204 (103/101)	Omega-3 (2.32 g/d EPA + DHA) versus. corn oil/6 months	Primary: Arm muscle circumference	Moderate/high
Salari Sharif 2010/Iran [22]	Osteoporotic post-menopausal women. Age (Mean): 60.0 (5.6), int., 63 (8.9) control	25 (13/12)	Omega-3 capsules (0.9 g/d n3 fats) versus unclear placebo/6 months	Secondary: OC, BAP, PTH, PYD	Moderate/high
Sinn 2012/Australia [53]	Older people with mild cognitive impairment. Mean age (sd): 74.88 (5.06) intEPA, 74.22 (7.00) IntDHA, 73 (3.96) = LAgroup	54 (18, 18/18)	EPA-rich FO (1·67 g EPA + 0·16 g DHA/d) versus DHA-rich FO (1·55 g DHA + 0·40 g EPA/d) versus safflower oil (2·2 g LA/d)/6 months	Primary: SF-36 physical functioning (results not reported)	Low
Smith 2015/USA [75]	Healthy older adults. Mean age (sd) yrs: 68 (5) int., 69 (7) control	60 (40/20)	Omega-3 capsules (3.36/d EPA + DHA) versus corn oil/6 months	Primary: Thigh Muscle mass. Secondary: hand grip, 1-RM strength	Moderate/high
Stammers 1992/UK [51]	Patients with clinical diagnosis of osteoarthritis. Mean age (sd) yrs: 67 (NR) int., 69 (NR) control.	86 (44/42)	Cod liver oil (786 mg/d EPA) versus olive oil/24 weeks	Primary: VAL of disability	Moderate/high
Sufolom3 2010/France [56]	People with a history of MI, unstable angina or ischaemic stroke. Mean age (sd): 61.1 (8.8) int., 60.8 (8.7) control	2501(1248/1253)	Omega-3 capsules (0.6 g/d EPA + DHA) versus liquid paraffin capsules/4 years	Primary: SF-36-physical functioning	Low
Tardivo 2015/Brazil [44]	Post-menopausal women with metabolic syndrome. Mean age (sd) years: 55.1 (6.6) int., 55.0 (7.3) control	87 (44/43)	Omega-3 capsules (0.9 g/d EPA + DHA) versus nil/6 months	Primary: Muscle mass %	Moderate/high
Tartiban 2011/Iran [45]	Sedentary post-menopausal women. Mean age (sd) yrs: 59.7 (2.3) int with exercise, 63.1 (7.5) int alone, 61.4 (6.9) exercise alone, 58.9 (8.1) no int	79** (41/38)	FO capsules (0.9 g/d EPA + DHA) versus nil (± exercise)/6 months	Primary: BMD Secondary: OC, CTX, PTH	Moderate/high
Vanlint 2012/Australia [46]	Sedentary post-menopausal women. Mean age (sd) yrs: 59.2 (NR) overall, not reported by arm.	40 (20/20)	Algal oil capsules (0.4 g/d DHA) versus corn oil/12 months	Primary: BMD Secondary: CTX	Moderate/high
Wang 2016/China [76]	Type 2 diabetic patients with abdominal obesity. Mean age (sd): 64.6 (5.5) int., 66.3 (5.1) control	100 (50/50)	FO capsules/d (2.4 g/d EPA + DHA) versus corn oil capsules/6 months	Primary: Muscle mass, lean mass	Moderate/high

Table 1 (continued)

Study/location	Participants	N (I/C)	Intervention/duration	Outcome measures	Summary risk of bias
WELCOME 2014/UK [77]	Patients with NAFLD. Mean age (sd): 48.6 (11.1) int., 54 (9.6) control.	103 (51/52)	Omega-3 capsules (3.36 g/d EPA + DHA) versus olive oil capsules/15–18 months	Primary: Lean mass	Moderate/high
Omega-6 intervention studies					
Glamt 1993/UK and Finland [49]	People with mild diabetic neuropathy. Age, mean (sd) yrs: control 52.9 (11.4), intervention 53.3 (11.1)	111 (54/57)	EPO (0.48 g/d GLA) versus paraffin/1 year	Secondary: Arm and leg muscle strength	Moderate/high
Mixed PUFA intervention studies					
Bassey 2000/UK [38]	Healthy post-menopausal women aged 50–65 years. Mean age (SD): 58 (4.6) int., 55 (4.6) control.	45 (21/24)	EPO + FO capsules plus calcium versus calcium (4.4 g/d PUFA)/12 months	Primary: BMD. Secondary: Leg extensor power OC, BSAP, NTX, uHyp, PTH,	Moderate/high
Kruger 1998/South Africa [43]	Women from old age homes with osteoporosis/osteopenia. Age, mean (sd) yrs: control 77.2 (6.4), intervention 78.66 (5.77)	60 (29/31)	EPO + FO (4.5 g/d PUFA, 4.1 n6, 0.4 n3) versus coconut oil/18 months	Primary: BMD. Secondary: walking speed, hand grip, OC, NTX, BAP, PTH, PICP, DPD, urinary Ca	Moderate/high
PREDIMED-Reus 2013/Spain [47, 48, 78]	Diabetic (or with CVD risk) men 55–80 years and women 60–80 years. Mean age (sd) years: 68.4 (6.0) int., 67.8 (6.5) control	175 (85/90)[§]	30 g/d mixed nuts (rich in ALA and LA) versus extra-virgin olive oil (+Med diet advice)/1 year	Primary: BMD Secondary: OC, CTX, P1NP, PTH, BAP, urinary Ca/creatinine, DPD	Moderate/high
PREDIMED-Canaria 2013/Spain [50, 78]	Diabetic (or with CVD risk) men 55–80 years and women 60–80 years	234 (102/112)[§]	30 g/d mixed nuts (rich in ALA and LA) versus extra-virgin olive oil (+Med diet advice)/2 years	Primary: FFM	Moderate/high

BMD bone mineral density, *BAP* bone-specific alkaline phosphatase, *CTX* cross-linked C-telopeptide, *DPD* deoxypyridinoline, *FFM* fat-free mass, *FIM + FAM* functional independence measure and functional assessment measure, *FO* fish oil, *NAFLD* non-alcoholic fatty liver disease, *NTX* N-telopeptide of type 1 collagen, *OC* osteocalcin, *PICP* procollagen type I, *PTH* parathyroid hormone, *PYD* urinary total pyridinoline, *SPPB* short physical performance battery, *uHyp* urinary hydroxyproline, *VAL* visual analogue line

*A third arm of low omega-3 dose was not used

**Studies provided two comparisons

[§]A third low fat arm, not discussed here. These are sub-cohorts of the same study (PREDIMED) reporting on different study centres

were conducted in Europe, four in North America, four each in Asia and Australia and one each for South America and Africa. Eight RCTs included only post-menopausal women [22, 38–46], two of which were of osteopenic or osteoporotic women [22, 43]. Sample sizes ranged from 25 to 2501 (mean 252, median 100 participants), and intervention duration ranged from 24 weeks to 4 years (mean 12.9 months).

Twenty-three studies were omega-3 interventions, of which 21 provided LCn-3 (EPA and/or DHA) and two provided ALA [39, 40]. Effects of increasing mixed total PUFA was evaluated by three studies [38, 43, 47, 48], whilst omega-6 was assessed in by one [49]. The intervention was supplementary capsules in 23 studies with the remaining five providing supplementary oils, nuts or seeds [39, 40, 47, 48, 50, 51]. No studies provided dietary advice only. Doses ranged from 0.4 to 5.8 g/d LCn-3 and 3.5 to 9.1 g/d ALA. The omega-6 study provided 0.48 g/d GLA and two mixed PUFA studies provided ~ 4.5 g/d (PUFA dose was unclear in one study).

Data from three studies could not be used in the meta-analysis. EPOCH and Sinn did not report numerical data for functional outcomes [52, 53], whilst OmegAD only provided arm muscle circumference as medians and inter-quartile range [54]. Six included RCTs, assessing effects of omega-3 [46, 53, 55–59], were judged to be at low summary risk of bias (Fig. 2).

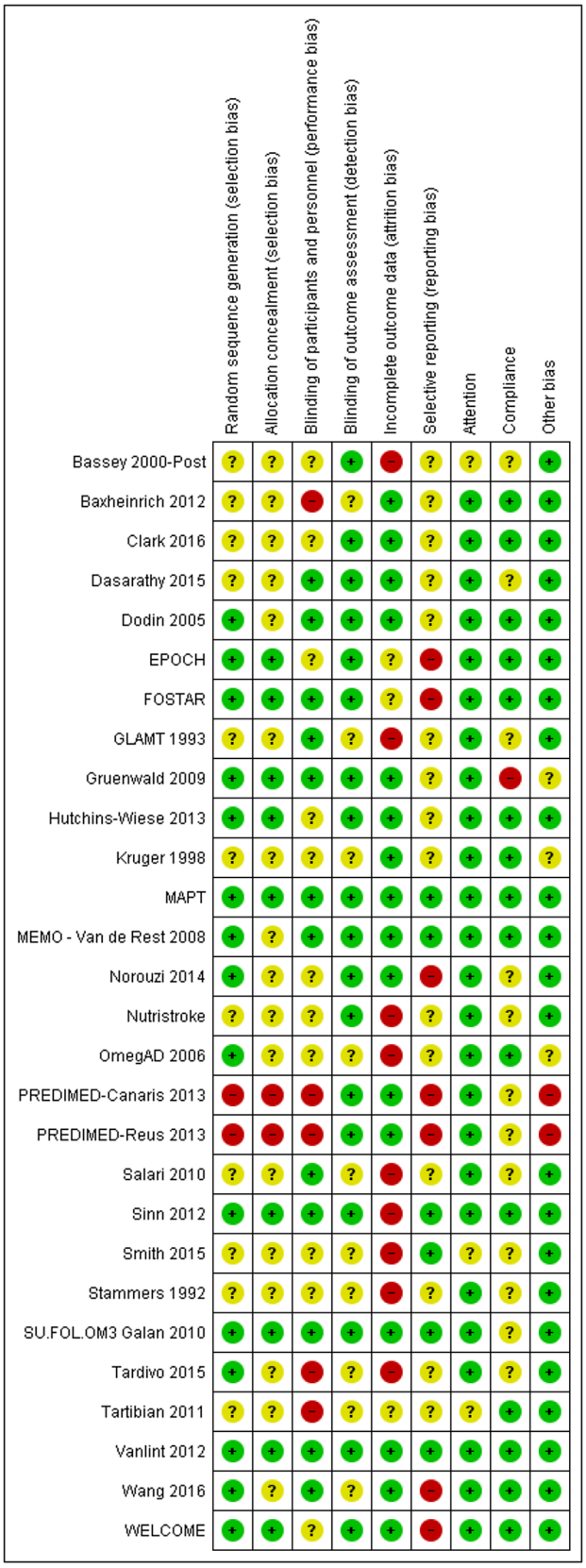

Fig. 2 Risk of bias summary for each included study

Effects of Higher Omega-3

GRADE assessment of quality of evidence is shown in Table 2, and the meta-analysis results in Additional Table 1. No studies reported data on BMC, sarcopenia, dynapenia or myopenia incidence.

Fractures

The effect of increasing omega-3 fats on fracture incidence is unclear as the evidence is of very low quality (downgraded once for risk of bias, twice for imprecision). One RCT [42] reported the incidence of one fracture (RR 0.16, 95% CI 0.01 to 3.91, 126 participants).

Bone Density

Increasing omega-3 intake may have little or no effect on total bone mass, with data available from one small study [60]. Total bone mass increased < 2% from baseline (0.2 kg, 95% CI − 2.8 to 3.2). Evidence was of low quality, downgraded once each for risk of bias (the study was not at low summary risk of bias) and imprecision (as the 95% CI included both important benefits and harms).

Table 2 Grade table for effects of omega-3 on musculoskeletal health and functional status in older adults

Higher versus lower omega-3 for musculoskeletal health and functional status in older adults						
Patient or population: older adults with or without musculoskeletal health problems Setting: community or institutional Intervention: Higher omega-3 intake Comparison: lower omega-3 intake						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (Grade)	Comments
	Risk with lower omega-3	Risk with higher omega-3				
Fracture incidence	24 per 1000	4 per 1000 (0 to 95)	RR 0.16 (0.01 to 3.91)	126 (1 RCT)	⨁◯◯◯ very low[a,b,c]	The effect of increasing omega-3 fats on fracture incidence is unclear as the evidence is of very low quality. Downgraded once for risk of bias, twice for imprecision
Lumbar BMD, g/cm^2	The mean lumbar BMD was 1.15 g/cm^2	The mean lumbar BMD in the intervention group was 0.03 g/cm^2 higher (0.02 lower to 0.07 higher)	–	463 (4 RCTs)	⨁⨁◯◯ low[d,e]	Increasing omega-3 may slightly increase lumbar BMD (as change was > 2% of baseline). Downgraded once each for inconsistency and imprecision
Femoral neck BMD, g/cm^2	The mean femoral neck BMD was 0.97 g/cm^2	The mean femoral neck BMD in the intervention group was 0.04 g/cm^2 higher (0 to 0.08 higher)	–	463 (4 RCTs)	⨁◯◯◯ very low[d,e,f]	The effect of increasing omega-3 fats on femoral neck BMD is unclear as the evidence is of very low quality. Downgraded once each for risk of bias, inconsistency and imprecision
Total proximal femur BMD, g/cm^2	The mean total proximal femur BMD was 0.87 g/cm^2	The mean total proximal femur BMD in the intervention group was 0.03 g/cm^2 higher (0.3 lower to 0.36 higher)	–	37 (1 RCT)	⨁◯◯◯ very low[b,g]	The effect of increasing omega-3 fats on proximal femur BMD is unclear as the evidence is of very low quality. Downgraded once for indirectness and twice for imprecision
Muscle mass (various measures)	Data combined using SMD	No suggestion of a statistically significant effect, SMD = 0.38, suggesting small-to-moderate effect size	–	476 (7 RCTs)	⨁◯◯◯ very low[h,I,j]	The effect of increasing omega-3 fats on muscle mass is unclear as the evidence is of a very low quality. Downgraded once each for risk of bias, inconsistency and indirectness

Table 2 (continued)

Higher versus lower omega-3 for musculoskeletal health and functional status in older adults						
Patient or population: older adults with or without musculoskeletal health problems Setting: community or institutional Intervention: Higher omega-3 intake Comparison: lower omega-3 intake						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (Grade)	Comments
	Risk with lower omega-3	Risk with higher omega-3				
Total bone mass, kg	The mean total bone mass (kg) (omega3) as 24.6 kg	The mean total bone mass in the intervention group was 0.2 kg higher (2.8 lower to 3.2 higher)	–	37 (1 RCT)	⨁⨁◯◯ low[a,k,l,m]	Increasing omega-3 intake may have little or no effect on total bone mass. One trial only. Downgraded for risk of bias and imprecision
Measures of functional status (various measures)	Data combined using SMD	No suggestion of a statistically significant effect, SMD = −0.04 suggesting little or no effect	–	4166 (9 RCTs)	⨁⨁◯◯ low[e,n]	Increasing omega-3 may have little or no effect on various measures of functional status. Downgraded once each for indirectness and publication bias

GRADE Working Group grades of evidence High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

CI confidence interval, *RR* risk ratio, *MD* mean difference, *SMD* standardised mean difference

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

[a]Risk of bias: the single included study was not at low summary risk of bias. Downgraded once

[b]Indirectness: a single study including only post-menopausal women was included. Downgraded once

[c]Imprecision: only one event in a single included study, downgraded twice

[d]Inconsistency: $I^2 > 70\%$. Results show considerable heterogeneity that was not explained by limiting to studies at low risk of bias, downgraded once

[e]Imprecision: the 95% CI does not exclude null, downgraded once

[f]Risk of bias: limiting the analysis to studies at low risk of bias changes the insignificant positive effect, downgraded once

[g]Imprecision: the 95% CI includes both important benefits and important harms. Downgraded twice

[h]Risk of bias: none of the included studies was at an overall low risk of bias, downgraded once

[i]Inconsistency: $I^2 > 60\%$, downgraded once

j. Indirectness: Studies reported different measures of muscle mass, downgraded once

[k]Inconsistency only one study included, not downgraded

[l]Indirectness: only a single small study including diabetic patients, not downgraded

[m]Imprecision: the 95% CI included both important harms and benefits, downgraded once

[n]Publication bias: three of the ten identified RCTs provided no useable data. Downgraded once

Bone Mineral Density (BMD)

Effects of increasing omega-3 fats on proximal femur BMD are unclear as the evidence is of very low-quality downgraded once for indirectness, twice for imprecision. Increasing omega-3 may slightly increase lumbar spine BMD by 2.6% (MD 0.03 g/cm^2, 95% CI −0.02 to 0.07, 463 participants, low-quality evidence, downgraded once each for inconsistency and imprecision) and femoral neck BMD by 4.1% (MD 0.04 g/cm^2, 95% CI 0.0 to 0.08, 463 participants, very low-quality evidence, downgraded once each for risk of bias, inconsistency and imprecision). Four omega-3 studies (5 comparisons, of which 4 were in post-menopausal women) reported effects on BMD (Fig. 3). There was little or no effect of omega-3 on BMD at any site when sensitivity analyses were limited to RCTs at low summary risk of bias (Additional Table 1). We ran a post hoc sensitivity analysis limiting to the three studies of at least 1 year (as BMD changes slowly). This led to losing the effect on lumbar spine BMD (MD 0.00 g/cm2, 95% CI −0.04 to 0.04, 384 participants) and decreasing the effect shown on femoral neck BMD (MD 0.01 g/cm^2, 95% CI 0.0 to 0.02, 384 participants).

As the same studies reported BMD at several sites, SMD was not used to combine results.

Skeletal Muscle Mass

The effect of increasing omega-3 fats on skeletal muscle mass is unclear as the evidence is of a very low quality. Indices of skeletal muscle mass were reported in nine studies as percentage, percentage change or in kilograms, so we used SMD to combine measures, suggesting a small statistically significant improvement in indices muscle mass with higher omega-3 and a small-to-moderate effect size (Fig. 4). The evidence was undermined by high heterogeneity (SMD 0.38, 95% CI 0.05 to 0.70, 7 studies, 476 participants, I^2 67%), risk of bias (as no included studies were at low summary risk of bias) and indirectness (measures varied between studies). We identified one study with missing data [54] which reported slightly higher median arm muscle circumference in the omega-3 arm compared to control (change of −0.1 cm in males and +0.1 cm in females, compared to −0.3 cm in placebo for males and females combined).

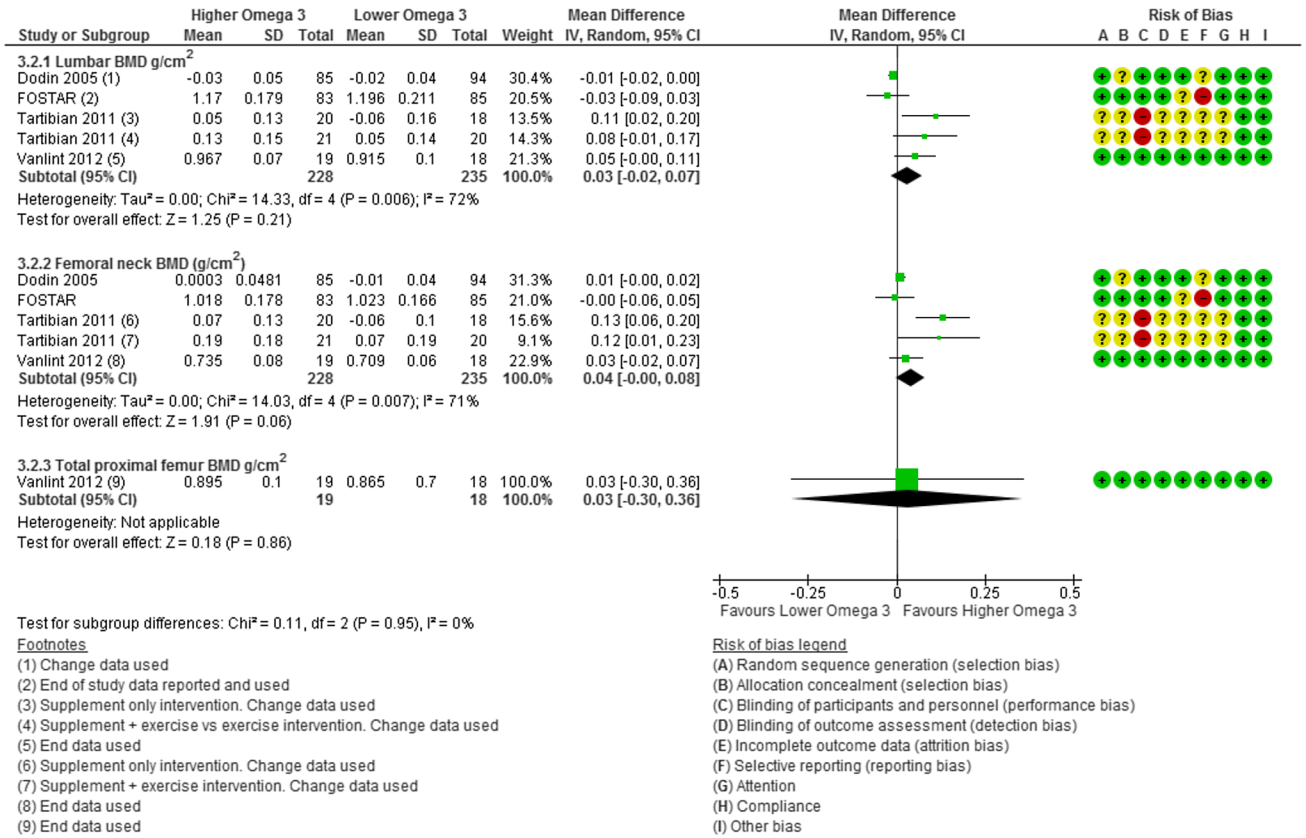

Fig. 3 Effect of high versus low omega-3 on BMD at different sites

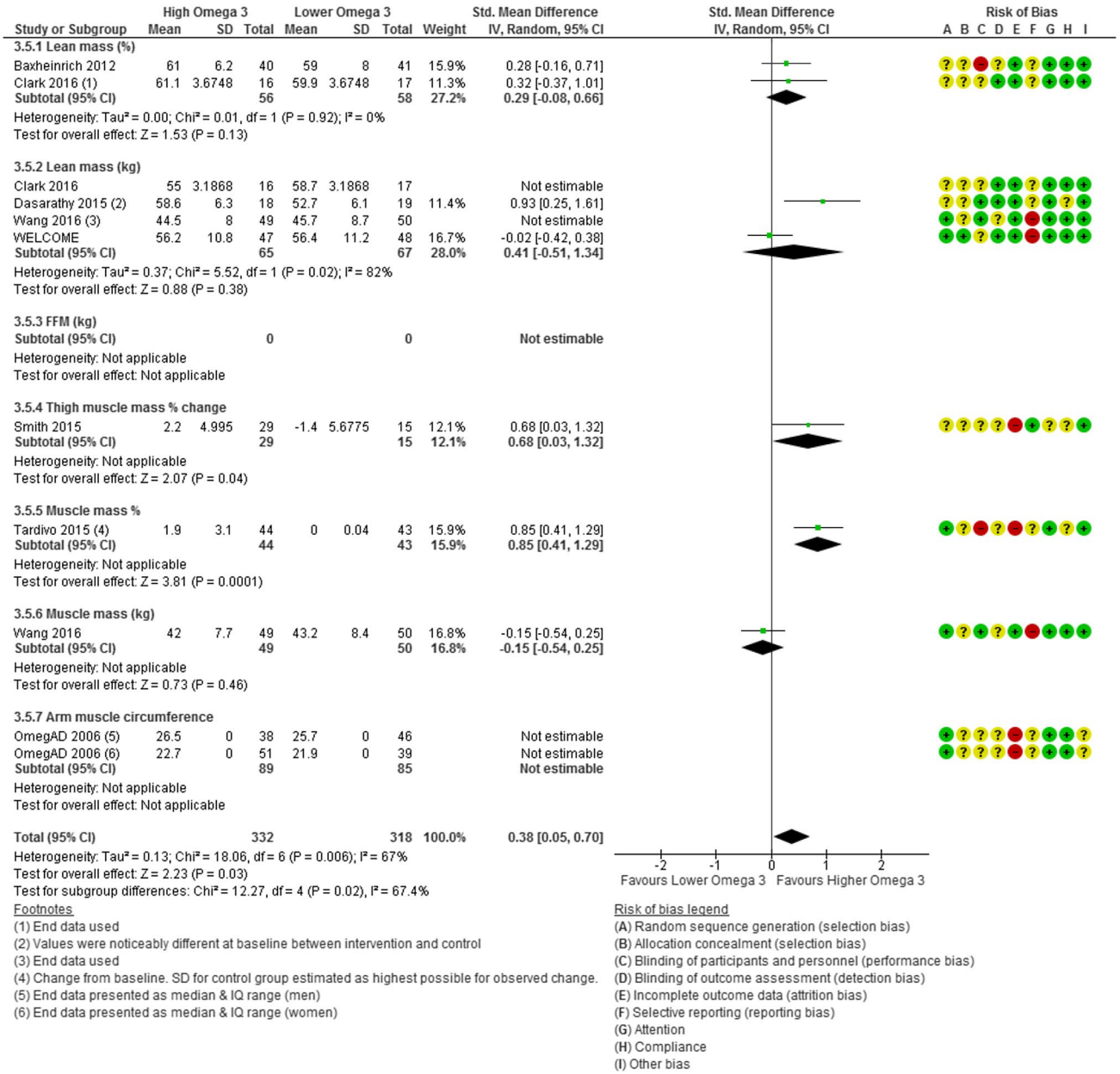

Fig. 4 Effect of high versus low omega-3 on various measures of skeletal muscle mass in different sites

Functional Status

Increasing omega-3 may have little or no effect on functional status (low-quality evidence, downgraded once each for indirectness and publication bias). Ten RCTs measured functional status using various scales, of which eight presented numerical results of which one presented means without variance. We used SMD to combine the remaining seven RCTs [9 comparisons, SMD-0.04, 95% CI −0.11, 0.02, I^2 0% (Fig. 5)]. This SMD equates to little or no effect, and using MAPT Short Physical Performance Battery Score to re-express SMD suggests MD 0.08 equates to 0.7% increase from baseline on the SPPB scale. The three studies without usable data suggested non-statistically significant effects [53, 58] or provided no data [52].

Secondary Outcomes

Measures of Physical Performance/Strength

Two studies reported measures of handgrip strength (% change or kg), neither was at low summary risk of bias. Combining these using SMD did not suggest a statistically significant effect of increased omega-3. Other measures

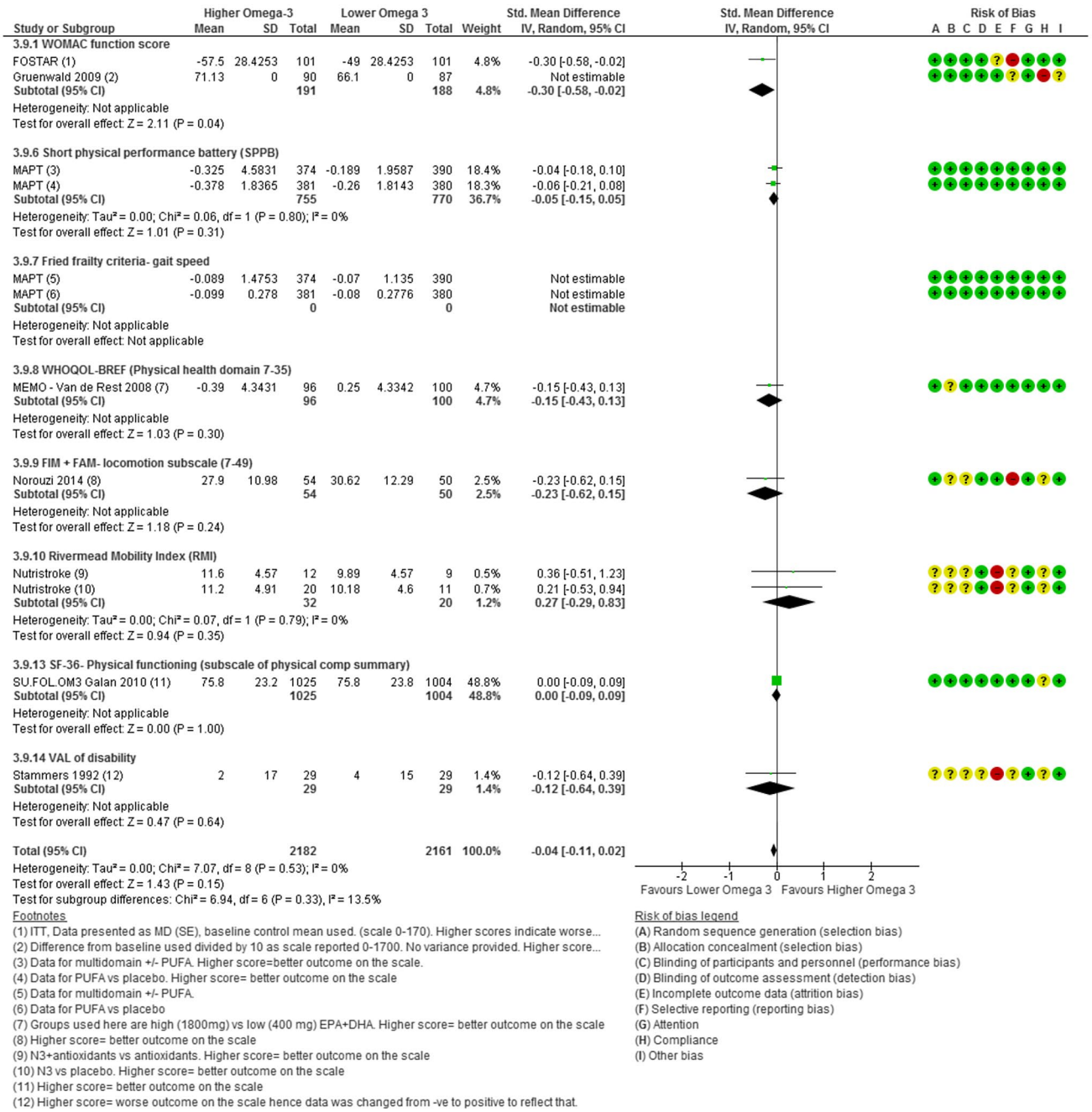

Fig. 5 Effect of high versus low omega-3 on various measures of functional status

assessed within the two RCTs included leg extensor power, walking speed and repeated chair rises, but no single measure was reported by both studies. These two studies suggested improvement in the measures used with high omega-3 PUFA and combining data from the two studies using SMD suggested a positive effect of high omega-3 PUFA on physical performance (SMD 0.47, 95% CI 0.09, 0.85, 161 participants, I^2 17%).

Bone formation markers were reported in three studies, none of which was at low summary risk of bias. One study author provided raw data that allowed inclusion in the meta-analysis [22]. Osteocalcin was the most frequently reported marker (3 studies, 4 comparisons, with heterogeneous data, I^2 55%) suggesting a small increase with increased omega-3. There was little or no effect on other markers (Additional Table 1).

Bone resorption markers were reported in four studies [22, 42, 45, 46]; C-terminal telopeptide of type 1 collagen (CTX) was reported in two studies (3 comparisons) whilst N-telopeptide of type 1 collagen (NTX) and urinary total pyridinoline (PYD) in one study each. There was a suggestion of a decrease of CTX with increased omega-3, and an increase in urinary PYD, but these were non-statistically significant, and from small studies. Only the smallest trial was at low summary risk of bias and suggested no effect of omega-3 on CTX.

Various other markers of bone turnover were reported with parathyroid hormone being the most commonly reported (3 RCTs, 4 comparisons) with no significant effect of high omega-3 (Additional Table 1).

Effects of Omega-6

Primary Outcomes

No omega-6 studies reported on any primary outcome, so GRADE assessment was not carried out. Meta-analysis results are shown in Additional Table 2.

Secondary Outcomes

The only included omega-6 study [49] used GLA supplementation, randomised 84 participants and was not at low summary risk of bias. It provided data on two outcomes related to physical performance measures, arm and leg muscle strength, using scales of 0 to 2500 or 2000, respectively, suggesting little or no effect. The paper is unclear about whether higher or lower scores indicated greater strength, though both measures suggested small statistically significant increases (Additional Table 2).

Effects of Mixed Total PUFA

GRADE assessment of quality of evidence is shown in Table 3, and meta-analysis results in Additional Table 3.

Primary Outcomes

No trials assessing effects on fracture incidence, total bone mass, BMC, sarcopenia, dynapenia or myopenia incidence or measures of functional status were identified.

Bone Density

Increasing total PUFA may have little or no effect on BMD (low-grade evidence, downgraded once each for risk of bias and indirectness). Three mixed PUFA studies reported BMD as an outcome (Fig. 6), but no two studies reported on the same site (total, femoral neck, lumbar or calcaneal reported). Combining the three trials across sites (allowing one entry from the study with multiple measures) suggested little or no effect (< 2% change from baseline). For individual sites, there was a suggestion that increasing total PUFA increased femoral neck BMD (MD 0.07 g/cm^2, 95% CI 0.03 to 0.1, 1 RCT, 60 participants), but there were no suggested effects at any other site. No studies were at low summary risk of bias.

Skeletal Muscle Mass

Increasing total PUFA may have little or no effect on fat-free mass (downgraded once each for risk of bias and indirectness). Fat-free mass was reported in one study [50] with 214 participants, and change from baseline was < 2% (MD − 0.5 kg, 95% CI − 1.63 to 0.63).

Secondary Outcomes

No included trial reporting secondary outcomes was at low summary risk of bias.

Measures of Physical Performance/Strength

Only one small UK study of healthy post-menopausal women [38] at moderate-to-high summary risk of bias reported a small non-significant decline in leg extensor power in the mixed PUFA intervention group compared to the control (MD − 8 W, 95% CI − 23.8–7.8, 42 participants).

Bone Turnover Markers

Bone formation markers were reported in three studies, none at low summary risk of bias, with little or no effect for all except a suggestion of a reduction in C1NP with higher PUFA (Additional Table 3). Osteocalcin was reported by all three studies suggesting little or no effect (MD 0.52 µg/L, 95%CI − 1.99–0.95, 195 participants, I^2 45%). Serum bone-specific alkaline phosphatase was reported in all three studies, but one study reported it as a percentage (so could not be combined). There was no significant effect on either measure. Other markers reported by a single study included serum type 1 procollagen and procollagen.

Various markers of bone resorption were reported in three studies, but none were at low summary risk of bias. All suggested little or no effect except that there were small non-statistically significant falls of NTX/CR and CTX and urinary hydroxyproline with higher PUFA intake. The deoxypyridinoline/creatinine ratio was the only marker reported in two studies, other markers were reported by single studies. Parathyroid hormone was the most frequently reported bone turnover marker, reported by three studies. Pooled results suggested a small non-statistically significant increase in parathyroid hormone with increased PUFA.

Table 3 Grade table for effects of total PUFA on musculoskeletal health and functional status in older adults

Higher versus lower total PUFA for musculoskeletal health and functional status in older adults						
Patient or population: older adults with or without musculoskeletal health problems Setting: community or institutional Intervention: Higher total PUFA intake Comparison: Lower total PUFA intake						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with lower total PUFA	Risk with higher total PUFA				
Fracture incidence				0		No evidence found
BMD (total body, lumbar and calcaneal combined), g/cm^2	Mean BMD at baseline was 0.9 g/cm^2	The mean BMD in the intervention group was no different (0.01 g/cm^2 lower to 0.02 higher)	–	245 (3 RCTs)	⨁⨁◯◯ low[a,b,c]	Increasing total PUFA may have little or no effect on BMD. Data combined from studies reporting BMD at various sites. Downgraded once each for risk of bias and indirectness
Muscle mass, fat-free mass, kg	The mean fat-free mass at baseline was 50 kg	The mean fat-free mass in the intervention group was 0.5 kg lower (1.63 lower to 0.63 higher)	–	214 (1 RCT)	⨁⨁◯◯ low[a,c,d]	Increasing total PUFA may have little or no effect on fat-free mass. Downgraded once each for risk of bias and indirectness
Total bone mass, kg				0		No evidence found
Measures of functional status				0		No evidence found

GRADE Working Group grades of evidence High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

CI confidence interval, *SMD* standardised mean difference, *MD* mean difference

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

[a]Risk of bias: none of the included studies was at low summary risk of bias, downgraded once

[b]Indirectness: various sites of measurement combined, downgraded once

[c]Imprecision: the 95% CI does not exclude the null value, but did not include important benefits or harms. Not downgraded

[d]Indirectness: single study included, downgraded once

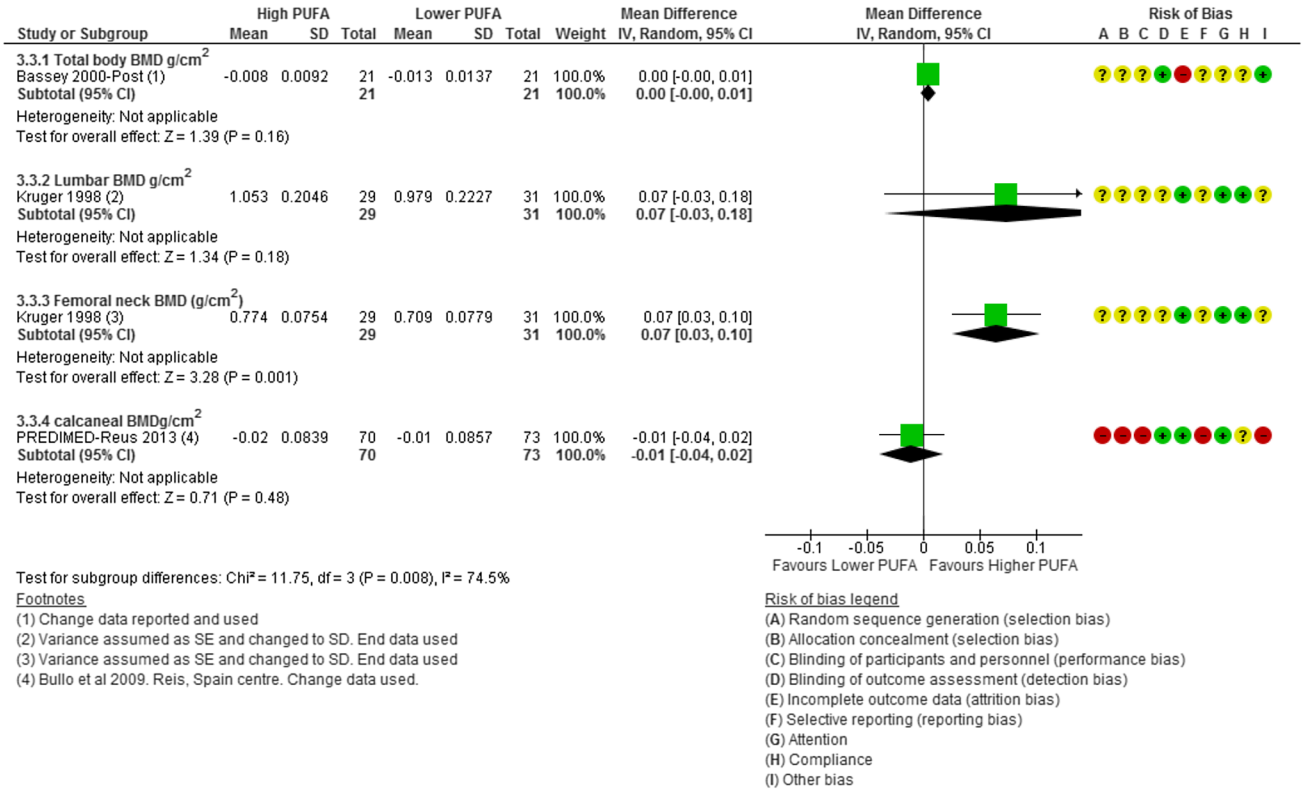

Fig. 6 Effect of high versus low mixed PUFA on BMD in different sites

Discussion

We have systematically reviewed the long-term effects of omega-3, omega-6 and total PUFA supplementation on risk factors for sarcopenia and fracture: functional status, bone density and skeletal muscle mass. We identified and included 28 RCTs (31 comparisons, 7288 participants), of which six were at low summary risk of bias. Twenty-three studies reported on the effects of increasing omega-3 fatty acids, but effects were unclear (as the evidence was of very low quality) for fracture incidence, total proximal femur BMD and skeletal muscle mass. Low or very low-quality data suggested that increasing omega-3 may increase lumbar spine and femoral neck BMD but has little or no effect on total bone mass or measures of functional status. A few small trials suggested increases in physical performance and osteocalcin with increased omega-3 but data were of limited quality. The single eligible study on omega-6 did not report on any primary outcomes, and was not at low summary risk of bias. As far as it could be interpreted, this study suggested little or no effect on arm and leg muscle strength of omega-6. Three RCTs (4 comparisons) assessed effects of increasing mixed total PUFA and none were at low summary risk of bias. None reported on fracture incidence, total bone mass or measures of functional status. The existing data suggested that increasing total PUFA may have little or no effect on BMD (when effects at different sites were combined) or fat-free mass. Data on secondary outcomes were very limited but suggested reductions in leg extensor power, C1NP, NTX/CR, CTX and urinary hydroxyproline, and a small increase in parathyroid hormone with more PUFA. There was considerable heterogeneity in populations studied and doses of fatty acids supplemented.

Observational data have suggested positive associations between intake of total PUFAs, total omega-6 and total omega-3 and BMD [61, 62]. This systematic review suggests that increasing omega-3 has little or no effect on functional status, though it may increase BMD a little. There is some evidence from reviews of shorter duration trials that omega-3 improves skeletal muscle outcomes [21] and decreases osteocalcin [19]. However, if such effects are not maintained over the longer term their utility is very limited.

To our knowledge, this is the first systematic review to evaluate all PUFA interventions on both bone and skeletal muscle health as well as functional status, important risk factors for sarcopenia, osteoporosis and increased fragility fractures. This review included trials irrespective of whether their primary aim was to assess skeletal muscle or bone outcomes. This allowed us to evaluate effects of PUFA supplementation on various measures of sarcopenia.

This was beneficial as sarcopenia has been poorly defined until recently [63, 64], and no studies assessed sarcopenia as a diagnosis. Our review excluded studies with multifactorial or multi-supplement interventions. Although this limited the evidence base used, it ensures that any effects seen are specifically related to PUFA supplementation. Our minimum intervention period was 24 weeks, as previous studies have suggested this length of time is the minimum required to allow equilibration of most body compartments with an altered fatty acid balance, and allow time for bone and muscle changes to become detectable [65, 66]. Limitations included limited numbers of relevant trials, and limited numbers of trials at low summary risk of bias. Whilst we excluded studies in individuals with overt clinical conditions that may influence the metabolism and utilisation of unsaturated fatty acids, not all studies described the proportion of individuals with, for instance, type 2 diabetes. Whilst the presence of type 2 diabetes may influence the results of supplementation studies with PUFA, we were unable to quantify these effects in the data available. This, along with heterogeneous results, has led to the evidence produced being of low or very low quality so overall the evidence to address effects of omega-3, omega-6 and total PUFA on functional, muscle and bone outcomes is limited. The inclusion of all PUFA nutritional interventions regardless of their nature (i.e. supplemental, food provision or dietary advice) could be viewed as a limitation restricting the comparability of the results, however, all interventions in the included studies aimed to increase one or more PUFA.

Despite the limitations of our study due to the lack of comprehensive evidence from trials with low risk of bias, thus limiting the conclusions from our study the importance of PUFA on musculoskeletal heath and outcomes deserves further research. The lack of studies relating greater intakes of PUFA to risk factors for sarcopenia is due to the relatively recent recognition and evolving definitions for this condition [64] as well as to the combination of exercise and dietary interventions which means it is not possible to isolate the effects of PUFA intake alone.

Recommendations for future research include larger-scale studies in populations likely to have low intakes as well as circulating concentrations of EPA and DHA. ALA interventions are also unlikely to be effective in those already consuming high concentrations of EPA and DHA due to their competition with ALA as substrates for the desaturase, elongase pathway responsible for conversion from ALA to EPA and then DHA [67]. So these studies should be limited to populations consuming small quantities of EPA and DHA. Future studies determining the effects of omega-3 PUFA on BMD would require a duration of 12 months or longer to enable detection of measurable changes and the intervention to be of sufficient scale to detect the effects these interventions. We also recommend taking baseline measurements of intake and circulating concentrations of PUFA. Reporting from trials should also include the proportion of individuals with metabolic conditions such as type 2 diabetes that may impact on the utilisation and metabolism of PUFA.

In conclusion, we found low-quality evidence that omega-3 may increase BMD by a small amount, but there were no other clear effects of omega-3 or total PUFA on skeletal muscle, bone or functional outcomes. Evidence of the effects of omega-6 supplementation on bone or skeletal muscle outcomes was insufficient to warrant any conclusions. Further trials assessing effects of omega-3, omega-6 and mixed PUFA on musculoskeletal outcomes are warranted, but only if the trials are methodologically strong (at low summary risk of bias) and appropriately powered.

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Author Contributions AW, AA and LH conceived this review; AA wrote the first draft of the protocol and submitted the protocol draft to PROSPERO; LH drafted the searches which were developed, refined, run and de-duplicated by the Cochrane Heart Group. AA and LH assessed full text papers for inclusion; LH searched trials registers and assessed entries for inclusion; AA and RS carried out data extraction and assessed risk of bias. LH and AA carried out data checks; AA and LH entered data into RevMan, ran meta-analyses and carried out sensitivity analyses. AA wrote the first draft of the review. AA and LH carried out GRADE assessment and interpretation. All authors contributed to the manuscript and agreed the final version.

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Compliance with Ethical Standards

Conflict of interest All authors have completed the Osteoporosis International's authorship and disclosure form and declare: some authors had financial support via the University of East Anglia from the World Health Organization for the submitted work, and LH and AA were funded to attend WHO meetings to present the results of other reviews in this series; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical Approval No ethical approval was required.

Human and Animal Rights and Informed Consent This article does not contain any studies with human participants or animals performed by any of the authors. Therefore, no consent form was needed.

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