Omega-3, omega-6 and polyunsaturated fat for cognition: systematic review & meta-analysis of randomised trials

Structured Abstract

Objectives: Neurocognitive function may be influenced by polyunsaturated fat intake. Many older adults consume omega-3 supplements hoping to prevent cognitive decline. We assessed effects of increasing omega-3, omega-6 or total polyunsaturated fats on new neurocognitive illness and cognition.

Design and inclusion criteria: We carried out a systematic review and meta-analysis of randomised controlled trials in adults, with duration ≥24 weeks, assessing effects of higher vs lower omega-3, omega-6 or total polyunsaturated fats and outcomes: new neurocognitive illness, newly impaired cognition, and/or continuous measures of cognition.

Methods: We searched Medline, Embase, Cochrane CENTRAL and trials registers (final update of ongoing trials December 2018). We duplicated screening, data extraction and risk of bias assessment. Neurocognitive measures were grouped to enable random-effects meta-analysis. GRADE assessment, sensitivity analyses and subgrouping by dose, duration, type of intervention and replacement were used to interrogate our findings.

Results: Searches generated 37,810 hits, from which we included 38 RCTs (41 comparisons, 49,757 participants). Meta-analysis suggested no or very little effect of long-chain omega-3 on new neurocognitive illness (RR 0.98, 95% CI 0.87 to 1.10, 6 RCTs, 33,496 participants, I^2

36%), new cognitive impairment (RR 0.99, 95% CI 0.92 to 1.06, 5 RCTs, 33,296 participants, I^2 0%) or global cognition assessed using the Mini-Mental State Examination (MD 0.10, 95% CI 0.03 to 0.16, 13 RCTs, 14,851 participants, I^2 0%), all moderate-quality evidence. Effects did not differ with sensitivity analyses, we found no differential effects by dose, duration, intervention type or replacement. Effects of increasing ALA, omega-6 or total PUFA were unclear.

Conclusions: This extensive trial dataset enabled assessment of effects on neurocognitive illness and cognitive decline not previously adequately assessed. Long-chain omega-3 probably has little or no effect on new neurocognitive outcomes or cognitive impairment.

Implications: Long-chain omega-3 supplements do not help older adults protect against cognitive decline.

Introduction

Older adults, including those living in long-term care, are at high risk of cognitive impairment, and neurocognitive ill-health.[1-3] Fifty million people worldwide were living with dementia in 2018, a number predicted to rise to 152 million in 2050.[4] Neurocognitive disorders, including dementias, are major causes of health and social care cost, disability adjusted life years and mortality worldwide.[5-7] Dementia costs worldwide are one trillion US dollars annually and rising, with 66% of new cases in low- and middle-income countries.[4]

There is keen interest in potential cognitive protection offered by polyunsaturated fats, particularly omega-3,[8-10] which is one of the most common dietary supplements. US adults' long-chain omega-3 intakes are greater from dietary supplements (0.72 g/d EPA and DHA) than foods (0.41 g/d).[11] Polyunsaturated fatty acids, especially docosahexaenoic acid (DHA, one of the long-chain omega-3 fats, found in oily fish and arachidonic acid, an omega-6), are key structural components of the brain and central nervous system and may help maintain membrane integrity and neuronal function.[9] DHA may also be neuroprotective via anti-inflammatory mechanisms, competing with pro-inflammatory omega-6.[9] These mechanisms suggest that long-chain omega-3 fats (LCn3) may be protective, and omega-6 fats neutral or harmful, to cognition.

However, LCn3 supplements (though not ALA) may harm neurocognition by another mechanism. Marine-origin foods and LCn3 supplements are at risk of contamination by heavy metals, organochlorines, polychlorinated biphenyls (PCBs) and polycyclic aromatic hydrocarbons (PAHs), all known to harm human health.[12, 13] Possible impacts on human health from ingesting unsafe levels of PCBs and/or methyl mercury include reduced cognitive

function and neurological disorders.[13, 14] Systematic reviews of observational data suggest higher omega-3 intake,[15] and higher omega-3 to omega-6 ratio, are associated with better cognition.[16] However, reverse causation and confounding by other lifestyle factors are feasible and could explain such relationships even in the absence of health benefits from increasing omega-3 intakes; for example poor cognition may lead to poorer quality dietary intake.

A 2012 Cochrane review assessed effects of omega-3 fats on neuro-cognition. That review found no trials of incident dementia and included three RCTs assessing effects on cognition, concluding that longer studies were required to allow time for greater cognitive changes to occur.[17] Our review aimed to systematically review effects of higher vs lower intakes of LCn3, alpha-linolenic acid (ALA), omega-6 and total polyunsaturated fatty acids (PUFA) on new neurocognitive outcomes, new impaired cognition, and cognitive function in randomised controlled trials (RCTs) of at least 6 months duration. This review was commissioned to inform the development of World Health Organization (WHO) guidance on polyunsaturated fatty acid intake.

Methods

This systematic review and meta-analysis is one of a series assessing health effects of omega-3, omega-6 and total PUFA,[18-26] its protocol was registered on PROSPERO (CRD42017019049). Detailed methods for the review series are reported elsewhere,[23] and briefly summarised for this review below.

We included randomised controlled trials (RCTs) that compared higher versus lower omega-3, omega-6 and/or total PUFA intakes in adults (18+ years, not pregnant or seriously ill) with or without current or previous diagnosis of any type of neurocognitive illness or impairment, unlimited by language, publication type or publication date. The intervention could consist of foodstuffs, oral supplements (oil, capsules, or provided foodstuffs) or advice that increased or decreased omega-3, omega-6 and/or total PUFA intake, or (if no specific aim was stated) achieved a change of ≥10% of baseline intake. Studies were excluded if they carried out multiple risk factor interventions on lifestyle or dietary factors other than PUFA. Interventions to raise or lower PUFA intake had to be compared with usual diet, no advice, no supplementation or placebo (as appropriate), or compared raised versus lowered PUFA intake. Trial duration minimum was 24 weeks, which reflects metabolic studies suggesting 6 months is the minimum duration of supplementation required to ensure equilibration of LCn3 into most body compartments, including the brain.[27] Studies were included if they collected data on any primary outcome, even if study objectives were not primarily neuro-cognitive. Primary outcomes were new neurocognitive illness, newly impaired cognition, global cognition, executive function, processing speed and memory (including verbal, spatial and other memory and attention).

We searched Cochrane CENTRAL, Medline and Embase to 27th April 2017, ClinicalTrials.com and the World Health Organization International Clinical Trials Registry Platform to September 2016, and reassessed all ongoing trials in December 2018. We checked included trials of relevant systematic reviews, and wrote to authors of included studies for additional studies and trial data (including unpublished summary outcome data). See methods paper for detailed search strategies.[23]

Study inclusion, data extraction and assessment of risk of bias (on a specially developed form) were conducted independently in duplicate. We extracted study-level data and assessed Cochrane risk of bias domains plus risk from compliance problems and attention bias.[23, 28] We considered trials to be at low summary risk of bias where we judged randomisation, allocation concealment, blinding of participants, personnel and outcome assessors adequate (all other trials were considered at moderate or high risk of bias).

Analysis and Interpretation

Main analyses assessed effects of omega-6, LCn3, ALA and total PUFA interventions on primary outcomes using random effects meta-analysis with risk ratio or mean differences in Review Manager version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark).[29] Pre-specified sensitivity analyses included fixed effects analysis, limiting analysis to studies at low summary risk of bias, limiting to studies at low risk for compliance issues, and limiting to trials randomising at least 100 participants. Pre-specified subgroup analysis was conducted for outcomes with at least 10 included studies to assess whether effects differed by intervention type (dietary advice, supplementary capsules, supplementary foods or a combination), replacement, dose, duration, baseline dementia (primary prevention where <50% diagnosed with cognitive problems, secondary prevention where ≥50% diagnosed with

cognitive problems) and anti-dementia medication use in ≥50% participants.[23] We planned to sub-group by number of anti-dementia medications used, baseline intake of omega-3, omega-6 or total PUFA, and omega-3/omega-6 ratio, but this information was not available in most trials so was not attempted. We assessed heterogeneity between trials using I^2, and small study bias using funnel plots and knowledge of missing data.[30]

Because of the diversity of metrics used to measure cognitive function, pooled analysis was often only possible by grouping similar measures. We standardised groupings by adopting neurocognitive domains suggested by others,[31-33] placing data in a domain (and subdomain) by researching the derivation, purpose and supported interpretation for each metric (Table 1). The direction of scales in forest plots was standardised so that a lower score signified lower levels of cognitive ability and different scales were combined meta-analytically using standardised mean differences. Within each cognitive domain we ordered tests so that the best, most commonly used and most immediate tests were higher in Table 1. Outcomes were preferred in this order in forest plots: thus, if a single study reported several tests within a single domain all test results were displayed in the forest plot but only the first results for that study (those nearest the top of the forest plot and Table 1) were pooled in meta-analysis, ensuring that the most useful tests had as much available data as possible. Data from individual participants were never counted more than once in any single meta-analytical pooling.

Effect sizes were interpreted as agreed with the World Health Organization (WHO) Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health and pre-specified for this set of reviews[23]. RR <0.92 or >1.08 was considered a relevant clinical effect (RR 0.92 to 1.08 was considered "little or no effect"), while a mean difference between arms of

≥5% of baseline was required for a relevant clinical effect for continuous measures. Outcome data were interpreted using GRADE assessment,[23] Where GRADE suggested data of very low-quality we did not interpret effect sizes. Where data were of low-quality we used the term "may", moderate-quality evidence warranted "probably" in describing effects.

WHO funded the research, and the WHO NUGAG Subgroup on Diet and Health was involved in its design, but not in data collection, analysis, interpretation or the decision to publish. The exception is that GRADE assessment was drafted by LH then discussed and agreed with NUGAG as part of guidance development. All researchers had full access to all the data (within a shared database) and take responsibility for the accuracy and integrity of the data.

Results

The broader search strategy for the full set of reviews generated 37,810 hits, de-duplicated to 19,772 titles and abstracts from which 364 RCTs (reported in 1020 papers) of omega-3, omega-6 or total PUFA with a duration of at least 24 weeks were found.[23] From this set of trials we included 38 RCTs (41 comparisons, including 49,757 participants) that assessed outcomes of interest to this review (see Figure 1 of our database paper for PRISMA flowchart;[23] Table 2 in this paper presents brief characteristics of included RCTs).

Trials were published from 1978 to 2018; only two did not take place in high income countries. Mean duration was 21 months. Thirty six comparisons compared higher with lower LCn3, two compared higher with lower ALA[34-36], 1 omega-6[37], one total PUFA[38-40] and one increased both omega-6 and total PUFA[41]. All trials were of capsular supplements except for four LCn3 trials (one of supplementary margarine[34, 35], one of advice to eat more oily fish [41], and two providing fish sausages[42, 43]), both ALA trials (supplementary margarine[34, 35] and yogurt with added canola[36]), the omega-6 trials (provided emulsified oil[37] or advice to increase specific oils and margarines[41]) and total PUFA trial (dietary advice plus oil or nut supplements[38-40]). LCn3 doses ranged from 150mg/day to 4.4 g/day, but most were in the range 400-2400 mg/d (Table 2). Participants included people with normal and impaired cognition at baseline. Fifteen comparisons were at low summary risk of bias, see Figure 1 for risk of bias assessments by trial and domain. Key findings are summarised here, results are presented in full with references, forest plots and GRADE assessments in the Appendix.

Six RCTs reported adverse neurological outcomes, including dementia, low cognitive function, neurological hospitalisation and motor neurone disease[41, 44-48]. Meta-analyses suggested that increasing LCn3 had little or no effect on new neurocognitive diagnosis (RR

193 0.98, 95% CI 0.87 to 1.10, I^2 36%, >33,000 participants of whom 2622 developed a
194 neurocognitive illness, moderate-quality evidence) and little or no effect on new cognitive
195 impairment (RR 0.99, 95% CI 0.2 to 1.06, I^2 0%, >33,000 participants of whom 2551
196 developed impaired cognition, moderate-quality evidence), Figure 2. This lack of effect did
197 not alter in sensitivity analyses or when subgrouping by dose, duration or replacement by
198 LCn3 of other nutrients.
199
200 Nineteen trials provided assessment of LCn3 on global cognition using at least one scale,
201 including >20,000 participants for ≥6 months, in people with normal cognition to moderate
202 dementia at baseline. Effects in the 11 different scales provided different answers (test for
203 subgroup differences p<0.00001), so we ran our assessment including 13 trials (14,851
204 participants) using Mini-Mental State Examination (MMSE, which runs from 0, very poor
205 cognition, to 30, or normal cognition [49]). Increasing LCn3 led to a very small improvement in
206 MMSE, altering it by <1% of baseline (MD 0.10, 95% CI 0.03 to 0.16, I^2 0%, Figure 3,
207 unaltered in sensitivity analyses, moderate-quality evidence), but we are aware of high levels
208 of missing data and the funnel plot suggested small study bias (Figure A2 in the Appendix).
209 If we added small studies to correct this bias we would move the MD closer to zero (no
210 effect). Subgrouping did not suggest differences in effect by LCn3 dose, duration,
211 replacement (of MUFA, omega-6 or non-fat), intervention type (supplemental foods or
212 capsules), baseline cognitive status (normal or impaired cognition), or cognitive medication
213 use.
214
215 Six trials (including 1757 participants) assessed executive function, five trials (including
216 1426 participants) assessed effects of LCn3 on processing speed, and eleven (including 5698
217 participants) assessed memory. Meta-analysis suggested little or no effect for all of these

measures (as well as the sub-categories of memory, all moderate- or low-quality evidence, see Appendix for further information).

We found no trials assessing effects of ALA on new neurocognitive outcomes or cognitive decline, executive function, processing speed or any type of memory. Two trials assessed effects of ALA on global cognition, the ALA assessment in Alpha-Omega (assessing MMSE in 2522 participants) and Rebello (measuring ADAS-Cog in 4 participants at study end).[34, 36] As Rebello was so small we did not combine these data and use SMD. Alpha-Omega suggested little or no effect of increasing ALA on MMSE (MD 0.14, 95% CI -0.03 to 0.31, a change of 1% from baseline MMSE, low-quality evidence).

Only one RCT noted new cognitive outcomes following two years of omega-6 intervention in 2033 men, reporting 2 cases of dementia and 5 of motor neurone disease, insufficient data on which to assess health effects. One small trial increased omega-6 and assessed global cognition (EDSS mentation), but did not provide any measure of variance so statistical significance was unclear. We found no trials of omega-6 reporting executive function, processing speed, verbal, spatial or other memory, or attention.

Two RCTs noted new neurocognitive outcomes following ≥2 years of increased PUFA, including 20 cases of dementia, 62 of mild cognitive impairment and 5 of motor neurone disease. Effects of increasing PUFA on new neurocognitive diagnosis were unclear as the evidence was of very low-quality. Two cohorts of a single large trial (PREDIMED) assessed global cognition using the MMSE in a subset (629) of participants. Effects of increasing PUFA on global cognition was unclear as the evidence was of very low quality while the effect size was <1% of baseline, MMSE MD -0.14, 95% CI -0.44 to 0.16. Some PREDIMED

participants were assessed for verbal memory, spatial memory and executive function. Data were limited from this trial, which was at moderate to high summary risk of bias, suggesting changes <5% of baseline for verbal memory and executive function. However, there was a larger change in spatial memory, suggesting an improvement in spatial memory with more PUFA (assessed using the Color Trail Test part 1, MD 7.17, 95% CI 0.48 to 13.86, I^2 0%). No trials assessed effects of increasing total PUFA on processing speed.

Discussion

Increasing LCn3 probably has little or no effect on new neurocognitive outcomes, new impaired cognition, global cognition, executive function, processing speed or memory. Increasing ALA may have little or no effect on global cognition, but we found no RCTs of ALA reporting other neurocognitive outcomes. The effects of increasing omega-6 or total PUFA on new neurocognitive outcomes, cognitive decline and global cognition, executive function, processing speed or memory are unclear.

Recent systematic reviews have assessed effects of omega-3 fats on cognition in different ways, but all included many fewer RCTs than this review, limiting their ability to accurately assess effect sizes. Yurko-Mauro et al. reported significant between-group benefits for episodic memory after DHA supplementation, based on results reported in only five RCTs (describing <1000 participants).[33] However, Yurko-Mauro et al. pooled all reported measures of episodic memory from each trial, which means that many, but not all, participants were included four or five times in a single meta-analyses. This is statistically inappropriate as it over-counts effects in some participants.[33] They did not find between-group differences for semantic or working memory outcomes. Zhang et al. pooled data from six pre-2015 RCTs and found statistically significant but clinically unimportant differences in MMSE (WMD = 0.15; 95% CI: 0.04-0.26; p = 0.006), results similar to this review.[50] It was unclear why they used WMD (rather than MD) to combine the single scale. Both Yurko-Mauro et al. and Zhang et al. included short RCTs (<24 weeks duration) ineligible for our review and less able to accurately assess changes in cognition over time than longer trials. A 2013 systematic review of nutritional interventions for Alzheimer's Disease suggested that long-chain omega-3 supplementation improved verbal fluency (in two small trials), might support cognition in very mild AD (in one trial) but did not alter neuropsychiatric symptoms,

delay the rate of cognitive decline, or affect memory, global cognition or brain volume (each in individual trials).[51] A 2017 network meta-analysis assessing the utility of nutritional strategies in managing Alzheimer's Disease included six trials of omega-3[52-54] ranked omega-3 as the worst of their nutritional interventions (the efficacy of omega-3 was compared with antioxidants, B-vitamins, inositol, medium-chain triglyceride, polymeric formulas, polypeptide, and vitamin D).[55] A 2018 systematic review of RCTs by Butler et al. assessing effects of over-the-counter nutritional supplements found insufficient evidence to recommend any supplement for cognitive protection in adults (including omega-3).[56] That review included only 9 trials compared to our 38 RCTs. A recent Cochrane review of effects of omega-3 for treatment of dementia found only three RCTs and no convincing evidence of beneficial effects on cognition or quality of life.[57]

We found statistically significant but clinically unimportant effects of LCn3 on MMSE scores, differing by <1% of baseline. The MMSE asks verbal questions to detect impaired thinking and was developed, and is most validated, for dementia screening.[58] The three trials contributing 94% of the weight to this analysis included 13,503 participants and were all of at least 3 years duration. The largest was 6 years long, suggesting that the reason for the small effect size was not that trials were too short or too small. Doses of LCn3 were 0.40, 0.84 and 1.04g/d, 0.84/d in the largest single RCT. Eating three portions of fish per week, one of which is oily (current healthy eating advice), provides approximately 0.4g/d LCn3. Data on effects of LCn3 will be strengthened with publication of VITAL-Cog, which randomised almost 4000 participants aged 60+ years for 5 years with a primary outcome of change in cognitive function.[59] VITAL cardiovascular outcomes were published in late 2018, but cognitive outcomes are not expected until late 2020.

We used subgrouping to assess whether effects differed according to whether supplementary capsules, foods rich in specific PUFAs or foods supplemented with specific PUFAs were provided. There were no suggestions that effects of foods were different from those of capsules, but as most trials were of capsules there was little power to assess differential effects. As effects would be greater when omega-6 is replaced by LCn3 if the omega-3 to omega-6 ratio theory is important, we also assessed whether effects differed by replacement (see for example Figure A4), but no important differences were observed. We did not find different effects in trials of higher LCn3 doses or of longer durations, as noted in the Appendix page 3, as would be expected if some included trials are too short or of too low a dose.

We were interested in both potential benefits and harms, and found moderate-quality evidence of little or no effect of LCn3 on neurocognitive outcomes or cognitive ability. We found neither benefits nor harms, and low-quality evidence of little or no effect of ALA on global cognition. Evidence of any effect of ALA, omega-6 and total PUFA on neurocognitive outcomes and cognition are lacking. Other potential reasons for increasing polyunsaturated fat intake, including effects on cardiovascular diseases, cancers, inflammatory bowel disease, body weight, diabetes and glucose metabolism, depression and anxiety and all-cause mortality, have been considered elsewhere in our series of systematic reviews.[18-20, 23, 60-64]

We devised domains to group similar metrics and undertake pooled analysis building on previous literature; however, our groups are not definitive. We did not set out to devise an authoritative logic model for to group neurocognitive measures. Any such grouping is likely to be imperfect. While alternative clustering or order of neurocognitive measures may have

yielded slightly different numerical summaries, the lack of clinical effect from PUFA interventions that we report is consistent across many different measures. We have tried to be transparent about the statistical significance of individual measures as reported in the original studies (see Tables and Figures in the Appendix), as well as the rationale used when pooling similar measures, to look for possible effects of LCn3, ALA, omega-6 and total PUFA.

Conclusions and implications

People concerned about their cognitive health should be advised that taking long-chain omega-3 supplements is not helpful for cognition, but neither is it harmful. No further trials of supplementary LCn3 should be initiated until VITAL-COG has reported, but methodologically strong and long duration trials of increased oily fish intake, nuts and foods high in ALA, and increased omega-6 and total PUFA intake are needed to further inform dietary advice for cognition.

Ethical approval: No ethical approval was required.

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Figure titles

Figure 1. Risk of bias assessment for each included trial by risk of bias domain

Figure 2. Effects of increased LCn3 on neurocognitive outcomes individually and grouped, random effects meta-analysis.

Figure 3. Effects of increased LCn3 on measures of global cognition, random effects meta-analysis. (Different measures not combined as the test for subgroup differences suggested severe heterogeneity between tests.)

613 **Table 1. Cognitive measures allocated to cognitive domains and subgroups**

Cognitive domains	Sub-domain	Measures*
Diagnosis of cognitive decline		• Dementia diagnosis • MCI (Mild cognitive impairment) • TICS (Telephone Interview for Cognitive Status), score <30 • EDSS (Expanded Disability Status Scale), mentation change
Global cognition		• MMSE (Mini-Mental State Examination) • ADAS- Cog (Alzheimer's Disease Assessment Scale – Cognitive subscale) • CDR (Clinical Dementia Rating scale) • CIBIC-Plus (Clinician's Interview-Based Impression of Change with caregiver input) • HDS (Hasegawa Dementia Scale) • FTICS Score – French Telephone Interview for Cognitive Status • BCAT (Brief Cognitive Assessment Tool), total score, cognitive function • IQ (Intelligence Quotient) • Global brain volume change • Global cognitive function z-score (study-specific batteries)
Executive function		• Working memory – 2 back accuracy • Working memory – 2 back response time • BCAT working memory • BCAT mental arithmetic efficiency • SOC (Stockings of Cambridge) problem solved • Numeric working memory % accuracy • Digit Span Forward • Executive function z score (study-specific batteries)
Memory	Verbal	• CANTAB (Cambridge Neuropsychological Test Automated Battery), VRM (verbal recognition memory), immediate recall, total correct • CANTAB VRM, free recall, total correct • CVLT (California Verbal Learning Test) • RAVT (Rey Verbal Learning Test), immediate recall • CANTAB VRM, delayed recall, total correct • RAVT, delayed recall • Verbal Fluency
	Spatial	• CANTAB SWM (spatial working memory), between errors • BCAT SIE (Space Imagery Efficiency) • CANTAB PRM (pattern recognition memory), delayed, number correct • Corsi blocks span score • Color Trail test part 1
	Attention	• DSST (Digit symbol substitution test) • Stroop overall % accuracy • Attention z-score (study-specific batteries)

	Others	• MMSE, Memory section • Lexical Fluency • Memory Functioning, mean within group change • BCAT Recognition Memory • Memory z-score (study-specific batteries)
Processing Speed		• BCAT, perceptual speed • Stroop total correct RT • Processing speed z-score (study-specific batteries)

614 * Not every test within each domain or outcome group was applied for every intervention

615

Table 2. Brief characteristics of, and references for, included studies.

Study	Participant age profile	Participant characteristics & cognition	Duration	Country	Comparison	Number randomised		Summary Risk of Bias
						Intervention	Control	
ADCS-Quinn 2010 [65]	Mean 76 yrs	Individuals with mild to moderate Alzheimer disease (I)	18 m	USA	DHA vs. n6	238	164	Low
Alpha-Omega ALA [34, 35]	60-80 yrs	60-80 year olds with previous MI (N)	40 m	Netherlands	ALA vs. MUFA	(1257)	(1265)	Low
Alpha-Omega EPA+DHA [34, 35]	60-80 yrs	60-80 year olds with previous MI (N)	40 m	Netherlands	EPA+DHA vs. MUFA	1240	1282	Low
AREDS 2 2014 [48, 66]	50-85 yrs	People at high risk of progression to advanced age-related macular degeneration (N)	5 yrs	USA	EPA+DHA vs. nil	2147	2056	Low
ASCEND 2018 [44]	≥40 yrs	People with diabetes, without apparent vascular disease (N)	7.4 yrs	UK	EPA+DHA vs. MUFA	7740	7740	Low
Baleztena 2015 [67]	75 yrs +	Institutionalised older adults without cognitive problems (N)	1 yr	Spain	EPA+DHA vs. nil	49	49	MoH
Bo 2017 [68]	≥ 60 yrs	Older adults with mild cognitive impairment (I)	6 m	China	EPA+DHA vs. MUFA	44	42	MoH
Boespflug 2016 [69]	62-80 yrs	Older adults with subjective memory impairment (I)	6 m	USA	EPA+DHA vs. LA	15	12	MoH
Chiu 2008 [70]	70-81 yrs	Older adults with Alzheimer's Disease or Mild Cognitive Impairment (I)	6 m	Taiwan	EPA+DHA vs. MUFA	24	22	MoH
Chiu 2010 (NCT01235533)	60 yrs +	Older people with Late-Life Depression (N)	11 m	Taiwan	EPA+DHA vs. MUFA	nr	nr	MoH
DART 1989 (fat) [41]	<70 yrs	Men recovering from an MI (N)	2 yrs	UK	n6 vs. mixed fats	(1018)	(1015)	MoH
DART 1989 (fish) [41]	<70 yrs	Men recovering from an MI (N)	2 yrs	UK	EPA+DHA vs. nil	1015	1018	MoH

Study	Participant age profile	Participant characteristics & cognition	Duration	Country	Comparison	Number randomised		Summary Risk of Bias
						Intervention	Control	
EPOCH 2011 [71]	65-90 yrs	Healthy older adults with no cognitive impairment (N)	18 m	Australia	EPA+DHA vs. MUFA	195	196	Low
Hashimoto 2012 [43]	Mean 72.5 yrs	Healthy older people (N)	1 yr	Japan	EPA+DHA vs. MUFA	57	54	MoH
Hashimoto 2016 [42]	Mean 88 yrs	Healthy older people (N)	1 yr	Japan	high DHA vs. low DHA	43	32	MoH
Jackson 2016 [72]	Mean 60 yrs	Healthy adults with subjective memory deficit (MMSE ≥26, MAC-Q score > 24) (I)	6 m	UK	high DHA vs. low DHA+PUFA	33	32	MoH
Lee 2012 [73]	≥60 yrs	Elderly individuals living in low to middle socioeconomic public flats (N)	1 yr	Malaysia	EPA+DHA vs. LA	18	18	MoH
MAPT 2017 [74]	≥70 yrs	People without dementia but with memory complaint, IADL limitation or slow gait speed (mixed)	3 yrs	France, Monaco	EPA+DHA vs. non-fat	432	420	Low
MEMO Van de Rest 2008 [75]	≥ 65 yrs	Independently living people (N)	6 m	Netherlands	EPA+DHA vs. MUFA	96	103	MoH
MIDAS 2010 [76]	≥ 55 yrs	Healthy older people with subjective memory complaints (no dementia diagnosis) (I)	24 wks	USA	EPA+DHA vs. LA	242	243	Low
Nutristroke Antiox [77]	Mean 65 yrs	People who had survived a stroke (N)	1 yr	Italy	EPA+DHA vs. nil	18	16	MoH
Nutristroke No antiox [77]	Mean 65 yrs	People who had survived a stroke (N)	1 yr	Italy	EPA+DHA vs. nil	20	18	MoH
OFAMS Torkildsen 2012 [78]	Mean 38.6 yrs	People with relapsing remitting multiple sclerosis (N)	6 m	Norway	EPA+DHA vs. LA	46	46	MoH
OmegAD 2008 [52-54]	Mean 73 yrs	People with mild to moderate Alzheimer's disease (I)	6 m	Sweden	EPA+DHA vs. LA	103	101	MoH

Study	Participant age profile	Participant characteristics & cognition	Duration	Country	Comparison	Number randomised		Summary Risk of Bias
						Intervention	Control	
OPAL Dangour 2010 [79]	70-79 yrs	Healthy cognitively normal adults (N)	2 yrs	UK	EPA+DHA vs. MUFA	434	433	Low
ORIGIN 2013 [80]	Mean 64 yrs	People at high risk of CV events and impaired glucose metabolism (N)	6 yrs	Multiple	EPA+DHA vs. MUFA	6319	6292	Low
Paty 1978 [37]	Mean 45 yrs	Patients with multiple sclerosis (N)	2.5 yrs	Canada	LA vs. MUFA	38	38	MoH
Pomponi 2014 [81]	Mean 64 yrs	Adults with mild to moderate Parkinson's disease (N)	6 m	Italy	EPA+DHA vs. LA	12	12	MoH
PREDIMED 2013 [38-40]	Mean 67 yrs	People with several CVD risk factors (N)	56 m	Spain	high PUFA vs. low PUFA	2454	2543	MoH
Puri 2005 [82]	Mean 50 yrs	People with Huntington's Disease (N)	1 yr	Multiple	EPA vs. non-fat	67	68	Low
Raitt 2005 [46]	Mean 62.5 yrs	People with heart rhythm problems (N)	2 yrs	USA	EPA+DHA vs. MUFA	100	100	MoH
Rebello 2015 [36]	58-78 yrs	Healthy older people	24 wks	USA	ALA vs. mixed fats	3	3	MoH
Romero 2013 [83]	Mean 72.5 yrs	People with mild cognitive impairment (I)	6 m	Spain	EPA+DHA vs. nil	15	15	MoH
Schattin 2016 [84]	Median 67 yrs	Older adults (N)	26 wks	Italy	EPA+DHA vs. MUFA	29	29	Low
SCIMO Von Schacky 1999 [47]	Mean 58 yrs	People with coronary artery disease (N)	2 yrs	Germany	EPA+DHA vs. mixed fats	112	111	Low
Shinto 2014 [85]	Mean 75.6 yrs	People with probable Alzheimer dementia (I)	1 yr	USA	EPA+DHA vs. LA	13	13	MoH
Sinn 2012 [86]	Mean 74.5 yrs	Older people with mild cognitive impairment (I)	6 m	Australia	EPA+DHA vs. LA	18	18	Low
Stonehouse 2013 [87]	Mean 33.3 yrs	Healthy men and women (N)	6 m	New Zealand	DHA vs. MUFA	115	113	MoH
SU.FOL.OM3 Galan 2010 [88-90]	Mean 61 yrs	People with a history of CVD (N)	4 yrs	France	EPA+DHA vs. non-fat	1248	1253	Low

Study	Participant age profile	Participant characteristics & cognition	Duration	Country	Comparison	Number randomised		Summary Risk of Bias
						Intervention	Control	
Terano 1999 [91]	Mean 83 yrs	Older adults living in a care home with mild to moderate dementia (I)	1 yr	Japan	EPA+DHA vs. nil	10	10	MoH
Zhang 2017 [92]	Mean 74.5 yrs	Otherwise healthy elderly people with mild cognitive impairment (I)	1 yr	China	EPA+DHA vs. LA	120	120	MoH
Total 38 RCTs, 41 comparisons			*Mean 20.5 months*		*36 LCn3, 2 ALA, 1 omega-6, 1 PUFA, 1 both omega-6 & PUFA*	*24942 (24901 of LCn3)*	*24815 (24774 of LCn3)*	*14 Low*

Notes: yr = year, N = recruited assuming normal cognition, I = recruited assuming impaired cognition, MoH = Moderate or High summary risk of bias, Low = low summary risk of bias, m = months, wks = weeks, LA: Linoleic acid, MUFA: monounsaturated fatty acid, nr = not reported

Figure 1 eps format

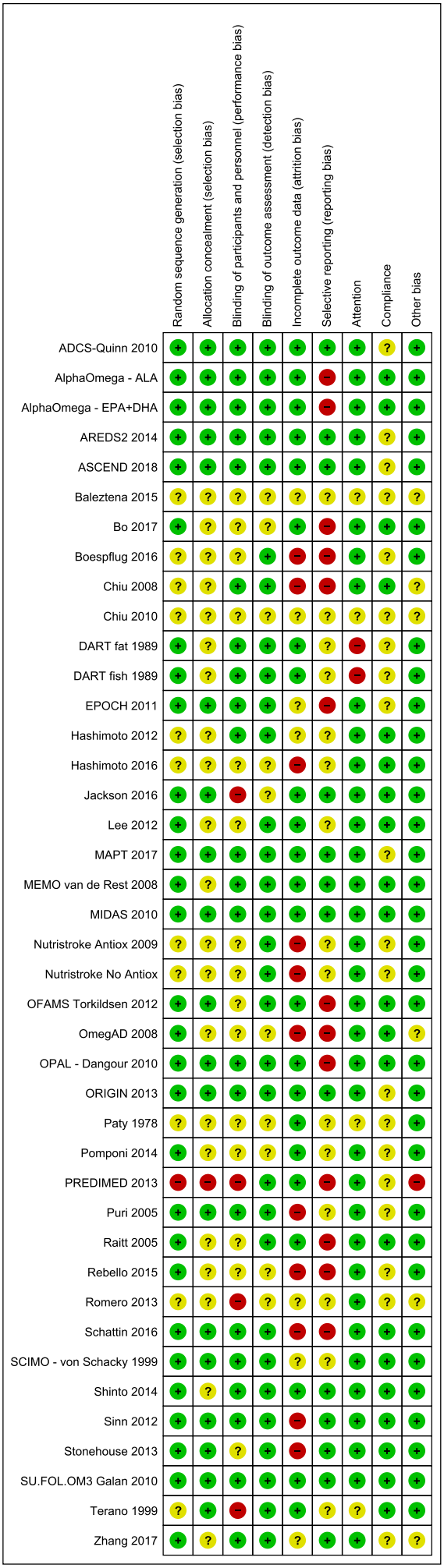
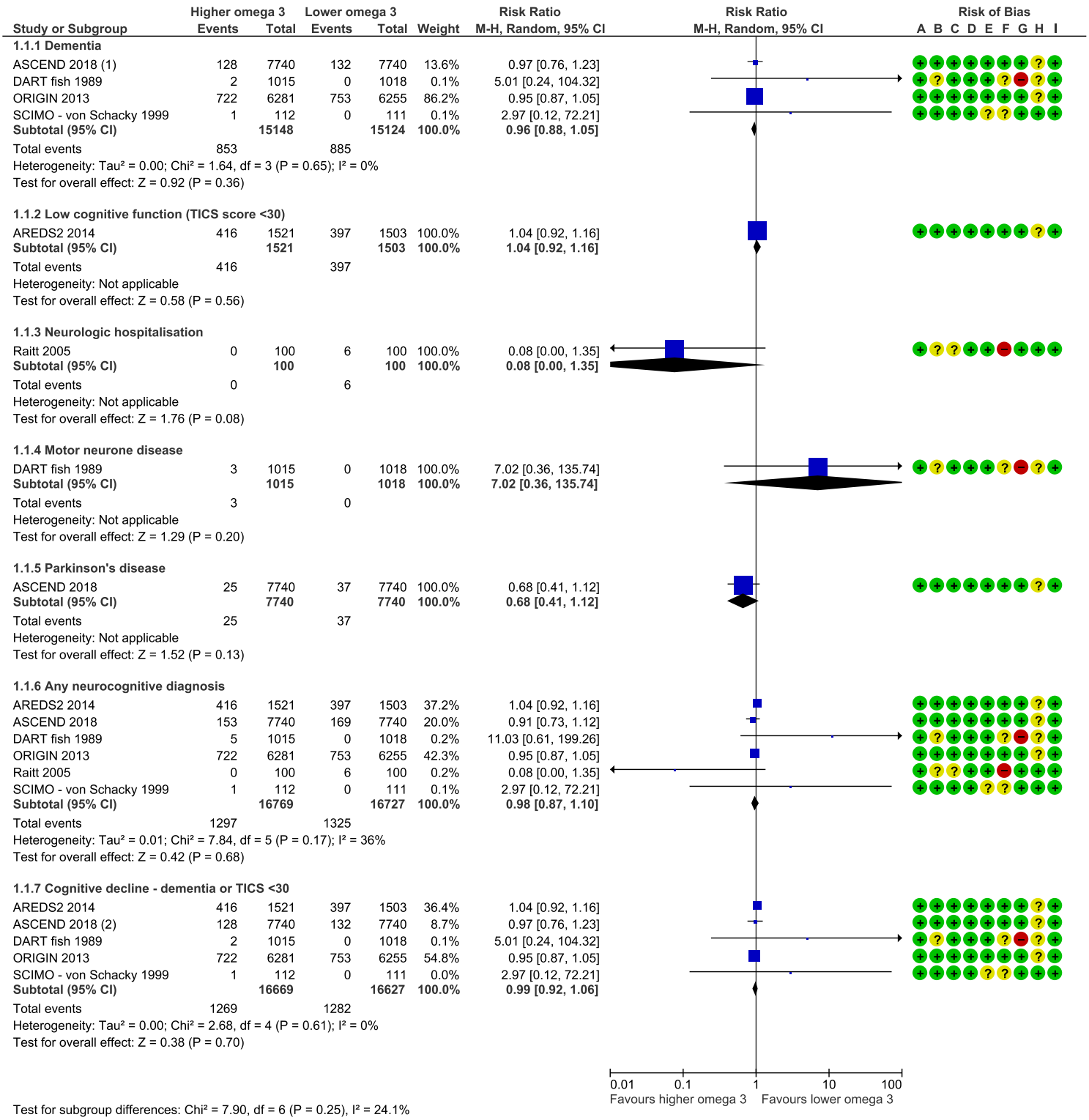


Figure 2 eps format



Test for subgroup differences: Chi² = 7.90, df = 6 (P = 0.25), I² = 24.1%

Footnotes

(1) Mental impairment including any dementia or memory loss diagnosis

(2) Mental impairment including any dementia or memory loss diagnosis

Risk of bias legend

(**A**) Random sequence generation (selection bias)

(**B**) Allocation concealment (selection bias)

(**C**) Blinding of participants and personnel (performance bias)

(**D**) Blinding of outcome assessment (detection bias)

(**E**) Incomplete outcome data (attrition bias)

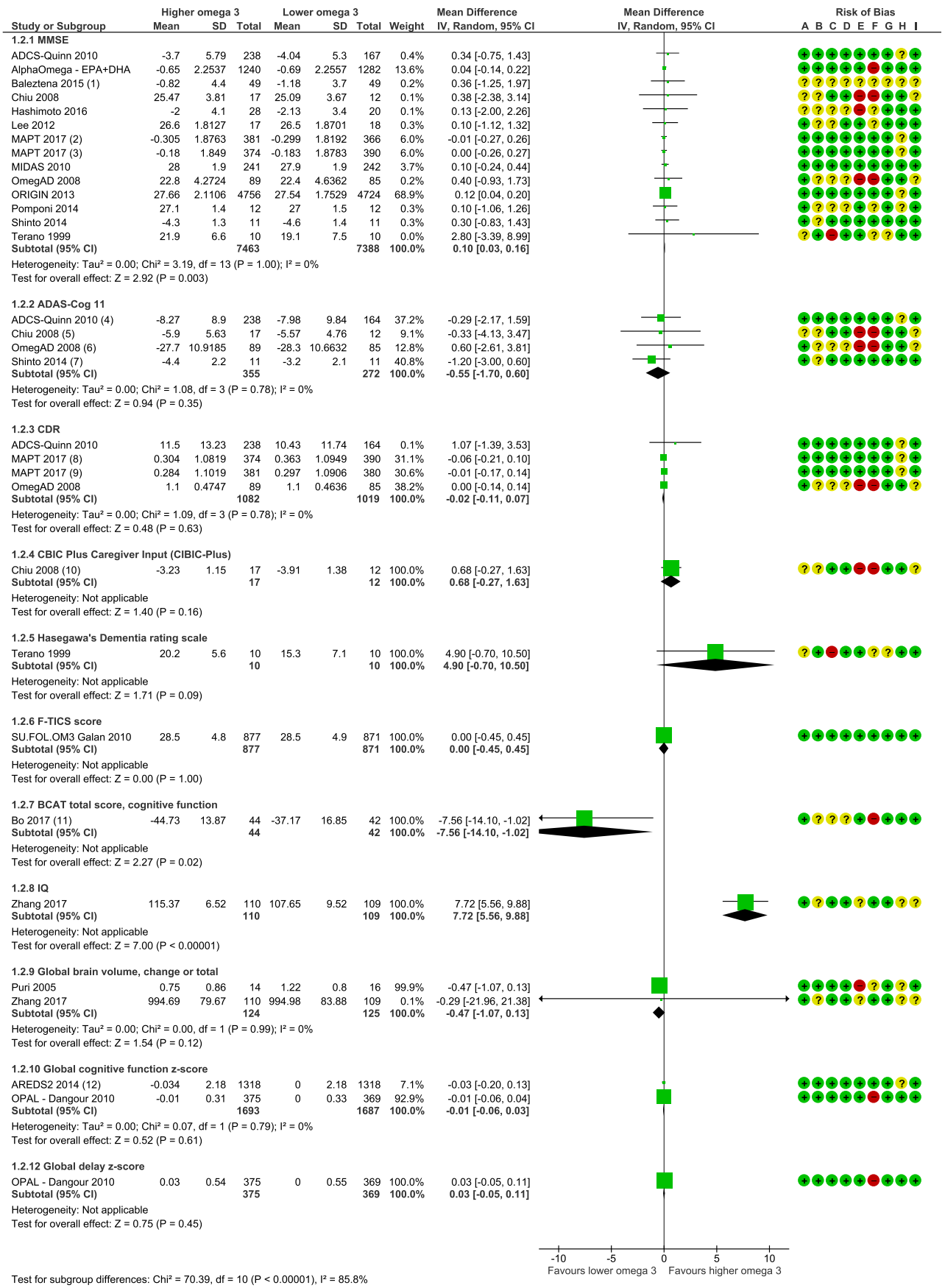
(**F**) Selective reporting (reporting bias)

(**G**) Attention

(**H**) Compliance

(**I**) Other bias

Figure 3 eps format



Test for subgroup differences: Chi² = 70.39, df = 10 (P < 0.00001), I² = 85.8%

Footnotes

(1) SDs unlikely, calculated assuming SEs
(2) PUFA vs placebo arms only
(3) Multidomiain intervention plus PUFA vs Multidomain intervention plus placebo arms only
(4) multiplied mean by -1
(5) multiplied mean by -1
(6) multiplied mean by -1
(7) multiplied mean by -1
(8) Multidomiain intervention plus PUFA vs Multidomain intervention plus placebo arms only
(9) PUFA vs placebo arms only
(10) multiplied by -1
(11) multiplied mean by -1
(12) Composite score of all cognitive tests

Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Attention
(**H**) Compliance
(**I**) Other bias