Omega-3, omega-6 and polyunsaturated fat for cognition: systematic 1 review & meta-analysis of randomised trials 2 3 4 **Structured Abstract** 5 6 **Objectives:** Neurocognitive function may be influenced by polyunsaturated fat intake. Many 7 older adults consume omega-3 supplements hoping to prevent cognitive decline. We 8 assessed effects of increasing omega-3, omega-6 or total polyunsaturated fats on new 9 neurocognitive illness and cognition. 10 Design and inclusion criteria: We carried out a systematic review and meta-analysis of 11 12 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 13 illness, newly impaired cognition, and/or continuous measures of cognition. 14 15 Methods: We searched Medline, Embase, Cochrane CENTRAL and trials registers (final 16 update of ongoing trials December 2018). We duplicated screening, data extraction and risk 17 of bias assessment. Neurocognitive measures were grouped to enable random-effects meta-18 analysis. GRADE assessment, sensitivity analyses and subgrouping by dose, duration, type 19 20 of intervention and replacement were used to interrogate our findings. 21 22 **Results:** Searches generated 37,810 hits, from which we included 38 RCTs (41 comparisons, 23 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, I² 24

25	36%), new	cognitive i	mpairment	(RR 0.99,	95% C	I 0.92 to	1.06, 5 F	RCTs, 33,296

26 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, I² 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.

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32	Conclusions: This extensive trial dataset enabled assessment of effects on neurocognitive
33	illness and cognitive decline not previously adequately assessed. Long-chain omega-3
34	probably has little or no effect on new neurocognitive outcomes or cognitive impairment.
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36	Implications: Long-chain omega-3 supplements do not help older adults protect against

37 cognitive decline.

38 Introduction

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40	Older adults, including those living in long-term care, are at high risk of cognitive
41	impairment, and neurocognitive ill-health. ¹⁻³ Fifty million people worldwide were living
42	with dementia in 2018, a number predicted to rise to 152 million in 2050. ⁴ Neurocognitive
43	disorders, including dementias, are major causes of health and social care cost, disability
44	adjusted life years and mortality worldwide. ⁵⁻⁷ Dementia costs worldwide are one trillion US
45	dollars annually and rising, with 66% of new cases in low- and middle-income countries. ⁴
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47	There is keen interest in potential cognitive protection offered by polyunsaturated fats,
48	particularly omega-3, ⁸⁻¹⁰ which is one of the most common dietary supplements. US adults'
49	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

52 key structural components of the brain and central nervous system and may help maintain

53 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.

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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.

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A 2012 Cochrane review assessed effects of omega-3 fats on neuro-cognition. That review 70 found no trials of incident dementia and included three RCTs assessing effects on cognition, 71 concluding that longer studies were required to allow time for greater cognitive changes to 72 occur.¹⁷ Our review aimed to systematically review effects of higher vs lower intakes of 73 74 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 75 controlled trials (RCTs) of at least 6 months duration. This review was commissioned to 76 77 inform the development of World Health Organization (WHO) guidance on polyunsaturated fatty acid intake. 78

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81 Methods

82 This systematic review and meta-analysis is one of a series assessing health effects of omega-

83 3, omega-6 and total PUFA,¹⁸⁻²⁶ its protocol was registered on PROSPERO

84 (CRD42017019049). Detailed methods for the review series are reported elsewhere,²³ and

85 briefly summarised for this review below.

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We included randomised controlled trials (RCTs) that compared higher versus lower omega-87 3, omega-6 and/or total PUFA intakes in adults (18+ years, not pregnant or seriously ill) with 88 89 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 90 foodstuffs, oral supplements (oil, capsules, or provided foodstuffs) or advice that increased or 91 92 decreased omega-3, omega-6 and/or total PUFA intake, or (if no specific aim was stated) achieved a change of $\geq 10\%$ of baseline intake. Studies were excluded if they carried out 93 94 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, 95 no supplementation or placebo (as appropriate), or compared raised versus lowered PUFA 96 97 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 98 into most body compartments, including the brain.²⁷ Studies were included if they collected 99 100 data on any primary outcome, even if study objectives were not primarily neuro-cognitive. 101 Primary outcomes were new neurocognitive illness, newly impaired cognition, global cognition, executive function, processing speed and memory (including verbal, spatial and 102 103 other memory and attention).

105 We searched Cochrane CENTRAL, Medline and Embase to 27th April 2017,

106 Clinical Trials.com and the World Health Organization International Clinical Trials Registry

107 Platform to September 2016, and reassessed all ongoing trials in December 2018. We

108 checked included trials of relevant systematic reviews, and wrote to authors of included

109 studies for additional studies and trial data (including unpublished summary outcome data).

110 See methods paper for detailed search strategies.²³

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112Study inclusion, data extraction and assessment of risk of bias (on a specially developed

113 form) were conducted independently in duplicate. We extracted study-level data and assessed

114 Cochrane risk of bias domains plus risk from compliance problems and attention bias.^{23, 28}

115 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

117 (all other trials were considered at moderate or high risk of bias).

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119 Analysis and Interpretation

Main analyses assessed effects of omega-6, LCn3, ALA and total PUFA interventions on 120 primary outcomes using random effects meta-analysis with risk ratio or mean differences in 121 Review Manager version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark).²⁹ Pre-122 123 specified sensitivity analyses included fixed effects analysis, limiting analysis to studies at 124 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 125 for outcomes with at least 10 included studies to assess whether effects differed by 126 127 intervention type (dietary advice, supplementary capsules, supplementary foods or a combination), replacement, dose, duration, baseline dementia (primary prevention where 128 <50% diagnosed with cognitive problems, secondary prevention where $\geq 50\%$ diagnosed with 129

130cognitive problems) and anti-dementia medication use in ≥50% participants.23 We planned to131sub-group by number of anti-dementia medications used, baseline intake of omega-3, omega-1326 or total PUFA, and omega-3/omega-6 ratio, but this information was not available in most133trials so was not attempted. We assessed heterogeneity between trials using I², and small134study bias using funnel plots and knowledge of missing data.

135

Because of the diversity of metrics used to measure cognitive function, pooled analysis was 136 often only possible by grouping similar measures. We standardised groupings by adopting 137 neurocognitive domains suggested by others,³¹⁻³³ placing data in a domain (and subdomain) 138 by researching the derivation, purpose and supported interpretation for each metric (Table 1). 139 140 The direction of scales in forest plots was standardised so that a lower score signified lower 141 levels of cognitive ability and different scales were combined meta-analytically using 142 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 143 preferred in this order in forest plots: thus, if a single study reported several tests within a 144 single domain all test results were displayed in the forest plot but only the first results for that 145 study (those nearest the top of the forest plot and Table 1) were pooled in meta-analysis, 146 ensuring that the most useful tests had as much available data as possible. Data from 147 individual participants were never counted more than once in any single meta-analytical 148 149 pooling.

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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 reviews²³. 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

155	\geq 5% of baseline was required for a relevant clinical effect for continuous measures. Outcome
156	data were interpreted using GRADE assessment, ²³ Where GRADE suggested data of very
157	low-quality we did not interpret effect sizes. Where data were of low-quality we used the
158	term "may", moderate-quality evidence warranted "probably" in describing effects.
159	
160	WHO funded the research, and the WHO NUGAG Subgroup on Diet and Health was
161	involved in its design, but not in data collection, analysis, interpretation or the decision to
162	publish. The exception is that GRADE assessment was drafted by LH then discussed and
163	agreed with NUGAG as part of guidance development. All researchers had full access to all
164	the data (within a shared database) and take responsibility for the accuracy and integrity of
165	the data.

168 **Results**

169 The broader search strategy for the full set of reviews generated 37,810 hits, de-duplicated to

170 19,772 titles and abstracts from which 364 RCTs (reported in 1020 papers) of omega-3,

171 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

173 outcomes of interest to this review (see Figure 1 of our database paper for PRISMA

174 flowchart;²³ Table 2 in this paper presents brief characteristics of included RCTs).

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176 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 177 LCn3, two compared higher with lower ALA³⁴⁻³⁶, 1 omega-6³⁷, one total PUFA³⁸⁻⁴⁰ and one 178 increased both omega-6 and total PUFA⁴¹. All trials were of capsular supplements except for 179 four LCn3 trials (one of supplementary margarine^{34, 35}, one of advice to eat more oily fish ⁴¹, 180 and two providing fish sausages^{42, 43}), both ALA trials (supplementary margarine^{34, 35} and 181 yogurt with added canola³⁶), the omega-6 trials (provided emulsified oil^{37} or advice to 182 increase specific oils and margarines⁴¹) and total PUFA trial (dietary advice plus oil or nut 183 184 supplements³⁸⁻⁴⁰). 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 185 cognition at baseline. Fifteen comparisons were at low summary risk of bias, see Figure 1 for 186 187 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. 188

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190 Six RCTs reported adverse neurological outcomes, including dementia, low cognitive

191 function, neurological hospitalisation and motor neurone disease^{41, 44-48}. Meta-analyses

192 suggested that increasing LCn3 had little or no effect on new neurocognitive diagnosis (RR

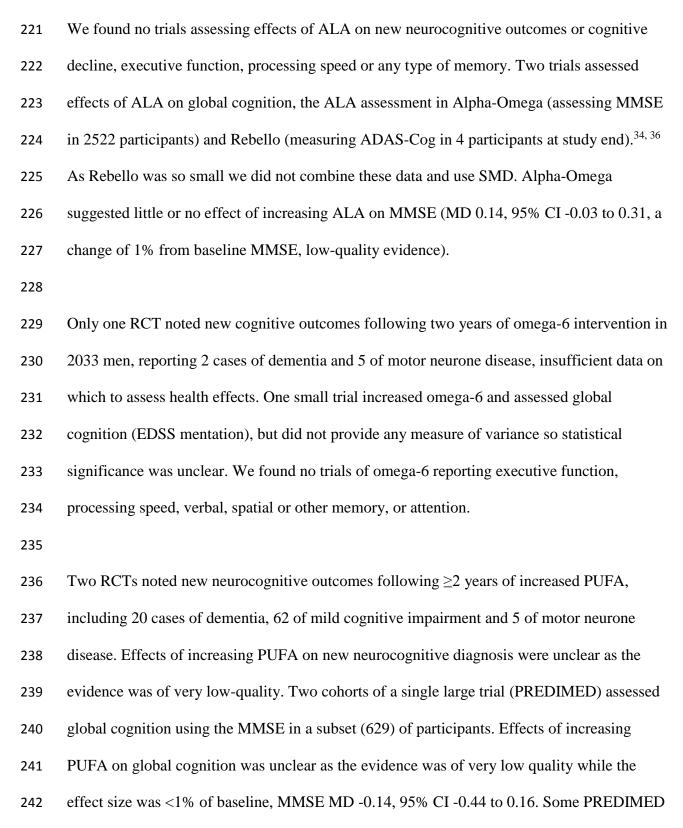
0.98, 95% CI 0.87 to 1.10, I² 36%, >33,000 participants of whom 2622 developed a
neurocognitive illness, moderate-quality evidence) and little or no effect on new cognitive
impairment (RR 0.99, 95% CI 0.2 to 1.06, I² 0%, >33,000 participants of whom 2551
developed impaired cognition, moderate-quality evidence), Figure 2. This lack of effect did
not alter in sensitivity analyses or when subgrouping by dose, duration or replacement by
LCn3 of other nutrients.

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Nineteen trials provided assessment of LCn3 on global cognition using at least one scale, 200 201 including >20,000 participants for ≥ 6 months, in people with normal cognition to moderate dementia at baseline. Effects in the 11 different scales provided different answers (test for 202 203 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 cognition, to 30, or normal cognition ⁴⁹). Increasing LCn3 led to a very small improvement in 205 MMSE, altering it by <1% of baseline (MD 0.10, 95% CI 0.03 to 0.16, I² 0%, Figure 3, 206 207 unaltered in sensitivity analyses, moderate-quality evidence), but we are aware of high levels of missing data and the funnel plot suggested small study bias (Figure A2 in the Appendix). 208 209 If we added small studies to correct this bias we would move the MD closer to zero (no effect). Subgrouping did not suggest differences in effect by LCn3 dose, duration, 210 replacement (of MUFA, omega-6 or non-fat), intervention type (supplemental foods or 211 212 capsules), baseline cognitive status (normal or impaired cognition), or cognitive medication 213 use. 214 Six trials (including 1757 participants) assessed executive function, five trials (including 215 1426 participants) assessed effects of LCn3 on processing speed, and eleven (including 5698 216

217 participants) assessed memory. Meta-analysis suggested little or no effect for all of these

218 measures (as well as the sub-categories of memory, all moderate- or low-quality evidence,219 see Appendix for further information).



243	participants were assessed for verbal memory, spatial memory and executive function. Data
244	were limited from this trial, which was at moderate to high summary risk of bias, suggesting
245	changes <5% of baseline for verbal memory and executive function. However, there was a
246	larger change in spatial memory, suggesting an improvement in spatial memory with more
247	PUFA (assessed using the Color Trail Test part 1, MD 7.17, 95% CI 0.48 to 13.86, $I^2 0\%$).
248	No trials assessed effects of increasing total PUFA on processing speed.
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252 **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.

259

260 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 261 assess effect sizes. Yurko-Mauro et al. reported significant between-group benefits for 262 263 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 264 265 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 266 inappropriate as it over-counts effects in some participants.³³ They did not find between-267 group differences for semantic or working memory outcomes. Zhang et al. pooled data from 268 six pre-2015 RCTs and found statistically significant but clinically unimportant differences in 269 MMSE (WMD = 0.15; 95% CI: 0.04-0.26; p = 0.006), results similar to this review.⁵⁰ It was 270 271 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 272 review and less able to accurately assess changes in cognition over time than longer trials. A 273 2013 systematic review of nutritional interventions for Alzheimer's Disease suggested that 274 long-chain omega-3 supplementation improved verbal fluency (in two small trials), might 275 276 support cognition in very mild AD (in one trial) but did not alter neuropsychiatric symptoms,

277 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 278 strategies in managing Alzheimer's Disease included six trials of omega-3⁵²⁻⁵⁴ ranked omega-279 280 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, 281 polypeptide, and vitamin D).⁵⁵ A 2018 systematic review of RCTs by Butler et al. assessing 282 effects of over-the-counter nutritional supplements found insufficient evidence to recommend 283 any supplement for cognitive protection in adults (including omega-3).⁵⁶ That review 284 285 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 286 beneficial effects on cognition or quality of life.⁵⁷ 287

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We found statistically significant but clinically unimportant effects of LCn3 on MMSE 289 scores, differing by <1% of baseline. The MMSE asks verbal questions to detect impaired 290 thinking and was developed, and is most validated, for dementia screening.⁵⁸ The three trials 291 contributing 94% of the weight to this analysis included 13,503 participants and were all of at 292 least 3 years duration. The largest was 6 years long, suggesting that the reason for the small 293 effect size was not that trials were too short or too small. Doses of LCn3 were 0.40, 0.84 and 294 1.04g/d, 0.84/d in the largest single RCT. Eating three portions of fish per week, one of 295 296 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 297 almost 4000 participants aged 60+ years for 5 years with a primary outcome of change in 298 cognitive function.⁵⁹ VITAL cardiovascular outcomes were published in late 2018, but 299 cognitive outcomes are not expected until late 2020. 300

302 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 303 provided. There were no suggestions that effects of foods were different from those of 304 305 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 306 omega-6 ratio theory is important, we also assessed whether effects differed by replacement 307 308 (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 309 310 Appendix page 3, as would be expected if some included trials are too short or of too low a dose. 311

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313 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 314 found neither benefits nor harms, and low-quality evidence of little or no effect of ALA on 315 global cognition. Evidence of any effect of ALA, omega-6 and total PUFA on 316 neurocognitive outcomes and cognition are lacking. Other potential reasons for increasing 317 polyunsaturated fat intake, including effects on cardiovascular diseases, cancers, 318 inflammatory bowel disease, body weight, diabetes and glucose metabolism, depression and 319 320 anxiety and all-cause mortality, have been considered elsewhere in our series of systematic reviews.18-20, 23, 60-64 321

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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 327 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

- 329 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.

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333 Conclusions and implications

People concerned about their cognitive health should be advised that taking long-chain

335 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
- 337 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
- 339 dietary advice for cognition.
- 340
- 341 **Ethical approval:** No ethical approval was required.

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603	Figure titles
604	
605	Figure 1. Risk of bias assessment for each included trial by risk of bias domain
606	
607	Figure 2. Effects of increased LCn3 on neurocognitive outcomes individually and grouped, random
608	effects meta-analysis.
609	
610	Figure 3. Effects of increased LCn3 on measures of global cognition, random effects meta-analysis.
611	(Different measures not combined as the test for subgroup differences suggested severe heterogeneity
612	between tests.)

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

Cognitive	Sub-domain	Measures*
domains		
Diagnosis of		Dementia diagnosis
cognitive decline		• 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) Clobal basis values abases
		Global brain volume change Clabal consisting for sting a construction of the structure of the struc
Executive function		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)
	• BCAT, perceptual speed
	Stroop total correct RT
	• Processing speed z-score (study-specific batteries)
	Others

614

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

Study	Participant age profile	Participant characteristics &	Duration	Country	Comparison	Number randomised		Summary Risk of
		cognition				Intervention	Control	Bias
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	\geq 60 yrs	Older adults with mild cognitive impairment (I)	6 m	China	EPA+DHA vs. MUFA	44	42	МоН
Boespflug 2016	62-80 yrs	Older adults with subjective memory impairment (I)	6 m	USA	EPA+DHA vs. LA	15	12	МоН
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	МоН
DART 1989 (fat) ⁴¹	<70 yrs	Men recovering from an MI (N)	2 yrs	UK	n6 vs. mixed fats	(1018)	(1015)	МоН
DART 1989 (fish) ⁴¹	<70 yrs	Men recovering from an MI (N)	2 yrs	UK	EPA+DHA vs. nil	1015	1018	MoH

SR of omega-3, omega-6 & total PUFA for cognition, page 26

Study	Participant age profile	Participant characteristics &	Duration C	Country	Comparison	Number randomised		Summary Risk of
	8	cognition				Intervention	Control	Bias
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 \geq 26, MAC-Q score > 24) (I)	6 m	UK	high DHA vs. low DHA+PUFA	33	32	МоН
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	МоН
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	\geq 65 yrs	Independently living people (N)	6 m	Netherlands	EPA+DHA vs. MUFA	96	103	MoH
MIDAS 2010 ⁷⁶	\geq 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

SR of omega-3, omega-6 & total PUFA for cognition, page 27

Study	Participant age profile	Participant characteristics &	Duration	Country	Comparison	Number rai	ndomised	Summary Risk of
		cognition				Intervention	Control	Bias
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 &	Duration	Country	Comparison			Summary Risk of
		cognition				Intervention	Control	Bias
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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Attention	Compliance	Other bias
ADCS-Quinn 2010	•	•	•	•	•	•	•	?	•
AlphaOmega - ALA	•	•	•	•	•	•	•	•	•
AlphaOmega - EPA+DHA	•	•	•	•	•	•	•	•	÷
AREDS2 2014	•	•	•	•	•	•	•	?	•
ASCEND 2018	•	•	•	•	•	•	•	?	•
Baleztena 2015	?	?	?	?	?	?	?	?	?
Bo 2017	•	?	?	?	•	•	•	•	•
Boespflug 2016	?	?	?	•			•	?	•
Chiu 2008	?	?	•	•		•	•	+	?
Chiu 2010	?	?	?	?	?	?	?	?	?
DART fat 1989 DART fish 1989	•	? ?	•	•	•	?		?	•
EPOCH 2011	•	•	•	•	• ?		•	•	•
Hashimoto 2012	?	?	•	•	• ?	•	•	•	•
Hashimoto 2016	?	?	?	?	•	?	•	•	•
Jackson 2016	•	•	•	?	•	•	•	•	•
Lee 2012	•	?	?	•	•	?	•	•	•
MAPT 2017	•	•	•	•	•	•	•	?	•
MEMO van de Rest 2008	•	?	•	•	•	•	•	•	•
MIDAS 2010	•	•	•	+	•	•	•	•	÷
Nutristroke Antiox 2009	?	?	?	÷		?	•	?	+
Nutristroke No Antiox	?	?	?	•	•	?	•	?	•
OFAMS Torkildsen 2012	•	•	?	•	•	•	•	•	•
OmegAD 2008	•	?	?	?	•	•	•	•	?
OPAL - Dangour 2010	•	•	•	•	•	•	•	•	•
ORIGIN 2013	•	•	•	•	•	•	•	?	•
Paty 1978	?	?	?	?	•	?	?	?	•
Pomponi 2014	•	?	?	?	•	?	•	?	•
PREDIMED 2013				•	•	•	•	?	
Puri 2005 Raitt 2005	•	•	+ ?	•	•	?	•	? +	•
Ralit 2005 Rebello 2015	•	' ?	' ?	•			•	•	•
Romero 2013	• ?	• ?		• ?	?	• ?	•	• ?	• ?
Schattin 2016	•	•	•	•	•	•	•	•	•
SCIMO - von Schacky 1999	•	•	•	•	?	?	•	•	•
Shinto 2014	•	?	•	•	•	•	•	•	•
Sinn 2012	•	•	•	•	•	•	•	•	•
Stonehouse 2013	•	•	?	•	•	•	•	+	•
SU.FOL.OM3 Galan 2010	•	•	•	+	•	•	•	•	+
Terano 1999	?	•	•	•	•	?	?	•	•
Zhang 2017	•	?	•	+	?	•	•	?	?

Figure 2 eps format

11.10 Emerantia ASCEND 2018 (1) (122 7740 132 7	Study or Subgroup	Higher om Events	nega 3 Total	Lower on Events	-	Weight	Risk Ratio M-H, Random, 95% C	Risk Ratio M-H, Random, 9	Risk of Bias 5% CI A B C D E F G H I
ASCERD 2018 (1) 128 7740 132 7740 136%, 0.07 (076, 123) ART Ish 1999 2 1015 0 1018 0.1%, 0.50 [027, 103] Subtoal (25%, C1) 1514 100, 7% 0.26 [0.8, 1.05] Subtoal (25%, C1) 1514 100, 7% 0.26 [0.8, 1.05] Heavoganety, Tar = 0.00, Chr = 1.01, df = 3 (P = 0.65); F = 0% Heavoganety, Tar = 0.00, Chr = 1.01, df = 3 (P = 0.65); F = 0% Heavoganety, Tar = 0.00, Chr = 1.01, df = 3 (P = 0.65); F = 0% Heavoganety, Tar = 0.00, Chr = 1.01, df = 3 (P = 0.65); F = 0% Heavoganety, Tar = 0.00, Chr = 1.01, df = 3 (P = 0.65); F = 0% Heavoganety, Tar = 0.00, Chr = 1.01, df = 3 (P = 0.65); F = 0% Heavoganety, Not applicable Test for owerst Heavoganety, Not applicable Test for owerst Heavoganety Heavoganety Not applicable Test for owerst Heavo							, , / · · / · ·		
DART Ish 1989 2 1015 0 1016 0.1% 0.0 (0.4, 104.32) SCIMO - von Schnaby 1999 1 112 0 111 0.1% 2.27 (0.4, 7.2.21) SCIMO - von Schnaby 1999 1 1544 1512 100.0% SCIMO - von Schnaby 1999 1 1544 1512 100.0% SCIMO - von Schnaby 1999 1 1544 1512 100.0% SCIMO - von Schnaby 1999 1 154 1512 100.0% SCIMO - von Schnaby 1999 1 152 0 171 100.0% SCIMO - von Schnaby 1999 1 152 0 171 100.0% SCIMO - von Schnaby 1999 1 152 0 171 100.0% SCIMO - von Schnaby 1999 1 152 0 170 100.0% SCIMO - von Schnaby 1999 1 152 0 1016 100.0% SCIMO - von Schnaby 199 1 152 0 1016 100.0% SCIMO - von Schnaby 199 1 152 0 177 40 100.0% SCIMO - von Schnaby 199 1 152 0 177 40 100.0% SCIMO - von Schnaby 199 1 152 0 177 40 100.0% SCIMO - von Schnaby 199 1 152 0 171 0.00 % SCIMO - von Schnaby 199 1 152 0 1111 0.1% SCIMO - von Schnaby 199 1 152 0 1111 0.1% SCIMO - von Schnaby 199 1 152 0 1111 0.1% SCIMO - von Schnaby 199 1 152 0 1111 0.1% SCIMO - von Schnaby 199 1 152 0 1111 0.1% SCIMO - von Schnaby 199 1 152 0 1111 0.1% SCIMO - von Schnaby 199 1 152 0 1111 0.1% SCIMO - von Schnaby 199 1 152 0 1111 0.1% SCIMO - von Schnaby 199 1 152 0 1111 0.1% SCIMO - von Schnaby 199 1 152 0 1111 0.1% SCIMO - von Schnaby 199 1 152 0 1111 0.1% SCIMO - von Schnaby 199 1 152 0 1111 0.1% SCIMO - von Schnaby 199 1 152 0 111 0.1% SCIMO - von Schnaby 199 1 152 0 111 0.1% SCIMO - von Schnaby 199 1 152 0 111 0.1% SCIMO - von Schnaby 199 1 152 0 111 0.1% SCIMO - von Schnaby 199 1 152 0 111 0.1% SCIMO - von Schnaby 199 1 152 0 111 0.0% SCIMO - von Schnaby 199 1 152 0 111 0.0% SCIMO - von Schnaby 199 1 152 0 111 0.0% SCIMO - von Schnaby 199 1 152 0 111 0.0% SCIMO - von Schnaby 199 1 152 0 111 0.0% SCIMO - von Schnaby 199 1 152 0 111 0.0% SCIMO - von Schnaby 199 1 152 0 111 0.0% SCIMO - von Schnaby 199 1 152 0 111 0.0% SCIMO - von Schnaby 199 1 152 0 111 0.0% SCIMO - von Schnaby 199 1 152 0 111 0.0% SCIMO - von Schnaby 199 1 152 0 111 0.0% SCIMO - von Schnaby 199 1 152 0 111 0.0% SCIMO - von Schnaby 199 1 152 0 111 0.0% SCIMO - von Schnaby 199 1	ASCEND 2018 (1)	128	7740	132	7740	13.6%	0.97 [0.76, 1.23]	+	
SCMD-over Schedury 1999 1 112 0 111 0.1% 2.27 (0.12, 72, 21) Untercognetity. Trail = 0.00; Ch ⁺ = 1.44, df = 3 (P = 0.55); F = 0% Test for overall effect: Z = 0.29; (P = 0.36) 1.1.2 Low cognitive function (TCS score <30) KL2 Low cognitive function (TCS score <30) KL3 Reversely; Not applicable Test for overall effect: Z = 0.56; P = 0.66; 1.1.4 Motor neurone disease DART Ent 1989 Subtolal (95%; C1) 100 6 100 100.0% Cost (0.00, 1.35) L1.4 Motor neurone disease DART Ent 1989 Subtolal (95%; C1) 1015 0 1018 100.0% Total events 3 0 Heterogenety; Not applicable Test for overall effect: Z = 1.76; (P = 0.08) 1.1.4 Motor neurone disease DART Ent 1989 Subtolal (95%; C1) 1015 0 1018 100.0% Total events 3 0 Heterogenety; Not applicable Test for overall effect: Z = 1.76; (P = 0.08) 1.1.4 Motor neurone disease DART Ent 1989 Subtolal (95%; C1) 1015 1018 100.0% Total events 3 0 Heterogenety; Not applicable Test for overall effect: Z = 1.52; (P = 0.20) 1.1.4 Motor neurone disease DART Ent 1989 Subtolal (95%; C1) 1015 1018 100.0% Cost (0.41, 1.12) Cost (0.5, 135, 74] Total events 3 0 Heterogenety; Not applicable Test for overall effect: Z = 1.52; (P = 0.13) 1.1.4 Roty neurocognitive diagnosis SUBMO 2018 153 7740 160 7740 20.0% 0.95 (0.84; 1.14] SUBMO 2018 153 7740 160 7740 20.0% 0.95 (0.87, 1.16] SUBMO 2018 153 7740 160 7740 20.0% 0.95 (0.87, 1.16] SUBMO 2018 153 7740 160 7740 20.0% 0.95 (0.87, 1.16] SUBMO 2018 153 7740 160 7740 20.0% 0.95 (0.87, 1.16] SUBMO 2018 153 7740 160 7740 20.0% 0.95 (0.87, 1.16] SUBMO 2018 153 7740 160 7740 20.0% 0.95 (0.87, 1.16] SUBMO 2018 153 7740 160 7740 20.0% 0.95 (0.87, 1.16] SUBMO 2018 153 7740 160 7740 20.0% 0.95 (0.87, 1.16] SUBMO 2018 153 7740 160 7740 20.0% 0.95 (0.87, 1.16] SUBMO 2018 153 7740 160 7740 20.0% 0.95 (0.87, 1.16] SUBMO 2010 Ch ⁺ 2 2.84, 1753 27740 87, 0.97	. ,	2	1015	0	1018	0.1%			
Subtola (95% Cf) 154 (95% Cf) 154 (95% Cf) 1521 (95% Cf) 1512 (95% Cf) 1513 (95% Cf) 153 (95% Cf) 1553 (9	ORIGIN 2013	722	6281	753	6255	86.2%	0.95 [0.87, 1.05]		
Total events 9.83 B85 Hereorganeity: Two overall offect: $Z = 0.22$ ($P = 0.36$); $P = 0\%$ Test for overall offect: $Z = 0.52$ ($P = 0.65$); $P = 0\%$ Hit2 Low cognitive function (TLCS score <30) Ht2ES2 2014 416 1521 397 1503 100.0% 1.04 [0.92, 1.16] Subtolal (9% C) 416 1521 397 1503 100.0% 1.04 [0.92, 1.16] Test for overall offect: $Z = 0.52$ ($P = 0.56$) H1.3 Neurologic hospitalisation Fast 2005 2014 100 100 5 100 100.0% 0.09 [0.00, 1.35] Hereorganeity: Not applicable Test for overall offect: $Z = 1.76$ ($P = 0.06$) Hereorganeity: Not applicable Test for overall offect: $Z = 1.76$ ($P = 0.06$) Hereorganeity: Not applicable Test for overall offect: $Z = 1.72$ ($P = 0.06$) Hereorganeity: Not applicable Test for overall offect: $Z = 1.72$ ($P = 0.06$) Hereorganeity: Not applicable Test for overall offect: $Z = 1.72$ ($P = 0.02$) H.1.5 Parkinson's disease SocKDM 2016 25 7740 7740 100.0% 0.68 [0.41, 1.12] Total events 3 0 Hereorganeity: Not applicable Test for overall offect: $Z = 1.52$ ($P = 0.13$) H.1.6 Any neuroconglitive diagnosis ART fini 1989 5 1015 0 1016 100.0% 0.68 [0.41, 1.12] Total events 25 37 Hereorganeity: Not applicable Test for overall offect: $Z = 1.52$ ($P = 0.13$) H.1.6 Any neuroconglitive diagnosis ART Constant $S = 0.00$ ($O = 0.00$ 100 6 100 0.2% 0.058 [0.61, 1.12] SCIMD : 0.01 C, Dir $P = AK$, if $z = 0.77$; P = 30%. SCIMD : 0.01 C, Dir $P = AK$, if $z = 0.77$; P = 30%. SCIMD : 0.01 C, Dir $P = AK$, if $z = 0.77$; P = 30%. SCIMD : 0.01 C, Dir $P = AK$, if $z = 0.77$; P = 30%. SCIMD : 0.01 SOL 24 2 = 0.08] H.1.7 Compative defined are	SCIMO - von Schacky 1999	1	112	0	111	0.1%	2.97 [0.12, 72.21]		·
Heerogeneity: Tar 2 = 0.00; Ch ² = 1.64; df = 3 (P = 0.68); P = 0%; Text for varial effect: 2 = 0.32 (P = 0.38) 1.1.2 Low cognitive function (TICS score <30) AREDS 2 2014 416 1521 397 1503 100.0% 1.04 [0.52, 1.16] 1.04 [0.52, 1.16] 1.1.3 Neurologic hospitalisation Rati 2005 0 1 100 6 100 100.0% 0.08 [0.00, 1.35] 0.08 [0.00, 1.35] 1.1.3 Neurologic hospitalisation Rati 2005 0 1 100 7 100 100.0% 0.08 [0.00, 1.35] 1.1.4 Normal effect: 2 = 1.58 (P = 0.58) 1.1.4 Neurologic hospitalisation Rati 2005 0 1 1015 0 1018 100.0% 7.02 [0.36, 135, 74] 1.1.4 Normal effect: 2 = 1.52 (P = 0.20) 1.1.4 Neurologic hospitalisation Rati Roward effect: 2 = 1.52 (P = 0.20) 1.1.4 Neurologic hospitalisation Rati Roward effect: 2 = 1.52 (P = 0.20) 1.1.5 Parkinson's disease ASCEND 2016 25 7740 37 7740 100.0% 0.68 [0.41, 1.12] 1.1.6 Any neurocognitive diagnosis AREDS2 2014 416 1521 397 1503 37.2% 1.04 [0.92, 1.16] ASCEND 2016 153 7740 100 1018 0.01% 0.91 [0.73, 1.12] ASCEND 2016 153 7740 100 1018 0.01% 0.91 [0.73, 1.12] ASCEND 2016 153 7740 100 0% 0.93 [0.87, 1.10] CRGM 2013 722 6281 753 6285 42.3% 0.98 [0.87, 1.59] CRGM 2013 722 6281 753 6285 42.3% 0.98 [0.87, 1.59] CRGM 2013 722 6281 753 6285 42.3% 0.98 [0.87, 1.59] CRGM 2013 722 6281 753 6285 42.3% 0.98 [0.87, 1.59] CRGM 2013 722 6281 753 6285 42.3% 0.98 [0.87, 1.59] CRGM 2013 722 6281 753 6285 42.3% 0.98 [0.87, 1.59] CRGM 2013 722 6281 753 6285 42.3% 0.98 [0.87, 1.59] CRGM 2013 722 6281 753 6285 42.3% 0.98 [0.87, 1.59] CRGM 2013 722 6281 753 6285 42.3% 0.98 [0.87, 1.59] CRGM 2013 722 6281 753 6285 42.4% 0.95 [0.57, 1.59] CRGM 2016 27 (0.188 26, 1.40 (P = 0.58) 1.1.7 Cognitive decline -desmati 102 770 180 38.4% 1.04 [0.92, 1.16] CRGM 2013 722 6281 753 6285 42.4% 0.98 [0.87, 1.59] CRGM 2013 722 6281 753 6285 42.4% 0.96 [0.7, 1.59] CRGM 2013 722 6281 753 6285 44.8% 0.96 [0.50, 1.59] CRGM 2013 722 6281 753 6285 44.8% 0.96	Subtotal (95% CI)		15148		15124	100.0%	0.96 [0.88, 1.05]	•	
Tast for overfall effect: $Z = 0.92 (P = 0.36)$ 1.1 2. Low cognitive function (TICS score -30) AREDS2 2014 416 1521 397 1503 100.0% 1.04 [0.52, 1.16] Subtotal (95% C) 416 1521 397 1503 100.0% 1.04 [0.52, 1.16] Total events 416 397 Teat for overfall effect: $Z = 0.56$) 1.1.3 Neurologic hospitalisation Tata for overfall effect: $Z = 0.56$) 1.1.3 Neurologic hospitalisation Total events 0 6 Helerogeneity: Not applicable Test for overfall effect: $Z = 1.76 (P = 0.08)$ 1.1.4 Motor neurone disease DART fish 1686 3 1015 0 1016 100.0% 7.02 [0.36, 135.74] 7.02 [0.36, 10.7, 1.12] 7.03 [0.01, 135] 7.740 100.0% 0.58 [0.41, 1.12] 7.04 [0.02, 1.16] 7.04 [0.02, 1.16] 7.05 [0.01, 135] 7.740 100.0% 0.58 [0.41, 1.12] 7.04 [0.02, 1.16] 7.04 [0.02, 1.16] 7.05 [0.01, 135] 7.740 100.0% 0.58 [0.41, 1.12] 7.05 [0.01, 135 [0.01, 115] 7.05 [0.01, 12, 22.71] 7.05 [0.01, 12, 22.71] 7.00.0% 0.98 [0.87, 1.10] 7.01 [0.01, 12, 22.71] 7.02 [0.02, 1.22, 22.1] 7.02 [0.02, 1.22, 22.1] 7.02 [0.02, 1.22, 22.1] 7.03 [0.02, 1.22] 7.04 [0.02, 1.22] 7.05 [0.02, 1.22] 7.04 [0.02, 1.22] 7.05 [0.02,	Total events	853		885					
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Subtotal (95% Cl) 16669 16627 100.0% 0.99 [0.92, 1.06] Total events 1269 1282 Heterogeneity: Tau² = 0.00; Chi² = 2.68, df = 4 (P = 0.61); l² = 0%									
Total events 1269 1282 Heterogeneity: Tau² = 0.00; Chi² = 2.68, df = 4 (P = 0.61); l² = 0%				0				4	
Heterogeneity: Tau ² = 0.00; Chi ² = 2.68, df = 4 (P = 0.61); l ² = 0%		1269		1282			,		
			= 4 (P -		0%				
				5.51), 1 -	070				
0.01 0.1 1 10 100									
Fest for subgroup differences: Chi ² = 7.90, df = 6 (P = 0.25), l ² = 24.1% Favours higher omega 3 Favours lower omega 3	est for subgroup differences:	Chi² = 7.90.	df = 6 (F	P = 0.25), l ²	² = 24.1%			Favours higher omega 3 Favo	urs lower omega 3

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

itudy or Subgroup	Highe Mean	r omega SD	3 Total	Lowe Mean	er omega SD		Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% Cl	Risk of Bias
.2.1 MMSE										
DCS-Quinn 2010	-3.7	5.79	238	-4.04	5.3	167	0.4%	0.34 [-0.75, 1.43]		
IphaOmega - EPA+DHA	-0.65	2.2537	1240	-0.69	2.2557	1282	13.6%	0.04 [-0.14, 0.22]		222222222
Baleztena 2015 (1)	-0.82	4.4	49	-1.18 25.09	3.7	49	0.2% 0.1%	0.36 [-1.25, 1.97]		
hiu 2008	25.47	3.81	17		3.67 3.4	12 20		0.38 [-2.38, 3.14]		2222020
ashimoto 2016 ee 2012	-2 26.6	4.1 1.8127	28 17	-2.13 26.5	3.4 1.8701	20 18	0.1% 0.3%	0.13 [-2.00, 2.26]		
APT 2017 (2)	-0.305	1.8763	381	20.5 -0.299	1.8192	366	0.3% 6.0%	0.10 [-1.12, 1.32] -0.01 [-0.27, 0.26]	Ļ	
APT 2017 (2) APT 2017 (3)	-0.305	1.849	374	-0.299	1.8783	390	6.0%	0.00 [-0.26, 0.27]	ļ	
IDAS 2010	-0.18	1.049	241	27.9	1.0703	242	3.7%	0.10 [-0.24, 0.44]	4	
megAD 2008	22.8	4.2724	89	22.4	4.6362	85	0.2%	0.40 [-0.93, 1.73]		
RIGIN 2013	27.66	2.1106	4756	27.54	1.7529	4724	68.9%	0.12 [0.04, 0.20]		
mponi 2014	27.1	1.4	12	27.04	1.7 02.5	12	0.3%	0.10 [-1.06, 1.26]		
into 2014	-4.3	1.4	11	-4.6	1.4	11	0.3%	0.30 [-0.83, 1.43]		
rano 1999	21.9	6.6	10	19.1	7.5	10	0.0%	2.80 [-3.39, 8.99]		?
btotal (95% CI)	21.9	0.0	7463	19.1	7.5	7388	100.0%	0.10 [0.03, 0.16]		
terogeneity: Tau ² = 0.00;	Chi ² = 3.19	, df = 13		00); l² = (0%	/ 500	100.070	0.10 [0.03, 0.10]		
st for overall effect: Z = 2.	.92 (P = 0.0	03)								
.2 ADAS-Cog 11 CS-Quinn 2010 (4)	-8.27	8.9	238	-7.98	9.84	164	37.2%	-0.29 [-2.17, 1.59]		
u 2008 (5)	-5.9	5.63	17	-5.57	4.76	12	9.1%	-0.33 [-4.13, 3.47]		
negAD 2008 (6)		10.9185	89		10.6632	85	12.8%	0.60 [-2.61, 3.81]		
into 2014 (7)	-27.7	2.2	11	-28.3	2.1	11	40.8%			
btotal (95% CI)	-4.4	2.2	355	-3.Z	2.1	272		-1.20 [-3.00, 0.60] -0.55 [-1.70, 0.60]		
	01.12			0.10.00		212	100.0%	-0.55 [-1.70, 0.60]		
erogeneity: Tau² = 0.00; at for overall effect: Z = 0.			P = 0.7	8); I ² = 0 ⁴	%					
3 CDR										
CS-Quinn 2010	11.5	13.23	238	10.43	11.74	164	0.1%	1.07 [-1.39, 3.53]	- +-	•••••
PT 2017 (8)		1.0819	374	0.363	1.0949	390	31.1%	-0.06 [-0.21, 0.10]	↓	
PT 2017 (9)		1.1019	381	0.297	1.0906	380	30.6%	-0.01 [-0.17, 0.14]	÷	
eqAD 2008		0.4747	89	1.1	0.4636	85	38.2%	0.00 [-0.14, 0.14]		
ototal (95% CI)			1082		2	1019	100.0%	-0.02 [-0.11, 0.07]		
erogeneity: Tau ² = 0.00;	$Chi^2 = 1.00$	/ df = ٦		8)· I2 - 00	%					
for overall effect: Z = 0.			0.7	⊖, i = 0°	70					
4 CBIC Plus Caregiver		,								
iu 2008 (10)	-3.23	1.15	17	-3.91	1.38		100.0%	0.68 [-0.27, 1.63]		??+++
btotal (95% CI)			17			12	100.0%	0.68 [-0.27, 1.63]	◆	
terogeneity: Not applicabl	le									
st for overall effect: Z = 1.		6)								
	,									
.5 Hasegawa's Dementi	-									
ano 1999	20.2	5.6	10	15.3	7.1			4.90 [-0.70, 10.50]	+	? • • • • ? ? • •
btotal (95% CI)			10					4.90 [-0.70, 10.50]		
terogeneity: Not applicabl	le									
st for overall effect: Z = 1.		9)								
		'								
2.6 F-TICS score										
	20 E	10	077	20 E	4.0	071	100.0%	0.00 [0.45 0.45]		
J.FOL.OM3 Galan 2010	28.5	4.8	877	28.5	4.9		100.0%	0.00 [-0.45, 0.45]	—	
ubtotal (95% CI)			877			871	100.0%	0.00 [-0.45, 0.45]	▼	
eterogeneity: Not applicabl	le									
est for overall effect: Z = 0.	.00 (P = 1.0	0)								
2.7 BCAT total score, co										
o 2017 (11)	-44.73	13.87	44	-37.17	16.85		100.0%	-7.56 [-14.10, -1.02]	←	•???••••
ubtotal (95% CI)			44			42	100.0%	-7.56 [-14.10, -1.02]		
eterogeneity: Not applicabl	le									
st for overall effect: Z = 2.	.27 (P = 0.0	2)								
		,								
2.8 IQ										
nang 2017	115.37	6.52	110	107.65	9.52	100	100.0%	7.72 [5.56, 9.88]		$\bullet ? \bullet \bullet ? \bullet \bullet ? ?$
ubtotal (95% CI)	110.07	0.02	110	107.00	9.32		100.0%	7.72 [5.56, 9.88]		
. ,	le		110			103	100.070	1.12 [0.00, 9.00]		
terogeneity: Not applicabl		0001								
st for overall effect: Z = 7.	.00 (P < 0.0	0001)								
0 Global hasin	obc	tot-l								
2.9 Global brain volume,	-									
ri 2005	0.75	0.86	14	1.22	0.8	16	99.9%	-0.47 [-1.07, 0.13]		
ang 2017	994.69	79.67		994.98	83.88	109	0.1%	-0.29 [-21.96, 21.38]	· · · · · · · · · · · · · · · · · · ·	a 5 a a 5 6 a a 5 6
btotal (95% CI)			124			125	100.0%	-0.47 [-1.07, 0.13]	•	
eterogeneity: Tau ² = 0.00;	Chi ² = 0.00	, df = 1 (l	P = 0.9	9); l ² = 0 ⁴	%					
st for overall effect: Z = 1.										
	,									
2.10 Global cognitive fur	nction z-sc	ore								
REDS2 2014 (12)	-0.034		1318	0	2.18	1318	7.1%	-0.03 [-0.20, 0.13]	4	
PAL - Dangour 2010	-0.01	0.31	375	0	0.33	369	92.9%	-0.01 [-0.06, 0.04]		ĠĞĞĞĞĞĞĞ
btotal (95% CI)	0.01	5.51	1693	v	0.00	1687	100.0%	-0.01 [-0.06, 0.04]	—	
terogeneity: Tau ² = 0.00;	$Chi^2 = 0.07$	df = 1 /		9)· 12 - 00	%			[
st for overall effect: Z = 0.			5.7	-,0						
		,								
.12 Global delay z-score	е									
PAL - Dangour 2010	0.03	0.54	375	0	0.55	360	100.0%	0.03 [-0.05, 0.11]		
btotal (95% CI)	0.00	0.04	375	5	5.00	369	100.0%	0.03 [-0.05, 0.11]		
	lo		2.0				//			
erogeneity: Not applicabl		5)								
t for overall effect: Z = 0.	.15 (P = 0.4	·0)								
									-10 -5 0 5 10	
									Favours lower omega 3 Favours higher omega 3	
st for subgroup difference	es: Chi² = 70	0.39, df =	10 (P	< 0.0000	1), l² = 85	.8%			the second se	
otnotes									Risk of bias legend_	
) SDs unlikely, calculated :	assuming S	SEs							(A) Random sequence generation (selection bias)	
) PUFA vs placebo arms o									(B) Allocation concealment (selection bias)	
		VIC MALE	idom - '	inter :-	tion n!	nlass -	ormo '	N.		vo bias)
) Multidomiain intervention	i pius PUFA	n vs multi	uomair	rinterven	nion plus	piacebo	anns onl	у	(C) Blinding of participants and personnel (performance)	e uids)
) multiplied mean by -1									(D) Blinding of outcome assessment (detection bias)	
) multiplied mean by -1									(E) Incomplete outcome data (attrition bias)	
) multiplied mean by -1									(F) Selective reporting (reporting bias)	
) multiplied mean by -1									(G) Attention	
		Ve More	idom-'	intor	tion plus		armo'	N .		
) Multidomiain intervention		∧ vs i∕lulti	uomair	i interven	nion plus	piacebo	arms onl	у	(H) Compliance	
) PUFA vs placebo arms o	лпу								(I) Other bias	
0) multiplied by -1										
1) multiplied mean by -1										
 Composite score of all of 	cognitive to	sts								
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PRISMA checklist

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